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ORIGINAL RESEARCH

Thyroid Dysfunction After Intensity-Modulated Radiotherapy and PD-1 Inhibitor Treatment for Locally Advanced Nasopharyngeal Carcinoma

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Purpose: Analyze the incidence and risk factors of thyroid dysfunction in patients with advanced nasopharyngeal carcinoma (LA-NPC) after intensity-modulated radiotherapy (IMRT) and PD-1 inhibitor treatment and their relationship with treatment efficacy and prognosis.

Methods: Eighty-five LA-NPC patients treated with IMRT and PD-1 inhibitors were retrospectively collected from March 1, 2019, to May 30, 2022. The incidence of thyroid dysfunction after combination therapy was analyzed. The Kaplan–Meier method was used to analyze the relationship between thyroid dysfunction and patient prognosis. Logistic regression analysis was used to screen independent risk factors for thyroid dysfunction.

Results: As of data cutoff (May 31, 2024), the median follow-up time was 27.8 months (range: 25.6 to 32.0 months). The median time of onset of thyroid dysfunction was 8.26 months. The incidence of thyroid dysfunction is 47.06% (40/85), with clinical hypothyroidism being the main cause at an incidence rate of 28.24% (24/85) and clinical hyperthyroidism at an incidence rate of 3.53% (3/85). The incidence of grade 1 thyroid immune-related adverse events (irAEs) was 29.41% (25/85), and the incidence of grade 2 thyroid irAEs was 17.65% (15/85). Patients with thyroid dysfunction had longer overall survival, progression-free survival, and distant metastasis-free survival at both one and two years compared to patients with normal thyroid function, but the difference was not statistically significant ($p > 0.05$). Multivariate logistic regression analysis showed that pretreatment lactate dehydrogenase (LDH) ($p = 0.079$) is an independent predictor of thyroid dysfunction after radiotherapy in combination with immunotherapy for LA-NPC.

Conclusion: The study found that the addition of immunotherapy increases the risk and shortens the onset time of thyroid dysfunction in LA-NPC patients treated with chemoradiotherapy. Pretreatment LDH may serve as an independent risk factor for thyroid dysfunction for LA-NPC patients.

Keywords: nasopharyngeal carcinoma, IMRT, PD-1 inhibitor, thyroid dysfunction, survival

Introduction

Nasopharyngeal carcinoma (NPC) is prevailing in southern coastal areas of China, with nearly 60% of patients in the middle or advanced stage at the initial diagnosis.[1] Some researches proposed that NPC is an ecological disease: a multidimensional spatiotemporal "unity of ecology and evolution" pathological ecosystem.[2] Radiotherapy is the main treatment for NPC patients. Intensity-modulated radiotherapy (IMRT) combined with chemotherapy for locally advanced NPC (LA-NPC) has achieved great results, with a 5-year survival rate of over 80%.[3] Furthermore, the National Comprehensive Cancer Network (NCCN) and CSCO guidelines recommend concurrent chemoradiotherapy (CCRT) for patients of LA-NPC.[4–6] In recent years, with the widespread application of immunotherapy, PD-1 inhibitors combined with chemoradiotherapy have significantly improved the prognosis of recurrent or metastatic nasopharyngeal

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carcinoma.[7–9] PD-1 inhibitors have been recommended as the first and second-line treatment for recurrent or metastatic NPC by the 2021 Chinese Society of Clinical Oncology (CSCO) guidelines.[4] Additionally, clinical studies of PD-1 inhibitors in the first-line treatment of LA-NPC (NCT03930498, NCT03984357, NCT04769076, NCT05707819, NCT05229315) are also being widely conducted. The preliminary results reported by the 2023 American Society of Clinical Oncology showed that Sintilimab combined with CCRT treatment increased the 3-year event-free survival rate of patients from 76% to 86.1% and reduced the risk for distant metastasis-free survival (DMFS) and locoregional recurrence-free survival (LRFS) by 48% and 43% in LA-NPC (CONTINUUM) (NCT03700476).[10]

The thyroid gland is the largest endocrine organ in the human body. Radical radiotherapy for nasopharyngeal carcinoma routinely requires irradiation of the cervical lymph node area, which will inevitably irradiate the thyroid gland and cause radiation damage to the thyroid gland. Studies have reported that hypothyroidism occurred 9.4–15.4 months after IMRT treatment in NPC, with an incidence of 39%–69%.[11–13] At the same time, anti-PD-1 immunotherapy drugs also cause hypothyroidism, which is reported to be one of the most common immune-related adverse events (irAEs) in the application of PD-1 inhibitors.[14–16] Interestingly, studies have reported that patients with hypothyroidism had significantly better survival when undergoing IMRT[12,17,18] and anti-PD-1 immunotherapy.[15] With the increasing application of anti-PD-1 immunotherapy in the comprehensive treatment of nasopharyngeal carcinoma, whether there is a risk of synergistic aggravation of hypothyroidism caused by anti-PD-1 immunotherapy and radiotherapy has become one of the focuses of experts' attention, and there is no unified conclusion yet. Therefore, we analyzed 85 patients who received PD-1 inhibitors combined with radiotherapy, aiming to analyze the incidence of thyroid dysfunction after treatments and trying to clarify the clinical outcomes for patients with thyroid dysfunction after comprehensive treatment.

Methods

Patients

We retrospectively collected 85 cases of LA-NPC patients treated at the Affiliated Cancer Hospital of Guizhou Medical University (formerly Guizhou Cancer Hospital) from March 1, 2019, to May 30, 2022. Patients must meet the following inclusion criteria: (1) Age is ≥18 and ≤65 years old; (2) Pathological type is non-keratinizing carcinoma (WHO standard); (3) the American Joint Committee on Cancer 8th Edition Clinical Stage System diagnosed locally advanced nasopharyngeal carcinoma as T4N1 and T1-4N2-3; (4) ECOG score is 0–1; (5) adequate organ function; (6) baseline thyroid function, amylase and lipase levels, pituitary function, inflammatory infection indicators, and electrocardiogram test results were normal; (7) patients signed informed consent and demonstrated good compliance during the treatment; Exclusion criteria: (1) positive viral hepatitis B surface antigen and hepatitis B virus quantification> 1×10^3 copies/mL or anti-hepatitis C virus antibody positive; (2) anti-HIV antibody positive or diagnosed with acquired immunodeficiency syndrome; (3) Hypothyroidism or hyperthyroidism requiring treatment; (4) Severe illness cannot tolerate treatment. The study was approved and carried out by the Ethics Committee of the Affiliated Cancer Hospital of Guizhou Medical University ((formerly Guizhou Cancer Hospital)) on December 15, 2018 (Ethics No. SL-201812195).

Treatment

All patients were treated with IMRT technology. Target volume delineation was performed according to NCCN and CSCO guidelines.[4,5] The prescription doses for the primary gross tumor volume (GTV) and the involved lymph nodes (GTVnd) were 69.96 grays (Gy)/33 fractions(f), the high-risk clinical target volume (CTV) was 60.06 Gy/33f, and the low-risk CTV was 50.96 Gy/28f. In the case of 85 LA-NPC patients, the treatment mode consisted of induction chemotherapy (IC) combined with CCRT. The specific regimen included three cycles of gemcitabine plus cisplatin (GP) combined with three cycles of concurrent cisplatin and PD-1 inhibitors (toripalimab, nivolumab, or sintilimab) every three weeks. The dose for the IC regimen was 80 mg/m^2 cisplatin on day one and 1000 mg/m^2 gemcitabine on days one and eight; in addition to this, there was a dose of 100 mg/m^2 cisplatin in the CCRT regimen. The PD-1 inhibitors' doses were as follows: 200 mg for sintilimab, 240 mg for toripalimab and 360 mg for nivolumab.

Study Variables

The 85 LA-NPC patients were examined for thyroid function, including thyroglobulin antibodies (TG-Ab), thyroid peroxidase antibodies (TPO-Ab), total thyroxine (TT4), total triiodothyronine (TT3), free thyroxine (FT4), free triiodothyronine (FT3), and thyroid-stimulating hormone (TSH) before IC treatment, before each PD-1 inhibitors treatment, every 3 months for 2 years after radiotherapy, and every 6 months for 3 to 5 years after radiotherapy. The normal reference range for thyroid function is TSH: 0.270–4.200 μIU/mL and FT4: 12.000–22.000 pmol/L. Thyroid dysfunction refers to the absence of FT4 and TSH within normal reference ranges, including hypothyroidism and hyperthyroidism. Clinical hypothyroidism is defined as increased TSH and decreased FT4, while subclinical hypothyroidism is defined as increased TSH and normal FT4. Clinical hyperthyroidism is diagnosed with decreased TSH and increased FT4, while subclinical hyperthyroidism is diagnosed with decreased TSH and normal FT4. Pretreatment plasma EBV DNA concentrations were measured using quantitative polymerase chain reaction, with EBV-DNA concentrations above 500 copies/mL defined as EBV-DNA positive. Serum lactate dehydrogenase (LDH) was routinely measured, with the normal upper limit set at <240 IU/L in our center. Thyroid nodules are diagnosed based on the findings of the thyroid ultrasound diagnostic report.

Study Endpoints

The primary endpoint of this study is to observe changes in thyroid function after treatment with IMRT and PD-1 inhibitors. The severity grading of thyroid injury follows the Common Terminology Criteria for Adverse Events 5.0, which is commonly used in clinical trials. Grade 1 is mild, and the patient has no symptoms or only mild symptoms, which are only detected during clinical or diagnostic testing and do not require treatment. Grade 2 is moderate, which is the lowest indication for local or non-invasive treatment, and patients have age-related instrumental limitations in daily life and activities. Grade 3 refers to severe or medically significant symptoms that do not immediately endanger life. This is an indication that patients need hospitalization or extended hospitalization. Thyroid damage at this level is disabling, and the patient's ability to take care of themselves and their daily life and activities is limited. Grade 4 is life-threatening and patients need to receive emergency treatment. Grade 5 indicates patient death. The secondary observation index included short-term effects and the survival rate. All the patients received a complete treatment evaluation of tumor response after 3 cycles of induction chemotherapy and one month after concurrent chemoradiotherapy. Short-term effects include Complete Response (CR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (PD). The Response Evaluation Criteria in Solid Tumors 1.1 were used for short-term efficacy. The survival rates include Overall Survival (OS), Progression-Free Survival (PFS), LRFS, and DMFS. The OS rate is the time from diagnosis to death due to any cause. The LRFS rate is the survival rate from the start of treatment to the occurrence of local-regional recurrence or death. The DMFS rate is the survival rate from the start of treatment to the time of distant metastasis or death. The PFS rate is the survival rate from the start of treatment to the time of tumor progression or death.

Statistical Analysis

The treatment composition, patient characteristics, short-term efficacy, and the incidence of thyroid dysfunction were expressed as percentages (%). The survival effect was analyzed using Kaplan–Meier survival curve and logistic regression analysis. Multivariable analysis was conducted using the logistic regression model. p values <0.05 were considered significant.

Results

Baseline Characteristics

We enrolled a total of 85 LA-NPC patients in the study. The last follow-up was conducted on 31 May 2024, with a median follow-up time of 27.8 months (range: 25.6 to 32.0 months). The median age was 50.0 years (IQR 42.0–53.0). All the patients received 3 cycles of induction chemotherapy (IC) combined with PD-1 inhibitors followed by CCRT. Among them, fourteen (14/85, 16.47%) patients received sintilimab immunotherapy and six (6/85, 7.06%) patients underwent nivolumab treatment. The vast majority of these patients, precisely 65 (65/85, 76.47%), underwent

toripalimab immunotherapy. As of data cut off, out of 85 patients, 40 (40/85,47.06%) have developed thyroid dysfunction, while 45 have normal thyroid function. Among thyroid dysfunction, there are 24(24/85,28.24%) cases of clinical hypothyroidism, 8(8/85,9.41%) cases of subclinical hypothyroidism, 3(3/85,3.53%) cases of hyperthyroidism, and 5(5/85,5.88%) cases of subclinical hyperthyroidism. The clinical characteristics of 85 patients with clinical hypothyroidism, subclinical hypothyroidism, clinical hyperthyroidism, subclinical hyperthyroidism, and normal thyroid function treated by IMRT and PD-1 inhibitors are presented in Table 1.

Incidence and Severity Grading of Thyroid-Related irAEs

The median time of onset for thyroid dysfunction was 8.26 months, with the earliest occurrence being 1 month after treatment with IMRT combined with PD-1 inhibitors and the latest occurrence so far being 26 months. Figure 1A presents a comprehensive overview of the incidence rates of clinical hypothyroidism, subclinical hypothyroidism, clinical hyperthyroidism, and subclinical hyperthyroidism in 4 cohorts of patients at various time points. As the follow-up duration increases, there is a noticeable upward trend in the incidence rates. The incidence of grade 1 thyroid irAEs after IMRT and PD-1 inhibitors treatment was 29.41% (25/85), and the incidence of grade 2 thyroid irAEs was 17.65% (15/85), with no grade 3–5 thyroid irAEs (Figure 1B).

Short-Term Efficacy

All 85 patients completed all treatment plans and were eligible for efficacy evaluation. Nine patients (37.5%) with clinical hypothyroidism were evaluated for CR, and 15 patients (62.5%) were evaluated for PR. There were 4 patients (50.0%) of CR and 4 patients (50.0%) of PR in the subclinical hypothyroidism group. In the hyperthyroidism group,2 patients (66.67%) of CR and 1 patient (33.33%) of PR. There were 3 patients (60.0%) of CR and 2 patients (40.0%) of PR in the subclinical hyperthyroidism group. The last group consisted of 20 patients (44.44%) of CR, 24 patients (53.33%) of PR and 1 patient (2.23%) of SD in the group with normal thyroid function. In hypothyroidism group, 1

Table 1 Baseline Characteristics of 85 Patients

Characteristics	Clinical Hypothyroidism	Subclinical Hypothyroidism	Clinical Hyperthyroidism	Subclinical Hyperthyroidism	Normal Thyroid Function
n	24	8	3	5	45
Sex, n (%)					
Female	10 (47.62%)	0 (0%)	1 (33.33%)	2(40.0%)	14 (31.11%)
Male	14 (52.38%)	8 (100%)	2 (66.67%)	3(60.0%)	31 (68.89%)
Age, median (years)	50	48	46	40	49
Smoking, n (%)					
No	11 (45.83%)	0 (0%)	1 (33.33%)	2(40.0%)	20 (44.448%)
Yes	13 (54.17%)	8 (100%)	2 (66.67%)	3(60.0%)	25 (55.56%)
ECOG, n (%)					
0	23 (95.83%)	8 (100%)	3 (100%)	3(60.0%)	41 (91.11%)
1	1 (4.17%)	0 (0%)	0 (0%)	2(40.0%)	4 (8.89%)
T stage, n (%)					
T2	0 (0%)	0 (0%)	0 (0%)	1(20.0%)	1 (2.22%)
T3	8 (33.33%)	4 (50.0%)	1 (33.33%)	2(40.0%)	18 (40.0%)
T4	16 (66.67%)	4 (50.0%)	2 (66.67%)	2(40.0%)	26 (57.78%)
N stage, n (%)					
N1	3 (12.5%)	0(0%)	1 (33.33%)	0(0%)	8 (17.78%)
N2	13 (54.17%)	7 (87.5%)	2 (66.67%)	4(80.0%)	24 (53.33%)
N3	8 (33.33%)	1 (12.5%)	0(0%)	1(20.0%)	13 (28.89%)
Total stage, n (%)					
III	7 (29.17%)	4 (50.0%)	1 (33.33%)	2(40.0%)	15 (33.33%)
IVa	17 (70.83%)	4(50.0%)	2 (66.67%)	3(60.0%)	30 (66.67%)

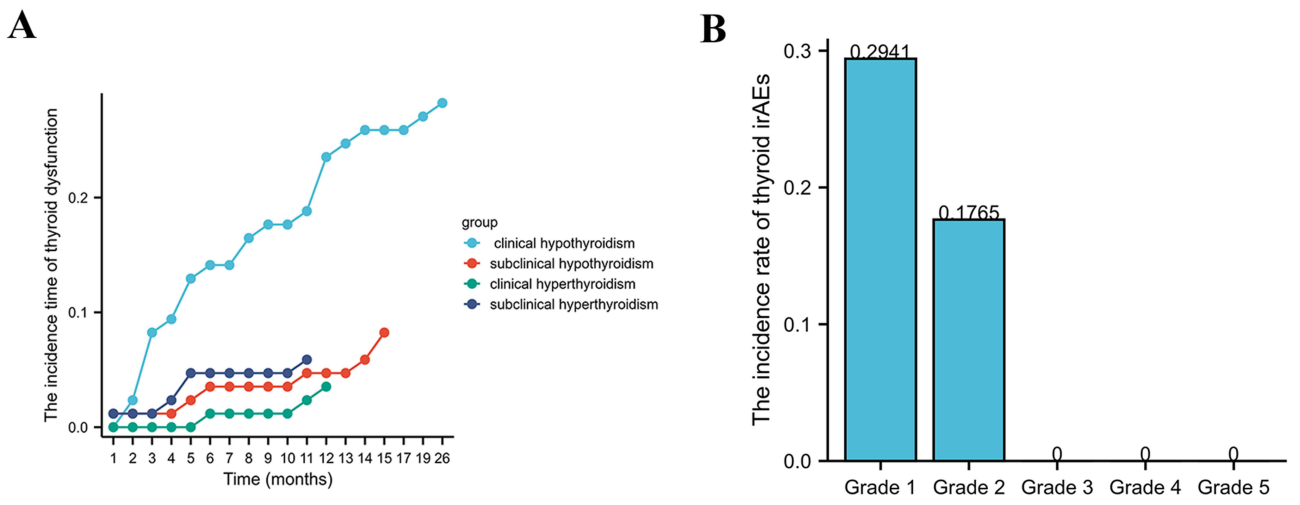

Figure 1 (**A**). The incidence time of thyroid dysfunction in patients with nasopharyngeal carcinoma. (**B**) The incidence rate of thyroid irAEs after IMRT and PD-1 inhibitors treatment.

patient (4.17%) died of distant metastasis, and 1 patient (4.17%) died of nasopharyngeal hemorrhage caused by local recurrence. In the normal thyroid function group, 3 patients (6.67%) died of distant metastasis, 1 patient (2.22%) died of severe pulmonary infection and shock, and 1 patient (2.22%) died of stroke (Table 2).

Survival Outcomes

In the 85 patients, the 1-year OS and 3-year OS were 97.6% and 87.2%, respectively (Figure 2A). To further explore whether thyroid dysfunction affected patients' survival, we compared the survival of 40 patients with thyroid dysfunction with 45 normal thyroid function patients. The 2-year OS and 3-year OS were 87.6% and 82.5% in the thyroid dysfunction patients and 84.9% and 75.6% in the normal thyroid patients, respectively (Hazard ratio(HR)=0.51, 95% confidence interval(CI)0.10–2.66, p = 0.425); The 2-year PFS and 3-year PFS were 91.4% and 85.0% in the thyroid dysfunction patients and 83.5% and 75.6% in the normal thyroid patients, respectively (HR=0.46,95% CI 0.09–2.40, p = 0.359); The 2-year DMFS and 3-year DMFS were 93.8% and 85.0% in the thyroid dysfunction patients, and 87.4% and 75.6% in the normal thyroid patients, respectively (HR=0.40,95% CI 0.04–3.93, p = 0.434) (Figures 2B–2D). We also tried to figure out whether there are differences in survival rates between the four thyroid dysfunction sub-groups and the normal group, but no significant difference was found in patient survival between the five subgroups (Supplementary Figure 1).

Table 2 Response to Treatment in the Five Groups of Patients

Variable	Clinical Hypothyroidism, n=24	Subclinical Hypothyroidism, n=8	Clinical Hyperthyroidism, n=3	Subclinical Hyperthyroidism, n=5	Normal Thyroid Function, n=45
Response to the whole treatment					
CR	9(37.5%)	4(50.0%)	2(66.67%)	3(60.0%)	20(44.44%)
PR	15(62.5%)	4(50.0%)	1(33.33%)	2(40.0%)	24(53.33%)
SD	0(0%)	0(0%)	0(0%)	0(0%)	1(2.23%)
Overall survival					
Death — no. (%)	2(8.34%)	0(0%)	0(0%)	0(0%)	5(11.11%)
Disease progressive					
Distant	1(4.17%)	0(0%)	0(0%)	0(0%)	3(6.67%)
Recurrence	1(4.17%)	0(0%)	0(0%)	0(0%)	0(0%)

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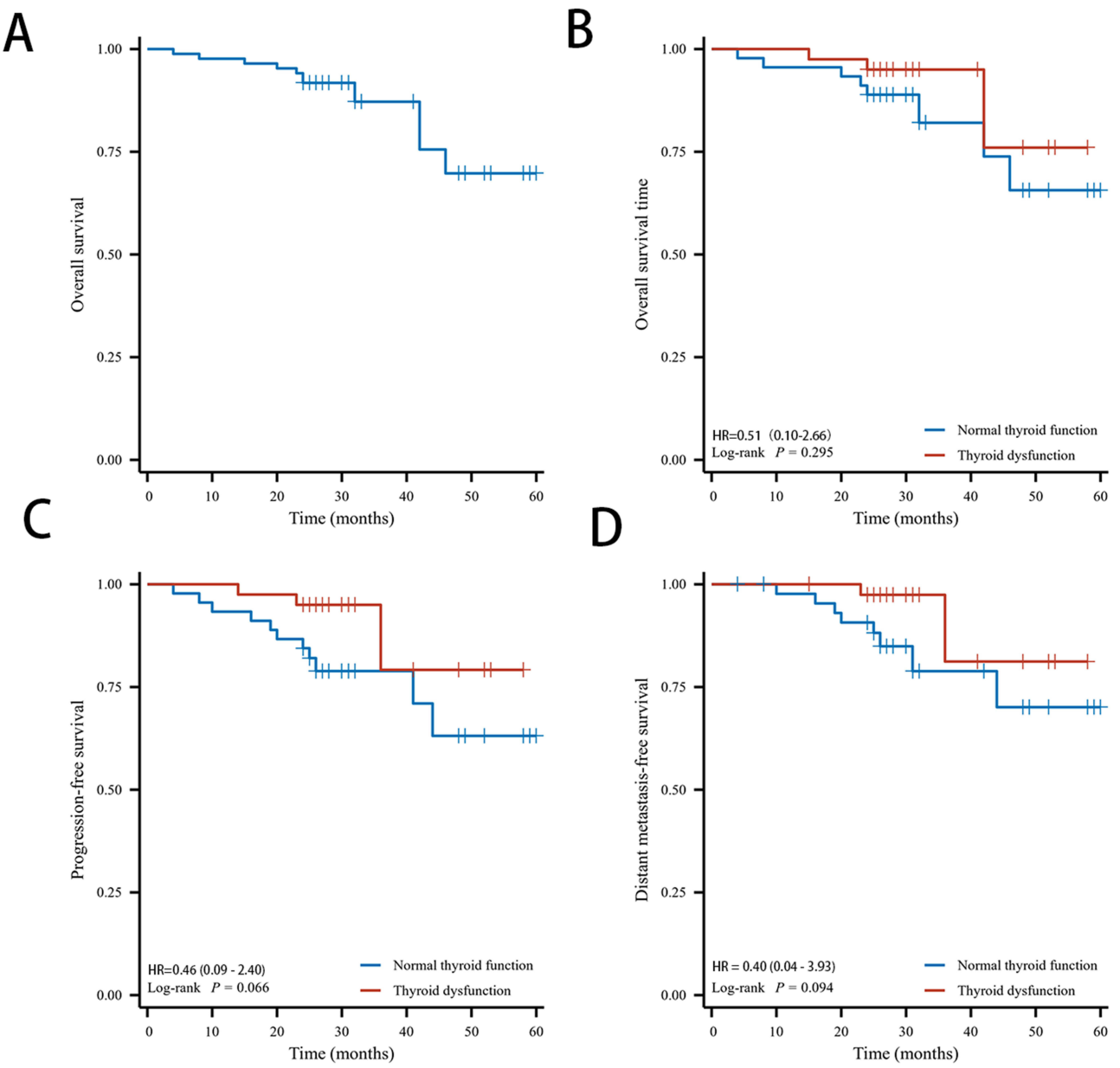

Figure 2 (**A**). The Overall survival curves of 85 patients. (**B**) OS curve of thyroid dysfunction and normal thyroid function patients. (**C**) PFS curve of two group patients. (**D**) DMFS curve of two group patients.

Prognostic Analysis

In addition to including general characteristics such as patient sex, age, T and N stage, total stage in the multivariable logistic analysis, pre-treatment EBV DNA copies and thyroid nodules are also included for analysis in this study. Univariate logistic regression analysis showed that pre-treatment LDH and pre-treatment thyroid nodules were influencing factors for thyroid dysfunction in LA-NPC patients treated with radiotherapy and immunotherapy, while the final multivariate logistic regression showed that only pre-treatment LDH was an independent influencing factor for thyroid dysfunction (Table 3).

Discussion

Thyroid dysfunction after radiotherapy of nasopharyngeal carcinoma is one of the most common complications after radiotherapy. Although intensity-modulated radiotherapy (IMRT) can minimize the average thyroid dose during treatment, studies

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Table 3 Results of Multivariable Analysis of Thyroid Dysfunction After IMRT and PD 1 Inhibitors for Nasopharyngeal Carcinoma

Variables	Total (%)	Univariate		Multivariate	
		OR (95% CI)	P	OR (95% CI)	P
Gender					
Male	58	Reference			
Female	27	1.066 (0.427–2.660)	0.891		
Age					
<50	42	Reference			
≥50	43	0.655 (0.278–1.542)	0.332		
T stage					
T2	2	Reference			
T3	33	0.833 (0.048–14.482)	0.900		
T4	50	0.923 (0.055–15.592)	0.956		
N stage					
N1	12	Reference			
N2	50	0.710 (0.263–1.918)	0.499		
N3	23	0.462 (0.123–1.732)	0.252		
Total stage					
III	29	Reference			
IVA	56	0.929 (0.378–2.279)	0.871		
LDH					
Negative	51	Reference		Reference	
Positive	34	8.589 (3.150–23.420)	< 0.001	7.480 (2.686–20.836)	< 0.001
Pretreatment EBV DNA					
Positive	68	Reference			
Negative	17	1.000 (0.345–2.900)	1.000		
Thyroid nodule					
No	66	Reference		Reference	
Yes	19	4.308 (1.386–13.392)	0.012	3.083 (0.878–10.825)	0.079

have shown that the 12 to 24 months after radiotherapy is still the high incidence period for hypothyroidism after radiotherapy.[19] In recent years, the combination of radiotherapy and PD-1 inhibitors has brought great new hope to many patients. More and more preclinical and clinical data involve the combination of radiotherapy and immune checkpoint inhibitors.[20,21] One of the most common irAEs reported in the application of PD-1 inhibitors is hypothyroidism in endocrine diseases.[22–24] The relationship between the incidence and clinical characteristics of thyroid dysfunction caused by the combination of IMRT and PD-1 inhibitors in the treatment of LA-NPC, as well as its relationship with survival, has been rarely reported currently. Therefore, thyroid immune-related events may be used as an indicator to predict the survival and prognosis of NPC. Our research suggest that the prevalence of thyroid dysfunction is 47.06%, with a median onset time of 8.26 months, and there is an observed tendency for extended OS, PFS, and DMFS in patients with thyroid dysfunction compared to those with normal thyroid function. This conclusion is consistent with previous studies.[25] However, how PD-1 inhibitors efficacy and thyroid dysfunction are connected remains unclear. Several studies also suggested that some immune pathways involving NK or T cells may influence thyroiditis with an anti-cancer effect, but the underlying mechanisms remain unknown.[26,27] In a word, the specific mechanisms between thyroid dysfunction and antitumor effects still need to be further explored.

Our results showed that 28.24% patients had clinical hypothyroidism, 9.41% had subclinical hypothyroidism, 3.53% had clinical hyperthyroidism, and 5.88% had subclinical hyperthyroidism as the data cut off. The incidence of clinical hypothyroidism in this study is significantly higher than 14.1% in previous studies that patients were treated with IMRT alone.[28] This suggests that radiotherapy and immunotherapy may synergize with each other to further increase the incidence of hypothyroidism. The incidence of grade 1 thyroid irAEs after IMRT and PD-1 inhibitors treatment was 29.41%, and the incidence of grade 2 thyroid irAEs was 17.65%. The rate of thyroid dysfunction was higher than

previous studies. In the POLARIS-02 study,[7] the incidence of hypothyroidism in patients with recurrent or metastatic NPC treated with toripalimab was 23.7%, with 10% experiencing grade 1 thyroid irAEs and 13.7% experiencing grade 2 thyroid irAEs. Fang[29] et al studied camrelizumab alone or in combination with GP for NPC, and the results showed that camrelizumab alone treated grade 1–2 thyroid irAEs incidence was 32%, and 1 case of hyperthyroidism was reported. However, all the above data are from studies of recurrent or metastatic NPC. In the nonmetastatic NPC study,[15] in the immunotherapy camrelizumab combination with chemoradiotherapy patients, the thyroid dysfunction rate was 28.485%, clinical hypothyroidism plus subclinical hypothyroidism was 51.064%, and 38.298% incidence rate of hyperthyroidism. Hypothyroidism occurred median onset time difference of 32 days. Our results of hyperthyroidism patients were lower and thyroid dysfunction occurred later. In a study of 404 patients with nonmetastatic NPC treated with IMRT, the 3-, 5- and 7-year cumulative incidence rate of hypothyroidism was 39.4%, 49.1%, and 54.7%, respectively.[12] Among our 85 patients, 50 were in the N2 stage, and 23 were in the N3 stage. The thyroid gland is within the radiation range, and it is PD-1 inhibitors combined with chemoradiotherapy, so the incidence of thyroid dysfunction is higher than in other studies, with a median OS of 20 months.

Regarding short-term efficacy, no significant difference was observed between the thyroid dysfunction group and the normal group in this study, and no difference was observed between the subgroups of thyroid dysfunction either. Presently, few studies have reported the relationship between thyroid dysfunction and the short-term efficacy of PD-1 inhibitors combined with concurrent chemoradiotherapy. In a word, how ICI efficacy and thyroid irAEs are connected remains unknown. Our regimen of three cycles of induction chemotherapy with GP plus PD-1 inhibitors followed by concurrent cisplatin plus PD-1 inhibitors resulted in a 3-year OS of 87.2%. Compared with the GP induction chemotherapy in the NPC study, the 3-year OS was 94.6%.[30] We are in the standard GP scheme based on PD-1 inhibitor therapy did not improve the OS. The vast majority of patients achieve CR and PR. Patients with thyroid dysfunction had longer OS, PFS, and DMFS at 3 years compared to patients with normal thyroid function. To our knowledge, few studies had reported the association between thyroid dysfunction and survival in IMRT in combination with PD-1 inhibitors for LA-NPC. However, in non-small cell lung cancer studies, thyroid dysfunction during PD-1 inhibitor treatment could be used as a potential marker for the prognosis.[31–36]

Unlike previous studies on hypothyroidism after radiotherapy,[37–39] the logistic regression analysis showed that there was no statistically significant difference in the impact of T, N stages on thyroid dysfunction. It may mainly because the incidence of hypothyroidism increased sharply after the addition of immunotherapy, and the original relationship between clinical stage and the occurrence of radiation-induced hypothyroidism was significantly weakened. Multifactor logistic regression analysis showed that pretreatment LDH is an independent risk factors for thyroid dysfunction after radiotherapy combined with immunotherapy for LA-NPC patients. BIONDI[40] also found that the increased thyroid-stimulating hormone levels may indirectly increase LDH levels, and LDH levels may indicate the reserve of thyroid function. Patients with higher LDH levels before radiotherapy may experience a higher incidence of hypothyroidism after radiotherapy and immunotherapy, which may be related to the low reserve of thyroid function. In addition to this, some studies[41] also found that the size of thyroid nodules is an independent risk factor for predicting the incidence of hypothyroidism in patients with normal thyroid function, suggesting a possible relationship between thyroid nodules and the occurrence of hypothyroidism. However, we did not find a significant correlation between thyroid nodules and thyroid dysfunction in LA-NPC patients in this study. It is well known that pretreatment EBV DNA is a strong prognostic indicator for NPC patients.[42–44] We also tried to find out whether there is a correlation between pretreatment EBV DNA and thyroid dysfunction in LA-NPC patients treated with radiotherapy and immunotherapy. Unfortunately, multivariate logistic regression analysis suggested that pretreatment EBV DNA was not a strong predictor of thyroid dysfunction.

Conclusions

In conclusion, the incidence of thyroid dysfunction in patients with LA-NPC is significantly increased after IMRT combined with PD-1 inhibitors. Pretreatment LDH is an independent risk factor for thyroid dysfunction after radiotherapy combined with immunotherapy for LA-NPC patients. We also observed a tendency of longer OS, PFS, and DMFS in patients with thyroid dysfunction, in which that thyroid dysfunction may be one of the potential prognostic markers for LA-NPC treated with IMRT combined with immunotherapy. Nevertheless, large prospective randomized clinical studies are required to further validate these conclusions. Several limitations of our study should also be noted:

First of all, the sample size is small. Second, the radiotherapy dosimetry data are incompletely preserved and are not included in the final analysis. We are planning to expand the sample size and continue to improve radiotherapy dosimetry factors in the subsequent enrollment of new cases.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request. All requests for data will be reviewed by the Affiliated Cancer Hospital of Guizhou Medical University to verify if the request is subject to any intellectual property or confidentiality obligations.

Ethics and Consent

This study was conducted in accordance with the declaration of Helsinki. A written informed consent was obtained from all participants. The study was approved and carried out by the Ethics Committee of the Affiliated Cancer Hospital of Guizhou Medical University ((formerly Guizhou Cancer Hospital)) on December 15, 2018 (Ethics No. SL-201812195).

Consent for Publication

Consent for publication was obtained from every individual whose data are included in this manuscript.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors claimed that there are no conflicts of interest.

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