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Effect and safety of immunotherapy among elder patients (age ≥ 65) with recurrent or metastatic nasopharyngeal carcinoma

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Abstract

Background The use of immune checkpoint inhibitors (ICIs) combined with chemotherapy constitutes the first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (RM-NPC). However, elderly patients are underrepresented in the majority of related clinical trials.

Patients and methods This retrospective study included RM-NPC patients aged 65 years or older who received immunotherapy between January 2015 and February 2022. Cox regression models were utilized to compare the outcomes. Comorbidity assessments (ACE-27, CCI, and ACCI) were used for the geriatric evaluation.

Results Among the 95 of 243 patients included in this analysis (71 men), the median follow-up time was 29.3 months. Patients receiving local therapy had longer progression-free survival (PFS) (HR 0.352; 95% CI: 0.145–0.853; $p = .021$). No significant differences in survival outcomes or toxicity profiles were observed between age groups or among the ICI agent groups.

Conclusions The findings suggest that immunotherapy is efficacious and safe for treating RM-NPC in elderly patients. The combination of ICIs and local therapy significantly prolonged survival and could be an option for this vulnerable population.

Keywords Nasopharyngeal carcinoma, Geriatric oncology, Recurrence, Metastasis, Local therapy, Survival

Introduction

Nasopharyngeal carcinoma (NPC) is a specific type of head and neck carcinoma that arises from the epithelium of the nasopharynx. The geographic distribution of NPC is unbalanced, and more than 70% of new cases are in East Asia and Southeast Asia [1]. Additionally, 41.9% of patients with NPC are diagnosed at the age ≥ 60, whereas 17.5% of patients diagnosed at the age after 70 [2]. Approximately 63.1% to 75.8% of elderly NPC patients have stage III or IV disease [3]. Older NPC patients have poorer survival than younger patients do [4, 5]. As ageing is a global trend, the number of elderly NPC patients increases. Hence, it is important to choose the optimal treatment for aged NPC patients.

Intensity-modulated radiotherapy (IMRT) is recommended as the standard treatment for non-metastatic elderly NPC patients, whereas the choice of anticancer treatment for aged recurrent or metastatic NPC (RM-NPC) patients is individualized [3]. Salvage surgery or reradiation may be feasible in elderly NPC patients with locoregional recurrence, whereas palliative chemotherapy is the first-line treatment for aged patients

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with metastatic NPC [3, 6, 7]. The meta-analysis, which included 26 trials and 7,080 patients with NPC, revealed that aged patients had worse survival benefits from chemotherapy than younger patients did [8]. Elderly NPC patients who received RT alone had survival time comparable to those of to the patients treated with RT and chemotherapy [9]. However, when elderly NPC patients do not have severe comorbidities, radiotherapy with concurrent chemotherapy (CRT) improves 5-year overall survival, cancer-specific survival, disease-free survival, and locoregional relapse-free survival compared with RT alone [4]. Hence, careful and comprehensive geriatric evaluation must be performed before selecting chemotherapy as treatment [3].

Recently, randomized clinical trials have validated the efficacy of immune checkpoint inhibitors (ICIs), such as programmed death-ligand 1 (PD-1) inhibitors as first-line treatments for RM-NPC [10–13]. Compared with the placebo group, toripalimab plus chemotherapy improved the median progression-free survival (PFS) of RM-NPC patients from 8.2 months to 21.4 months [10], whereas camrelizumab [11] and tislelizumab [12] had similar survival benefits. Toripalimab with gemcitabine and cisplatin was approved by the National Medical Products Administration (NMPA) of China and the US Food and Drug Administration (FDA) as the first-line treatment for RM-NPC. Even though the 3 above mentioned trials recruited patients aged between 18 and 75 years (1 trial recruited participants aged 18 years or older), the proportion of elderly patients aged ≥ 65 years was less than 15%, and age-specific survival and treatment-related adverse events were not reported in detail [10–13]. Moreover, only patients who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 could be enrolled in the above trials [10–12], leading to some of the elderly RM-NPC patients being under-represented.

In this context, we retrospectively studied the efficacy and safety of immunotherapy in elderly RM-NPC patients aged ≥ 65 while also exploring the prognostic factors and the value of geriatric assessments in this setting.

Materials and methods

Patient selection

We retrospectively studied the clinical effectiveness and safety of ICIs in elderly adults with RM-NPC. Patients were enrolled between January 2015 and February 2022 from Sun Yat-sen University Cancer Center (SYSUCC). We extracted demographic data, clinicopathologic parameters, clinical outcomes, and follow-up data from medical records. Patients ≥ 65 years of age treated with immunotherapy were eligible for analysis. NPC patients who had not received treatment before immunotherapy were excluded (Supplementary Fig. 1). All of the demographic and clinicopathologic parameters were collected before ICI therapy. The last follow-up date was February 29, 2024.

Comorbidity assessment

The influence of comorbidities was assessed via the Adult Comorbidity Evaluation 27 (ACE-27), Charlson Comorbidity Index (CCI), and Age-Adjusted CCI (ACCI), which are valuable tools that are widely used to predict outcomes for various medical conditions. The ACE-27 contains a 27-item comorbidity index, which is scored into 3 grades (grade 1 = minimal, grade 2 = moderate, grade 3 = severe). The overall score of ACE-27 is defined as the highest-ranking single ailment. If two or more comorbidities are scored as moderate in different organs, the overall ACE-27 score will be assessed as severe. The CCI includes 17 weighted comorbidities, and the ACCI is a modified version of the CCI that adjusts for age. Although the comorbidity indices evaluate points for tumors, we did not grade a patient's NPC as a comorbidity. The ACE-27, CCI, and ACCI scores were retrospectively calculated by reviewing the medical records.

Treatment

Prior treatments were documented before immunotherapy. All NPC patients with recurrence or metastasis received immunotherapy, including toripalimab, camrelizumab, tislelizumab, and others. The following treatments were conducted in patients undergoing immunotherapy. There were various combinations of ICIs. First, since systemic therapy is the first-line treatment for RM-NPC, the combination of ICIs with chemotherapy or targeted therapy was included as a candidate risk factor for survival benefit. Dose reduction chemotherapy means that patients have reduced chemotherapy, and platinum-containing chemotherapy means that patients receive chemotherapy with cisplatin, carboplatin, and other platinum. The drugs for chemotherapy contained gemcitabine, paclitaxel, fluorouracil, and others. Targeted therapy included anti-epidermal growth factor receptor agents (nimotuzumab or cetuximab), anti-vascular endothelial growth factor agent (bevacizumab), and anti-angiogenesis agent (endostatin, apatinib, or anlotinib). Local therapy includes surgery and radiotherapy targeting local recurrent or metastatic lesions. For nasopharyngeal recurrence, salvage surgery is recommended as the primary treatment for patients with a diagnosis of the rT1-2 stage. The surgery to either the nasopharynx or metastatic foci was documented. The patient received radiotherapy of the nasopharynx delivered at 60–70 Gy in 1.8–2 Gy per fraction using IMRT or tomography, and the radiotherapy plans for the metastatic sites were personalized.

Outcomes

The clinical outcomes included overall survival (OS), PFS, subsequent-line treatment-free survival (sTFS) and restricted mean survival time (RMST). OS was defined as the period from the start of ICI therapy to death or the last follow-up date. PFS was defined as the period from the start of ICI therapy to progression, death or the last follow-up date. sTFS was defined as the period from the start of ICI therapy to the time of subsequent-line treatment or death. RMST is the measure of average survival during the specified follow-up period. Tumor responses were retrospectively and blindly via the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). The objective response rate (ORR) was defined as the proportion of patients who had a complete response (CR) or partial response (PR) with measurable disease before immunotherapy. Adverse events (AEs) were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events version (CTCAE) 5.0.

Statistical analysis

The clinical and pathological characteristics were analyzed by the *t-test*, *chi-squared* test, or *Fisher's* exact test. The *Kaplan–Meier* method, *Logrank* test, and the RMST were applied to compare patient survival curves. The cut-off for RMST was set to 24 months, according to the minimum follow-up time in this study. We evaluated the correlation with survival benefit between patient groups using the univariate Cox proportional hazards model while including factors with $P < 0.100$ at univariate analysis into the multivariate Cox regression. The final Cox models were determined by backward stepwise selection. The proportional hazard assumption was verified with *Schoenfeld*'s residuals. A two-sided value of $P < 0.05$ was considered statistically significant. All statistical tests were performed using R software (version 4.3.1).

Results

Patient characteristics

From January 2015 to February 2022, 95 patients met the inclusion criteria. There were 71 (74.7%) men and 24 (25.3%) women. All patients started ICI therapy when they were 65 years of age or older. The median age was 67 years (ranging from 65 to 78). A total of 89 (93.7%) patients had the nonkeratinizing undifferentiated NPC. Approximately three-quarters of the patients (74.7%) had a Karnofsky performance status (KPS) score ≥ 90. The differences were among the three comorbidity indexes. Patients with ACE-27 scores of 0 or 1 accounted for 53.7% (51/95) of the cases, and those with CCI scores of 0 and ACCI scores of 0 to 3 accounted for 78.9% (75/95) and 89.5% (85/95), respectively. Before immunotherapy, 48 (50.5%) patients were diagnosed with local recurrence of the nasopharynx, 22 (23.2%) patients had recurrent with metastases, and 25 (26.3%) patients were primary metastatic. Most patients (91/95) received radiotherapy prior to immunotherapy. Induction chemotherapy, concurrent chemotherapy, and adjuvant chemotherapy were observed in 63.2% ($n = 48$), 61.8% ($n = 47$), and 25.0%($n = 19$) of the 76 patients who had undergone prior chemotherapy, respectively. The most common site of metastasis was bone ($n = 23$, 24.2%), followed by liver ($n = 22$, 23.2%) and lung ($n = 16$, 16.8%) (Table 1).

ICIs were the first-line therapy for 67 (70.5%) patients. Fifty-eight (61.1%) patients were treated with toripalimab, and 16 (16.8%) patients were treated with tislelizumab. The median number of ICI cycles was 6(range: 1–40). A total of 78.9% ($n = 75$) of patients were treated with systemic therapy, whereas 21.1% ($n = 20$) of patients received local therapy. Radiotherapy was performed on 14 patients, while 6 patients underwent surgery. The proportions of patients receiving the combination of chemotherapy and targeted therapy were 86.3% ($n = 82$) and 18.9% ($n = 18$), respectively. Even though platinum-containing chemotherapy was the main type of chemotherapy, 30.5% (25/82) of patients did not receive platinum as an anti-cancer agent. Among the 82 patients who had both chemotherapy and immunotherapy together, 51.2% ($n = 42$) experienced reduction doses of chemotherapy (Table 1).

Risk factors for RM-NPC patients aged ≥ 65 years who received immunotherapy

For the entire cohort, the median follow-up time was 29.3 (interquartile range, IQR: 21.1–39.7) months. The median OS, PFS, and sTFS were 16.5 months, 11.7 months, and 9.1 months, respectively. In addition, 66 (69.5%) patients had measurable lesions to evaluate the tumor response using RECIST v1.1. There were 36 (54.5%) patients who achieved an objective response (4 CR, 32 PR), while 26 patients who achieved SD as the best response.

PFS was significantly longer with local therapy than without local therapy (hazard ratio [HR] 0.352; [95% confidence interval (CI): 0.145–0.853]; $p = 0.021$) (Table 2, Fig. 1A). The 2-year RMST analysis revealed the same trend in PFS (with minus without local therapy, 5.312 [95% CI: 2.024–8.600] months; $p = 0.002$) (Fig. 1B). The baseline characteristics were balanced between patients who received local therapy and those who did not, except for the combination of chemotherapy (Supplementary Table 1). Patients with liver metastasis had a poorer PFS than patients without metastatic foci of the liver did (HR 2.291; 95% CI: 1.118–4.693; $p = 0.024$) (Table 2, Fig. 1C).

Favorable sTFS was observed for patients who completed ≥ 4 ICI cycles versus those who complete < 4 ICI cycles (HR 0.362; 95% CI: 0.180- 0.727; $p = 0.004$)

Table 1 Patient characteristics

Characteristics		No. (%)			*p* Value
		Overall	Age < 70	Age ≥ 70	
Patients		95	70	25	
Sex	Male	71 (74.7)	52 (74.3)	19 (76.0)	1.000
	Female	24 (25.3)	18 (25.7)	6 (24.0)	
Smoke	Never	63 (67.7)	43 (63.2)	20 (80.0)	0.199
	Current or Former	30 (32.3)	25 (36.8)	5 (20.0)	
Alcohol	Never	79 (84.9)	59 (86.8)	20 (80.0)	0.630
	Current or Former	14 (15.1)	9 (13.2)	5 (20.0)	
Allergy	No	87 (93.5)	67 (98.5)	20 (80.0)	**0.006**
	Yes	6 (6.5)	1 (1.5)	5 (20.0)	
KPS	< 90	23 (24.2)	18 (25.7)	5 (20.0)	0.738
	≥ 90	71 (74.7)	51 (72.9)	20 (80.0)	
	NA	1(0.1)	1(1.4)	0(0.0)	
ACE27	< 2	51 (53.7)	41 (58.6)	10 (40.0)	0.172
	≥ 2	44 (46.3)	29 (41.4)	15 (60.0)	
CCI	0	75 (78.9)	54 (77.1)	21 (84.0)	0.663
	≥ 1	20 (21.1)	16 (22.9)	4 (16.0)	
ACCI	< 4	85 (89.5)	62 (88.6)	23 (92.0)	0.920
	≥ 4	10 (10.5)	8 (11.4)	2 (8.0)	
EBV DNA	Negative	22 (23.1)	16 (22.9)	6 (24.0)	1.000
	Positive	68 (71.6)	50 (71.4)	18 (72.0)	
	NA	5 (5.3)	4 (5.7)	1 (4.0)	
Histology	Keratinized squamous cancer	3 (3.2)	3 (4.3)	0 (0.0)	0.567
	Differentiated non-keratinized	2 (2.1)	1 (1.4)	1 (4.0)	
	Undifferentiated non-keratinized	89 (93.7)	65 (92.9)	24 (96.0)	
	Unclassified	1 (1.1)	1 (1.4)	0 (0.0)	
Location of metastases	Liver	22 (23.2)	13 (18.6)	9 (36.0)	0.134
	Bone	23 (24.2)	18 (25.7)	5 (20.0)	0.764
	Lung	16 (16.8)	12 (17.1)	4 (16.0)	1.000
Current disease stage	Local recurrent	48 (50.5)	38 (54.3)	10 (40.0)	0.382
	Recurrent with metastatic	22 (23.2)	14 (20.0)	8 (32.0)	
	Primary metastatic	25 (26.3)	18 (25.7)	7 (28.0)	
Prior chemotherapy[a]	Yes	76 (80.0)	63 (90.0)	13 (52.0)	**< 0.001**
Prior radiotherapy	Yes	91 (95.8)	70 (100.0)	21 (84.0)	**0.004**
Treatment line of ICI therapy	≥2	28 (29.5)	21 (30.0)	7 (28.0)	1.000
	1	67 (70.5)	49 (70.0)	18 (72.0)	
ICI type	Systemic	75 (78.9)	56 (80.0)	19 (76.0)	**0.031**
	Neoajuvant	3 (3.2)	0 (0.0)	3 (12.0)	
	Concurrent	6 (6.3)	6 (8.6)	0 (0.0)	
	Adjuvant	3 (3.2)	2 (2.9)	1 (4.0)	
	Others	8 (8.4)	6 (8.6)	2 (8.0)	
ICI agents	Camrelizumab	5 (5.3)	4 (5.7)	1 (4.0)	0.289
	Sintilimab	11 (11.6)	11 (15.7)	0 (0.0)	
	Tislelizumab	16 (16.8)	11 (15.7)	5 (20.0)	
	Toripalimab	58 (61.1)	41 (58.6)	17 (68.0)	
	Others	5 (5.3)	3 (4.3)	2 (8.0)	
ICI cycles	< 4	37 (38.9)	27 (38.6)	10 (40.0)	1.000
	≥ 4	58 (61.1)	43 (61.4)	15 (60.0)	
ICI maintenance	No	71 (74.7)	54 (77.1)	17 (68.0)	0.525

Table 1 (continued)

Characteristics		No. (%)			*p* Value
		Overall	Age < 70	Age ≥ 70	
	Yes	24 (25.3)	16 (22.9)	8 (32.0)	
Chemotherapy	No	13 (13.7)	10 (14.3)	3 (12.0)	1.000
	Yes	82 (86.3)	60 (85.7)	22 (88.0)	
Platinum – containing chemotherapy	No	38 (40.0)	26 (37.1)	12 (48.0)	0.476
	Yes	57 (60.0)	44 (62.9)	13 (52.0)	
Dose reduction chemotherapy	No	53 (55.8)	36 (51.4)	17 (68.0)	0.231
	Yes	42 (44.2)	34 (48.6)	8 (32.0)	
Target therapy	No	77 (81.1)	55 (78.6)	22 (88.0)	0.462
	Yes	18 (18.9)	15 (21.4)	3 (12.0)	
Local therapy	No	75 (78.9)	56 (80.0)	19 (76.0)	0.178
	Yes	20 (21.1)	14 (20.0)	6 (24.0)	

Abbreviations: *KPS* Karnofsky performance status, *ACE-27* Adult Co-morbidity Evaluation 27, *CCI* Charlson Comorbidity Index, *ACCI* Age-Adjusted CCI, *ICI* Immune checkpoint inhibitor

[a] Each patient was included only once in each specific category, but could appear in several different categories

Table 2 Univariate and Multivariate Cox Regression on Progression-Free Survival

Characteristics	Univariate analyses			Multivariate analyses		
	HR	95%CI	*p*	HR	95%CI	*p*
Age (≥ 70 vs < 70)	1.454	0.736–2.873	0.282			
Sex (Male vs Female)	1.133	0.554–2.318	0.732			
Smoke (current or former vs never)	1.454	0.742–2.848	0.276			
Alcohol (current or former vs never)	1.531	0.699–3.352	0.287			
Allergy (Yes vs No)	0.975	0.234–4.072	0.973			
Histology	1.996	0.394–10.116	0.404			
ACE27 (≥ 2 vs < 2)	1.032	0.551–1.934	0.922			
CCI (≥ 1vs 0)	0.866	0.361–2.081	0.748			
ACCI (≥ 4 vs < 4)	0.280	0.038–2.044	0.209			
Current disease stage	0.984	0.678–1.430	0.935			
Lung Metastasis (Yes vs No)	0.980	0.431–2.227	0.961			
Bone Metastasis (Yes vs No)	1.585	0.819–3.070	0.172			
Liver Metastasis (Yes vs No)	1.925	0.957–3.870	0.066	2.291	1.118–4.693	**0.024**
EBV DNA (negative vs positive)	1.442	0.560–3.710	0.448			
Treatment line of ICI therapy (≥ 2 vs 1)	0.769	0.401–1.473	0.428			
ICI cycles (≥ 4 vs < 4)	0.64	0.332–1.234	0.183			
ICI maintenance (Yes vs No)	1.015	0.517–1.992	0.965			
ICI type	0.806	0.612–1.062	0.125			
ICI agents	1.075	0.772–1.496	0.670			
Local therapy (Yes vs No)	0.404	0.169–0.967	**0.042**	0.352	0.145–0.853	**0.021**
Chemotherapy (Yes vs No)	1.439	0.602–3.437	0.413			
Platinum – containing chemotherapy (Yes vs No)	1.151	0.614–2.158	0.661			
Dose reduction chemotherapy (Yes vs No)	1.569	0.845–2.913	0.154			
Target therapy (Yes vs No)	1.054	0.502–2.213	0.889			

Abbreviations: *KPS* Karnofsky performance status, *ACE-27* Adult Co-morbidity Evaluation 27, *CCI* Charlson Comorbidity Index, *ACCI* Age-Adjusted CCI, *ICI* immune checkpoint inhibitor

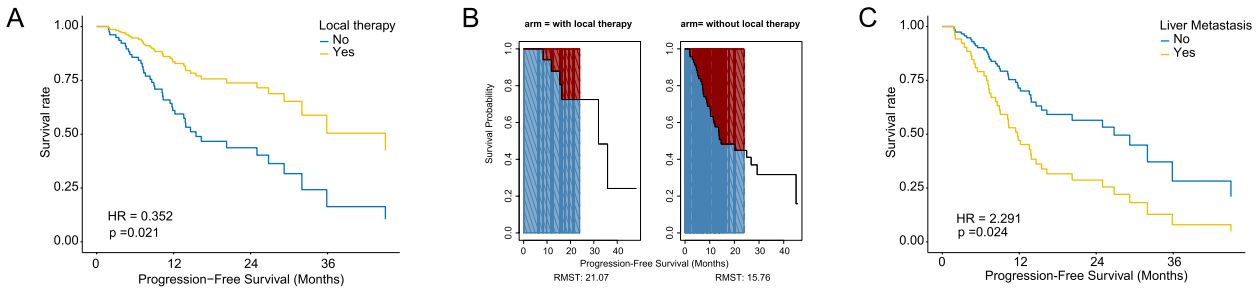

Fig. 1 Risk factors for Progression-Free Survival (PFS). **A** Multivariable Cox proportional hazards model of PFS in RM-NPC patients stratified by local therapy, adjusted by liver metastasis. **B** Restricted Mean Survival Curves for PFS between with and without local therapy. **C** Multivariable Cox proportional hazards model of PFS in RM-NPC patients stratified by liver metastasis, adjusted by local therapy

(Supplementary Table 2, Supplementary Fig. 2A). Patients who completed 4 or more cycles of ICI treatment also had longer sTFS in the first two years than those who completed < 4 ICI cycles (completed minus not completed, 4.716 [95% CI: 0.235–9.198] months; $p = 0.039$) (Supplementary Fig. 2B). Compared to patients who received local therapy, patients without local therapy tended to have poor sTFS (HR 0.025; 95%CI: 0.001 -1.022; $p = 0.051$) (Supplementary Table 2, Supplementary Fig. 2C). The RMST for patients in the local therapy arm was 19.663 months, which was longer than that for patients in the arm without local therapy (with minus without local therapy, 5.304 [95% CI: 1.226—9.381] months; $p = 0.011$) (Supplementary Fig. 2D).

No significant differences were observed for sex, current disease status, and other variables ($p > 0.05$ for all) on OS (Supplementary Table 3). We performed an RMST analysis of patients with or without liver metastasis because the Kaplan–Meier curve of liver metastasis was crossed (Supplementary Fig. 3), and the factor violated the proportional hazard assumption using *Schoenfeld*'s residuals ($p = 0.017$). Likewise, no significant differences were observed in the 2-year RMST between the groups with and without liver metastasis ($p = 0.313$).

Patients aged ≥ 70 years had comparable survival benefits from immunotherapy

In the cohort, 25 (26.3%) patients received immunotherapy at the age of ≥ 70 years. The baseline clinical and pathological parameters were similar between those aged < 70 years and those aged ≥ 70 years, except for a few characteristics (Table 1). More patients in the younger age group than in the older age group received prior chemotherapy (90.0% *vs.* 52.0%, $p < 0.001$) or radiotherapy (100.0% *vs.* 84.0%, $p = 0.004$). To our surprise, even though the rate of local therapy was comparable between the two age groups ($p = 0.892$), elderly patients were more likely to undergo surgery than younger patients (20% *vs.* 1.4%, $p = 0.005$). No significant differences were found in the survival benefit between those aged younger than 70 years and those in the other age group ($p < 0.05$, Fig. 2, Table 2, Supplementary Table 2,3). Given that the trend indicated a diminished PFS among patients aged ≥ 70 years compared with those younger than 70 years within the RM-NPC subgroup (Fig. 2B), the analysis of RMST validated this observation. At the 24-month assessment of RMST, there was no significant difference between adults aged under 70 years and those in the other group (17.5 months *vs.* 15.9 months, $p = 0.427$). The ORR of the elderly (57.1% *vs.* 53.3%, $p = 0.772$) was not significantly greater than that of the young patients.

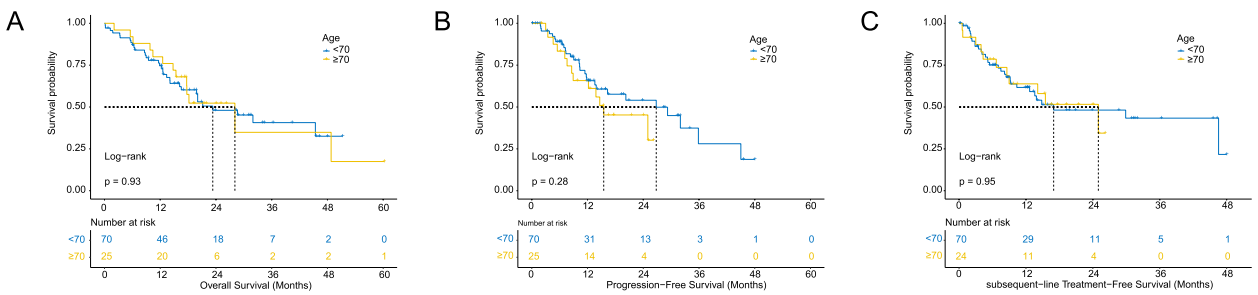

Fig. 2 Kaplan–Meier curves show the risk of OS (**A**), PFS (**B**) and sTFS (**C**) according to age groups

To identify potential survival advantages among elderly patients within the RM-NPC cohort, subgroup comparisons were conducted to compare PFS between patients aged under 70 years and those aged 70 years or above. As shown in Supplementary Fig. 4, the younger age group did not have longer PFS in any of the subgroups (all $p > 0.05$). No significant interactions were detected (all $p > 0.05$).

Toxicity of immunotherapy

Among 95 patients, 93 (97.9%) patients experienced AEs during ICI therapy, while CTCAE grade ≥ 3 AEs accounted for 25.3% (24/95) of all AEs (Table 3). The most common AEs of grade 3 or worse were anemia (in 17 [24%] patients aged < 70 years *vs.* 5 [20%] patients aged ≥ 70 years), leukopenia (15 [21%] *vs.* 2 [8%]), and neutropenia (12 [17%] *vs.* 3 [12%]). Therapy related to death was recorded in two (2.9%) of 70 patients aged younger than 70 years. Both patients died after one cycle of concurrent immunotherapy and chemotherapy. Immune-related AEs were observed in 23 (32.9%) patients in the younger age group and 9 (36%) patients in the elder age group. The incidence rates of AEs and irAEs were similar between the two age groups, except that a higher incidence of leukopenia was observed in the younger group ($p = 0.004$) (Table 3).

Discussion

In this retrospective study, we evaluated the clinical effectiveness and safety of immunotherapy in 95 NPC patients with recurrence or metastasis who were ≥ 65 years of age and who were receiving ICIs. To our knowledge, this analysis is the first study focused on aged RM-NPC patients who received ICIs to date. We found that there were only marginally statistically significant differences in clinical efficacy and toxic effects between patients aged under 70 years and those aged 70 years or above. Local therapy improved PFS and sTFS in elderly RM-NPC patients treated with anti-PD1 therapy.

Combining PD-1 immunotherapy with other agents is a promising strategy in RM-NPC patients because of the limited benefit of monotherapy with PD-1 inhibitors [13]. Adding toripalimab [10], camrelizumab [11], or tislelizumab [12] to chemotherapy significantly prolonged survival. However, in the phase III RATIONALE-309 study, subgroup analysis revealed that no improvement in PFS with tislelizumab-chemotherapy versus placebo-chemotherapy in patients aged ≥ 65 years [12]. Also, no improvement in OS was detected with the

Table 3 Adverse events in in older patients treated with immune checkpoint inhibitors

	Age < 70 ($n = 70$)			Age ≥ 70 ($n = 25$)		
	Grade 0	Grade 1 or 2	Grade 3 to 5	Grade 0	Grade 1 or 2	Grade 3 to 5
Any adverse event (%)	1 (1.4)	51 (72.9)	18 (25.7)	1 (4.0)	18 (72.0)	6 (24.0)
Anaemia (%)	6 (8.6)	47 (67.1)	17 (24.3)	3 (12.0)	17 (68.0)	5 (20.0)
Leukopenia (%)	32 (45.7)	23 (32.9)	15 (21.4)	21 (84.0)	2 (8.0)	2 (8.0)
Neutropenia (%)	48 (68.6)	10 (14.3)	12 (17.1)	20 (80.0)	2 (8.0)	3 (12.0)
Thrombocytopenia (%)	48 (68.6)	15 (21.4)	7 (10.0)	18 (72.0)	7 (28.0)	0 (0.0)
Infection (%)	39 (55.7)	22 (31.4)	9 (12.9)	18 (72.0)	6 (24.0)	1 (4.0)
Bleeding (%)	57 (81.4)	11 (15.7)	2 (2.9)	24 (96.0)	1 (4.0)	0 (0.0)
Nausea (%)	57 (81.4)	13 (18.6)	0 (0.0)	16 (64.0)	9 (36.0)	0 (0.0)
Diarrhoea (%)	64 (91.4)	5 (7.1)	1 (1.4)	23 (92.0)	1 (4.0)	1 (4.0)
Fatigue (%)	60 (85.7)	9 (12.9)	1 (1.4)	19 (76.0)	6 (24.0)	0 (0.0)
Dermatitis (%)	67 (95.7)	3 (4.3)	0 (0.0)	22 (88.0)	2 (8.0)	1 (4.0)
Fever (%)	64 (91.4)	6 (8.6)	0 (0.0)	23 (92.0)	1 (4.0)	1 (4.0)
Cardiac disorders (%)	55 (78.6)	11 (15.7)	4 (5.7)	21 (84.0)	4 (16.0)	0 (0.0)
Pneumonitis (%)	64 (91.4)	1 (1.4)	5 (7.1)	24 (96.0)	0 (0.0)	1 (4.0)
Creatinine increase (%)	54 (77.1)	13 (18.6)	3 (4.3)	19 (76.0)	5 (20.0)	1 (4.0)
Elevated ALT or AST concentrations (%)	38 (54.3)	30 (42.9)	2 (2.9)	18 (72.0)	7 (28.0)	0 (0.0)
Cognitive disturbance (%)	68 (97.1)	2 (2.9)	0 (0.0)	25 (100.0)	0 (0.0)	0 (0.0)
Sensory neuropathy (%)	62 (88.6)	8 (11.4)	0 (0.0)	24 (96.0)	1 (4.0)	0 (0.0)
Hypothyroidism (%)	45 (64.3)	25 (35.7)	0 (0.0)	18 (72.0)	7 (28.0)	0 (0.0)

Abbreviations: *ALT* Alanine aminotransferase, *AST* Aspartate transferase

pembrolizumab group versus the chemotherapy group in participants aged ≥ 65 years, according to the phase III KEYNOTE-122 study [13]. Our study suggested that adults aged ≥ 70 years had similar survival benefits as those aged < 70 years from immunotherapy. Chemotherapy was not an independent risk factor for survival in our cohort. Therefore, the role of chemotherapy-immunotherapy in elderly patients with RM-NPC requires further confirmation.

The median PFS in our research of elderly RM-NPC patients who received ICIs was 11.7 months, which is comparable to or longer than the results from younger patients in the JUPITER-02 trial (11.7 months) [14] and CAPTAIN-1st trial (9.7 months) [11]. Notably, the median follow-up time in these clinical trials was approximately half of what we achieved in our study. These findings illustrated that elderly NPC patients may have poorer survival outcomes than younger adults when treated with immunotherapy, a finding that aligns with several studies [3, 8]. More evidence is needed to validate these finding in the context of the immunotherapy era.

Among treatment-related risk factors, local therapy had a consistent and positive impact on survival. Local therapy improved the survival of recurrent or metastatic patients with solid tumors [15, 16], including NPC [7, 17, 18]. However, the efficacy of immunotherapy and local therapy has not been described in RM-NPC patients, let alone patients aged ≥ 65 years. In the present study, aged patients receiving local therapy prolonged the time from ICI treatment to progression and to the next line of therapy, which expanded the potential application of local therapy in elderly RM-NPC patients. Hence, in line with the recommendation of Chan et al. [3], we suggest that advanced age should not be a contraindication for RM-NPC patients to choose immunotherapy combined with local therapy on basis of our retrospective study.

The efficacy of different ICI agents in aged tumor patients has not been elucidated. Our study revealed the insight that there were no significant differences in survival periods among different immunotherapy drugs (Tables 2, 3, Supplementary Table 1), which was consistent with previous studies on aged patients with advanced non-small cell lung cancer (NSCLC) [19]. However, they retrospectively compared the survival benefits among the atezolizumab, nivolumab, and pembrolizumab groups, which were less frequently used in our cohort. The cost-effectiveness might be the explanation, even though KEYNOTE-122 [13] and NCI-9742 [20] showed that pembrolizumab and nivolumab had clinical activity in RM-NPC, respectively. On the one hand, the price of the above three anti-PD-(L)1 antibodies was much higher than that of camrelizumab, sintilimab, tislelizumab, and toripalimab in China. On the other hand, CTONG1901, a phase 2 prospective randomized controlled trial, demonstrated that sintilimab was as efficacious and safe as pembrolizumab in patients with NSCLC [21]. However, no direct comparison among other PD-1 inhibitors has been performed in RM-NPC patients or in older patients with RM-NPC. Hence, further prospective studies are needed to confirm the efficacy of different ICI agents in older RM-NPC patients.

Limitations

First, potential selection bias may exist because of the retrospective nature. Second, this was a single-center study from an endemic region. Third, owing to the small sample size, the number of subgroups or events identified in the study was relatively small. Fourth, the heterogeneity of treatment regimens may obscure true associations. In addition, these methods are insufficient for evaluating toxicity profiles because of the limited data on nonhematologic toxic effects. Hence, further prospective multicenter studies are needed to address the above limitations.

Conclusions

This retrospective study revealed that immunotherapy was efficacious and safe for RM-NPC patients aged ≥ 70 years compared with the younger patients (65 ≤ age < 70 years). When treated with a combination of PD-1 inhibitors and local therapy, patients exhibited longer PFS and sTFS. Patients who received different ICI regimens had comparable survival benefits. In other words, our findings suggest that immunotherapy combined with local therapy could be an option for elderly RM-NPC patients. Future prospective studies with larger sample sizes, standardized treatment protocols, and multi-institutional collaboration are necessary to confirm these findings and provide more definitive guidance on the optimal use of immunotherapy in this vulnerable population.

Abbreviations

ACE-27	Adult Co-morbidity Evaluation 27
ACCI	Age-Adjusted Charlson Comorbidity Index
AEs	Adverse events
CCI	Charlson Comorbidity Index
CR	Complete Response
CRT	Concurrent chemotherapy
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
ICI	Immune checkpoint inhibitor
IMRT	Intensity-modulated radiotherapy
NMPA	National Medical Products Administration
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed death-ligand 1
PFS	Progression-free survival
PR	Partial Response
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RM-NPC	Recurrent or metastatic nasopharyngeal carcinoma
RMST	Restricted mean survival time
RT	Radiotherapy
sTFS	Subsequent-line, treatment-free survival
SYSUCC	Sun Yat-sen University Cancer Center

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Authors' contributions

RL.X. and R.S. Conceptualization; RL.X., WL.C., HY.Z., YF.OY. Data curation; RL.X. and R.S. Methodology; RL.X. and WL.C. Analysis; RL.X. Writing and revising the manuscript. R.S. supervised the project. All authors discussed the results and commented on the manuscript.

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Data availability

The data that support the findings of this study are available on request from the corresponding author, sunrui@sysucc.org.cn, upon reasonable request.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the institutional review board of Sun Yat-sen University Cancer Center (IRB number: B2024-288–01) in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients at the time of primary diagnosis. When patients were unable to provide consent themselves, it was obtained from their legal guardian or an appropriate representative.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. Lancet. 2019;394(10192):64–80.
2. Lee AW, Sou A, Patel M, Guzman S, Liu L. Early onset of nasopharyngeal cancer in Asian/Pacific Islander Americans revealed by age-specific analysis. Ann Epidemiol. 2023;80:25–9.
3. Chan WL, Chow JCH, Xu ZY, Li J, Kwong WTG, Ng WT, Lee AWM. Management of nasopharyngeal carcinoma in elderly patients. Front Oncol. 2022;12:810690.
4. Liu H, Chen QY, Guo L, Tang LQ, Mo HY, Zhong ZL, Huang PY, Luo DH, Sun R, Guo X, et al. Feasibility and efficacy of chemoradiotherapy for elderly patients with locoregionally advanced nasopharyngeal carcinoma: results from a matched cohort analysis. Radiat Oncol. 2013;8:70.
5. Liang Y, Chen KH, Yang J, Zhang J, Peng RR, Qu S, Li L, Zhu XD. Acute toxicities and prognosis of elderly patients with nasopharyngeal carcinoma after intensity-modulated radiotherapy: prediction with nomogram. Cancer Manag Res. 2020;12:8821–32.
6. Ng WT, Soong YL, Ahn YC, AlHussain H, Choi HCW, Corry J, Gregoire V, Harrington KJ, Hu CS, Jensen K, et al. International recommendations on reirradiation by intensity modulated radiation therapy for locally recurrent nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 2021;110(3):682–95.
7. Liu YP, Wen YH, Tang J, Wei Y, You R, Zhu XL, Li J, Chen L, Ling L, Zhang N, et al. Endoscopic surgery compared with intensity-modulated radiotherapy in resectable locally recurrent nasopharyngeal carcinoma: a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet Oncol. 2021;22(3):381–90.
8. Blanchard P, Lee AWM, Carmel A, Wai Tong N, Ma J, Chan ATC, Hong RL, Chen MY, Chen L, Li WF, et al. Meta-analysis of chemotherapy in nasopharynx carcinoma (MAC-NPC): an update on 26 trials and 7080 patients. Clin Transl Radiat Oncol. 2022;32:59–68.
9. Wen YF, Sun XS, Yuan L, Zeng LS, Guo SS, Liu LT, Lin C, Xie HJ, Liu SL, Li XY, et al. The impact of adult comorbidity evaluation-27 on the clinical outcome of elderly nasopharyngeal carcinoma patients treated with chemoradiotherapy or radiotherapy: a matched cohort analysis. J Cancer. 2019;10(23):5614–21.
10. Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, Li J, Shi Y, Jin F, Xu R, et al. Toripalimab plus chemotherapy for recurrent or metastatic nasopharyngeal carcinoma: The JUPITER-02 randomized clinical trial. JAMA. 2023;330(20):1961–70.
11. Yang Y, Qu S, Li J, Hu C, Xu M, Li W, Zhou T, Shen L, Wu H, Lang 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;22(8):1162–74.
12. Yang Y, Pan J, Wang H, Zhao Y, Qu S, Chen N, Chen X, Sun Y, He X, Hu C, et al. Tislelizumab plus chemotherapy as first-line treatment for recurrent or metastatic nasopharyngeal cancer: a multicenter phase 3 trial (RATIONALE-309). Cancer Cell. 2023;41(6):1061–1072 e1064.
13. Chan ATC, Lee VHF, Hong RL, Ahn MJ, Chong WQ, Kim SB, Ho GF, Caguioa PB, Ngamphaiboon N, Ho C, et al. Pembrolizumab monotherapy versus chemotherapy in platinum-pretreated, recurrent or metastatic nasopharyngeal cancer (KEYNOTE-122): an open-label, randomized, phase III trial. Ann Oncol. 2023;34(3):251–61.
14. Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, Li J, Shi YR, Jin F, Xu R, et al. Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial. Nat Med. 2021;27(9):1536–43.
15. Mahvi DA, Liu R, Grinstaff MW, Colson YL, Raut CP. Local cancer recurrence: the realities, challenges, and opportunities for new therapies. CA Cancer J Clin. 2018;68(6):488–505.
16. Katipally RR, Pitroda SP, Juloori A, Chmura SJ, Weichselbaum RR. The oligometastatic spectrum in the era of improved detection and modern systemic therapy. Nat Rev Clin Oncol. 2022;19(9):585–99.
17. You R, Liu YP, Huang PY, Zou X, Sun R, He YX, Wu YS, Shen GP, Zhang HD, Duan CY, 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):1345–52.
18. Zhang MX, Liu T, You R, Zou X, Liu YL, Ding X, Duan CY, Xu HS, Liu YP, Jiang R, et al. Efficacy of local therapy to metastatic foci in nasopharyngeal carcinoma: large-cohort strictly-matched retrospective study. Ther Adv Med Oncol. 2022;14:17588359221112486.
19. Altan M, Singhi EK, Worst M, Carter BW, Leung CH, Lee JJ, Presley CJ, Lewis J, Rinsurongkawong W, Rinsurongkawong V, et al. Clinical effectiveness and safety of anti-PD-(L)1 therapy among older adults with advanced non-small cell lung cancer. Clin Lung Cancer. 2022;23(3):236–43.
20. Ma BBY, Lim WT, Goh BC, Hui EP, Lo KW, Pettinger A, Foster NR, Riess JW, Agulnik M, Chang AYC, et al. Antitumor activity of nivolumab in recurrent and metastatic nasopharyngeal carcinoma: an international, multicenter study of the mayo clinic phase 2 consortium (NCI-9742). J Clin Oncol. 2018;36(14):1412–8.
21. Maggie Liu SY, Huang J, Deng JY, Xu CR, Yan HH, Yang MY, Li YS, Ke EE, Zheng MY, Wang Z, et al. PD-L1 expression guidance on sintilimab versus pembrolizumab with or without platinum-doublet chemotherapy in untreated patients with advanced non-small cell lung cancer (CTONG1901): A phase 2, randomized, controlled trial. Sci Bull (Beijing). 2024;69(4):535–43.

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