

ORIGINAL RESEARCH ARTICLE

Incidence of mastoiditis in nasopharyngeal carcinoma following anti-PD-1 therapy: A propensity-matched analysis

Qi-Lun Guo^{1,2†}, Yong-Long Liu^{1,2†}, Wei-Jing Zhang^{2,3†}, Kai Wen^{1,2}, Hui-Feng Li^{1,2}, Rui You^{1,2}, Si-Yuan Chen^{1,2}, Jian Li⁴, Ming-Yuan Chen^{1,2} and Yi-Jun Hua^{1,2*}

¹Department of Nasopharyngeal Carcinoma, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Sun Yat-sen University Cancer Center, Guangzhou, China

²State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China

³Department of Medical Imaging, Sun Yat-sen University Cancer Center, Guangzhou, China

⁴Institute of Molecular Medicine and Experimental Immunology, University Clinic of Rheinische Friedrich-Wilhelms-University, Bonn, Germany

Abstract

Mastoiditis can be induced by radiotherapy and is closely associated with hearing loss. This study aimed to investigate the incidence of mastoiditis in patients with locally advanced nasopharyngeal carcinoma (LANPC) undergoing anti-programmed death 1 (PD-1) therapy. We retrospectively reviewed patients with primary locoregionally advanced nasopharyngeal carcinoma who received intensity-modulated radiotherapy and concurrent cisplatin-based chemotherapy with or without anti-PD-1 therapy from January 2020 to January 2022 in a single medical institution. Group A received neoadjuvant chemotherapy (NACT) + concurrent chemoradiotherapy (CCRT) + anti-PD-1 therapy, whereas Group B received the same treatment, except for anti-PD-1 therapy. We employed a propensity score matching method to match patients from each group in a 1:1 ratio. The severity of mastoiditis was assessed using magnetic resonance imaging, specifically grading mastoid opacification on a scale of 0 – 3. A total of 136 out of 259 eligible patients were propensity-matched, with 68 patients in Group A and 68 patients in Group B. No significant differences were observed in patient and tumor characteristics between the two groups. There were no significant differences in the incidence rates of severe mastoiditis between the two groups before NACT, before CCRT, at 0 months, and at 3 months following CCRT. However, the incidence rate of severe mastoiditis at 6 months following CCRT was significantly higher in Group A compared to Group B (35.3% vs. 20.6%, $P = 0.008$). Analysis of variance with repeated measures demonstrated that anti-PD-1 therapy did not increase the incidence rate of severe mastoiditis in LANPC patients compared to immunotherapy-free patients following CCRT ($P = 0.24$). LANPC patients receiving anti-PD-1 therapy did not significantly experience more severe mastoiditis during CCRT, but there was an increasing trend post-CCRT. Additional follow-up with a larger patient cohort is necessary to draw definitive conclusions.

Keywords: Nasopharyngeal carcinoma; Mastoiditis; Anti-PD-1 therapy; Propensity-score matching

†The authors contributed equally to the work.

*Corresponding author:

Yi-Jun Hua
(huayj@sysucc.org.cn)

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1. Introduction

Nasopharyngeal carcinoma (NPC) has been endemic in Southeast Asia and Southern China.¹⁻³ Mastoiditis presents as mastoid effusion and is a common occurrence in patients with NPC both before and after radical radiotherapy.⁴ Studies have shown an increase in the incidence of mastoiditis following nasopharyngeal radiation, ranging from 15% to 50%.¹ The increasing incidence of mastoiditis has reached plateau since the introduction of intensity-modulated radiotherapy (IMRT), which is highly adaptable for targeting the tumor. Current research indicates that the incidence of mastoiditis during radiotherapy is 20% before treatment, and 31%, 19%, and 17% at 3 months, 12 months, and 24 months after treatment, respectively.⁴⁻⁷ Mastoiditis in NPC patients significantly impacts their quality of life, leading to symptoms such as ear fullness, tinnitus, pain, otorrhea, and even hearing loss.⁸

Immune checkpoint inhibitors (ICIs) have demonstrated promising clinical outcomes in the treatment of various cancer types and have become a common approach for managing early cancer stages.^{9,10} Several studies have shown that programmed death 1 (PD-1) inhibitors are well tolerated in patients with relapsed or metastatic NPC (RM-NPC). These inhibitors exhibit tumoricidal activity when used alone or in combination with platinum-based chemotherapy.¹¹⁻¹⁵ While the associated risk factors of mastoiditis have been studied in the context of two-dimensional conventional radiotherapy (2D-CRT) and IMRT,^{7,16-18} the incidence rate of mastoiditis following immunotherapy remains unknown. Considering that immunotherapy can induce various immune-related adverse events (irAEs),^{19,20} our study aims to investigate whether mastoiditis, an inflammatory condition, can manifest as a type of irAE in NPC patients receiving immunotherapy. In addition, we aim to explore the associated incidence rate of this condition.

2. Materials and methods

2.1. Study population

This retrospective study included patients newly diagnosed with NPC and admitted to the Sun Yat-sen University Cancer Center (Guangzhou, China) between January 2020 and January 2022. This study was conducted in compliance with the institutional policy to protect the patients' private information and was approved by the Institutional Review Board of Sun Yat-Sen University Cancer Center. The treatment protocols adhered to the principles of the Declaration of Helsinki. The key inclusion criteria for this study are as follows: (1) Newly diagnosed NPC, pathologically confirmed, and previously untreated; and (2) NPC at the M0 stage. The exclusion criteria for this

study are as follows: (1) Previous diagnosis of malignant tumors or other concurrent malignancies; (2) distant metastasis at the time of diagnosis; and (3) interruption of radiotherapy or anti-PD-1 therapy. In this retrospective study, a total of 259 patients met the inclusion criteria and were enrolled (Figure 1).

2.2. Clinical staging

Demographic information (age, sex, Karnofsky Performance Status [KPS] score, and body mass index [BMI]) and current medical history (disease course, AJCC TNM 8 staging, World Health Organization [WHO] pathological type, and treatment regimen) were collected.²¹ Clinical tumor staging of T and N stages was determined by magnetic resonance imaging (MRI) and M stage by positron emission tomography-computed tomography (PET/CT) according to the criteria from the 8th edition of the American Joint Committee on Cancer TNM Staging Manual.²² At each follow-up time point, two blinded expert reviewers individually assessed the degree of mastoiditis through MRI in each patient using diagnostic criteria as well as their own individual clinical experience.

2.3. Treatment

2.3.1. Radiation therapy

All patients ($n = 259$) were treated with a full course of IMRT. The primary gross tumor volume of NPC (GTVnx) and metastatic retropharyngeal nodes was determined based on MRI and/or PET/CT imaging, endoscopic, and clinical findings. Enlarged retropharyngeal lymph nodes were also delineated in GTVnx. The gross tumor volume of the cervix node (GTVnd) was defined as the gross tumor volume of the neck metastasis lymph node. The clinical target high-risk volume (CTV1) was defined as a subclinical disease consisting of a 0.5 – 1.0 cm margin (0.2 – 0.3 margin posteriorly) surrounding the GTVnx, and it must include the whole nasopharynx wall, as well as the high-risk sites of microscopic extension. The clinical target low-risk volume (CTV2) consisted of CTV1 and a 0.5 – 1.0 cm margin (0.2 – 0.3 margin posteriorly) to encompass the low-risk sites of microscopic extension, the level of the lymph node and the elective neck area (all N0 patients routinely delineated bilateral IIa, IIb, III, and Va regions, whereas N1 – 3 patients additionally delineated ipsilateral IV, Vb, or supraclavicular fossa regions). The prescribed doses of PTVs of GTVnx, CTV1, CTV2, and CTVnd were mainly 69.96 Gy, 59.4 Gy, 54 Gy, and 69.96 Gy in 33 fractions, respectively. Patients were treated with one fraction daily, 5 days/week. The dose received by each organ at risk (OAR) was limited to tolerance according to the RTOG 0225 protocol.²³

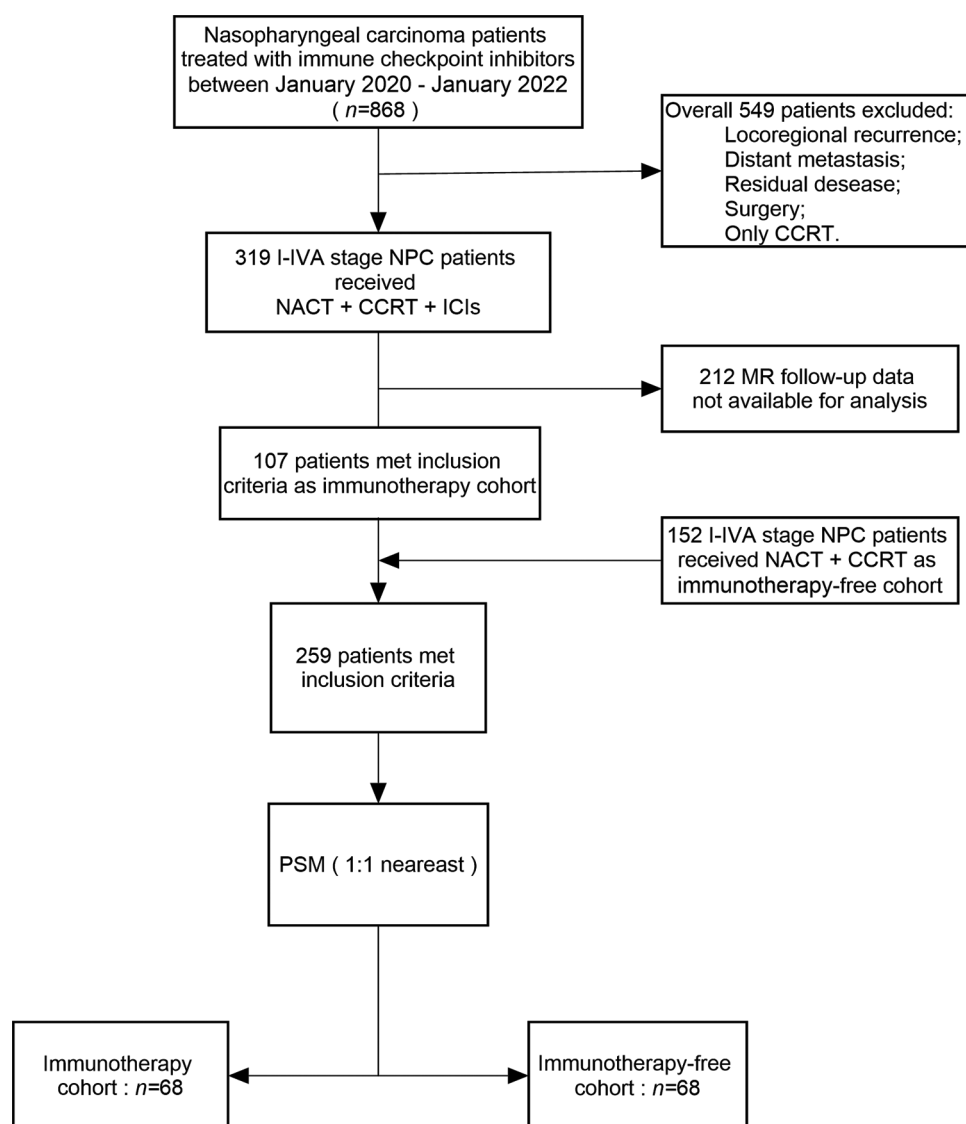


Figure 1. PSM flow diagram of the study selection process.

Abbreviations: CCRT: Concurrent chemoradiotherapy; ICI: Immune checkpoint inhibitor; MR: Magnetic Resonance NACT: Neoadjuvant chemotherapy; NPC: Nasopharyngeal carcinoma; PSM: Propensity score matching.

2.3.2. Chemotherapy

All patients ($n = 259$) received platin-based chemotherapy, which was given as neoadjuvant and concurrent therapy. For patients with locally advanced NPC (LANPC), guidelines recommend concurrent chemoradiotherapy (CCRT) followed by neoadjuvant chemotherapy (NACT) as the preferred standard of care.^{24,25} The NACT regimens included GP ($n = 111$), TP ($n = 8$), PF ($n = 8$), TPF ($n = 13$), or TPC ($n = 6$):

- (i) GP: 1.0 g/m² gemcitabine on days 1 and 8, and 80 mg/m² cisplatin on day 1
- (ii) TP: 260 mg/m² paclitaxel and 80 mg/m² cisplatin on day 1; 260 mg/m² paclitaxel and 30 mg/m² lobaplatin

on day 1; 70 mg/m² docetaxel and 70 mg/m² nedaplatin on day 1; 70 mg/m² docetaxel and 30 mg/m² lobaplatin on day 1

- (iii) PF: 80 mg/m² cisplatin on day 1 and 800 mg/m² fluorouracil civ on days 1 – 5
- (iv) TPF: 260 mg/m² paclitaxel or 60 mg/m² docetaxel on day 1, 60 mg/m² cisplatin on day 1, and 500 mg/m² fluorouracil civ on days 1 – 5
- (v) TPC: 200 mg/m² paclitaxel on day 1, 60 mg/m² cisplatin on day 1, and 1000 mg/m² capecitabine twice daily for 14 days every 3 weeks.

The cycles were repeated every 3 weeks for a total of 3 cycles, followed by radiotherapy performed concurrently

with platin-based chemotherapy. The reasons for deviating from the institutional guidelines included organ dysfunction suggesting intolerance to chemotherapy, patient refusal, and the discretion of the doctors in individual cases.

2.3.3. Anti-PD-1 therapy

At the time of the study, ICIs were gradually popularized and applied in LANPC. Camrelizumab, toripalimab, and tislelizumab were administered intravenously every 3 weeks at initial doses of 200 mg, 240 mg, and 200 mg, respectively, until disease progression or death.

2.4. MRI

All patients underwent standard MRI and were follow-up in our institution: 0 (before NACT), 2 (before CCRT), 4 (0 months after CCRT), 7 (3 months after CCRT), 10 (6 months after CCRT) months after diagnosis. All MRI examinations were performed on a 3.0T or 1.5T scanner (3.0T MRI system SIGNA PIONEER, GE Healthcare United States). The following sequences were obtained for each patient: unenhanced T1-weighted imaging (T1-WI) in the axial, coronal, and sagittal planes; unenhanced T2-weighted imaging (T2-WI) in the axial planes; enhanced T1-WI in the axial, coronal, and sagittal planes; diffusion-weighted magnetic resonance imaging (DWI). The parameters of these sequences are listed in Table A1 (Appendix). Digital Imaging and Communications in Medicine (DICOM) images of spin echo pre-enhanced axial T2-WI were selected for further analysis.

2.5. Image assessment and volume measurement

The magnetic resonance images collected from all target patients were compiled, and the image evaluation was independently conducted by two radiologists and one clinician. The radiologists and the clinician possess over 10 years of experience in diagnosing head and neck cancer through imaging. They received training in delineating mastoid opacity areas and independently outlined the corresponding mastoid contours. In case of any disagreements in their conclusions, consensus was reached through discussion. The diagnostic criteria for mastoiditis were based on Platzek *et al.*'s report,²⁶ including: (i) Fluid accumulation, increased contrast enhancement of the mastoid, and restricted diffusion in the mastoid, which were defined as signs of mastoiditis; (ii) subperiosteal fluid collection, extracranial contrast enhancement adjacent to the mastoid and restricted extracranial diffusion adjacent to the mastoid, which were interpreted as signs of a subperiosteal abscess; and (iii) all subperiosteal abscesses were defined as severe mastoiditis, regardless of the volume of the opacified structure.

Due to the variable mastoid turbidity ratio between the left and right mastoids in NPC patients, our study independently examined both mastoids. The MRI scanning images were imported into 3D Slicer 4.10 (www.slicer.org),²⁷ a widely used free and open-source multi-platform software package for medical and biomedical imaging research. Mastoid contours were manually delineated on each image based on T2-weighted axial images, and the mastoid volume was calculated using a volume rendering method. After outlining the mastoid profile, two investigators calculated the mean mastoid turbidity ratio, which serves as the basis for grading mastoiditis on each side. The mastoid turbidity ratio was scored as Grade 0 (<5% of the opacified structure's volume), 1 (6 – 33%), 2 (34 – 67%), or 3 (68 – 100%), as illustrated by Yao *et al.*⁷

2.6. Patient follow-up and statistical analysis

All patients underwent MRI examinations at the time of diagnosis and during relevant treatment phases. The primary focus of mastoiditis data collection centered on the 6-month period following radiotherapy. Propensity-score matching (PSM) was performed, incorporating known covariates (gender, age, KPS, BMI, pathology, T stage, N stage, and GTVnx), while accounting for potential confounding effects. Patients with missing data for the propensity-matched variables were excluded from the analysis. Nearest-neighbor 1:1 matching was employed, with a caliper set at 0.2. This process generated a new set of matched pairs, one each for immunotherapy and immunotherapy-free patients, and the covariates were evaluated using the Mann–Whitney *U* test, Chi-square test, or Fisher's exact test to assess the success of the matching algorithm. Based on whether or not they received anti-PD-1 therapy, the patients were categorized into the immunotherapy subgroup (Group A, *n* = 68) and the immunotherapy-free subgroup (Group B, *n* = 68) through propensity matching.

The primary outcome measure was the incidence rates of mastoiditis. Incidence rates of mastoiditis were calculated over time, and subgroups were compared using the Pearson's Chi-square test. The effect of anti-PD-1 treatment on the incidence of mastoiditis was assessed using repeated measures analysis of variance (ANOVA).

Statistical analyses were conducted using R version 4.1.2. Gender, KPS, WHO histological grade, T stage, N stage, and chemotherapy regimens are categorical variables and are presented as percentages (%). Continuous variables are expressed as median and interquartile range (IQR). All statistical tests were two-sided, and a *P* < 0.05 was considered statistically significant.

3. Results

3.1. Enrollment and demographics

Between January 2020 and January 2022 at the Sun Yat-sen University Cancer Center (Guangzhou, China), a total of 259 patients with histologically confirmed NPC met the predefined inclusion and exclusion criteria and were enrolled in the study. Out of the 259 eligible patients, 136 were included in the PSM group. In this overall PSM group ($n = 136$), the median age at diagnosis was 42.0 years (IQR: 34.0 – 52.0), and the median BMI was 22.6 kg/m² (IQR: 20.8 – 25.5). There were 95 male patients (69.9%), and 129 patients (94.9%) had a KPS score of 90. Most patients presented with T3/T4 tumors (89.7%) and the non-keratinizing type (WHO II type) (97.8%). The median GTVnx for the immunotherapy group and the immunotherapy-free group was 48.3 cm³ versus 46.5 cm³ ($P = 0.62$). Approximately equal proportions of patients had cN1 (37.5%, $n = 47$), cN2 (29.4%, $n = 54$), and cN3 (30.9%, $n = 42$) tumors.

Among the 136 patients in the PSM group, 68 patients belonged to Group B, receiving chemoradiotherapy alone, whereas the other 68 patients constituted Group A, receiving additional anti-PD-1 therapy. Among those in Group A, 47.1% ($n = 64$) received camrelizumab, 2.2% ($n = 3$) received toripalimab, and 0.7% ($n = 1$) received tislelizumab. The distribution of patients who received the first dose of anti-PD-1 therapy in the neoadjuvant, concurrent, and adjuvant phases was 35.3% ($n = 24$), 60.3% ($n = 41$), and 4.4% ($n = 3$), respectively. In Group A, more patients received neoadjuvant GP chemotherapy ($n = 42$, 61.8%) than TPC ($n = 13$, 19.1%), whereas in Group B, neoadjuvant GP chemotherapy ($n = 60$, 88.2%) was more common than PF ($n = 8$, 11.8%) therapy. It is noteworthy that none of the patients discontinued chemoradiotherapy during the course of our study. Table 1 provides a summary of the baseline demographic and clinical characteristics following PSM. Tumor characteristics were comparable between the two subgroups.

3.2. Incidence of mastoiditis after PSM

Patients were categorized into three groups based on the severity of mastoiditis before radiotherapy: G0M cohort, G1-2M cohort, and G3M cohort, representing grade 0, 1, or 2, and 3 mastoiditis, respectively, before treatment.⁷ Between January 2020 and January 2022, a total of 146 patients were initially screened for eligibility, resulting in the analysis of 292 mastoids for comparison. According to the diagnostic criteria previously established by Platzek *et al.*,²⁶ mastoiditis was newly confirmed in 93 (34.2%) out of 272 mastoids. Figure 2 illustrates the progression of grade 3 mastoiditis over time in an adult patient with biopsy-proven NPC, as observed on MRI.

Following PSM, for Group A versus Group B, the incidence of grade 3 mastoiditis was as follows: 18.4% versus 22.8% before NACT and 8.1% versus 8.1%, 13.2% versus 11.8%, 33.8% versus 23.5%, and 35.3% versus 20.6% before CCRT and at 0, 3, and 6 months following CCRT, respectively (Figure 3). The percentage of grade 3 mastoiditis was notably higher in Group A (35.3%) than in Group B (20.6%) 6 months after CCRT, and this difference was statistically significant ($P = 0.008$). Table 2 demonstrates that the distribution of mastoiditis severity was similar in both subgroups during NACT + CCRT, but mastoiditis in Group A became more severe 6 months after chemoradiotherapy.

3.3. Incidence of mastoiditis in G0M cohort

Mastoids with grade 0 were specifically selected before treatment, resulting in a total of 179 mastoids out of the initial 272. Among these, 96 mastoids were from Group A, and 83 mastoids were from Group B. Within the G0M cohort, the incidence rates of severe mastoiditis in Group A and Group B were as follows: 0.0% and 0.0% before NACT, 1.0% and 0.0%, 5.2% and 4.8%, and 29.2% and 18.1% before CCRT, and at 0, 3, and 6 months following CCRT, respectively (Figure 4). Notably, the percentage of grade 3 mastoiditis was significantly higher in Group A compared

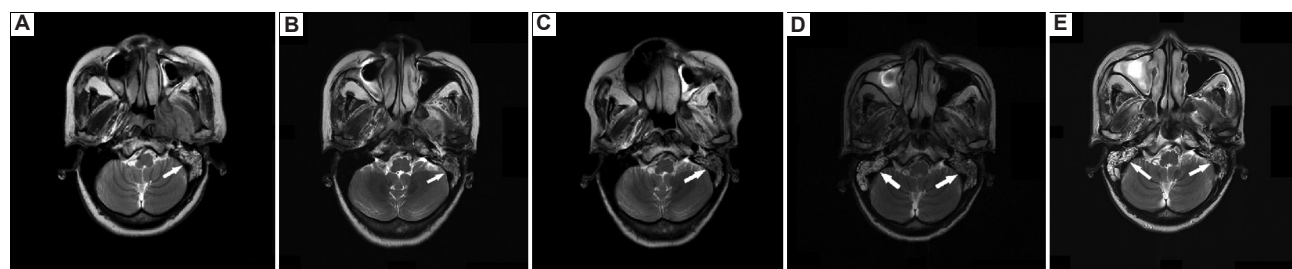


Figure 2. Axial T2-weighted MRI of an adult patient with biopsy-proven nasopharyngeal carcinoma revealing grade 3 mastoiditis (indicated by the white arrow) over the course of time: before NACT (A), before CCRT (B), and at 0 (C), 3 (D), and 6 (E) months after CCRT in conjunction with anti-PD-1 therapy.

Abbreviations: CCRT: Concurrent chemoradiotherapy; MRI: Magnetic resonance imaging; NACT: Neoadjuvant chemotherapy.

Table 1. Baseline characteristics (n=136 patients)

	Immunotherapy (Group A, n=68)	Immunotherapy-free (Group B, n=68)	P-value
Sex			0.85
Female	21 (30.9%)	20 (29.4%)	
Male	47 (69.1%)	48 (70.6%)	
Age (years)			0.87
Median (IQR)	43.5 (34.3 – 51.8)	41.0 (33.3 – 52.8)	
KPS			1.00
80	4 (5.9%)	3 (4.4%)	
90	64 (94.1%)	65 (95.6%)	
BMI (kg/m ²)			0.89
Median (IQR)	22.7 (20.5 – 25.6)	22.5 (21.0 – 25.3)	
Pathology ^a			1.00
1	2 (2.9%)	1 (1.5%)	
2	66 (97.1%)	67 (98.5%)	
T ^b			0.92
1	2 (2.9%)	2 (2.9%)	
2	6 (8.8%)	4 (5.9%)	
3	36 (52.9%)	36 (52.9%)	
4	24 (35.3%)	26 (38.2%)	
N			0.84
0	1 (1.5%)	2 (2.9%)	
1	25 (36.8%)	26 (38.2%)	
2	19 (27.9%)	21 (30.9%)	
3	23 (33.8%)	19 (27.9%)	
GTVnx (cm ³)			0.62
Median (IQR)	48.3 (30.9 – 72.2)	46.5 (33.4 – 69.4)	

Notes: ^aAccording to the World Health Organization (WHO); ^bAccording to the American Joint Committee on Cancer (AJCC), 8th edition. Abbreviations: BMI: Body mass index; GTVnx: Gross tumor volume of nasopharyngeal carcinoma; IQR: Interquartile range; KPS: Karnofsky Performance Status.

to Group B (29.2% vs. 18.1%, $P = 0.031$). Consequently, for newly diagnosed NPC patients without mastoiditis, anti-PD-1 therapy may represent a potential risk factor for the development of mastoiditis.

3.4. Repeated measures ANOVA

The trends in mean changes in the grade of mastoiditis are depicted in Figure A1 (Appendix). Repeated measures ANOVA analysis demonstrated that time ($F = 39.14$, $P < 0.001$) and the interaction between time and immunotherapy ($F = 7.25$, $P < 0.001$) had a significant impact on the incidence of severe mastoiditis during the treatment course in the G0-3M cohort. However, immunotherapy alone ($F = 1.40$, $P = 0.24$) had an insignificant impact on the incidence of severe mastoiditis during the treatment course within the G0-3M cohort. As outlined in Table 2, there was no significant difference in the proportion of

patients with grade 3 mastoiditis at the 3-month post-CCRT point between Groups A and B (33.8% vs. 23.5%, $P = 0.31$). However, a statistically significant difference in the proportion of patients with grade 3 mastoiditis at the 6-month post-CCRT point was observed between the two subgroups (35.3% vs. 20.6%, $P = 0.008$). In summary, the repeated measures ANOVA revealed significantly higher incidences of severe mastoiditis in Group A at the 6-month post-CCRT interval compared to Group B.

4. Discussion

Radiation-induced mastoiditis frequently arises in patients with NPC. Studies have revealed that this condition is more prevalent among those undergoing IMRT.⁷ PD-1 inhibitors have exhibited promising therapeutic outcomes in patients with RM-NPC. However, immunotherapy's capacity to elicit diverse irAEs prompts the inquiry

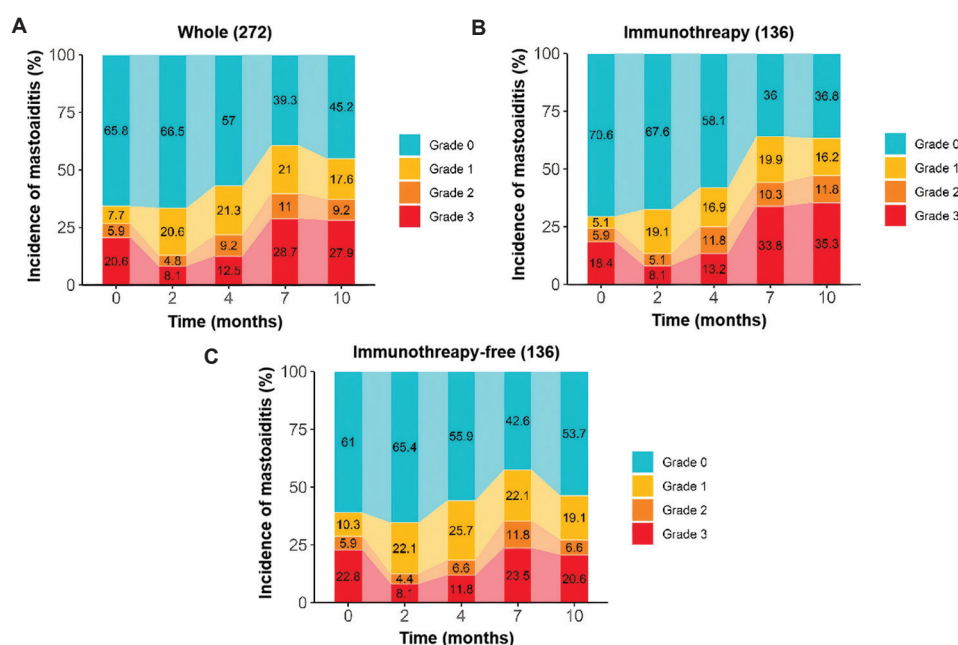


Figure 3. Stacked histograms depicting the incidence of grade 0 – 3 mastoiditis over time in LANPC patients ($n = 272$ mastoids). For the entire cohort (comprising the immunotherapy and immunotherapy-free groups), the incidence of grade 3 mastoiditis was 20.6% (18.4% vs. 22.8%) before NACT and 8.1% (8.1% vs. 8.1%), 12.5% (13.2% vs. 11.8%), 28.7% (33.8% vs. 23.5%), and 27.9% (35.3% vs. 20.6%) before CCRT and at 0, 3, and 6 months following CCRT, respectively. Immunotherapy (Group A), Immunotherapy-free (Group B).

Abbreviations: CCRT: Concurrent chemoradiotherapy; LANPC: Locally advanced nasopharyngeal carcinoma; NACT: Neoadjuvant chemotherapy.

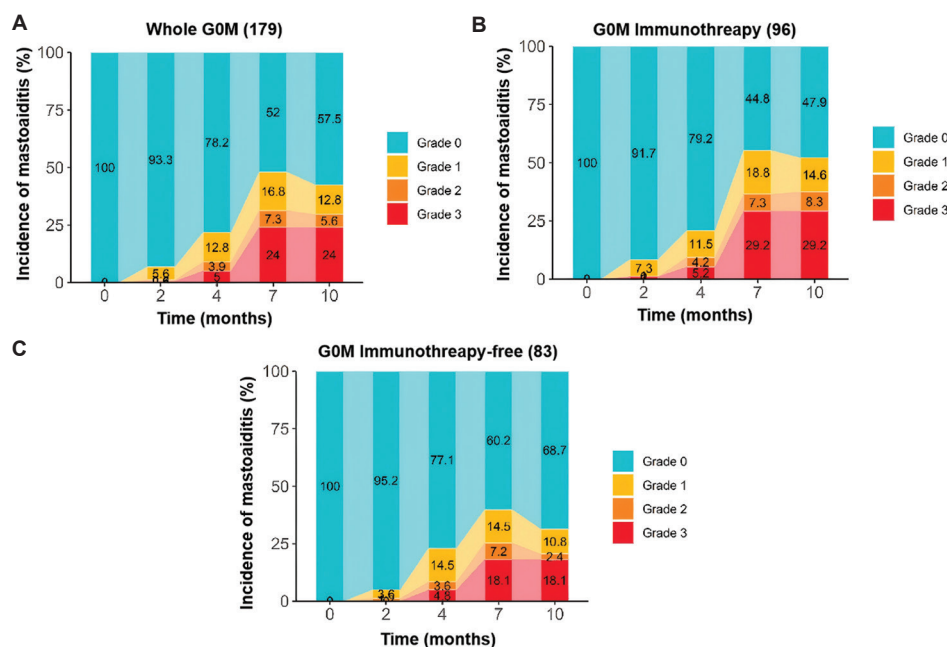


Figure 4. Stacked histograms depicting the incidence of grade 0 – 3 mastoiditis over time in LANPC patients ($n = 179$ mastoids) with grade 0 mastoiditis. Within the entire G0M group (comprising the immunotherapy and immunotherapy-free subgroups), the incidence of grade 3 mastoiditis was 0.0% (0.0% vs. 0.0%) before NACT and 0.6% (1.0% vs. 0.0%), 5.0% (5.2% vs. 4.8%), 24.0% (29.2% vs. 18.1%), and 24.0% (29.2% vs. 18.1%) before CCRT and at 0, 3, and 6 months following CCRT, respectively. Immunotherapy (Group A), Immunotherapy-free (Group B).

Abbreviations: CCRT: Concurrent chemoradiotherapy; LANPC: Locally advanced nasopharyngeal carcinoma; NACT: Neoadjuvant chemotherapy.

Table 2. Mastoiditis grade in the different treatment phases of patients' mastoids (*n*=272 mastoids)

	Immunotherapy (Group A, <i>n</i> =136) (%)	Immunotherapy-free (Group B, <i>n</i> =136) (%)	<i>P</i> -value
Before NACT			0.27
0	96 (70.6)	83 (61.0)	
1	7 (5.1)	14 (10.3)	
2	8 (5.9)	8 (5.9)	
3	25 (18.4)	31 (22.8)	
Before CCRT			0.94
0	92 (67.6)	89 (65.4)	
1	26 (19.1)	30 (22.1)	
2	7 (5.1)	6 (4.4)	
3	11 (8.1)	11 (8.1)	
0 month after CCRT			0.20
0	79 (58.1)	76 (55.9)	
1	23 (16.9)	35 (25.7)	
2	16 (11.8)	9 (6.6)	
3	18 (13.2)	16 (11.8)	
3 months after CCRT			0.31
0	49 (36.0)	58 (42.6)	
1	27 (19.9)	30 (22.1)	
2	14 (10.3)	16 (11.8)	
3	46 (33.8)	32 (23.5)	
6 months after CCRT			0.008
0	50 (36.8)	73 (53.7)	
1	22 (16.2)	26 (19.1)	
2	16 (11.8)	9 (6.6)	
3	48 (35.3)	28 (20.6)	

Abbreviations: CCRT: Concurrent chemoradiotherapy; NACT: Neoadjuvant chemotherapy.

of whether it impacts the occurrence of mastoiditis subsequent to radiotherapy. We conducted a retrospective review of patients with primary locally advanced NPC who underwent IMRT and cisplatin-based chemotherapy from January 2020 to January 2022 at Sun Yat-sen University Cancer Center, with a subset receiving anti-PD-1 therapy. Out of the 259 eligible patients, 136 fulfilled the criteria for PSM. Our repeated measures ANOVA indicate that anti-PD-1 therapy recipients did not endure significantly exacerbated mastoiditis during CCRT, but there was an increasing trend post-CCRT.

NPC has led to an endemic in Southern China and East-southern Asia, with incidence rates soaring to as high as 20 – 30/100,000.^{28,29} Patients diagnosed with NPC, especially those with higher T stages, frequently present with mastoiditis as an initial manifestation, primarily characterized by symptoms such as tinnitus and hearing loss. While radiotherapy can trigger radiation-related

mastoiditis, its incidence tends to decrease post-treatment.^{7,18} Although advancements in tumor control, particularly with the introduction of IMRT, have improved overall NPC survival rates, there remains a need to enhance the quality of life for post-treatment individuals.²⁴ In recent years, with the advent of immunotherapy, anti-PD-1 agents such as camrelizumab and toripalimab have demonstrated clinical effectiveness in treating RM-NPC while maintaining a favorable safety profile in China.^{12,13} Immunotherapy is now widely acknowledged as a superior treatment option for LANPC.³⁰ Given the growing body of evidence linking inflammatory responses to ICI treatment,³¹ it is hypothesized that NPC patients receiving ICIs may experience an increased incidence of severe mastoiditis.

After several decades, however, the incidence rate of mastoiditis, closely associated with hearing issues and as a complication of NPC, has not significantly decreased. Our

study revealed that the incidence rate of NPC remains at 34.2%.^{4,7} NPC patients with mastoiditis often suffer from tinnitus, hearing loss, swelling, pain, and other debilitating symptoms, significantly impacting their quality of life.^{26,32,33} Therefore, there is an urgent need for therapeutic strategies to prevent and manage mastoiditis caused by NPC. MRI is particularly well-suited for detecting mastoiditis, offering superior opacities distinction compared to CT scans.^{34,35} MRI findings in NPC patients with mastoiditis can provide several valuable parameters, including those related to the tympanic cavity, mastoid antrum, and opacified air cells.^{26,34} Consequently, volume rendering based on these parameters can effectively detect and grade mastoiditis.

ICIs targeting PD-1, which have demonstrated promising therapeutic efficacy and hold a pivotal role in contemporary cancer treatment, exemplified by the humanized monoclonal antibodies pembrolizumab and nivolumab, have received approval for treating patients with relapsed squamous cell carcinoma of the head and neck following previous platinum-based therapy. These PD-1 therapies, including nivolumab, pembrolizumab, toripalimab, and camrelizumab, have shown promising antitumor activity and favorable tolerability in numerous phase 1/2 trials for recurrent or metastatic NPC.³⁶ However, the treatment of cancers with PD-1 pathway inhibitors can lead to irAEs, some of which can be severe or even life-threatening. Therefore, clinicians must be well-informed about the characteristics of irAEs associated with the use of these drugs.³⁷ Camrelizumab and toripalimab, both humanized anti-PD-1 antagonist IgG4 monoclonal antibodies (IgG4 mAbs), can give rise to various unpredictable irAEs that may affect different target organs. Nonetheless, irAEs related to mastoiditis have been rarely reported.¹⁹

The previously reported incidence rate of mastoiditis in NPC patients before treatment aligns with the results observed in our study (grade 3, 20.0% vs. 20.6%). Those studies also noted a temporary increase in morbidity 3 months after radiotherapy (31.0% vs. 28.7%).⁷ These findings collectively suggest that IMRT has the potential to induce mastoiditis. For the G0M cohort, the incidence rate of grade 3 mastoiditis in NPC patients without immunotherapy (18.1%) decreased at the 6-month post-CCRT point compared to the rates reported in prior studies (23.0%).⁹ With the advancements in radiotherapy techniques for NPC and the accumulation of clinical evidence and experience, anti-PD-1 therapies will continue to be widely used in the treatment of LANPC.⁹ In our study, 89.7% of NPC patients presented with stage T3/T4 tumors, and half of them underwent anti-PD-1 therapy. This may help explain why the incidence rate of grade 3

mastoiditis following radiotherapy has not decreased over the past decade.

To our knowledge, this study represents the first attempt to uncover the potential clinical impact of ICIs on the incidence of mastoiditis in NPC patients. We observed that after PSM, the incidence rate of grade 3 mastoiditis in the immunotherapy subgroup significantly decreased from 18.4% to 8.1% during NACT, followed by a gradual increase post-radiotherapy, rising from 8.1% to 35.3%. In contrast, the incidence rate of grade 3 mastoiditis in the immunotherapy-free subgroup declined during NACT, going from 22.8% to 8.1%, and then increased from 8.1% to 23.5% post-radiotherapy. Furthermore, among NPC patients with grade 0 mastoiditis before treatment, we noted a clear trend of increasing mastoiditis incidence rates in the immunotherapy subgroups compared to the immunotherapy-free subgroup, suggesting that immunotherapy might significantly elevate the mastoiditis incidence rate in NPC patients. However, the results of repeated measures ANOVA did not reveal a significantly higher incidence rate of mastoiditis in the immunotherapy subgroup. Therefore, we propose that for LANPC patients receiving anti-PD-1 therapy, relevant preventive follow-up and treatment strategies should be implemented to manage the mastoiditis incidence rate.²⁴ Taken together, the combination of anti-PD-1 therapy and radiotherapy may have the potential to induce mastoiditis in NPC patients, a phenomenon that warrants further attention and verification with a larger patient cohort.

The present study boasts several strengths. First, to the best of our knowledge, this study represents the first report on the incidence rate of mastoiditis in LANPC patients treated with ICIs. Second, all recruited NPC patients received standard treatment following the guidelines set by the Chinese Society of Clinical Oncology for NPC.³⁸ Third, the balanced matching between both subgroups enhances the robustness and credibility of our results, clearly demonstrating that anti-PD-1 therapy impacts the incidence rate of mastoiditis in NPC patients after receiving radiotherapy.

This study has several limitations. First, it is subject to inherent limitations associated with retrospective research. Second, the longest follow-up duration was limited to 6 months post-radiotherapy, and a longer period may be necessary to thoroughly investigate potential changes in the mastoiditis incidence rate. Third, detailed documentation of mastoiditis-related quality-of-life surveys was lacking, making it challenging to determine the subjective symptoms experienced by individual patients comprehensively.

5. Conclusions

Mastoiditis is a radiation-induced condition typically diagnosed through MRI. LANPC patients receiving anti-PD-1 therapy experience slightly severe mastoiditis compared to those not receiving anti-PD-1 therapy after CCRT in our study. To validate these findings, well-designed and large-scale studies are warranted.

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Conflict of interest

Yi-Jun Hua is an Editorial Board Member of this journal but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: Yi-Jun Hua, Ming-Yuan Chen

Formal analysis: Qi-Lun Guo, Yong-Long Liu, Wei-Jing Zhang

Investigation: Qi-Lun Guo, Kai Wen, Hui-Feng Li, Si-Yuan Chen, Jian Li

Methodology: Qi-Lun Guo, Yong-Long Liu, Wei-Jing Zhang, Rui You

Writing – original draft: Qi-Lun Guo, Yong-Long Liu, Kai Wen, Wei-Jing Zhang, Si-Yuan Chen, Hui-Feng Li

Writing – review & editing: Yi-Jun Hua, Jian Li, Ming-Yuan Chen

Ethics approval and consent to participate

This study was approved by the Institutional Ethical Review Board of the Sun Yat-sen University Cancer Center (Guangzhou, China, B2022-174-01), and was in compliance with the 2016/679 General Regulation on Personal Data Protection regarding the use of anonymized population data. As the current study was a retrospective

assessment of routine data, the Institutional Ethical Review Board of the Sun Yat-sen University Cancer Center waived the need for obtaining individual informed consent.

Consent for publication

Not applicable.

Availability of data

The datasets presented in this study can be found in online repositories (<http://www.researchdata.org.cn>; – RDDA2022934283).

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Appendix

Table A1. Parameters for the magnetic resonance sequences

Sequence obtained	Scanner	Scanning method	TE (ms)	Pixel size (mm)	FOV (mm)	ST/spacing (mm)
AX T2WI	Achieva	TSE	89.0	3.20×2.96	240×240	5.0/6.0
AX T2WI	TrioTim	TSE	89.0	3.84×3.07	240×240	5.0/6.0
AX T2WI	uMR 560	FSE	111.0	3.84×2.68	240×240	5.0/6.0
AX T2WI	uMR 780	FSE	113.0	3.84×2.68	240×240	5.0/6.0
AX T2WI	uMR 790	FSE	120.0	3.84×2.68	240×240	5.0/6.0
AX T2WI	Discovery MR750	FSE	93.0	3.84×3.20	240×240	5.0/6.0
AX T2WI	Discovery MR750W	FSE	120.0	3.84×3.20	240×240	5.0/6.0
AX T2WI	SIGNA Premier	FSE	75.0	3.84×3.20	240×240	5.0/6.0
AX T2WI	SIGNA Pioneer	FSE	86.0	3.84×2.88	240×240	5.0/6.0
AX T2WI	Ingenia CX	TSE	100.0	3.52×3.09	240×240	5.0/6.0
AX T2WI	Aera	TSE	77.0	3.84×2.60	240×225	5.0/6.0

Abbreviations: AX T2-WI: Axial T2-weighted image; FOV: Field of view; FSE: Fast spin-echo; ST: Slice thickness; TE: Echo time; TSE: Turbo spin-echo.

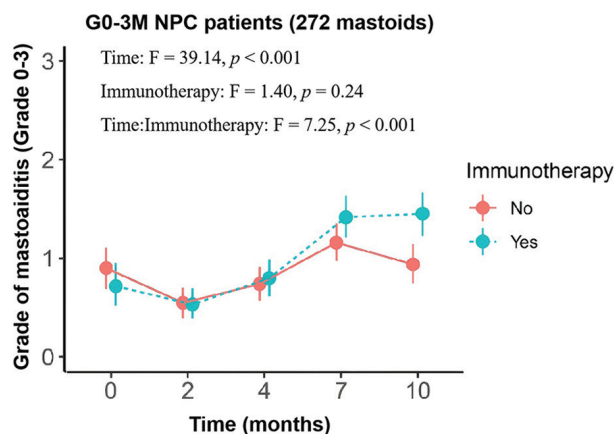


Figure A1. The analysis of variance conducted on the incidence of mastoiditis in G0-3M NPC patients ($n = 272$ mastoids) revealed that the main effects of time and the interaction of treatment and time were significant, whereas the main effect of treatment was not significant.