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Original Article

PD-1 inhibitors combined with chemotherapy versus chemotherapy alone: efficacy and prognostic analysis in recurrent metastatic nasopharyngeal carcinoma

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Abstract: Objective: To evaluate the prognostic value of combining PD-1 inhibitors (toripalimab or karelizumab) with chemotherapy for treating recurrent or metastatic nasopharyngeal carcinoma (R/M NPC). Methods: This study retrospectively analyzed 142 patients with R/M NPC diagnosed from January 2018 to January 2022. Patients were divided into PD-1 inhibitor combined with chemotherapy group (53 patients) and chemotherapy alone group (89 patients) according to the treatment regimen. Objective remission rate (ORR), progression-free survival (PFS), and treatment-related toxicity were evaluated in both groups. Results: The overall response rate (P=0.006) and objective remission rate (ORR) (P=0.002) were significantly higher in the combination chemotherapy group than in the chemotherapy-alone group. The incidences of hypothyroidism (P<0.001) and reactive capillary hyperplasia (P<0.001) were significantly higher in the combination chemotherapy group than in the chemotherapy-alone group. Cox regression analysis showed that treatment regimen (P<0.001), age (P<0.001), treatment duration (P=0.002), and number of treatment lines (P=0.034) were independent prognostic factors affecting patients' PFS. The prediction model constructed based on these prognostic factors had high accuracy in predicting 1-year and 2-year PFS (AUC 0.746 and 0.760, respectively). Conclusion: PD-1 inhibitors in combination with chemotherapy significantly improved the ORR and median PFS of patients with R/M NPC, while maintaining a favorable safety profile. Treatment regimen, age, number of lines and cycle of therapy were important independent prognostic factors for improving PFS in patients.

Keywords: Karelizumab, recurrent metastatic nasopharyngeal carcinoma, combination chemotherapy, prediction model, toripalimab

Introduction

Nasopharyngeal carcinoma (NPC), a malignant tumor originating from the nasopharyngeal epithelium, exhibits significant geographic variations in incidence. It is relatively common in regions such as North Africa, Southeast Asia, and Southern China, but rare in western countries, including Europe and the America [1, 2]. Worldwide, NPC accounts for 0.7% of all new cancer cases and 0.8% of all cancer deaths [3]. Despite its high sensitivity to radiotherapy and chemotherapy, leading to an optimistic prognosis for most patients, approximately 15-30% are at risk of local recurrence or distant metastasis after radical treatment. For these patients, the median overall survival is approximately 20 months, underscoring the challenges of treating recurrent or metastatic NPC (R/M NPC) [4].

Platinum-based doublet chemotherapy regimens have traditionally been the cornerstone of treatment for patients with R/M NPC as standard of care [5]. However, the advent of immunotherapy, particularly immune checkpoint inhibitors (ICIs), has changed the therapeutic landscape for R/M NPC by explicitly tar-

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geting the PD-1 and PD-L1 pathways [6]. PD-1, a critical immunosuppressive molecule, is primarily found on T, B, and natural killer cells [7]. Its ligand, PD-L1, expressed on various cell types, including epithelial and immune cells, interacts with PD-1 to inhibit T-cell function and induce apoptosis, allowing tumor cells to escape immune surveillance and clearance. PD-1 inhibitors, known for their unique mechanism of action and significant efficacy in multiple malignancies, have received considerable attention in tumor immunotherapy [8]. Toripalimab and karelizumab, both PD-1 inhibitors, have shown promise in activating the immune system to target and block the PD-1 pathway, thereby enhancing the anticancer capabilities of T cells [9, 10]. Toripalimab, a fully humanized anti-PD-1 monoclonal antibody, primarily treats non-small cell lung cancer, hepatocellular carcinoma, and esophageal cancer by preventing the PD-1/PD-L1 interaction [11]. Similarly, toripalimab works through a similar mechanism and has been shown to be effective against NPC, hepatocellular carcinoma and non-small cell lung cancer by reviving T-cell functionality to fight cancer cells [12].

Despite the significant efficacy of PD-1 inhibitors when used as monotherapy, their integration with conventional chemotherapy protocols, particularly platinum-based doublet chemotherapy, remains underexplored in both research and clinical practice in China. This emerging combination therapy holds promise for improving therapeutic outcome, particularly in prolonging progression-free survival (PFS) and overall survival (OS). Therefore, this study thoroughly investigates the efficacy and prognosis of combining PD-1 inhibitors (toripalimab or karelizumab) with chemotherapy in the treatment of R/M NPC. Our goal is to fill the current research gaps and provide a detailed and accurate treatment strategy for clinical application.

Methods and data

Case enrollment

The clinical data of patients with R/M NPC diagnosed between January 2018 and January 2022 were retrospectively analyzed following approval from the Medical Ethics Committee of the Second Affiliated Hospital of Shaanxi University of Chinese Medicine.

Inclusion criteria: 1) Diagnosis of non-keratinizing undifferentiated or differentiated type of cancer by CT, MRI, bone scan or pathology [13], with stage IV. 2) Age between 18 and 75 years with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0-1, indicating an excellent ability to perform daily activities [14]. 3) At least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [15]. 4) Complete clinical data available. Exclusion criteria: 1) Organ failure or acute infection. 2) Pretreatment abnormalities in hematologic, hepatic, renal, and cardiorespiratory function. 3) History of other malignancies or concurrent diagnosis of two or more neoplasms. 4) Treatment discontinuation for any reason.

According to the inclusion and exclusion criteria, a total of 142 eligible cases, including 53 patients who received PD-1 inhibitors in combination with chemotherapy (combination chemotherapy group), and 89 patients who received chemotherapy alone (chemotherapy alone group), were included in this study.

Treatment schedule

In the chemotherapy alone cohort, two primary regimens were used: the TP regimen, which combines paclitaxel (either paclitaxel liposome or albumin-bound paclitaxel) with a platinum-based agent (cisplatin or nedaplatin), and the GP regimen, which combines gemcitabine with a platinum agent (cisplatin or nedaplatin). Conversely, the combination chemotherapy group received a regimen containing a PD-1 inhibitor (either karelizumab or toripalimab) in addition to one of the above chemotherapy protocols, specifically pairing either karelizumab or toripalimab with the TP or GP regimen. Dosing was tailored to the patient's body surface area with the following regimens: paclitaxel liposomal (135-175 mg/m^2), albumin-bound paclitaxel (260 mg/m^2), gemcitabine (1 g/m^2), cisplatin (80 mg/m^2), nedaplatin (80 mg/m^2), combined with a fixed dose of karelizumab (200 mg) or toripalimab (240 mg). All treatments were administered intravenously on the first day of the treatment cycle. Each cycle lasted three weeks, with patients receiving at least two cycles until either disease progression or intolerable side effects occurred. Chest and abdominal CT scans and nasopharyngeal MRI

were performed after every two treatment cycles to monitor treatment efficacy and side effects. In addition, routine assessments, including blood tests, blood chemistry, electrocardiograms, coagulation profiles and thyroid function tests, were performed prior to treatment initiation. Supportive care measures such as premedication, allergy prevention, acid suppression, gastric protection, and antiemetic treatments were also implemented as part of the therapeutic protocol [16, 17].

Clinical data collection

Patient information was collected from the patient's electronic medical record, outpatient review record, and follow-up system. The main information included age, sex, distal metastasis, metastatic organs, number of metastases, pathology type, local recurrence, treatment duration, number of treatment lines, chemotherapy regimen, clinical efficacy, and toxicity statistics. In addition, patients were followed up primarily through medical record review and telephone callbacks. During the first 1-2 years following completion of treatment, imaging examinations were performed every 2-4 months; the frequency of imaging examinations was adjusted to every 3-6 months starting in the 3rd-4th year.

Assessment of efficacy

Efficacy was assessed using RECIST version 1.1 criteria, with the first assessment scheduled for the second cycle after treatment initiation [16]. Efficacy metrics included: complete remission (CR), defined as the disappearance of all target lesions for at least four weeks; partial remission (PR), defined as a 30% reduction in the sum of the longest diameters of all target lesions or more, and sustained for at least four weeks; stable disease (SD), defined as the degree of lesion shrinkage in the range between PR and PD; and progressive disease (PD), defined as an 20% increase in the sum of the smaller diameters of the target lesions or more, or the appearance of new lesions. The objective response rate (ORR), another efficacy measure, was calculated as the proportion of patients with 30% or greater lesion shrinkage. Long-term efficacy was assessed by focusing on PFS, which was calculated as the time from treatment initiation to disease progression, death or last follow-up. All adverse events were evaluated for toxicity during treatment according to the NCI CTCAE version 5.0 criteria [18], which includes hematologic toxicity, gastrointestinal reactions, liver function abnormalities, and thyroid function abnormalities to ensure patient safety and tolerability.

Outcome measures

Primary observational indexes: 1. Clinical efficacy was compared between the two patient groups in terms of ORR and overall clinical efficacy; 2. Independent prognostic factors affecting patient PFS were analyzed using Cox regression.

Secondary outcome measures: 1. The incidence of toxic side effects was compared between the two groups of patients; 2. The predictive value of Cox risk on patient PFS at 1-, 2- and 3-year was analyzed using time-dependent subject characteristics receiver operating characteristic (ROC).

The study process is illustrated in **Figure 1**.

Statistical analysis

Statistical analysis of all data was performed using SPSS 26.0 software. For quantitative data, a t-test or rank-sum test was chosen for comparative analysis according to the distributional characteristics of the data. Chi-square test was used to compare categorical data. For survival analysis, survival curves were plotted using the Kaplan-Meier method, and differences in survival between groups were assessed using the log-rank test. Univariate and multivariate survival analyses were performed using Cox regression models. Time-dependent ROC analysis was performed using the pROC package, and ggplot2 was used for image plotting. Differences were considered statistically significant ifat $P<0.05$.

Results

Comparison of baseline data

Comparison of baseline data between the two groups revealed no statistical difference in age, gender, distal metastasis, metastatic organs, number of metastases, pathologic type, local recurrence, duration of treatment, number of lines of treatment, or chemotherapy regimen between the two groups (all $P>0.05$, **Table 1**).

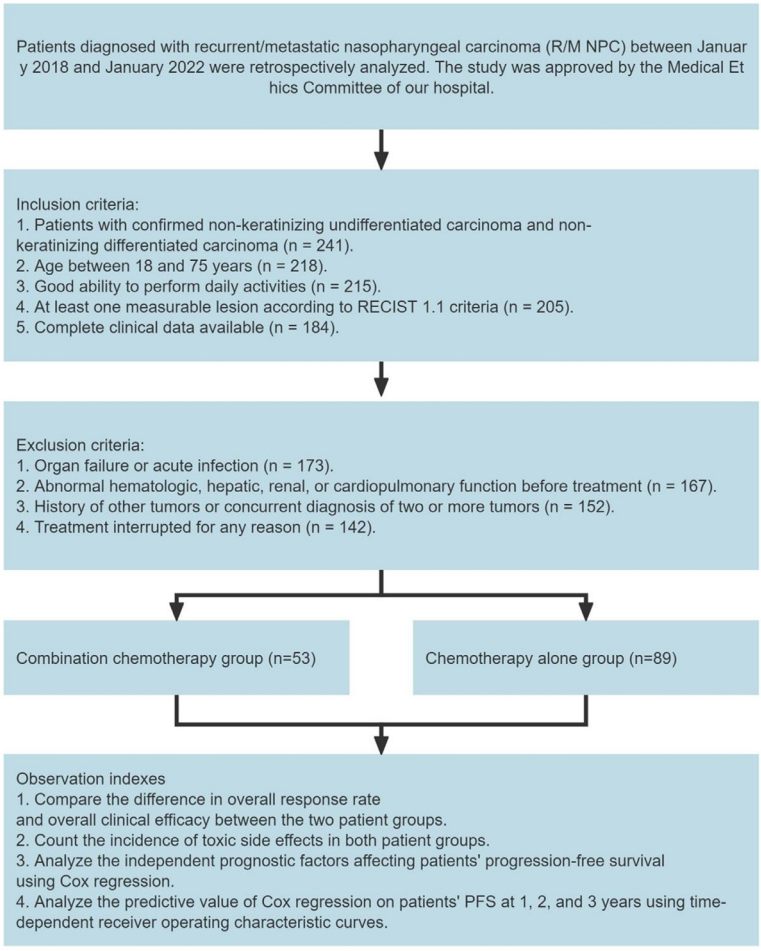

Figure 1. Study flowchart.

Clinical efficacy

A comparative analysis of clinical efficacy between the two groups revealed that the treatment effect was significantly better in the combination chemotherapy group than that in the chemotherapy-alone group (P=0.006). In addition, the ORR of patients in the combination chemotherapy group was also significantly higher than that of the chemotherapy-alone group (P=0.002, **Table 2**).

Comparison of toxic adverse events (AEs)

Comparison of AEs between the two groups showed that there were no significant differences in vomiting, leukopenia, thrombocytopenia, neutropenia, hemoglobinopenia, aminotransferase elevation, and rash between patients of the two groups (P>0.05, **Table 3**). However, the incidences of hypothyroidism (P<0.001) and reactive capillary hyperplasia (P<0.001) were significantly higher in the combination chemotherapy group than those of the chemotherapy-alone group (**Table 3**).

Cox regression analysis of factors influencing PFS in patients

The follow-up period ended in March 2024, and the median follow-up of patients was 15 months. Univariate Cox regression with multivariate Cox regression analysis showed that treatment regimen (P<0.001, OR: 2.24, 95% CI 1.505-3.334), age (P<0.001, OR: 2.164, 95% CI 1.425-3.287), treatment duration (P=0.002, OR: 0.549, and 95% CI 0.373-0.808), and number of treatment lines (P=0.034, OR: 0.667, 95% CI 0.459-0.97) were independent prognostic factors affecting patients' PFS (**Figure 2**).

Survival curve of independent prognostic factors for PFS

We then analyzed the relationship between the four independent prognostic factors and PFS using K-M survival curves. We found that the PFS of patients aged ≥50 years (P<0.001), on chemotherapy alone (P<0.001), receiving second-line therapy (P=0.018), and having a treatment period <4 weeks (P<0.001) were significantly lower than in their counterpart groups (**Figure 3**).

Cox regression modeling for predicting 1-, 2-, and 3-year PFS in patients

At the end of the study, we constructed a predictive model to predict patients' PFS at 1, 2, and 3 years based on the beta coefficients of the Cox regression model (Cox risk = treatment regimen * 0.806 + age * 0.772 + duration of treatment * -0.600 + number of treatment lines * -0.405). As a result, we found that the Cox regression model had an AUC of 0.746 for

Table 1. Comparison of baseline data between patients with different chemotherapy regimens

	Chemotherapy alone group (n=89)	Combination chemotherapy group (n=53)	χ^2-value	*P*-value
Age				
≥50 years	58	37	0.323	0.57
<50 years	31	16		
Gender				
Male	67	38	0.221	0.638
Female	22	15		
Distal transfer				
Yes	71	38	1.215	0.27
No	18	15		
Organ of diversion				
Pulmonary	48	27	0.528	0.768
Bones	22	16		
Others	19	10		
Number of transfers				
≥2	40	25	0.066	0.797
<2	49	28		
Pathological type				
Non-keratinizing differentiated carcinoma	33	15	1.144	0.285
Non-keratinizing undifferentiated carcinoma	56	38		
Localized relapse				
Yes	27	20	0.821	0.365
No	62	33		
Treatment cycle				
≥4 cycles	59	31	0.871	0.351
<4 cycles	30	22		
Number of treatment lines				
Front-line	52	33	0.204	0.652
Second-line	37	20		
Chemotherapy protocol				
TP	51	26	0.91	0.34
GP	38	27		

Note: TP, Paclitaxel and Cisplatin; GP, Gemcitabine and Cisplatin.

predicting patients' PFS at 1 year, 0.760 at 2 years, and 0.677 at 3 years (**Figure 4**; **Table 4**).

Discussion

Nasopharyngeal carcinoma (NPC) exhibits a high incidence in Southern China [19]. Due to the hidden location of the nasopharynx, approximately 70% to 80% of patients are diagnosed at a locally advanced stage, when radiotherapy alone is inadequate [20]. For patients with locally advanced NPC, treatment typically involves a combination of induction chemotherapy followed by concurrent radiotherapy. The main challenges following radical treatment are local recurrence and distant metastasis. Given the sensitivity of NPC to platinum-based chemotherapy, platinum-containing doublet chemotherapy has been established as the standard of care for R/M NPC [21].

This study evaluated the efficacy of doublet platinum-based chemotherapy in patients treated with PD-1 inhibitors compared to those who received chemotherapy alone. The results showed that the overall efficacy and ORR in

Table 2. Clinical efficacy assessment

Group	CR	PR	SD	PD	ORR
Chemotherapy alone group (n=89)	6	32	41	10	38 (42.69%)
Combination chemotherapy group (n=53)	2	35	14	2	37 (69.81%)
χ^2/Z value		2.747			9.800
P-value		0.006			0.002

Note: CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease.

Table 3. Comparison of the occurrence of toxic side effects

	Chemotherapy alone group (n=89)	Combination chemotherapy group (n=53)	χ^2-value	*P*-value
Vomiting	42	23	0.193	0.661
Leucopenia	65	36	0.422	0.516
Thrombocytopenia	42	27	0.187	0.665
Centropenia	47	23	1.177	0.278
Decreased hemoglobin	85	50	0.096	0.756
Aminotransferase (TT) increase	40	22	0.159	0.690
Hypothyroidism	0	10	18.065	<0.001
Erythra	3	4	1.236	0.266
Reactive capillary hyperplasia	0	8	14.236	<0.001

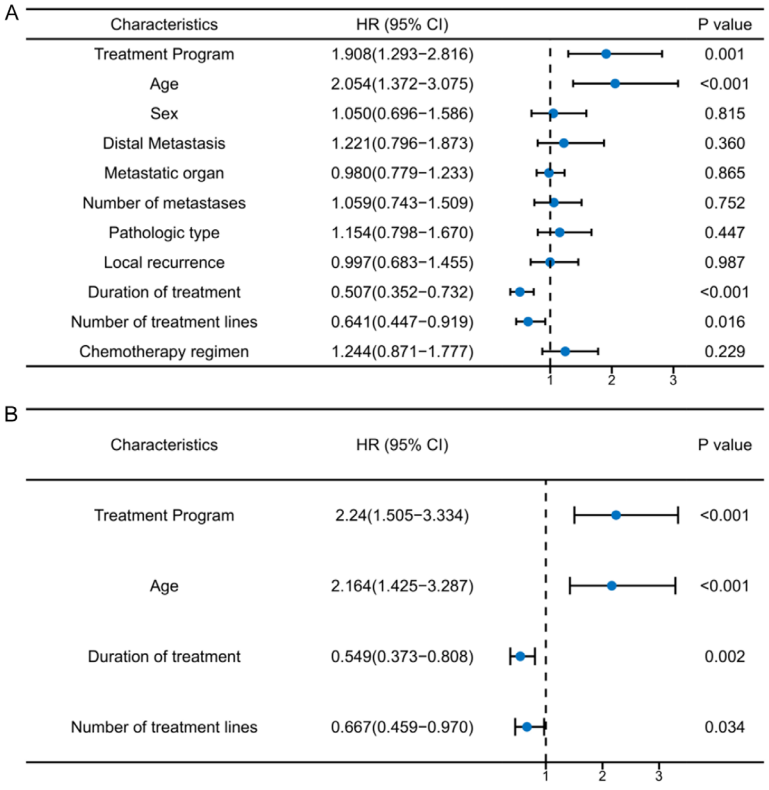

Figure 2. Analysis of prognostic factors affecting patients' PFS. A. One-way Cox regression analysis of prognostic factors affecting patients' PFS. B. Multifactorial Cox regression analysis of prognostic factors affecting patients' PFS. Note: PFS, progression-free survival.

the chemotherapy-alone group were significantly lower than those of the combination chemotherapy group. Previous research by Jin et al. [22] showed that the efficacy of combination chemotherapy with PD-1 inhibitors was significantly better than that of immunotherapy alone in R/M NPC patients who failed first-line chemotherapy. Similarly, interim analyses from the CAPTAIN 1ST trial [23] and the JUPITER-02 trial [24] confirmed the superior efficacy of PD-1 inhibitors in combination with GP regimens compared to placebo in combination with GP regimens for the treatment of R/M NPC.

The improved therapeutic efficacy of combining PD-1 inhibitors with chemotherapy in R/M NPC patients is primarily attributed to the ability of PD-1 inhibitors to alleviate immune suppression by tumor

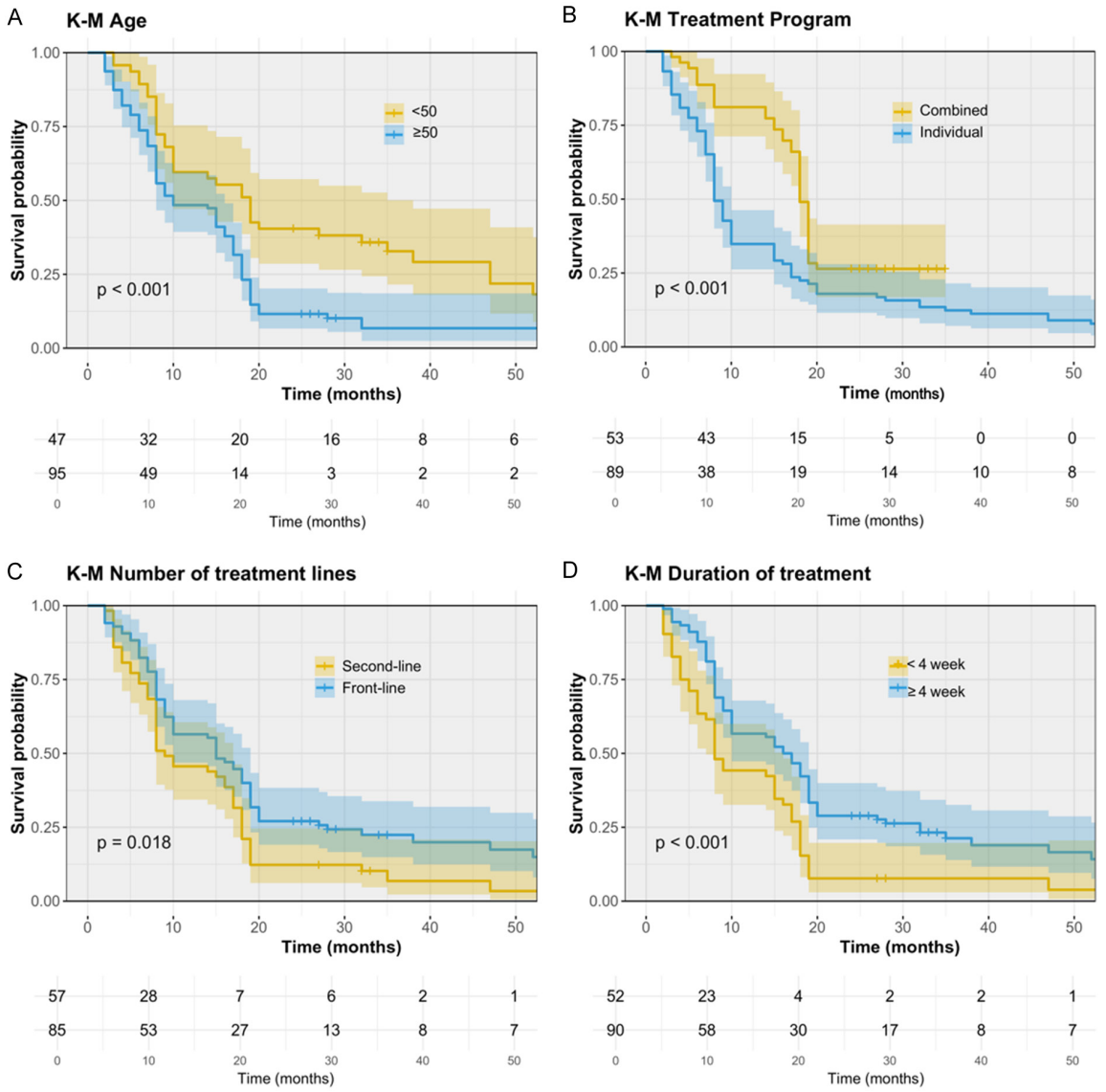

Figure 3. K-M survival curves of independent prognostic factors for PFS. A. Comparison of PFS in patients of different ages. B. Comparison of PFS in patients with different treatment regimens. C. Comparison of PFS in patients with different numbers of treatment lines. D. Comparison of PFS in patients with different treatment duration. Note: PFS, progression-free survival.

cells. By blocking the binding of PD-1 to PD-L1, these inhibitors restore T-cell activity, thereby improving tumor cell recognition and elimination [25]. In addition, PD-1 inhibitors have a synergistic effect when used with chemotherapeutic agents. Chemotherapy directly eliminates tumor cells and modifies the tumor microenvironment, promoting immune response and reducing tumor resistance to chemotherapy, providing a novel therapeutic mechanism [26].

However, this study also noted a higher incidence of hypothyroidism and reactive capillary hyperplasia as toxic side effects in the combination chemotherapy group, which may be due to the immunomodulatory mechanism of PD-1 inhibitors and their interactions with chemotherapy. These effects, individual patient differences, and the intensity of the treatment regimen can contribute to an increase in immune-related side effects [27]. Despite the benefits of combination chemotherapy in improving outcome, this highlights the importance of careful patient evaluation when using PD-1 inhibitors with chemotherapy for R/M NPC to balance maximal tumor suppression with maintaining quality of life.

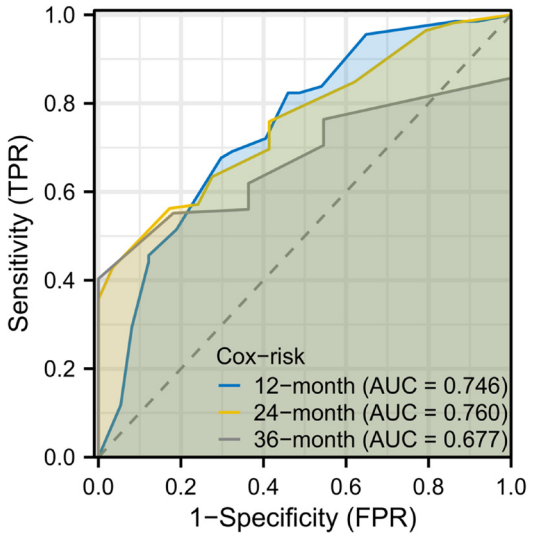

Figure 4. Time-dependent ROC curves of Cox regression model in predicting patients' PFS at 1, 2, and 3 years. Note: ROC, receiver operating characteristic; PFS, progression-free survival.

Disease progression in patients with R/M NPC leads to exacerbating symptoms, fewer treatment options and a worsening prognosis, culminating in a significant decrease in quality of life [28]. Therefore, it is imperative to investigate the factors that influence the PFS of patients. In this study, Cox regression analysis identified treatment regimen, age, treatment duration, and number of treatment lines as independent prognostic factors for PFS. Compared to multimodal combination therapies, the efficacy of chemotherapy alone, especially in resistant or advanced tumors, may be limited due to its inability to target different tumor growth pathways and susceptibility to drug resistance, resulting in shorter PFS. Yang et al. [29] highlighted the benefits of adding tocilizumab to the GP regimen as a first-line treatment for R/M NPC, noting a significant improvement in median PFS with combination therapy over chemotherapy alone and a significant reduction in the risk of death or disease progression, underscoring the critical role of PD-1 inhibitors in combination regimens.

Age-related biological changes, such as altered gene expression, reduced immune function, and decreased cell proliferation, may complicate treatment and lead to reduced PFS [30]. In addition, multiple chronic diseases in elderly patients may limit treatment options and tolerability [31]. The choice of second-line therapy indicates either initial treatment failure or disease recurrence, increasing drug resistance and disease burden, thereby compromising treatment efficacy [32]. Short treatment cycles, possibly due to inadequate treatment duration or premature discontinuation due to side effects or disease worsening, may affect treatment outcome [33].

The study achieved a significant milestone by developing a model to predict 1-, 2-, and 3-year PFS based on these four prognostic factors. This follows the work of Zhang et al. [34], who developed a model using 3 microRNAs to predict survival of nasopharyngeal cancer patients with mean AUC values above 0.7 for predicting OS, DFS, and DMFS. Our time-dependent ROC curve analysis showed high predictive accuracy for 1-year and 2-year PFS, with AUC values of 0.746 and 0.760, respectively. This indicates a robust predictive performance of the model and its ability to accurately classify patients into different prognostic groups. Although the AUC value for predicting 3-year PFS decreased to 0.677, it still suggests some predictive utility. Furthermore, sensitivity and specificity analyses showed that specificity increased over time, especially for 2-year and 3-year PFS prediction, highlighting the ability of the model to effectively identify high-risk patients.

Although the current study was fruitful in exploring treatment outcomes in patients with R/M NPC, it was influenced by several limitations. Firstly, the retrospective design, limited sample size, and lack of diversity, coupled with the single-center study scope, constrained the broad applicability and accuracy of the results. These limitations highlight future research directions, including the adoption of a prospective study design, increasing the sample size, and conducting multicenter studies to improve the external validity and reliability of the findings. Additionally, we were unable to systematically collect BMI data for all patients at the beginning of the study, which prevented its inclusion in the final data analysis. BMI is an important factor in assessing the overall health status of patients and could influence treatment tolerance, efficacy, and overall prognosis. The absence of BMI data may affect the interpretation of our study results, as variations in BMI may impact the outcome. We acknowledge this limitation and recommend that future studies systematically collect and analyze BMI data to

Table 4. Time-dependent ROC curve values

Variant	AUC	Confidence interval	Cumulative survival rate	Cumulative incidence	Cut-off	Sensitivity	Specificity
Cox-risk (1 year)	0.746	0.666-0.826	52.11%	47.89%	0.401	67.65%	70.27%
Cox-risk (2 years)	0.760	0.6756-0.8441	21.13%	78.87%	0.573	42.86%	96.55%
Cox-risk (3 years)	0.677	0.5723-0.781	16.20%	83.80%	0.573	40.34%	100.00%

Note: ROC, Receiver operating characteristic; AUC, Area under curve.

better understand its impact on treatment outcome. By addressing these limitations, we aim to enhance the robustness and comprehensiveness of future research in this area.

In conclusion, PD-1 inhibitors in combination with chemotherapy provides significant efficacy improvement for patients with R/M NPC, especially in ORR and median PFS, while maintaining a favorable safety profile. Treatment regimen, age, number of treatment lines, and treatment duration are independent prognostic factors affecting PFS in patients.

Disclosure of conflict of interest

None.

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References

[1] Su ZY, Siak PY, Lwin YY and Cheah SC. Epidemiology of nasopharyngeal carcinoma: current insights and future outlook. Cancer Metastasis Rev 2024; 3: 1-9.

[2] Shield KD, Ferlay J, Jemal A, Sankaranarayanan R, Chaturvedi AK, Bray F and Soerjomataram I. The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. CA Cancer J Clin 2017; 67: 51-64.

[3] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-249.

[4] Yang Y, Pan J, Wang H, Zhao Y, Qu S, Chen N, Chen X, Sun Y, He X, Hu C, Lin L, Yu Q, Wang S, Wang G, Lei F, Wen J, Yang K, Lin Z, Guo Y, Chen S, Huang X, Wu Y, Liang L, Chen C, Bai F, Ma X, Zhang Y, Leaw S, Zhang L and Fang W. Tislelizumab plus chemotherapy as first-line treatment for recurrent or metastatic nasopharyngeal cancer: a multicenter phase 3 trial (RATIONALE-309). Cancer Cell 2023; 41: 1061-1072.e1064.

[5] Zhu Y, Yang S, Zhou S, Yang J, Qin Y, Gui L, Shi Y and He X. Nimotuzumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone in patients with recurrent or metastatic nasopharyngeal carcinoma. Ther Adv Med Oncol 2020; 12: 1758835920953738.

[6] Wang S, Chen S, Zhong Q and Liu Y. Immunotherapy for the treatment of advanced nasopharyngeal carcinoma: a promising new era. J Cancer Res Clin Oncol 2023; 149: 2071-2079.

[7] Chen Y, Ding X, Bai X, Zhou Z, Liu Y, Zhang X, Yu J and Hu M. The current advances and future directions of PD-1/PD-L1 blockade in head and neck squamous cell carcinoma (HNSCC) in the era of immunotherapy. Int Immunopharmacol 2023; 120: 110329.

[8] Xu JY, Wei XL, Wang YQ and Wang FH. Current status and advances of immunotherapy in nasopharyngeal carcinoma. Ther Adv Med Oncol 2022; 14: 17588359221096214.

[9] MacDonald K, Pondel M and Abraham I. Cost-efficiency and budget-neutral expanded access modeling of the novel PD-1 inhibitor toripalimab versus pembrolizumab in recurrent or metastatic nasopharyngeal carcinoma. J Med Econ 2024; 27: 1-8.

[10] Zhu Y, Liu K, Ding D, Wang K, Liu X and Tan X. Chemo-immunotherapy regimes for recurrent or metastatic nasopharyngeal carcinoma: a network meta-analysis and cost-effectiveness analysis. Front Pharmacol 2022; 13: 858207.

[11] Tang YK, Xu Z, Ye ZM, Li SR and Zhou Q. Cost-effectiveness analysis of tislelizumab in combination with chemotherapy for the first-line treatment of patients with metastatic or recurrent nasopharyngeal carcinoma in China. Head Neck 2024; 46: 5-14.

[12] Zhao Z, Chen T, Zhou Z, Guo R and Liu Q. Cost-effectiveness of camrelizumab combined with chemotherapy in the first-line treatment of recurrent or metastatic nasopharyngeal carcinoma in China. BMJ Open 2023; 13: e071832.

[13] He Q, Huang Y, Yuan L, Wang Z, Wang Q, Liu D, Li L, Li X, Cao Z, Wang D and Yang M. A promising predictive biomarker combined EBV NDA with PNI for nasopharyngeal carcinoma in non-

endemic area of China. Sci Rep 2023; 13: 11700.

[14] Kodama H, Kadowaki S, Nakazawa T, Matsubara Y, Narita Y, Honda K, Masuishi T, Taniguchi H, Ando M, Koide Y, Tachibana H, Kodaira T, Sawabe M, Terada H, Beppu S, Nishikawa D, Suzuki H, Hanai N and Muro K. Safety and efficacy of gemcitabine plus cisplatin against recurrent/metastatic nasopharyngeal carcinoma: a retrospective study. Anticancer Res 2024; 44: 1227-1232.

[15] Chiang CL, Lam TC, Li JCB, Chan KSK, El Helali A, Lee YYP, Law LHT, Zheng D, Lo AWI, Kam NW, Li WS, Cheung AKW, Chow JCH, Chan SPC, Lai JWY, Lee SWM, Kong FS, Ng WT, Kwong DLW and Lee AWM. Efficacy, safety, and correlative biomarkers of bintrafusp alfa in recurrent or metastatic nasopharyngeal cancer patients: a phase II clinical trial. Lancet Reg Health West Pac 2023; 40: 100898.

[16] Liang H, Jiang YF, Liu GY, Wang L, Wang JW, Lu N, Xia WX, Ke LR, Ye YF, Duan JL, Bei WX, Dong SH, Li WZ, Liu LT, Zhao C, Xie C and Xiang YQ. Camrelizumab and apatinib plus induction chemotherapy and concurrent chemoradiotherapy in stage N3 nasopharyngeal carcinoma: a phase 2 clinical trial. Nat Commun 2024; 15: 1029.

[17] Ding X, Zhang WJ, You R, Zou X, Wang ZQ, Ouyang YF, Peng L, Liu YP, Duan CY, Yang Q, Lin C, Xie YL, Chen SY, Liu YL, Gu CM, Xie RQ, Huang PY, Hong MH, Hua YJ and Chen MY. Camrelizumab plus apatinib in patients with recurrent or metastatic nasopharyngeal carcinoma: an open-label, single-arm, phase II study. J Clin Oncol 2023; 41: 2571-2582.

[18] Freites-Martinez A, Santana N, Arias-Santiago S and Viera A. Using the common terminology criteria for adverse events (CTCAE - Version 5.0) to evaluate the severity of adverse events of anticancer therapies. Actas Dermosifiliogr (Engl Ed) 2021; 112: 90-92.

[19] Ji MF, Sheng W, Cheng WM, Ng MH, Wu BH, Yu X, Wei KR, Li FG, Lian SF, Wang PP, Quan W, Deng L, Li XH, Liu XD, Xie YL, Huang SJ, Ge SX, Huang SL, Liang XJ, He SM, Huang HW, Xia SL, Ng PS, Chen HL, Xie SH, Liu Q, Hong MH, Ma J, Yuan Y, Xia NS, Zhang J and Cao SM. Incidence and mortality of nasopharyngeal carcinoma: interim analysis of a cluster randomized controlled screening trial (PRO-NPC-001) in southern China. Ann Oncol 2019; 30: 1630-1637.

[20] Lee AWM, Ng WT, Chan JYW, Corry J, Mäkitie A, Mendenhall WM, Rinaldo A, Rodrigo JP, Saba NF, Strojan P, Suárez C, Vermorken JB, Yom SS and Ferlito A. Management of locally recurrent nasopharyngeal carcinoma. Cancer Treat Rev 2019; 79: 101890.

[21] Peng PJ, Lv BJ, Wang ZH, Liao H, Liu YM, Lin Z, Con YY and Huang PY. Multi-institutional prospective study of nedaplatin plus S-1 chemotherapy in recurrent and metastatic nasopharyngeal carcinoma patients after failure of platinum-containing regimens. Ther Adv Med Oncol 2017; 9: 68-74.

[22] Jin T, Zhang Q, Jin QF, Hua YH and Chen XZ. Anti-PD1 checkpoint inhibitor with or without chemotherapy for patients with recurrent and metastatic nasopharyngeal carcinoma. Transl Oncol 2021; 14: 100989.

[23] Yang Y, Qu S, Li J, Hu C, Xu M, Li W, Zhou T, Shen L, Wu H, Lang J, Hu G, Luo Z, Fu Z, Qu S, Feng W, Chen X, Lin S, Zhang W, Li X, Sun Y, Lin Z, Lin Q, Lei F, Long J, Hong J, Huang X, Zeng L, Wang P, He X, Zhang B, Yang Q, Zhang X, Zou J, Fang W and Zhang L. 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; 22: 1162-1174.

[24] Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, Li J, Shi YR, Jin F, Xu R, Pan J, Qu S, Li P, Hu C, Liu YC, Jiang Y, He X, Wang HM, Lim WT, Liao W, He X, Chen X, Liu Z, Yuan X, Li Q, Lin X, Jing S, Chen Y, Lu Y, Hsieh CY, Yang MH, Yen CJ, Samol J, Feng H, Yao S, Keegan P and Xu RH. Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial. Nat Med 2021; 27: 1536-1543.

[25] Wang F, Jin Y, Wang M, Luo HY, Fang WJ, Wang YN, Chen YX, Huang RJ, Guan WL, Li JB, Li YH, Wang FH, Hu XH, Zhang YQ, Qiu MZ, Liu LL, Wang ZX, Ren C, Wang DS, Zhang DS, Wang ZQ, Liao WT, Tian L, Zhao Q and Xu RH. Combined anti-PD-1, HDAC inhibitor and anti-VEGF for MSS/pMMR colorectal cancer: a randomized phase 2 trial. Nat Med 2024; 30: 1035-1043.

[26] Zhang T, Zhu C, Zhang N, Zhang L, Wang S, Xun Z, Xu Y, Yang X, Lu X and Zhao H. Lenvatinib combined with PD-1 inhibitor plus Gemox chemotherapy versus plus HAIC for advanced biliary tract cancer. Int Immunopharmacol 2024; 129: 111642.

[27] Hui-Mei P, Guang-Ming H, Xiao-Ling Q, Hong-Liang Z and Si-Jun W. Reactive cutaneous capillary endothelial proliferation caused by camrelizumab: sixteen case reports. Indian J Dermatol 2023; 68: 318-326.

[28] Alshamsan B, Gad AM, Alata MK, Alzahrani M, Elhassan T and Atallah JP. Capecitabine monotherapy as palliative treatment for patients with recurrent/metastatic nasopharyngeal cancer. J Oncol 2022; 2022: 6860413.

[29] Yang Y, Pan J, Wang H, Qu S, Chen N, Chen X, Sun Y, He X, Hu C and Lin LJAoO. 1210 rationale 309: a randomized, global, double-blind, phase III trial of tislelizumab (TIS) vs placebo, plus gemcitabine+ cisplatin (GP), as first-line treatment for recurrent/metastatic nasopharyngeal cancer (RM-NPC). Ann Oncol 2021; 32: S1430.

[30] Zeng X, Liu G, Pan Y and Li Y. Development and validation of immune inflammation-based index for predicting the clinical outcome in patients with nasopharyngeal carcinoma. J Cell Mol Med 2020; 24: 8326-8349.

[31] Wu B, Ni LQ, Wang Y, Yang HH and Zhao SK. Low prognostic nutritional index is associated with poor outcome in middle-aged and elderly patients with non-metastatic nasopharyngeal carcinoma: a retrospective cohort study. Support Care Cancer 2022; 30: 8895-8904.

[32] Jiang Y, Chen C, Liu G, Fang T, Lu N, Bei W, Dong S, Li W, Xia W, Liang H and Xiang Y. Combination strategy exploration for prior treated recurrent or metastatic nasopharyngeal carcinoma in the era of immunotherapy. Sci Rep 2024; 14: 1768.

[33] Zupančič T, Zakotnik B and Kuhar CG. Outcome of patients with recurrent/metastatic squamous cell head and neck cancer treated with platinum-based chemotherapy with or without cetuximab in real-world practice. Mol Clin Oncol 2021; 15: 190.

[34] Zhang SQ, Liu J, Chen HB, Dai WJ, Zhou LQ, Xie CW and Li JC. A novel three-microRNA signature for predicting survival in patients with nasopharyngeal carcinoma. J Dent Sci 2022; 17: 377-388.