

# Cervical nodal necrosis is an independent survival predictor in nasopharyngeal carcinoma: an observational cohort study

Yangkun Luo<sup>1</sup>  
Jing Ren<sup>2</sup>  
Peng Zhou<sup>2</sup>  
Yang Gao<sup>3</sup>  
Guangquan Yang<sup>1</sup>  
Jinyi Lang<sup>1</sup>

<sup>1</sup>Department of Radiation Oncology,

<sup>2</sup>Department of Radiology, Sichuan Cancer Hospital, Chengdu,

<sup>3</sup>Department of Radiation Oncology, Zigong No 4 People's Hospital of Sichuan Province, Zigong, Sichuan, People's Republic of China

**Purpose:** Most nasopharyngeal carcinoma (NPC) patients present with locoregionally advanced disease at the time of diagnosis; however, there is a lack of consensus on specific prognostic factors potentially improving overall survival, especially in late-stage disease. Herein, we conducted a retrospective study to evaluate various potential prognostic factors in order to provide useful information for clinical treatment of T3/T4-stage NPC.

**Patients and methods:** A total of 189 previously untreated NPC patients were enrolled in the current study. All patients received intensity-modulated radiotherapy. Survival, death, relapse-free survival (both local and regional), and metastasis were recorded during follow-up. Factors affecting patient survival were assessed by using univariate and multivariate analyses.

**Results:** The median follow-up time was 69 months. The 5-year local-regional recurrence-free survival, distant metastasis-free survival, progression-free survival (PFS), and overall survival (OS) of the entire group were 89.8%, 71.5%, 66.3%, and 68.9%, respectively. Univariate analysis revealed significant differences in the 5-year PFS (58.5% vs 72.5%,  $P=0.015$ ) and OS (59.5% vs 75.8%,  $P=0.033$ ) rates of patients with and without cervical nodal necrosis (CNN). Subgroup analyses revealed that CNN was associated with poorer distant metastasis-free survival and PFS among patients with N2 stage ( $P=0.046$  and  $P=0.005$ ) and with poorer PFS among patients with T3 or III stage (all  $P=0.022$ ). Multivariate analysis revealed CNN to be an independent prognostic factor for PFS and OS (PFS: adjusted hazard ratio, 1.860; 95% CI: 1.134–3.051;  $P=0.014$ ; OS: adjusted hazard ratio, 1.754; 95% CI: 1.061–2.899;  $P=0.028$ ).

**Conclusion:** CNN is a potential independent negative prognostic factor in NPC patients. Our results suggest that stratification of NPC patients based on their CNN status should be considered as part of NPC disease management.

**Keywords:** nasopharyngeal carcinoma, cervical nodal necrosis, prognostic factor, chemotherapy, intensity-modulated radiotherapy

## Introduction

Nasopharyngeal carcinoma (NPC), a type of head-and-neck squamous cell carcinoma, is a relatively rare disease that develops in the epithelial layer of the nasopharynx.<sup>1</sup> While its incidence in the Western world is low, the rate of NPC is paradoxically much higher in parts of southern China. NPC presents with a variation of nonspecific symptoms including trismus, pain, otitis media, nasal regurgitation, hearing loss, and cranial nerve pulses,<sup>1</sup> which when added to the anatomical complexity of the nasopharynx confound and delay diagnosis; therefore, most patients with NPC have locally advanced disease and up to 85% have regional node metastasis at the time of diagnosis.<sup>2,3</sup> This underscores the need for improving diagnostic methods for early detection of NPC.

Correspondence: Jinyi Lang  
#55, Section 4, Renmin South Road,  
Chengdu 610041, Sichuan Province,  
People's Republic of China  
Tel/fax +86 28 8542 0692  
Email langji610@163.com

Unlike other head-and-neck squamous cell carcinomas, NPC is sensitive to both radiation and chemotherapy. The standard treatment in early-stage disease is radiotherapy (RT), with high survival rates (64%–95%) typically observed. For locally advanced NPC, concurrent chemotherapy (CCT)/adjuvant chemotherapy (ACT) in addition to RT improves survival rates, but its efficacy is relatively lower (44%–68%), thus resulting in a poor prognosis for these patients.<sup>4,5</sup> The prognosis for NPC depends on staging based on tumor size, lymph node involvement, and metastasis (TNM), which specifically takes into account affected lymph nodes in the lower cervical and supraclavicular regions.<sup>6,7</sup>

With the aim of improving survival rates, previous studies have identified multiple prognostic factors for NPC, including TNM staging, age, sex, treatment modality, and anatomical involvement of the skull base and cranial nerves.<sup>6,8–12</sup> To further clarify and expand on these factors as they specifically relate to late-stage patients, we retrospectively reviewed the survival of patients with T3/T4-stage NPC and examined clinical factors affecting prognosis. Our comprehensive study examined newly diagnosed, previously untreated, non-metastatic patients who underwent chemotherapy/RT with a  $\geq 5$ -year follow-up period, aiming to identify additional prognostic factors that would provide useful information for clinical management of late T-stage NPC patients.

## Patients and methods

### Patients and pretreatment evaluations

A total of 189 newly diagnosed, histologically confirmed, non-metastatic, T3/T4-stage NPC patients treated at our hospital were enrolled in this study between October 2004 and November 2010. This retrospective study was approved by the ethics committee of Sichuan Cancer Hospital. Written informed consent from patients was obtained. All patients underwent a pretreatment workup that included complete medical history and physical evaluations; hematological and biochemistry profile analyses; and endoscopy, computed tomography (CT), and magnetic resonance imaging (MRI) of the nasopharynx and neck, chest CT or radiography, abdominal ultrasound, and emission CT. Patients who did not complete the full course of radiation therapy were excluded. Medical records and imaging studies were analyzed retrospectively, and all patients were restaged according to the American Joint Committee on Cancer (AJCC) 2010 staging system.<sup>13</sup>

### Radiotherapy

All patients underwent intensity-modulated RT (IMRT) with 6 MV photons. Target volumes were consistent with

the International Commission on Radiation Units and Measurements Reports 50 and 62.<sup>14,15</sup> RT planning was designed and optimized using the CORVUS 3.4–4.2 inverse treatment planning system (Peacock; Nomos, Deer Park, IL, USA). The gross tumor target of the nasopharynx (GTVnx) and right/left lymph nodes (GTVln) were outlined based on CT and MRI scans. Clinical target volume (CTV) 1 included the GTVnx with a 5–10 mm margin and high-risk structures. CTV2 was designed to include regions of the nasopharyngeal cavity, maxillary sinus, pterygopalatine fossa, posterior ethmoid sinus, parapharyngeal space, skull base, anterior third of clivus, inferior sphenoid sinus, and cavernous sinus. CTVln included the lymphatic drainage regions (bilateral retropharyngeal nodes and levels II, III, and V<sub>A</sub>). The prescribed radiation doses were defined as follows: 66–76 Gy for GTVnx; 60–70 Gy for GTVln; 60–66 Gy for CTV1; 54–60 Gy for CTV2; and 50–54 Gy for CTVln using the simultaneous integrated boost technique, each divided into 30–33 deliveries. The dose limits for normal organs were set according to the Radiation Therapy Oncology Group protocol 0225.<sup>5</sup> The prescribed dose encompassed at least 95% of the target volume. Not >1% of the nasopharynx gross target volume received  $\leq 93\%$  of the prescribed dose, and the maximum dose of the treatment plan was within the target volume. The IMRT plan was implemented with dynamic intensity-modulated coplanar arc irradiation using a MIMI multi-leaf collimator (NOMOS Corporation, Sewickley, PA, USA). All patients received radiation in the lymphatic drainage areas of the lower neck using <sup>60</sup>Co split-field techniques or 6 MV X-ray split-beam techniques, with a prescription dose of 46–50 Gy. All patients were treated with one fraction daily for 5 d/wk, for a total of 6–7 weeks.

### Chemotherapy and targeted therapy

Chemotherapy strategies included induction chemotherapy (NACT), CCT, and ACT. Cisplatin-based CCT was recommended to medically fit patients. Some patients did not receive CCT due to advanced age, heart disease, hepatitis, severe diabetes, inadequate renal function, patient refusal, or economic factors. NACT regimens were either TP (docetaxel 75 mg/m<sup>2</sup>, day 1 + cisplatin 80 mg/m<sup>2</sup>, day 1) or PF (cisplatin 100 mg/m<sup>2</sup>, day 1 + 5-fluorouracil 1,000 mg/m<sup>2</sup>/d, days 1–5) every 3 weeks for one to two cycles. CCT included cisplatin 80 mg/m<sup>2</sup> every 3 weeks for two to three cycles. Concurrent TP and PF regimens were identical to the induction chemotherapy regimen. After completion of radiation, one to two cycles of ACT were administered to patients who had residual disease. The ACT was docetaxel 75 mg/m<sup>2</sup>

day 1 + cisplatin 80 mg/m<sup>2</sup> day 1, or cisplatin 30 mg/m<sup>2</sup> days 1–3 + 5-fluorouracil 750 mg/m<sup>2</sup> days 1–5. Patients received targeted therapy, including cetuximab and nimotuzumab. Cetuximab was administered at an initial dose of 400 mg/m<sup>2</sup>, followed by weekly doses of 250 mg/m<sup>2</sup> concurrent with RT or induction chemotherapy. Nimotuzumab was administered at 200 mg/wk during RT.

## Imaging protocol

CT was performed with a dual-helix CT imager (Picker MX Marconi Twin flash, Cleveland, OH, USA). Each patient underwent a localized, contrast-enhanced CT scan, with the cranial vertex as the upper limit and 2 cm below the inferior margin of the clavicular head as the lower limit. The scanning layer thickness was 3 mm, and the layer interval was 2.5 mm. MRI was performed using a 1.5T system (Magnetom Avanto, Siemens, Germany). The area from the cranial vertex to 2 cm below the inferior margin of the clavicle head was examined with a head-and-neck combined coil. T1-weighted fast spin-echo images in the axial planes and T2-weighted fast spin-echo fat-suppressed images in the axial and coronal planes were obtained before injection of contrast material. After intravenous administration of gadopentetate dimeglumine (Schering AG, Berlin, Germany) at a dose of 0.1 mmol/kg of body weight, axial and sagittal T1-weighted fat-suppressed spin-echo sequences were performed sequentially. The scanning layer was 3 mm, and the layer interval was 2.5 mm.

## Image assessment and criteria for assessing lymph node metastases

Two radiologists specialized in head-and-neck cancer reviewed all imaging data independently. The aforementioned criteria of diagnosing lymph node metastasis were implemented as follows:<sup>16</sup> 1) transverse plane images showed lymph nodes with minimal axial diameter  $\geq 10$  mm (11 mm for submaxillary and jugulodigastric lymph nodes); 2) central necrosis or ring enhancement; 3) grouped lymph nodes of three or more with minimal axial diameter  $\geq 8$  mm; 4) extracapsular extension (characterized by heterogenous hyperintensity on the edges of lymph nodes, partial or total loss of surrounding fat, and fusion of lymph nodes); and 5) retropharyngeal lymph node (RLN): a) in the lateral group, minimal axial diameter  $\geq 5$  mm, b) any size in the medial group, and c) central necrosis in retropharyngeal nodes of any size.

The criteria for diagnosing cervical nodal necrosis (CNN) were, according to recommendations by King et al,<sup>17</sup>

focal area of low attenuation with or without a surrounding rim of enhancement on CT imaging and focal area of high signal intensity on T2-weighted images or focal area of low signal intensity on T1-weighted images with or without a surrounding rim of enhancement on MRI.

## Patient assessments and follow-up

All patients were evaluated weekly while undergoing RT, examined in follow-up appointments that were scheduled up to 1 month after completion of RT, and thereafter every 3 months in years 1–2, every 6 months in years 3–5, and finally annually. Each follow-up included a flexible fiberoptic endoscopy, ultrasound of the abdomen, chest X-ray, and basic serum chemistry. Either CT or MRI of the head and neck was performed after completion of IMRT and every 6 months thereafter.

## Statistical analysis

All analyses were performed using the Statistical Package for Social Sciences, Version 17.0 (SPSS Inc., Chicago, IL, USA). The  $\chi^2$  test was used to analyze the relationship between CNN and T, N, and clinical stages. Actuarial rates were calculated using the Kaplan–Meier method and differences compared using the log-rank test, with the following endpoints assessed: local-regional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), progression-free survival (PFS), and OS. All the endpoints were defined as the interval from the date of treatment initiation to the date of the failure or death, or last follow-up. Variables with  $P < 0.1$  were imputed in a multivariate Cox regression model to calculate adjusted hazard ratio (HR) and its corresponding 95% CI and  $P$ -value. Two-tailed  $P$ -values  $< 0.05$  were considered statistically significant.

## Results

### Patients and treatments

From October 2004 to November 2010, 189 T3/T4-stage NPC patients were enrolled in this study. Clinical characteristics (Table 1) include study population demographics, disease staging, and treatment stratification. The male patient population was substantially greater than the female population (75.7% vs 24.3%, respectively), and the median age of all patients was 46 years, with 98 patients being  $\leq 46$  years old. All patients were restaged according to the AJCC 2010 system; 86 patients (45.5%) and 103 patients (54.5%) were classified as T3 and T4 stages, respectively. A total of 41 patients had nodal 1 involvement, 130 patients had nodal 2 involvement, and the rest had nodal 3 involvement.

**Table 1** Clinical characteristics of 189 patients with T3/T4-stage NPC

Characteristics	n (%)
Age (years)	
Range	12–76
Median	46
Sex	
Male	143 (75.7)
Female	46 (24.3)
T stage	
T3	86 (45.5)
T4	103 (54.5)
N stage	
N1	41 (21.7)
N2	130 (68.8)
N3	18 (9.5)
Clinical stage	
III	77 (40.7)
IV	112 (59.3)
Cervical nodal necrosis	
No	104 (55.0)
Yes	85 (45.0)
Chemotherapy	
Concurrent	99 (52.4)
Concurrent + adjuvant	21 (11.1)
Concurrent + induction	56 (29.6)
Induction + concurrent + adjuvant	7 (3.7)
Radiotherapy alone	6 (3.2)
Targeted therapy	
No	151 (79.9)
Yes	38 (20.1)

**Abbreviation:** NPC, nasopharyngeal carcinoma.

All patients received IMRT. Chemotherapy was administered in some form to 183 patients. Specifically, 56 patients received NACT, 21 patients received ACT, 99 patients received CCT, and seven patients received NACT + CCT + ACT. Six patients did not receive chemotherapy. A total of 38 patients received targeted drug therapy.

## Treatment outcomes

The median follow-up time was 69 months (range, 12–107 months). A total of 65 failures were observed that involved distant metastasis alone ( $n=45$ ), local recurrence ( $n=10$ ), regional recurrence ( $n=3$ ), locoregional recurrence ( $n=1$ ), local recurrence and distant metastasis ( $n=4$ ), and regional recurrence and distant metastasis ( $n=2$ ). The main treatment failure was distant metastasis; the total distant metastases were observed in 51 patients (78.5%). The 5-year LRFS, DMFS, PFS, and OS rates of the entire group were 89.8%, 71.5%, 66.3%, and 68.9%, respectively. The 5-year LRFS, DMFS, PFS, and OS rates for T3 stage were 92.3%, 78.3%, 74.4%, and 77.4%, respectively. The 5-year LRFS,

DMFS, PFS, and OS rates for T4 stage were 87.2%, 65.8%, 59.4%, and 62%, respectively.

## Univariate and multivariate analyses

The effects of clinical characteristics, including age, sex, TNM staging, chemotherapy strategies, and CNN on patient survival, were evaluated statistically taking into account the following survival endpoints: LRFS, DMFS, PFS, and OS were calculated using the Kaplan–Meier method with log-rank test. As shown in Table 2, the univariate analysis suggests that factor influencing the 5-year LRFS rate is sex ( $P=0.021$ ), factors influencing DMFS rate are T stage ( $P=0.040$ ) and chemotherapy ( $P=0.027$ ), factors influencing PFS rate are T stage ( $P=0.044$ ), chemotherapy ( $P=0.033$ ), and CNN ( $P=0.015$ ), and factors influencing OS rate are T stage ( $P=0.032$ ), chemotherapy ( $P=0.040$ ), and CNN ( $P=0.033$ ).

For multivariate analysis, variables with  $P<0.1$  in univariate analysis were imputed in a multivariate Cox regression model. As shown in Table 3, the following factors were significantly associated with treatment outcomes according to multivariate analysis: sex ( $HR=2.985$ ,  $P=0.017$ ) was significantly associated with LRFS; T stage ( $HR=1.856$ ,  $P=0.038$ ) and chemotherapy ( $HR=0.200$ ,  $P=0.001$  and  $HR=0.268$ ,  $P=0.008$ ) were significantly associated with DMFS; T stage ( $HR=1.808$ ,  $P=0.024$ ), chemotherapy ( $HR=0.255$ ,  $P=0.005$  and  $HR=0.326$ ,  $P=0.022$ ), and CNN ( $HR=1.860$ ,  $P=0.014$ ) were significantly associated with PFS; and T stage ( $HR=2.071$ ,  $P=0.008$ ), chemotherapy ( $HR=0.256$ ,  $P=0.013$ ), and CNN ( $HR=1.754$ ,  $P=0.028$ ) were significantly associated with OS.

## CNN is a negative prognostic factor of survival in NPC

The incidence of CNN in this study was 45% (85 of 189 patients). The incidence of CNN in N1, N2, and N3 stages was 31.7%, 45.4%, and 72.2%, respectively ( $\chi^2=8.325$ ,  $P=0.016$ ). No differences were observed for CNN in T and overall stages ( $\chi^2=1.611$ ,  $P=0.204$  and  $\chi^2=0.498$ ,  $P=0.481$ , respectively). As shown in Figure 1, patients with CNN had a reduced LRFS (87.4% vs 91.6%) and DMFS (66.1% vs 75.7%). However, the differences in LRFS and DMFS between the two groups were not significant ( $P=0.095$  and  $P=0.134$ ). Patients with CNN had a significantly reduced PFS (58.5% vs 72.5%,  $P=0.015$ ) and OS (59.5% vs 75.8%,  $P=0.033$ ) compared to patients without CNN.

To further evaluate the impact of CNN on prognosis in NPC, we performed subgroup analysis according to TNM staging. Patients with CNN in the T3, N2, and III groups

**Table 2** Univariate analysis for various clinical endpoints

Characteristics	LRFS (%)	P-value <sup>a</sup>	DMFS (%)	P-value <sup>a</sup>	PFS (%)	P-value <sup>a</sup>	OS (%)	P-value <sup>a</sup>
Age (years)		0.199		0.788		0.271		0.230
≤46	92.2		72.2		69.4		71.0	
>46	87.0		70.6		62.8		66.6	
Sex		0.021		0.914		0.473		0.844
Male	91.0		71.7		67.3		67.5	
Female	86.2		70.6		66.2		74.0	
T stage		0.552		0.040		0.044		0.032
T3	92.3		78.3		74.4		77.4	
T4	87.2		65.8		59.4		62.0	
N stage		0.673		0.733		0.579		0.797
N1	90.8		75.9		70.3		77.1	
N2	89.4		68.1		63.3		65.4	
N3	90.9		88.5		80.5		73.8	
Clinical stage		0.862		0.094		0.136		0.090
III	91.6		77.4		73.0		76.3	
IV	88.2		67.5		61.5		63.7	
CNN		0.095		0.134		0.015		0.033
No	91.7		75.7		72.5		75.8	
Yes	87.4		66.1		58.5		59.5	
Chemotherapy		0.445		0.027 <sup>b</sup>		0.033		0.040 <sup>b</sup>
Concurrent	91.4		76.1		70.7		75.0	
Other regimens <sup>c</sup>	87.1		70.2		64.7		64.3	
Radiotherapy alone	100		16.7		16.7		25.0	
Targeted therapy		0.081		0.856		0.298		0.437
No	87.8		71.2		64.7		67.2	
Yes	97.2		72.8		72.8		75.3	

**Notes:** <sup>a</sup>Log-rank test. <sup>b</sup>Statistically significant difference between radiotherapy alone and concurrent or other regimens. <sup>c</sup>Other regimens indicated different chemotherapy regimen including concurrent + adjuvant, concurrent + induction, and induction + concurrent + adjuvant.

**Abbreviations:** CNN, cervical nodal necrosis; DMFS, distant metastasis-free survival; LRFS, local-regional recurrence-free survival; OS, overall survival; PFS, progression-free survival.

had a significantly reduced PFS (65.4% vs 82.9%, 49.7% vs 74.3%, and 63.2% vs 81.7%, respectively, and  $P=0.022$ ,  $P=0.005$ , and  $P=0.022$ , respectively) when compared with patients without CNN (Figure 2). No difference between with and without CNN for OS was observed in subgroups.

**Table 3** Multivariate analysis for various clinical endpoints

Endpoint	Characteristic	HR (95% CI)	P-value <sup>a</sup>
LRFS	Sex (female vs male)	2.985 (1.218–7.313)	0.017
DMFS	T stage (T4 vs T3)	1.856 (1.034–3.332)	0.038
	Chemotherapy	0.200 (0.075–0.531)	0.001 <sup>b</sup>
		0.268 (0.101–0.711)	0.008 <sup>c</sup>
PFS	T stage (T4 vs T3)	1.808 (1.083–3.019)	0.024
	CNN (yes vs no)	1.860 (1.134–3.051)	0.014
	Chemotherapy	0.255 (0.098–0.666)	0.005 <sup>b</sup>
		0.326 (0.125–0.850)	0.022 <sup>c</sup>
OS	T stage (T4 vs T3)	2.071 (1.211–3.543)	0.008
	Chemotherapy	0.256 (0.088–0.748)	0.013 <sup>b</sup>
	CNN (yes vs no)	1.754 (1.061–2.899)	0.028

**Notes:** <sup>a</sup>Multivariate Cox regression model. <sup>b</sup>Concurrent vs radiotherapy alone. <sup>c</sup>Other regimens vs radiotherapy alone.

**Abbreviations:** CI, confidence interval; CNN, cervical nodal necrosis; DMFS, distant metastasis-free survival; HR, hazard ratio; LRFS, local-regional recurrence-free survival; OS, overall survival; PFS, progression-free survival.

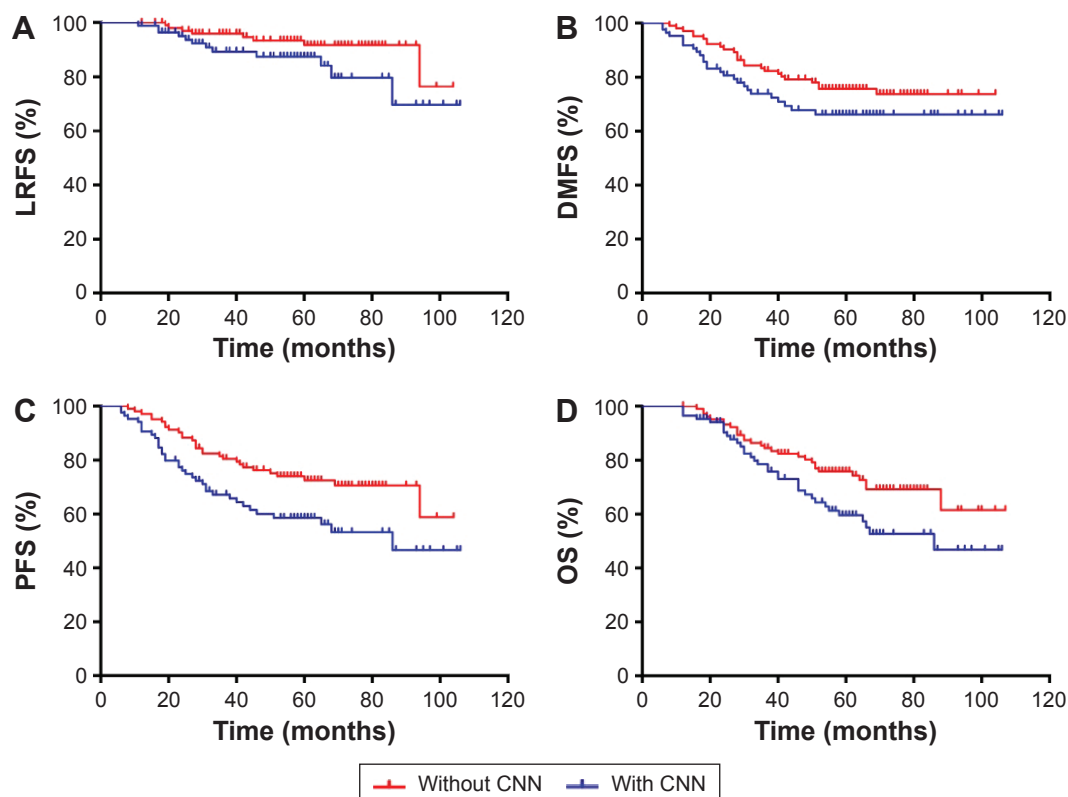
Interestingly, the difference between the DMFS of patients with and without CNN was statistically significant in the N2 group (58.5% vs 75.5%,  $P=0.046$ ), as shown in Figure 2.

## Discussion

In this study, we examined the effect of clinical characteristics associated with the survival of T3/T4-stage NPC patients. Our analyses determined that T stage, CNN, chemotherapy, and sex were associated with patient survival and/or metastasis. While other factors have been identified in prior studies,<sup>8–12</sup> our finding that CNN is a negative independent prognostic factor for PFS and OS in NPC has been rarely reported in literature. Stratification of NPC patients based on their CNN status should be considered as a part of T3/T4-stage NPC management.

The 5-year LRFS, DMFS, PFS, and OS rates of the entire group were 89.8%, 71.5%, 66.3%, and 68.9%, respectively. The 5-year LRFS, DMFS, PFS, and OS rates for T3 stage were 92.3%, 78.3%, 74.4%, and 77.4%, respectively. The 5-year LRFS, DMFS, PFS, and OS rates for T4 stage were 87.2%, 65.8%, 59.4%, and 62%, respectively. The results





**Figure 1** Kaplan-Meier curves depicting LRFS, DMFS, PFS, and OS between patients with and without CNN.

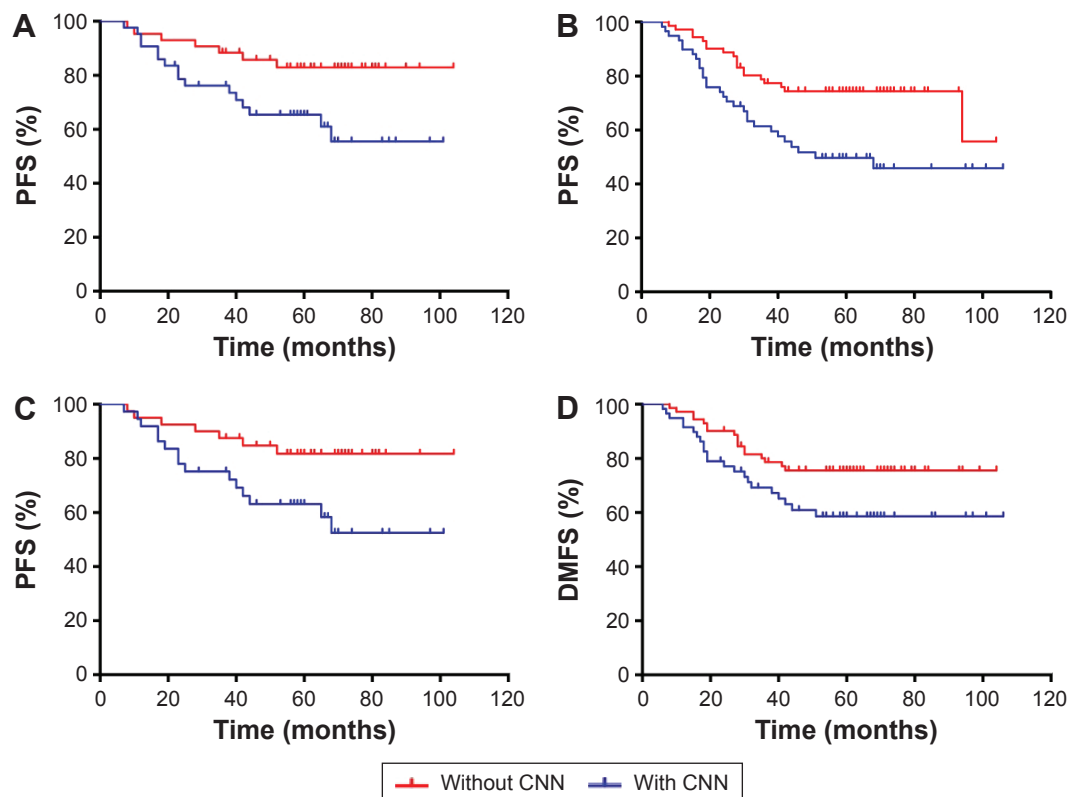
**Notes:** (A) The LRFS of patients with and without CNN. No difference was observed ( $P=0.134$ ). (B) The DMFS of patients with and without CNN. No difference was observed ( $P=0.134$ ). (C) The PFS of patients with and without CNN. The difference was significant ( $P=0.015$ ). (D) The OS of patients with and without CNN. The difference was significant ( $P=0.033$ ).

**Abbreviations:** CNN, cervical nodal necrosis; DMFS, distant metastasis-free survival; LRFS, local-regional recurrence-free survival; OS, overall survival; PFS, progression-free survival.

of our study are generally comparable to other studies.<sup>18–20</sup> In our observational cohort study, 20 patients experienced locoregional failure and total distant metastasis occurred in 51 patients. These results are also similar to those reported by previous studies.<sup>5,18</sup> Indeed, with excellent local treatment provided by IMRT, locoregional control has been markedly improved, and distant metastasis remained the main pattern of failure after treatment.

N stage is a negative prognostic factor in NPC patients; those with an advanced N stage were found to have a higher rate of distant metastasis.<sup>18,21,22</sup> According to the seventh edition of AJCC staging system,<sup>13</sup> N stage is stratified into four groups based on the nodal dimension, level, and laterality. As metastatic cervical lymph nodes are more accurately detected by imaging, more characters, such as extranodal neoplastic spread, nodal necrosis, and metastasis, to the RLN were studied. These previous results have shown that nodal characteristics affect both local disease recurrence and distant metastases, thus influencing patient survival.<sup>18,23–26</sup> In the current study, no significant differences were observed in LRFS,

DMFS, PFS, and OS for N1-, N2-, and N3-stage patients. This may be due to the retrospective study design, with a small sample size and intrinsically present selective bias. However, significant differences were observed in the 5-year PFS and OS rates of patients with and without CNN. In subgroup analyses, patients in the N2 stage with CNN had a poor DMFS compared to patients without CNN. Multivariate analysis identified CNN as an independent, negative prognostic factor for PFS and OS. Recently, a study by Lan et al<sup>24</sup> evaluated the prognostic value of CNN and determined that CNN negatively affected OS, DFS, RRFS, and DMFS in NPC patients. A study by Tang et al<sup>26</sup> also demonstrated that necrotic RLN metastases have a negative effect on treatment failure, distant failure, and locoregional recurrence in NPC patients. Our study is in agreement with those findings. Additionally, patients with CNN in the T3, N2, and III stages had a significantly reduced PFS when compared with patients without CNN. These results indicate that patients within the same T/N/M classification with different CNN statuses may have varying prognosis. Based on these findings, CNN has significant prognostic value for NPC



**Figure 2** Kaplan–Meier curves depicting PFS between patients with and without CNN in the T3, N2, and III subgroups and DMFS between patients with and without CNN in the N2 subgroup.

**Notes:** (A) The PFS of T3-stage patients with and without CNN. The difference was significant ( $P=0.022$ ). (B) The PFS of N2-stage patients with and without CNN. The difference was significant ( $P=0.005$ ). (C) The PFS of III-stage patients with and without CNN. The difference was significant ( $P=0.022$ ). (D) The DMFS of N2-stage patients with and without CNN. The difference was significant ( $P=0.046$ ).

**Abbreviations:** CNN, cervical nodal necrosis; DMFS, distant metastasis-free survival; PFS, progression-free survival.

patients. In clinical management of the individual patient, CNN status should be considered in addition to TNM staging when formulating treatment plans.

Identification of necrosis in head-and-neck lymph nodes has been routinely performed by contrast-enhanced CT, with MRI considered more superior for imaging the primary tumor rather than CNN. Lymph node central necrosis, viewed by CT preoperatively, was noted to be an indicator for extracapsular spread, while lymph node diameter was not influential.<sup>27,28</sup> However, a study by King et al<sup>17</sup> showed that MRI was at par with CT in the detection of CNN with similar diagnostic accuracies and sensitivities (MRI: 91%–99% accuracy and 93% sensitivity; CT: 92%–99% accuracy and 91% sensitivity). We therefore used both contrast-enhanced CT and MRI to improve both accuracy and sensitivity of imaging results, following recommendations set forth by King et al,<sup>17</sup> wherein a cervical node was diagnosed as necrotic if there was a focal area of low attenuation with or without a surrounding rim of enhancement on CT imaging and if there was a focal area of high signal intensity on T2-weighted images or a focal

area of low signal intensity on T1-weighted images (with or without a surrounding rim of enhancement on MRI). While the incidence of CNN in our study population was 45% (85 of 189 patients), other studies have reported CNN ranges from 20% to 44% in NPC patients.<sup>17,23,24,29</sup> Importantly, our study excluded early-stage patients, who were included in other studies; 45% reported herein is therefore reasonable. We report a higher incidence of observable CNN in advanced N-stage patients in cases we evaluated. Our results are partially consistent with a prior study,<sup>30</sup> suggesting that a greater incidence of CNN positively correlates with increasing nodal size. However, it is important to note that small nodes also showed necrosis characteristics on imaging. Unlike in head and neck cancer, pathologic confirmation of imaging findings is not possible in patients with NPC, as they are treated with RT (rather than surgery). However, due to the high accuracy of imaging diagnostics,<sup>17</sup> our results based on CT and MRI are reliable.

Limitations of our study include its retrospective design with a relatively small sample size, resulting in a relative

imbalance of patients in groups and subgroups. Additionally, chemotherapy regimens used in our study were not uniform, and possible prognostic factors, such as nodal dimension, distribution, and extranodal neoplastic spread, were not evaluated. These limitations may have potentially affected the outcomes observed. Therefore, our findings can only be taken as preliminary and require further confirmatory research.

## Conclusion

This study demonstrates that IMRT combined with chemotherapy can provide excellent local-regional control for T3/T4-stage NPC. Distant metastasis was the main pattern of treatment failure. In addition to other reported prognostic factors, CNN may be a potentially prognostic factor for poor survival in NPC patients. Our study suggests that stratification of patients based on their CNN status should be considered over the course of individual management. In addition, treatment modalities that effectively reduce the rate of distant metastasis and increase the survival rate of NPC patients with late stage need to be explored.

## Author contributions

YL planned the study and wrote the article. JR and PZ analyzed the image data. YG and GY collected the data. YL and YG did the statistical analysis. JL planned the study and wrote the article. All authors contributed toward data analysis, drafted and critically revised the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

## References

- Brennan B. Nasopharyngeal carcinoma. *Orphanet J Rare Dis*. 2006;1(5):506–511.
- Ho FC, Tham IW, Earnest A, Lee KM, Lu JJ. Patterns of regional lymph node metastasis of nasopharyngeal carcinoma: a meta-analysis of clinical evidence. *BMC Cancer*. 2012;12:98.
- Loong HH, Ma BB, Chan AT. Update on the management and therapeutic monitoring of advanced nasopharyngeal cancer. *Hematol Oncol Clin North Am*. 2008;22(6):1267–1278.
- Chou J, Lin YC, Kim J, et al. Nasopharyngeal carcinoma – review of the molecular mechanisms of tumorigenesis. *Head Neck*. 2008;30(7):946–963.
- Lee N, Harris J, Garden AS, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. *J Clin Oncol*. 2009;27(22):3684–3690.
- Sham JS, Choy D. Prognostic factors of nasopharyngeal carcinoma: a review of 759 patients. *Br J Radiol*. 1990;63(745):51–58.
- Ho JH. Stage classification of nasopharyngeal carcinoma: a review. *IARC Sci Publ*. 1978;(20):99–113.
- Yi JL, Gao L, Huang XD, et al. Nasopharyngeal carcinoma treated by radical radiotherapy alone: ten-year experience of a single institution. *Int J Radiat Oncol Biol Phys*. 2006;65(1):161–168.
- Leung TW, Tung SY, Sze WK, et al. Treatment results of 1070 patients with nasopharyngeal carcinoma: an analysis of survival and failure patterns. *Head Neck*. 2005;27(7):555–565.
- Lee AW, Sze WM, Au JS, et al. Treatment results for nasopharyngeal carcinoma in the modern era: the Hong Kong experience. *Int J Radiat Oncol Biol Phys*. 2005;61(4):1107–1116.
- Liu X, Liu LZ, Mao YP, et al. Prognostic value of magnetic resonance imaging-detected cranial nerve invasion in nasopharyngeal carcinoma. *Br J Cancer*. 2014;110(6):1465–1471.
- Xiao C, Wang L, Jiao Y, et al. Long-term results of concurrent chemoradiotherapy for T3/T4 locally advanced nasopharyngeal carcinoma. *Mol Clin Oncol*. 2013;1(3):507–510.
- Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17(6):1471–1474.
- ICRU. Prescribing, recording, and reporting photon beam therapy. ICRU Report 50. Bethesda, MD: ICRU; 1993.
- ICRU. Prescribing, recording and reporting photon beam therapy (supplement to ICRU report 50). ICRU Report 62. Bethesda, MD: ICRU; 1999.
- van den Brekel MW, Stel HV, Castelijns JA, et al. Cervical lymph node metastasis: assessment of radiologic criteria. *Radiology*. 1990;177(2):379–384.
- King AD, Tse GM, Ahuja AT, et al. Necrosis in metastatic neck nodes: diagnostic accuracy of CT, MR imaging, and US. *Radiology*. 2004;230(3):720–726.
- Sun X, Su S, Chen C, et al. Long-term outcomes of intensity-modulated radiotherapy for 868 patients with nasopharyngeal carcinoma: an analysis of survival and treatment toxicities. *Radiother Oncol*. 2014;110(3):398–403.
- Li J, Zou X, Wu YL, et al. A comparison between the sixth and seventh editions of the UICC/AJCC staging system for nasopharyngeal carcinoma in a Chinese cohort. *PLoS One*. 2014;9(12):e116261.
- Qiu WZ, Huang PY, Shi JL, Xia HQ, Zhao C, Cao KJ. Neoadjuvant chemotherapy plus intensity-modulated radiotherapy versus concurrent chemoradiotherapy plus adjuvant chemotherapy for the treatment of locoregionally advanced nasopharyngeal carcinoma: a retrospective controlled study. *Chin J Cancer*. 2016;35:2.
- Lai SZ, Li WF, Chen L, et al. How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? *Int J Radiat Oncol Biol Phys*. 2011;80(3):661–668.
- Wong FC, Ng AW, Lee VH, et al. Whole-field simultaneous integrated-boost intensity-modulated radiotherapy for patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2010;76(1):138–145.
- Mao YP, Liang SB, Liu LZ, et al. The N staging system in nasopharyngeal carcinoma with radiation therapy oncology group guidelines for lymph node levels based on magnetic resonance imaging. *Clin Cancer Res*. 2008;14(22):7497–7503.
- Lan M, Huang Y, Chen CY, et al. Prognostic value of cervical nodal necrosis in nasopharyngeal carcinoma: analysis of 1800 patients with positive cervical nodal metastasis at MR imaging. *Radiology*. 2015;276(2):536–544.
- Shi Q, Shen C, Kong L, et al. Involvement of both cervical lymph nodes and retropharyngeal lymph nodes has prognostic value for N1 patients with nasopharyngeal carcinoma. *Radiat Oncol*. 2014;9:7.
- Tang LL, Guo R, Zhou G, et al. Prognostic value and staging classification of retropharyngeal lymph node metastasis in nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. *PLoS One*. 2014;9(10):e108375.
- Zoumalan RA, Kleinberger AJ, Morris LG, et al. Lymph node central necrosis on computed tomography as predictor of extracapsular spread in metastatic head and neck squamous cell carcinoma: pilot study. *J Laryngol Otol*. 2010;124(12):1284–1288.



28. Randall DR, Lysack JT, Hudon ME, et al. Diagnostic utility of central node necrosis in predicting extracapsular spread among oral cavity squamous cell carcinoma. *Head Neck*. 2015;37(1):92–96.
29. Liu LZ, Zhang GY, Xie CM, Liu XW, Cui CY, Li L. Magnetic resonance imaging of retropharyngeal lymph node metastasis in nasopharyngeal carcinoma: patterns of spread. *Int J Radiat Oncol Biol Phys*. 2006;66(3):721–730.
30. Don DM, Anzai Y, Lufkin RB, Fu YS, Calcaterra TC. Evaluation of cervical lymph node metastases in squamous cell carcinoma of the head and neck. *Laryngoscope*. 1995;105(7):669–674.

### OncoTargets and Therapy

## Publish your work in this journal

OncoTargets and Therapy is an international, peer-reviewed, open access journal focusing on the pathological basis of all cancers, potential targets for therapy and treatment protocols employed to improve the management of cancer patients. The journal also focuses on the impact of management programs and new therapeutic agents and protocols on

Submit your manuscript here: <http://www.dovepress.com/oncotargets-and-therapy-journal>

patient perspectives such as quality of life, adherence and satisfaction. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Dovepress