BMC Cancer

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Nasopharyngeal necrosis following intensity-modulated radiation therapy of primary nasopharyngeal carcinoma—incidence rate and predictors of risk

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Abstract

Objectives This study aimed to investigate the incidence of post radiation nasopharyngeal necrosis (PRNN) in primary NPC after intensity modulated radiation therapy (IMRT) and identify the predictors of risk.

Methods Data of 5798 NPC patients who received IMRT-based treatment between April 2009 and December 2015 were retrospectively reviewed. PRNN was diagnosed by MRI or nasopharyngoscopy. Dosimetric factors were selected by the least absolute shrinkage and selection operator logistic regression and applied to Cox proportional hazards modeling with clinical predictors.

Results Among the 5798 patients, 53 developed PRNN—an incidence rate of 0.89%. Age > 55 years, diabetes, LDH > 170 U/L, and tumor volume of nasopharynx > 60.5 cm^3,were independently associated with risk of PRNN(all $p < 0.05$. Dosimetric analysis showed that $D_{0.5cc}^{EQD2}$ of 80.20 Gy might be the dose constraint for nasopharynx (sensitivity = 62.3%, 33 out of 53; specificity = 84.2%, 4897 out of 5925). Besides, the RTOG dose constraints of $V_{110\%}$ ($V_{77.0}$) should be less than 0.2% in case of increasing risk of PRNN(HR = 2.28, 95% CI: 1.26–4.41, $p = 0.01$).

Conclusion Nasopharyngeal necrosis is rare after primary IMRT. The independent risk factors for this rare complication include age > 55 years, diabetes mellitus, LDH > 170 U/L, tumor volume of nasopharynx > 60.5 cm^3, $D_{0.5cc}^{EQD2}$ > 80.20 Gy, and $V_{77.0}$ < 0.2% to the planning treatment volume of nasopharynx.

Keypoints High radiation dose may lead to devastating nasopharyngeal necrosis after primary IMRT. Real world analysis will provide valuable information for prevention.

Findings The aged, diabetes mellitus, large tumor volume, $D_{0.5cc}^{EQD2}$ > 80.20 Gy and $V_{77.0}$ < 0.2% to planning treatment volume increased the risk of nasopharyngeal necrosis.

Clinical relevance This real-world study provided valuable information for prevention of PRNN. Compared with RTOG protocol, $D_{0.5cc}^{EQD2}$ > 80.20 Gy is a reliable evidence-based new complement to dose constraint, especially for T3-4 disease, who received high prescribe dose in China.

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Keywords Nasopharyngeal necrosis, Nasopharyngeal carcinoma, Intensity modulated radiation therapy, Dose constraint, Least absolute shrinkage and selection operator logistic regression

Introduction

Nasopharyngeal carcinoma (NPC) is highly sensitive to ionizing irradiation, and radiation therapy remains the mainstay treatment for nonmetastatic NPC [1]. Currently, intensity modulated radiation therapy (IMRT) is the preferred technique for NPC as it can deliver high and homogenous dose to the target volume while minimizing the dose to surrounding organs [2]. With IMRT, the locoregional control rate of NPC is more than 90% [3]. Meanwhile, extensive application of chemotherapy has reduced the incidence of distant metastasis and significantly improved survival [4]. But with improved survival, there is increasing concern about treatment-related complications among long-term survivors. One serious complication is postradiation nasopharyngeal necrosis (PRNN), which manifests—months or years after exposure to irradiation—with necrosis of tissues around the nasopharynx, such as the mucosa, the musculus longus capitis, the parapharyngeal tissues, and the skull base [5]. Although PRNN after IMRT of primary NPC is uncommon, it can be life threatening [6], with mortality rates of 65.8% and 72.7% reported in patients with osteoradionecrosis and involvement of the internal carotid artery, respectively [7]. Identification of the risk factors for PRNN after IMRT might help prevent this dangerous complication.

Most previous studies on PRNN focused on patients with recurrent NPC in whom the incidence of PRNN after salvage radiotherapy is as high as 44.0% (11/25) [6]. Factors that have been found to be associated with PRNN include age, diabetes mellitus, original T classification, tumor volume [6, 8], anemia, hypoalbuminemia, and high C-reactive protein level [9]. Treatment modality may also influence risk of PRNN, as IMRT has been reported to be associated with higher risk of PRNN than conventional radiotherapy [9]. Further, cumulative radiation dose may be associated with the severity of necrosis [8, 9]. However, the heterogeneous treatments in previous studies make interpretation of the results difficult and, importantly, the predictors of risk of nasopharyngeal necrosis after IMRT of primary NPC remains largely uninvestigated. Besides, dosimetric analysis on PRNN is supposed to inspired dose constraint of nasopharynx. We therefore conceived a real-world retrospective study of a large homogenous cohort of IMRT-treated NPC patients. The purpose of this study was to identify the clinical and dosimetric factors associated with PRNN and provide evidence-based dose constraint of planning treatment volume of nasopharynx (PTVnx) for IMRT-treated NPC patients. We hope the results of this study will provide valuable information for prevention of PRNN.

Materials and methods

Patients

The study cohort was identified from a well-established big-data intelligence platform that contains the data of 10,126 patients with histologically proven, non-disseminated NPC diagnosed between April 2009 and December 2015 and treated with IMRT-based strategies at our institution. Patients were excluded if they 1) failed to undergone at least one follow-up magnetic resonance imaging (MRI) or nasopharyngscopy after IMRT and, 2) without available dosimetric and clinical data in the case records. A total of 5978 patients were eligible for this retrospective study (Fig. 1). All patients were restaged according to the 8th edition of the American Joint Commission on Cancer/Union for International Cancer Control staging system.

Treatment and follow-up

PTVnx delineation encompasses both the gross tumor lesion and the entire nasopharyngeal mucosa, consistent with IMRT guidelines for NPC (ICRU Report 83). In general,prescribed doses to PTVnx, was 66–77 Gy, in 1.84–2.43 Gy per fractions/28–38 fractions. Dose criteria for tumor region in RTOG 0225, RTOG 06151 and our institution included relative volume receiving more than110% dose (V110%) $\leq$20%, more than 115% dose (V115%) $\leq$5%, less than 95% dose (V95%) $\leq$2–5%, and less than 93% dose (V93%) $\leq$1% (Supplementary Table E1). However, exceptions may arise when encountering cavities within the PTVnx or when dose constraints are necessary for critical organs at risk (such as the brainstem or optic chiasm).

Following IMRT completion, patients underwent structured surveillance consisting of quarterly clinical evaluations during the initial 36-month post-treatment period, transitioning to biannual assessments thereafter. Each visit incorporated comprehensive monitoring of disease progression and radiation-induced sequelae through standardized protocols. MRI scans of the nasopharyngeal region and cervical lymph nodes, and/or endoscopic examinations of the nasopharyngeal region were systematically conducted according to the following schedule: baseline at 3 months post-radiotherapy, semiannual intervals through year 3, and annual examinations

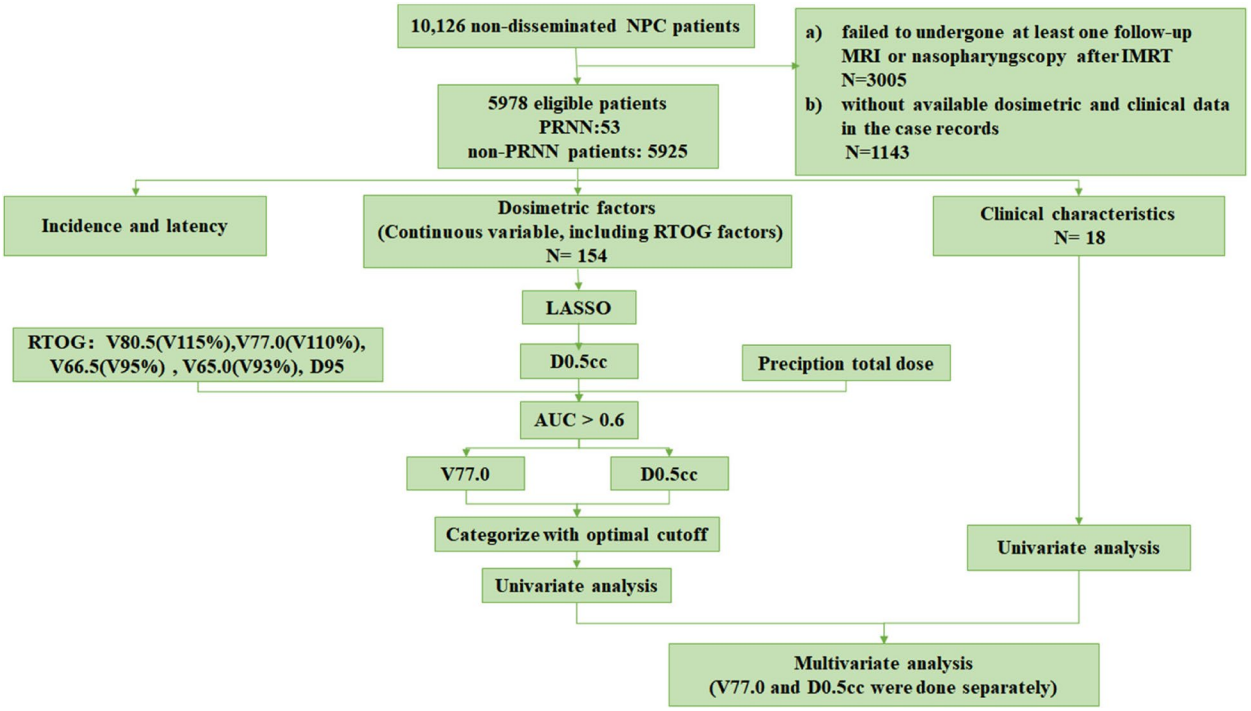


Fig. 1 Study flow chart

subsequently. The latency period to PRNN development was operationally defined as the temporal interval between radiotherapy initiation and initial radiographic or clinical confirmation of necrotic changes. Details of the radiation technique and chemotherapyare summarized in Supplementary materials.

Diagnosis and treatment of PRNN

The diagnosis of PRNN requires a multimodal synthesis of clinical manifestations, endoscopic features, radiological evidence, and histopathological exclusion of malignancy. Characteristic presentations included a triad of refractory headache (analgesic-resistant, duration >4 weeks), fetid nasal discharge, and recurrent epistaxis (≥ 2 episodes/week) [10–12]. All suspected cases underwent evaluation with high-definition nasopharyngoscopy (Fig. 2A-E) and contrast-enhanced MRI. Endoscopic examination identified necrotic ulcerations (diameter ≥5 mm) with irregular margins, with 43.6% of cases exhibiting pathognomonic bone exposure covered by purulent secretions [7, 11–14]. Radiological confirmation followed a double-blinded interpretation protocol: two head-and-neck radiologists (≥ 10 years'experience) independently analyzed contrast-enhanced T1-weighted MRI, focusing on mucosal discontinuity (defect ≥3 mm) and non-enhancing necrotic zones (signal intensity ratio <1.5 versus masseter muscle), with discordant cases resolved through consensus review (interobserver agreement, $\kappa = 0.81$) [12]. Histopathological validation mandated biopsy of ulcer margins, revealing acellular eosinophilic matrix on hematoxylin–eosin staining and negative immunohistochemistry for CK5/6 (excluding carcinoma) and CD68/CD163 (excluding granulomatous inflammation). Notably, all cases with histologically confirmed malignant ulcers were categorically excluded from PRNN diagnosis (specificity: 100%).

Therapeutic interventions were stratified based on lesion severity. For patients with extensive osteonecrosis ($N = 12$), endoscopic debridement served dual diagnostic (obtaining deep bone specimens) and therapeutic purposes (eradicating infected sequestra). Conservative management comprised twice-daily nasopharyngeal irrigation (2% hydrogen peroxide [5–10 mL] or saline [50–100 mL]) combined with culture-directed nitroimidazole antibiotics (metronidazole/ornidazole 500 mg three times daily). Parenteral nutritional support was administered for malnutrition (BMI <18.5 kg/m2), while febrile neutropenia cases received broad-spectrum antibiotic coverage.

Dosimetric data collection

Dose-volume histogram parameters

A comprehensive set of 154 dose-volume histogram (DVH) parameters was extracted (Supplementary Table.E2),

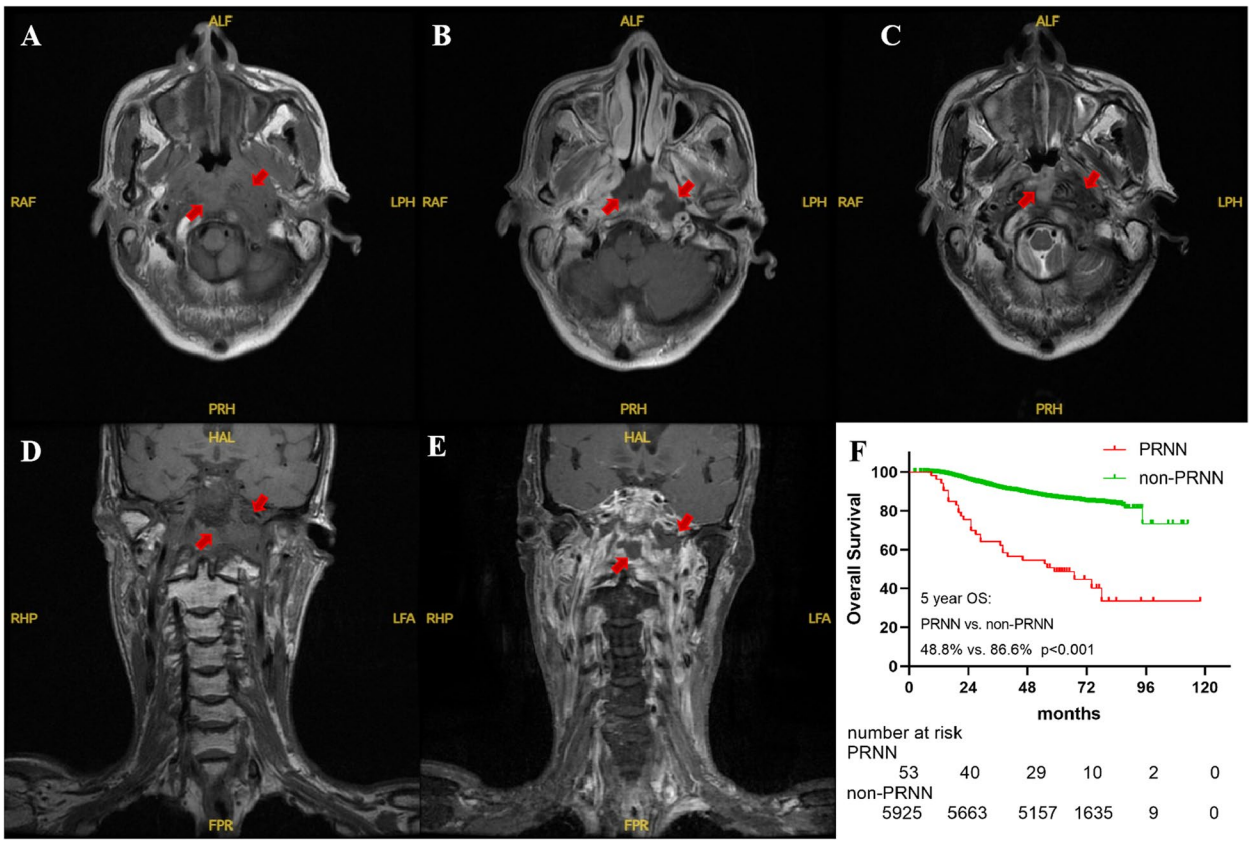


Fig. 2 MRI examination of PRNN and Overall survival in PRNN and non-PRNN groups. **A**: Transverse T1-weighted image; **B**: Transverse contrast-enhanced T1-weighted image; **C**: Transverse T2-weighted image; **D**: Coronal T1-weighted image; **E**: Coronal contrast-enhanced T1-weighted image; **F**: Kaplan–Meier curves of overall survival in PRNN and non-PRNN groups

encompassing: 1) Absolute dose metrics: Dmax/Dmean/Dmin; 2) Percentile doses: D_1 -D_{99} (1% increments); 3) Volume-based thresholds: $D_{0.5cc}$ to D_{10cc} (1cc increments); 4)Relative volume parameters: $V_{60}$to $V_{80.5}$ (0.5 Gy increments).

All doses were converted to equivalent 2 Gy fractionation (EQD2) using $\alpha/\beta = 10$ Gy for nasopharyngeal carcinoma, calculated as: $EQD2 = D \times (d + \alpha/\beta)/(2 + \alpha/\beta)$ where D= total dose, d= dose per fraction.

RTOG protocol cross-validation

Given the clinical adoption of RTOG 0225/0615 dose constraints, we implemented protocol-specific parameter translation:

RTOG 70 Gy reference:

$$V115\% \rightarrow V80.5\ Gy\ (70 \times 1.15)$$

$$V110\% \rightarrow V77.0\ Gy\ (70 \times 1.10)$$

$$V95\% \rightarrow V66.5\ Gy\ (70 \times 0.95)$$

$$V93\% \rightarrow V65.1\ Gy\ (70 \times 0.93)$$

Statistical analysis

Categorical variables were compared using $\chi 2$ or Fisher's exact tests, while continuous variables were analyzed with Mann–Whitney U tests after normality assessment (Shapiro–Wilk test). Survival curves were generated via Kaplan–Meier method and compared using log-rank tests. To address collinearity in dosimetric parameters, LASSO regression with tenfold cross-validation was applied prior to Cox proportional hazards modeling (backward elimination, $p < 0.05$ retention threshold). Variables were dichotomized based on median values (age), ROC-derived optimal cutoffs (tumor volume, hemoglobin, etc.), or established clinical thresholds (albumin, EBV DNA). Dynamic albumin levels during the treatment were classified into three tiers: 1) persistently normal (> 35 g/L throughout), 2) intermittent reduction (≥ 1 measurement < 35 g/L but never < 30 g/L), 3) critical hypoalbuminemia (≥ 1 measurement < 30 g/L).

Table 1 Baseline characteristics of patients with and without PRNN

Factor	Non-PRNN*	PRNN	Total	*P* value*
	5925(100%)	53(100%)	5978	
Age (y, median)				< 0.001
< = 55	4767(80.5%)	28(52.8%)	4795(80.2%)	
> 55	1158(19.5%)	25(47.2%)	1183(19.8%)	
Sex				0.536
Male	4298(72.5%)	41(77.4%)	4339(72.6%)	
Female	1627(27.5%)	12(22.6%)	1639(27.4%)	
Smoking				0.081
No	3859(65.1%)	28(52.8%)	3887(65.0%)	
Yes	2066(34.9%)	25(47.2%)	2091(35.0%)	
Drinking				1.000
No	5044(85.1%)	45(84.9%)	5089(85.1%)	
Yes	881(14.9%)	8(16.7%)	889(14.9%)	
Histology, WHO**				0.628
1	119(2.0%)	0(0%)	119(2.0%)	
2.1–2.2	5806(98.0%)	53(100%)	5856(98%)	
Hypertension				1.000
No	5401(91.2%)	49(92.5%)	5450(91.2%)	
Yes	524(8.8%)	4(7.5%)	528(8.8%)	
Diabetes				0.002
No	5714(96.4%)	46(86.8%)	5760(96.4%)	
Yes	211(3.6%)	7(13.2%)	218(3.6%)	
T stage***				< 0.001
T1-2	1872(31.6%)	6(11.3%)	1878(31.4%)	
T3-4	4053(68.4%)	47(88.7%)	4100(68.6%)	
N stage***				0.002
N0-1	3773(63.6%)	30(57.1%)	3803(63.6%)	
N2-3	2152(36.4%)	23(42.9%)	2175(36.4%)	
EBV DNA, copies/ml				0.270
< = 2000	2952(49.8%)	22(41.5%)	2974(49.7%)	
> 2000	2973(50.2%)	31(58.5%)	3004(50.3%)	
Induction Chemotherapy				1.000
No	2803(47.3%)	26(49.1%)	2829(47.3%)	
Yes	3122(52.7%)	27(50.9%)	3149(52.7%)	
Concurrent chemotherapy				0.358
No	1017(17.2%)	6(11.3%)	1023(17.1%)	
Yes	4908(82.8%)	47(88.7%)	4955(82.9%)	
primary tumor volume, cm^3				< 0.001
< = 60.5	4188(70.7%)	15(28.3%)	4360(73.0%)	
> 60.5	1737(29.3%)	38(71.7%)	1615(27.0%)	
Radiotherapy treatment time, day				0.005
< = 43	3388(57.2%)	20(37.7%)	3406(57.0%)	
> 43	2537(42.8%)	33(62.3%)	2569(43.0%)	
HGB, g/L				0.429
< = 126.5	847(14.3%)	5(9.4%)	852(14.3%)	
> 126.5	5078(85.7%)	48(90.6%)	5126(85.7%)	

Table 1 (continued)

Factor	Non-PRNN*	PRNN	Total	*P* value*
Dynamic ALB, g/L				0.013
< 30	4231(71.4%)	27(50.9%)	4258(71.2%)	
30–35	1354(22.9%)	19(35.8%)	1373(23.0%)	
> 35	340(57.4%)	7(13.2%)	347(5.8%)	
CRP, g/mL				0.012
< = 2.6	3934(66.4%)	26(49.1%)	3960(66.2%)	
> 2.6	1991(33.6%)	27(50.9%)	2018(33.8%)	
LDH, U/L				0.008
< = 170	2542(42.9%)	13(24.5%)	2555(42.7%)	
> 170	3383(57.1%)	40(75.5%)	3423(57.3%)	
Prescription dose^{EQD2}, Gy				0.002
< = 72.26	5826(98.3%)	48(90.6%)	5874(98.3%)	
> 72.26	99(1.7%)	5(9.4%)	104(1.7%)	
$D_{0.5cc}{}^{EQD2}$, Gy				< 0.001
< = 80.20	4887(84.2%)	20(37.7%)	5007(83.8%)	
> 80.20	938(15.8%)	33(62.3%)	971(16.2%)	
$V_{77.0}$($V_{110\%}$), %				< 0.001
< = 0.2	4055(68.4%)	19(35.8%)	4074(68.1%)	
> 0.2	1870(31.6%)	34(64.2%)	1904(31.9%)	

Abbreviations: *PRNN* Post radiation nasopharyngeal necrosis, *EBV* EpsteineBarr virus, *WHO* World Health Organization, *N* Node, *T* tumor, *HGB* Hemoglobin, *ALB* Albumin, *CRP* C-reactive protein, *LDH* Lactate dehydrogenase

* *P* values are from c2 test or Fisher exact test (for contingency tables with expected frequencies below 5), or ManneWhitney U test (continuous variables)

** WHO type 1 = keratinizing, WHO type 2.1 = nonkeratinizing (differentiated), WHO type 2.2 = nonkeratinizing (undifferentiated)

*** According to the eighth edition of American Joint Committee on Cancer staging system

Analyses were performed using SPSS 23.0 and R 3.4.4, with two-tailed $p < 0.05$ considered statistically significant.

Results

Patients

The 5978 patients were followed up for a median of 62.3 months (IQR, 54.3–72.2 months. While 53 patients developed PRNN, 5925 patients did not develop PRNN. Thus, the incidence rate of PRNN after primary IMRT was 0.89% (53/5978). Median time from completion of IMRT to diagnosis of PRNN was 7.1 months (IQR, 6.0–13.3 months). Table 1 summarizes the clinical characteristics of the PRNN and non-PRNN patients.

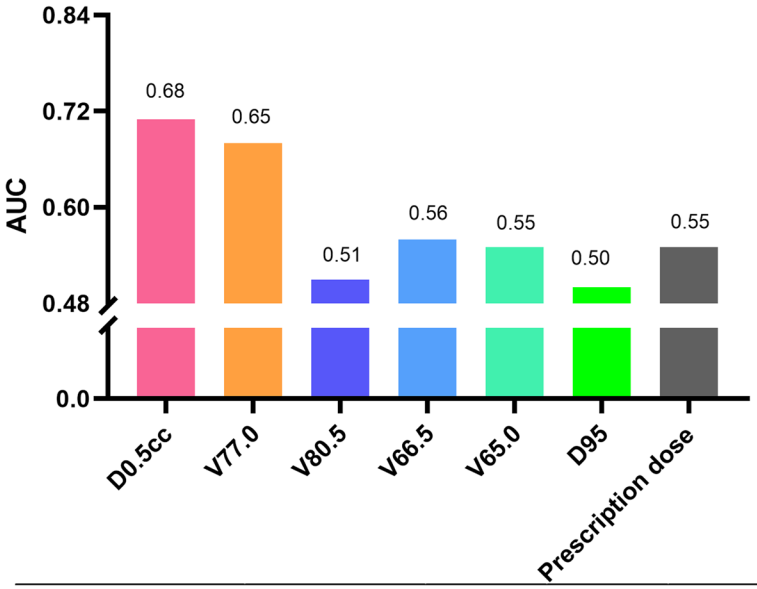
The crude incidence rates of PRNN in T1 - 2 was 0.32% (6/1877), and T3 - 4 disease was 1.15% (47/4100). Estimated 5-year overall survival rate was significantly lower for PRNN patients than for non-PRNN patients (48.8% vs. 86.6%, p < 0.001; Fig. 2F).

MRI data at diagnosis were available for 52 of the 53 patients with PRNN, in which 5 patients with only clival necrosis, 2 patients with pterygoid muscle necrosis. Internal carotid artery exposure was found in 15 patients, but only 2 received debridement. Osteoradionecrosis was found in 26 patients, but only 7 received debridement. Crude mortality rates of patients with and without osteoradionecrosis were 53.8% (14/26) and 57.7% (15/26), respectively. The crude mortality rate in patients with internal carotid artery exposure was 66.7% (10/15). Survival was not significantly different between subgroups with different features and treatments (Supplementary Table.E3).

Dosimetric parameters associated with PRNN

The elevated radiation doses to PTVnx in PRNN patients suggest a potential association between dosimetric parameters and PRNN risk. LASSO regression analysis identified $D_{0.5cc}{}^{EQD2}$ as an independent dosimetric predictor of PRNN, with an optimal cutoff of 80.20 Gy (sensitivity: 62.3% [33/53]; specificity: 84.2% [4897/5925]).

Figure 3 presents the AUCs and optimal cutoffs for RTOG parameters, along with their corresponding sensitivity and specificity. Notably, RTOG-related factors ($V_{80.5}$, $V_{66.5}$ and V_{65},) exhibited significantly lower predictive performance (AUCs) than $D_{0.5cc}{}^{EQD2}$. In contrast, $V_{77.0}$ demonstrated comparable predictive value, with an optimal cutoff of 0.2% (sensitivity: 64.2% [34/53]; specificity: 68.4% [4055/5925]) (Fig. 3).



Factor	AUC (95%CI)	Cutoff	Specificity	Sensitivity	P-value
D0.5cc*	0.71(0.63-0.79)	80.2 Gy	0.85	0.62	Reference
V77.0**	0.68(0.60-0.75)	0.20%	0.76	0.47	0.25
V80.5**	0.51(0.43-0.59)	NA	NA	NA	<0.01
V66.5**	0.56(0.48-0.65)	NA	NA	NA	<0.01
V65.0**	0.55(0.47-0.63)	NA	NA	NA	<0.01
D95**	0.50(0.43-0.57)	NA	NA	NA	<0.01
Prescription dose*	0.55(0.45-0.62)	NA	NA	NA	<0.01

Fig. 3 AUC of important dosimetric factor and cut-off value. * Converted to equivalent 2 Gy fractionation (EQD2) using α/β = 10 Gy. **Translated according to the recommend total dose of 70 Gy in protocols

Dosimetric parameters with AUC > 0.6 were dichotomized using their optimal cutoffs and included in univariate analysis. $D_{0.5cc}^{EQD2}$ > 80.20 Gy and $V_{77.0}$ > 0.2% were all significantly associated with PRNN risk (all $p < 0.01$; Fig. 4).

To assess their independent predictive value, each parameter was analyzed separately while adjusting for clinical factors. PRNN risk was significantly elevated in patients receiving:

$D_{0.5cc}^{EQD2}$ > 80.20 Gy (HR = 8.67, 95% CI: 4.97–15.12; $p < 0.01$; Fig. 5A); $V_{77.0}$ > 0.2% (HR = 3.88, 95% CI: 2.21–6.80; $p < 0.01$; Fig. 5B).

Clinical characteristics associated with PRNN

The variables listed in Table 1 (excluding histology type as all PRNN cases were WHO type 2.1–2.2) were first analyzed using univariable analysis (Fig. 4). Univariate analysis revealed several clinical factors significantly associated with PRNN: age > 55 years, diabetes mellitus, PTV > 60.5 cm3, and T3 - 4 disease (all $p < 0.01$). Additionally, patients who underwent IMRT for more than 43 days showed increased susceptibility to PRNN development ($p = 0.004$). Biochemical markers including elevated pretreatment levels of LDH (> 170 U/L) and C-reactive protein (> 2.6 g/L), along with reduced dynamic albumin levels (< 30 g/L), were also significantly correlated with PRNN (all $p < 0.01$).

Multivariate analysis identified three independent predictors of PRNN: age > 55 years, diabetes mellitus, LDH > 170 U/L and PTV > 60.5 cm3 (all $p < 0.05$) (Fig. 5).

Discussion

Nasopharyngeal necrosis is a devastating complication after radiotherapy of nasopharyngeal carcinoma [7, 12, 15], but there is limited information about its incidence and the dosimetric and clinical risk factors. In this study, we found that age > 55 years, diabetes, LDH > 170 U/L, primary tumor volume > 60.5 cm^3, and dosimetric factors ($D_{0.5cc}^{EQD2}$ > 80.20 Gy, $V_{77.0}$ > 0.2%) to PTV_{nx} were independent risk factors for this rare complication.

Radiotherapy method influences occurrence of PRNN. Li et al. showed higher risk of PRNN in patients treated with IMRT [9]. However, their study cohort included patients receiving primary radiotherapy and/or salvage

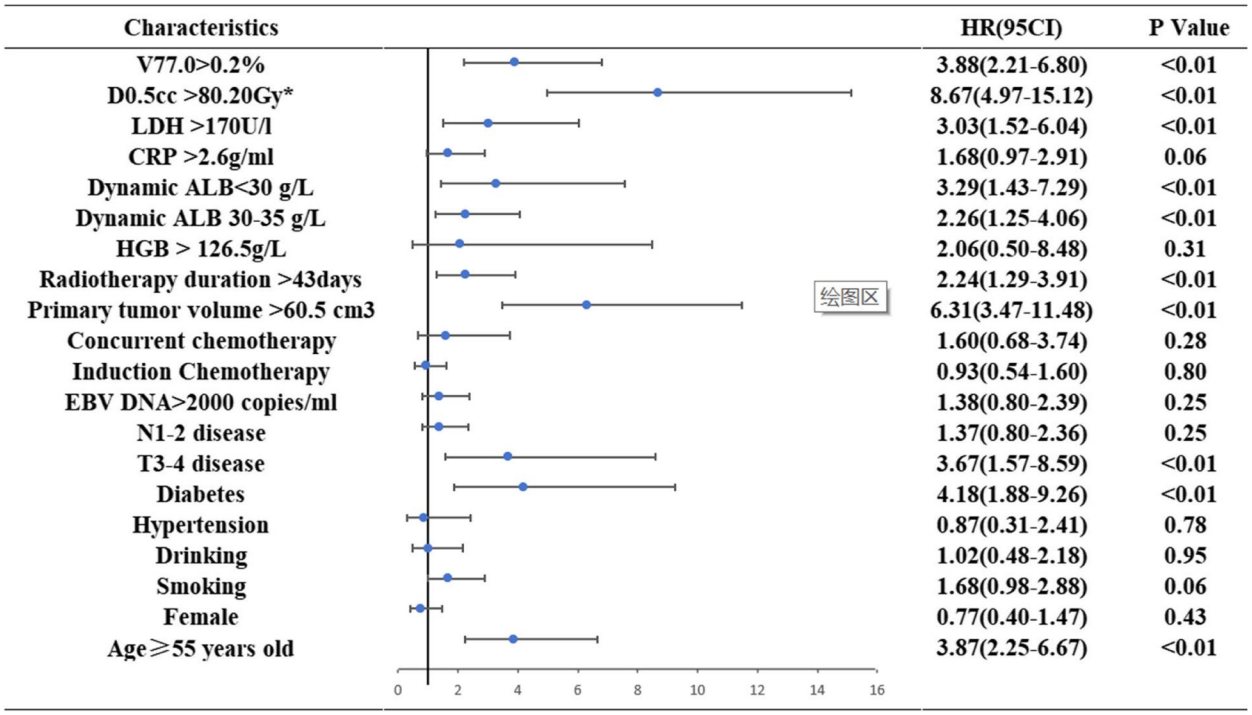


Fig. 4 Univariate analysis for covariates to estimate the risk of PRNN. Abbreviations: EBV = EpsteineBarr virus; N = node; T = tumor; HGB = hemoglobin, ALB = albumin, CR*P* = C-reactive protein; LDH = lactate dehydrogenase. * Converted to equivalent 2 Gy fractionation (EQD2) using α/β = 10 Gy

radiotherapy, which is itself a risk factor for PRNN. Theoretically, conformal dose delivery during IMRT in NPC means that the nasopharyngeal mucosa receives high radiation dose [16]. However, nasopharyngeal necrosis after primary radiotherapy in patients with NPC is rare, occurring in only 0.2%–0.3% of patients after conventional radiation therapy [17]. In our cohort, the crude incidence rate of PRNN after IMRT was 0.89%, which is higher than that reported after conventional radiation therapy. Li et al. found post-IMRT nasopharyngeal ulcers in 0.41% (25/6023) of their primary NPC patients [18], and higher dose is associated with higher incidence rate. Our study supported the finding and further investigate the impact of fraction schemes on PRNN.

Radiation dose has been cited as an important risk factor for necrosis in many studies [7, 11, 12, 19, 20]. In the 1980 s, one study reported that nasopharyngeal necrosis was more common at doses over 70 Gy (incidence of 18.4%) [21]. With advances in radiation technology, dose constraint criteria have changed. RTOG 0225 and RTOG 0615 protocols recommend a total dose of 70 Gy to PTV_{nx} for non-recurrent NPC, with satisfactory treatment outcomes and acceptable radiation-related toxicities demonstrated in patients from both the endemic and non-endemic regions [22–24]. Nasopharyngeal necrosis is rare after primary irradiation but more common following salvage irradiation, especially with cumulative doses over 120 Gy [12]. Yu et al. found that cumulative dose ≥ 141.5 Gy was an independent risk factor for lethal nasopharyngeal necrosis [8].

Dosimetric analysis for primary tumor dose constraint considered PRNN after primary irradiation is rare. A previous dosimetry study of 25 patients with PRNN after IMRT also proposed a D_{3cc} limit of 73.67 Gy [18], but various fraction schemes may also influence the result. Different fractionation schemes leads varied biological dose. In this study, we applied LASSO and multivariate analysis on calculated EQD2 dose, and found $D_{0.5cc}^{EQD2}$ > 80.20 Gy, $V_{77.0}$ < 0.2% the independently significant for PRNN. Moreover, $D_{0.5cc}^{EQD2}$ > 80.20 Gy ranked the best predictive dosimetric factor, which had more predictive value compared with dose constraints recommended by RTOG 0225/0615 [23, 24]. In China, T3 -4 disease received higher prescribe dose, which nearly up to 74 Gy based on extensive clinical experience. Radiation dose remained an independent risk predictor even

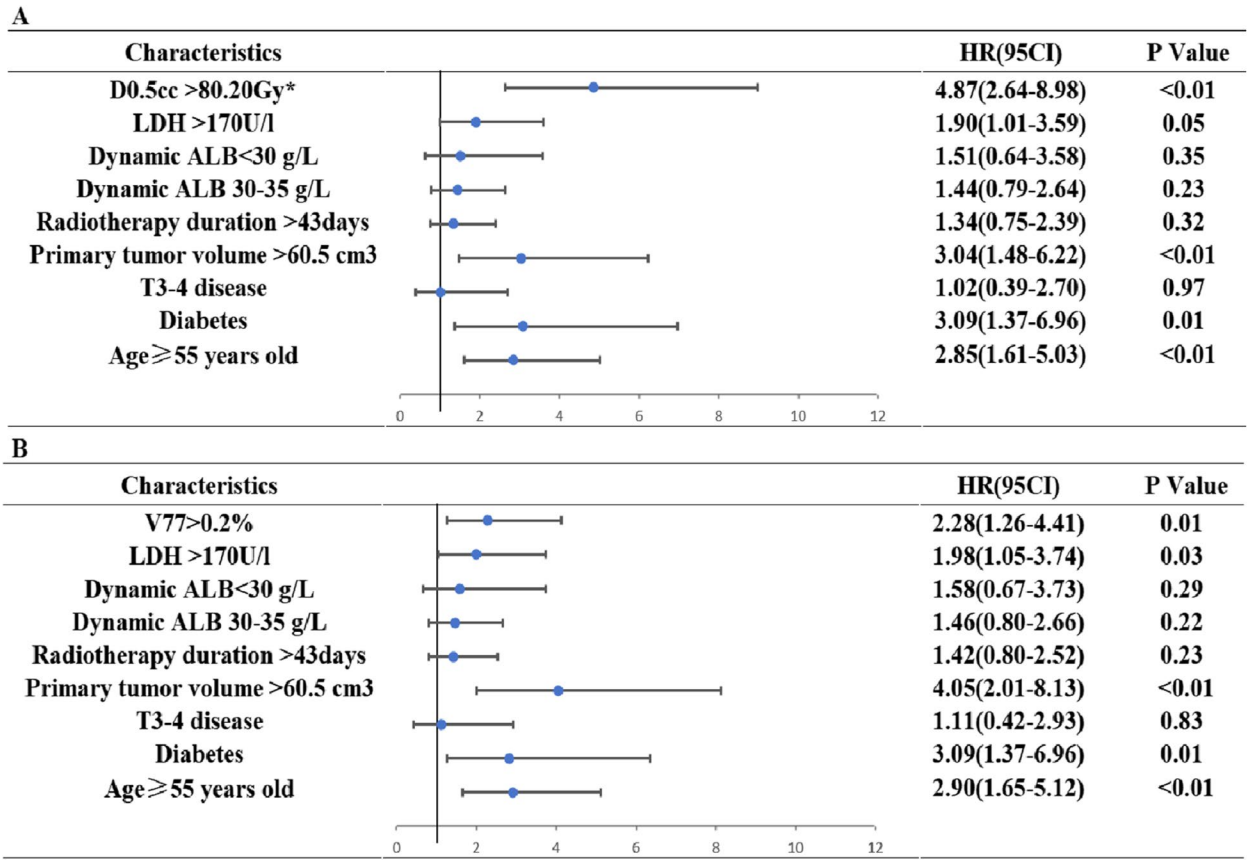


Fig. 5 Multivariate analysis for covariates to estimate the risk of PRNN. **A**: Multivariate analysis with clinical covariates and $D_{0.5cc}$; **B**: Multivariate analysis with clinical covariates and $V_{77.0}$($V_{110\%}$). *: Converted to equivalent 2 Gy fractionation (EQD2) using α/β = 10 Gy

after adjusting for T-stage and tumor volume parameters. The observed correlation between advanced T-stage/large tumor volume and PRNN risk appears secondary to compromised dosimetric optimization in anatomically complex cases, rather than representing direct biological causality. Therefore, we suggest $D_{0.5cc}{}^{EQD2} > 80.20$ Gy as a new complement for dose constraint of PTV_{nx} in patients receiving IMRT.

PRNN is postulated to develop from tissue breakdown and an irradiation-induced chronic non-healing wound of nasopharynx [25]. Morphological changes in mucosal epithelium and delayed mucosal wound healing in patients with old age and diabetes may promote development of necrosis [26, 27]. Nutritional status before, during, and after treatment was expected to impact nasopharyngeal necrosis, as it may affect adaptive radiotherapy and the actual dose delivered to the nasopharynx [7]. However, the correlation between low dynamic albumin levels and PRNN became insignificant in the multivariate analysis. A possible explanation is that nutritional status is itself influenced by factors such as age, diabetes, tumor burden, and radiation dose. After adjusting for dosimetric and other clinical factors, the weak causal relationship between nutritional status and PRNN may have been obscured.

Limitations

This study has several limitations. First, its retrospective design inherently introduces selection bias. Second, while identifying key dosimetric and clinical risk factors, we did not develop a predictive model, which remains an important avenue for future research. Third, the complex nasopharyngeal anatomy—surrounded by osseous and soft tissue structures—complicates precise estimation of normal tissue α/β ratios. Notably, our use of α/β = 10 (aligned with clinical protocols for tumor control in standard fractionated regimens) specifically reflects radiation planning conventions rather than representing the actual radiobiological parameters of normal tissue, as PRNN manifests in late-responding normal tissues typically associated with lower α/β values.

Conclusion

Nasopharyngeal necrosis is rare after primary IMRT. The independent risk factors for this rare complication include age >55 years, diabetes mellitus, LDH >170 U/L,tumor volume of nasopharynx >60.5 cm3, $D_{0.5cc}^{EQD2}$ > 80.20 Gy and $V_{77.0}$ < 0.2% to the planning treatment volume of nasopharynx.

Abbreviations

AUC	Area under the curve
$D_{0.5cc}$	Dose delivered to 0.5 cm^3 PTV_{nx}
D_{95}	Dose to 95% of PTV_{nx}
D_{max}	Maximum dose
D_{min}	Minimum dose
IMRT	Intensity-modulated radiation therapy
LDH	Lactate dehydrogenase
NPC	Nasopharyngeal carcinoma
PRNN	Postradiation nasopharyngeal necrosis
PTV	Planning treatment volume
PTV_{nx}	Planning treatment volume of nasopharynx
RTOG	Radiation Therapy Oncology Group
$V_{110\%}$	Relative volume of PTV receiving no less than 110% dose
$V_{77.0}$	Relative PTV_{nx} receiving more than 77 Gy

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14086-z.

Supplementary Material 1.

Authors' contributions

Xing-li Yang drafted the work, and substantively revised it, Li Lin and Jia Kou provided the acquisition of data, Sha-sha He help the revision, Dan-wan Wen analysis data, Yan Wang made interpretation of data, Xue-cen Wang and Yong Chen proved conception and guide the work.

Funding

This work was supported by National Natural Science Foundation of China [grant number 82373203].

Data availability

Key raw data were uploaded onto the Research Data Deposit public platform (https://www.researchdata.org.cn/) with the primary accession code RDDA2022847516 (https://www.researchdata.org.cn/Search.aspx?k=RDDA2022847516).

Declarations

Consent for publication

This retrospective study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center and The First Affiliated Hospital of Sun Yat-sen University in accordance with the Declaration of Helsinki, and the requirement for informed consent was waive.

Competing interests

The authors declare no competing interests.

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Received: 17 December 2024 Accepted: 3 April 2025
Published online: 29 April 2025

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