

Original Article

Prognostic value of retropharyngeal lymph node metastasis laterality in nasopharyngeal carcinoma and a proposed modification to the UICC/AJCC N staging system



Ling Huang^{a,1}, Yun Zhang^{b,1}, Yifei Liu^{b,1}, Haojiang Li^b, Shunxin Wang^c, Shaobo Liang^d, Jian Zhou^b, Chunyan Cui^b, Yin Sun^e, Minyuan Chen^f, Shuoyu Xu^b, Jianjun Li^{a,*}, Lizhi Liu^{b,*}

^aDepartment of Endoscopy, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine; ^bDepartment of Radiology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou 510060; ^cZhongshan School of Medical, Sun Yat-sen University; ^dDepartment of Radiation Oncology, Cancer Center, The First People's Hospital of Foshan Affiliated to Sun Yat-sen University; ^eDepartment of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine; and ^fDepartment of Nasopharyngeal Cancer, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou 510060, China

ARTICLE INFO

Article history:

Received 12 February 2019
Received in revised form 12 April 2019
Accepted 23 April 2019
Available online 10 June 2019

Keywords:

Retropharyngeal lymph nodes
Metastasis
Laterality
Prognostication
Nasopharyngeal carcinoma

ABSTRACT

Background and purpose: Metastasis laterality is used for N classification of cervical lymph nodes, but not retropharyngeal lymph nodes (RLNs). This study explored the prognostic value of laterality of RLN metastasis to provide suggestions for a better N standard classification.

Materials and methods: This retrospective study evaluated 1225 patients with new biopsy-confirmed nasopharyngeal carcinoma (NPC). Univariable and multivariable Cox regression models were used to assess overall survival (OS), progression-free survival (PFS), and distant metastasis-free survival (DMFS). A new N classification system was developed and compared to the 8th AJCC system. Kaplan-Meier methods with log-rank tests were used to compare OS, PFS, and DMFS between our proposed N stage and the AJCC N stages.

Results: The incidence of RLN metastasis was 38.7% (unilateral) and 27.5% (bilateral). In the N1 subgroup, metastasis laterality was associated with significant differences in the 5-year rates of OS (89.4% vs. 82.6%, $p = 0.016$), DMFS (91.5% vs. 82.9%, $p = 0.004$), and PFS (80.3% vs. 71.2%, $p = 0.016$). However, no significant differences in these outcomes were observed when we compared N2 disease to N1 bilateral RLN metastasis. Multivariate analysis confirmed that bilateral RLN metastasis independently predicted OS, DMFS, and PFS. The proposed classification broadened the differences in OS, DMFS, PFS between N1 and N2 disease.

Conclusion: Patients with NPC and unilateral RLN metastasis had better survival than did patients with bilateral RLN metastasis. Upgrading cases with bilateral RLN metastasis from N1 to N2 may help improve prognostication using the 8th AJCC system.

© 2019 Elsevier B.V. All rights reserved. Radiotherapy and Oncology 140 (2019) 90–97

Nasopharyngeal carcinoma (NPC), a squamous cell tumor of epithelial origin in the nasopharynx [1], is characterized by aggressive behaviors including early lymphatic spread and a high likelihood of distant metastasis [2]. The retropharyngeal lymph nodes (RLNs) are the first-echelon lymph nodes for NPC,

where its distribution and extent can be clearly defined using MRI [3–6].

Some studies have revealed differences in survival based on unilateral and bilateral RLN metastasis. Ma found that RLN metastasis from NPC could independently predict distant metastasis-free

* Corresponding authors at: Department of Endoscopy, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Esophageal Cancer Institute, Collaborative Innovation Center for Cancer Medicine, 651 Dong-Feng Road East, Guangzhou 510060, Guangdong Province, China (J. Li). Department of Radiology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, 651 Dongfeng Road East, Guangzhou 510060, People's Republic of China (L. Liu).

E-mail addresses: huangling@sysucc.org.cn (L. Huang), zhangyun@sysucc.org.cn (Y. Zhang), liuyf1@sysucc.org.cn (Y. Liu), lihaoj@sysucc.org.cn (H. Li), wangshx23@mail2.sysu.edu.cn (S. Wang), liangshb@sysucc.org.cn (S. Liang), zhoujian@sysucc.org.cn (J. Zhou), cui chy@sysucc.org.cn (C. Cui), sunying@sysucc.org.cn (Y. Sun), chenmy@sysucc.org.cn (M. Chen), xushuoy@sysucc.org.cn (S. Xu), lijj@sysucc.org.cn (J. Li), liulizh@sysucc.org.cn (L. Liu).

¹ These authors contributed equally to this work.

survival (DMFS), although no significant differences in the survival outcomes were observed between patients with unilateral or bilateral RLN metastasis [7]. Moreover, Tang reported that there were no significant differences in survival outcomes (disease-free, median disease-free, local relapse-free, or nodal relapse-free survival) between patients with unilateral or bilateral RLN metastasis in the N1 disease group [4,8]. RLN metastasis diagnosis was based on a minimum axial diameter (MID) of ≥ 5 mm, and the presence of RLN metastasis (regardless of laterality) was subsequently used to identify N1 disease in the 7th edition of the American Joint Committee on Cancer (AJCC) staging system and the 2008 Chinese staging system for NPC [9]. The 8th edition of the AJCC system incorporated several improvements for N classification, although RLN metastasis regardless of laterality remained a characteristic of N1 disease [10,11]. Nevertheless, the MID cut-off for identifying RLN metastasis was raised from 5 mm to 6 mm [3], while a MID of ≥ 6 mm was more accurate for prognostication among patients with RLN metastasis from NPC [12]. Thus, there remains controversy regarding whether the N classification should be assigned based on the 5-mm or 6-mm cut-off for identifying RLN metastasis.

Because RLN metastasis laterality is not considered in the 8th AJCC system and owing to the potential need to update the cut-off for identifying RLN metastasis, there is a requirement to reconsider the importance of metastasis laterality for NPC. Therefore, the present study aimed to determine whether laterality could be used to stratify cases with RLN metastasis from NPC, and whether the current system for staging NPC could be improved.

Methods

Study sample

This retrospective study evaluated 1225 patients with newly diagnosed, biopsy-confirmed non-metastatic NPC, who underwent intensity-modulated radiation therapy (IMRT) at the Sun Yat-sen University Cancer Center (792 patients) between January 11, 2010 and January 31, 2013 or the First People's Hospital of Foshan (433 patients) between April 27, 2010 and March 13, 2014. All patients were scanned using MRI; their disease was staged using the 8th edition of the AJCC staging system.

This study was approved by the committees of the Institutional Review Boards at Sun Yat-sen University Cancer Center and the First People's Hospital of Foshan. All data have been deposited at Sun Yat-sen University Cancer Center (www.researchdata.org.cn), with the Research Data Deposit (RDD) number as RDDA 2019000994.

MRI protocol

All patients underwent MRI of the head and neck regions using 1.5-T or 3.0-T MRI systems within 1 month before starting treatment. After accepting the combined head and neck coils, all patients underwent non-contrast-enhanced T1-weighted (T1WI) and T2-weighted (T2WI) scanning in the axial, coronal, and sagittal planes. A contrast agent (Gd-DTPA) was then injected into the patients' venous blood via an automatic high-pressure injector (0.1 mmol/kg) before the radiologists evaluated the contrast-enhanced T1WI results. The T1WI parameters were FSE, TR = 540 ms, and TE = 11.8 ms. The T2WI parameters were FSE, TR = 4000 ms, and TE = 99 ms. The scanning section thicknesses were 5 mm, 4 mm and, 2–3 mm for the axial, sagittal, and coronal planes, respectively; the slice gap was 1 mm.

Image assessment and criteria for RLN metastasis

All MRI scans were evaluated independently by 2 radiologists with >10 years of experience using MRI to diagnose NPC; any

disagreements were resolved via consensus. The diagnostic criteria for metastatic lymphadenopathy were: 1) a lateral RLN with a MID of ≥ 5 mm, any medial RLN node, or nodes with a MID of ≥ 11 mm in the digastric region or ≥ 10 mm in the cervical region; 2) any lymph nodes with central necrosis or a contrast-enhanced rim; and 3) nodal grouping with ≥ 3 contiguous and confluent lymph nodes that each had a MID of 8–10 mm [13–15]. Another set of analyses was planned to evaluate the higher MID cut-off for metastatic lymphadenopathy (a lateral RLN with a MID of ≥ 6 mm).

Treatment

All patients were treated using IMRT. The primary NPC gross tumor volume was defined as the primary tumor observed during the clinical examination and imaging, and was prescribed a dose of 66–72 Gy. The metastatic lymph node area was defined as the area with clinically and/or radiologically observed enlarged lymph nodes, and was prescribed a dose of 64–70 Gy. In addition to the IMRT, 685 of 792 patients (86.5%) with stage II–IV disease received cisplatin-based chemotherapy, and 363 of 433 patients (83.8%) with stage III–IVb disease received cisplatin-based chemotherapy. When possible, salvage treatments (including after-loading, surgery, and chemotherapy) were provided for patients with documented relapse or persistent disease.

Table 1
Patients' clinical characteristics.

Variables	All cases (N = 1225)	Chi-square P-value
Sex		0.212
Male	905 (73.9%)	
Female	320 (26.1%)	
Age		0.003
≥ 46 years	621 (50.7%)	
<46 years	604 (49.3%)	
WHO histological type		<0.001
Type 1	5 (0.4%)	
Type 2	41 (3.3%)	
Type 3	1179 (96.3%)	
T classification		0.547
T1	325 (26.5%)	
T2	157 (12.8%)	
T3	442 (36.1%)	
T4	301 (24.6%)	
N classification		0.031
N0	257 (21.0%)	
N1	679 (55.4%)	
N2	197 (16.1%)	
N3	92 (7.5%)	
Stage		0.940
I	110 (9.0%)	
II	275 (22.4%)	
III	464 (37.9%)	
IV	376 (30.7%)	
Chemotherapy		0.224
No	177 (14.4%)	
Yes	1048 (85.6%)	
CLNs		0.043
None	464 (37.9%)	
Unilateral	513 (41.9%)	
Bilateral	248 (20.2%)	
Regional lymph node		0.111
None	464 (37.9%)	
Upper cervical level	671 (54.8%)	
Lower cervical level	90 (7.3%)	

WHO: World Health Organization, CLNs: cervical lymph nodes, LNs: lymph nodes.

Table 2
Univariate analyses of variables related to overall, distant metastasis-free, and progression-free survival.

Characteristics	n (%)	OS	p-value	DMFS	p-value	PFS	p-value
Sex			0.030		0.634		0.335
Male	905 (73.9%)	84.27		86.69		76.52	
Female	320 (26.1%)	89.22		87.84		79.48	
Age			<0.001		0.150		0.007
<46 years	604 (49.3%)	90.67		88.50		80.84	
≥46 years	621 (50.7%)	80.64		85.48		73.86	
WHO histological type			0.825		0.595		0.472
Type 1	5 (0.4%)	80.00		80.00		60.00	
Type 2	41 (3.3%)	81.65		81.82		72.13	
Type 3	1179 (96.3%)	85.74		87.22		77.58	
T classification			<0.001		<0.001		<0.001
T1	325 (26.5%)	94.51		93.56		87.22	
T2	157 (12.8%)	84.65		87.33		78.87	
T3	442 (36.1%)	87.27		87.62		77.47	
T4	301 (24.6%)	73.72		78.47		65.28	
N classification			<0.001		<0.001		<0.001
N0	257 (21.0%)	92.47		94.79		88.61	
N1	679 (55.4%)	87.71		88.74		78.32	
N2	197 (16.1%)	77.19		78.08		68.04	
N3	92 (7.5%)	66.43		69.40		56.68	
Stage			<0.001		<0.001		<0.001
I	110 (9.0%)	97.70		98.02		93.16	
II	275 (22.4%)	93.63		93.64		86.77	
III	464 (37.9%)	87.66		87.77		78.17	
IV	376 (30.7%)	73.12		77.43		64.32	
Chemotherapy			0.144		0.002		0.050
No	177 (14.4%)	88.55		94.48		82.99	
Yes	1048 (85.6%)	85.11		85.76		76.37	
Regional lymph node			<0.001		<0.001		<0.001
None	257 (21.0%)	91.39		93.88		86.72	
Upper cervical level	878 (71.7%)	83.91		84.41		73.43	
Lower cervical level(level IV and Vb)	90 (7.3%)	66.05		68.96		56.09	
CLNs			<0.001		<0.001		<0.001
None	464 (37.9%)	91.39		93.88		86.72	
Unilateral	513 (41.9%)	85.52		85.56		74.32	
Bilateral	248 (20.2%)	74.19		76.85		65.58	
RLNs			<0.001		<0.001		<0.001
Non-bilateral	888 (72.5%)	88.97		91.84		81.51	
Bilateral	337 (27.5%)	76.58		83.49		66.15	
Size of metastatic LN			0.002		0.014		0.018
<6 cm	1208 (98.6%)	85.83		87.28		77.62	
≥6 cm	17 (1.4%)	69.33		64.71		54.30	

OS: overall survival (months), DMFS: distant metastasis-free survival (months), PFS: progression-free survival (months), WHO: World Health Organization, CLNs: cervical lymph nodes, RLNs: retropharyngeal lymph nodes.

Follow-up and outcomes

The median follow-up is 60.27 months (range = 1.43–83.4 months). All patients were assessed every 3 months during the first 2 years, and then every 6 months for a total follow-up of 5 years. The survival outcomes were defined as progression-free survival (PFS), distant metastasis-free survival (DMFS), and overall survival (OS). All outcomes were calculated from the start of treatment until the first instance of relapse at any site, death from any cause, or the last follow-up, as appropriate.

Statistical analysis

The OS, PFS, and DMFS rates, were analyzed using the Kaplan-Meier method and the log-rank test. Multivariate analyses were performed using the Cox proportional hazards model. Patients with bilateral or unilateral RLN metastasis were matched using logistic regression based on the following covariates: age, sex, T classification, N classification, histological type, disease stage, and the use of chemotherapy, induction chemotherapy, and targeted therapy. The chi-square test or Fisher's exact test was used to compare variables between the groups as appropriate. The likelihoods

of the survival outcomes were compared using the estimated hazard ratios (HRs) and 95% confidence intervals (CIs) from the Cox proportional hazard regression model; the concordance index (C-index) was used to evaluate predictive accuracy. Differences were considered statistically significant at two-tailed p-values of <0.05.

Results

Patient characteristics

We first used the criterion of MID ≥ 5 mm for metastatic RLNs. Patient characteristics are shown in Table 1.

RLN assessment

Based on a MID of ≥5 mm, no RLN involvement was observed for 414 patients (33.8%), unilateral RLN metastasis for 474 (38.7%), and bilateral RLN metastasis for 337 (27.5%). Among the patients with N1 disease, 132 patients (10.8%) had no RLN involvement, 362 (29.5%) had unilateral RLN metastasis, and 185 (15.1%) had bilateral RLN metastasis. Among the 474 patients with unilateral RLN metastasis, 139 (11.3%) had non-cervical lymph node

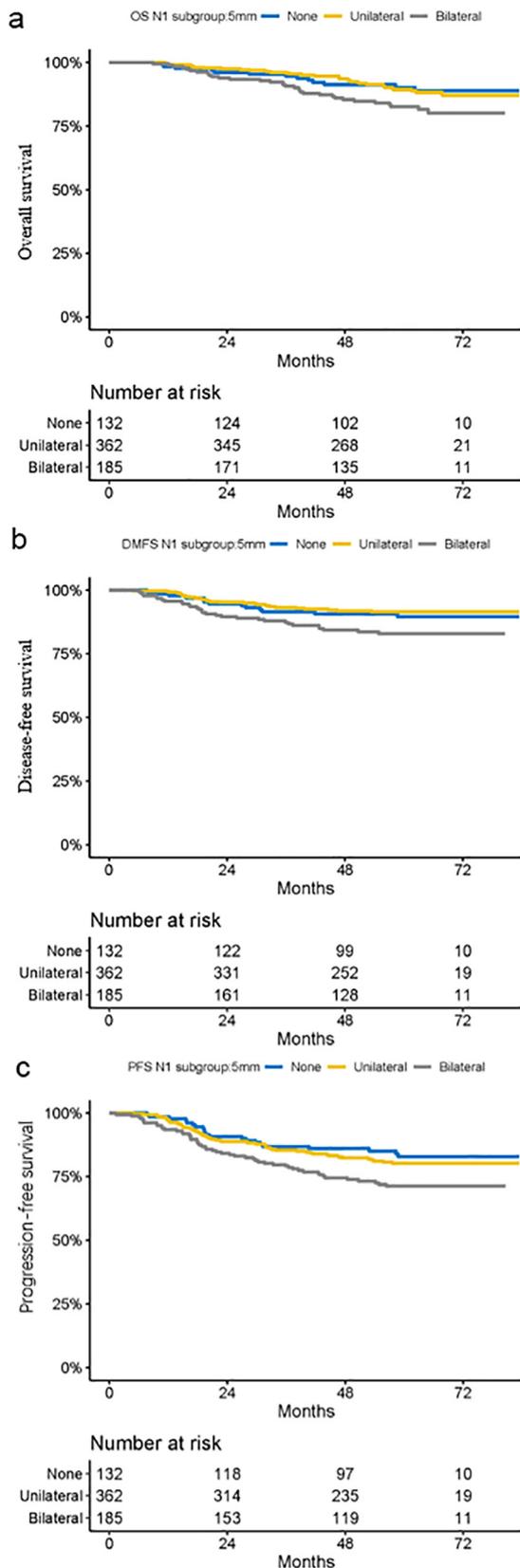


Fig. 1. Kaplan-Meier curves for overall(a), distant metastasis-free(b), and progression-free survival(c) according to N1 non-RLN metastasis, unilateral RLN metastasis, and bilateral RLN metastasis. OS: overall survival, PFS: progression-free survival, DMFS: distant metastasis-free survival.

(CLN) metastasis, 248 (20.2%) had unilateral CLN metastasis, and 87 (7.2%) had bilateral CLN metastasis. Among the 337 patients

with bilateral RLN metastasis, 60 (4.9%) had non-CLN metastasis, 137 (11.2%) had unilateral CLN metastasis, and 140 (11.4%) had bilateral CLN metastasis (Supplementary Table 1).

Prognostic values of unilateral and bilateral RLN metastasis

The results of univariate analyses revealed that OS, DMFS, and PFS were associated with RLN metastasis, age, T classification, CLN metastasis, and the regional lymph node (Table 2). When we compared N1 cases with unilateral or bilateral RLN metastasis, significant differences were observed in the 5-year rates of OS (89.4% vs. 82.6%, $p = 0.016$), DMFS (91.5% vs. 82.9%, $p = 0.004$), and PFS (80.3% vs. 71.2%, $p = 0.016$). However, when we compared N1 cases with no RLN metastasis or unilateral RLN metastasis, no significant differences were observed in the 5-year rates of OS (90.2% vs. 89.4%, $p = 0.913$), DMFS (89.5% vs. 91.5%, $p = 0.553$), or PFS (83% vs. 80.3%, $p = 0.466$) (Fig. 1). When we compared non-bilateral and bilateral RLN metastasis among cases of N1 disease, significant differences were observed in OS (89.6% vs. 82.6%, $p = 0.009$), DMFS (90.9% vs. 82.9%, $p = 0.003$), and PFS (81.0% vs. 71.2%, $p = 0.005$). However, when we compared patients with N1 disease with bilateral RLN metastasis and N2 disease, no significant differences were observed in OS ($p = 0.157$), DMFS ($p = 0.177$), and PFS ($p = 0.327$) (Supplementary Fig. 1). Multivariate analysis also revealed that the independent predictors of OS ($p < 0.01$), DMFS ($p < 0.01$) and PFS ($p < 0.01$) were T classification, regional lymph node, bilateral CLN metastasis, and bilateral RLN (Table 3).

Matched pair analyses

The results of the analyses were used to create 245 pairs of matched patients with unilateral or bilateral RLN metastasis, well-balanced considering age, sex, T classification, N classification, CLN metastasis, and the use of chemotherapy and targeted therapy (all $p > 0.05$). In this sample, survival was independently influenced by age (< 46 years vs. ≥ 46 years), sex (male vs. female), histological type (type I vs. type II vs. type III vs. type), T classification (T1 vs. T2 vs. T3 vs. T4), N classification (N1 vs. N2), CLN metastasis (unilateral vs. bilateral), induction chemotherapy (yes vs. no), chemotherapy (yes vs. no), and targeted therapy (yes vs. no). Among the matched pairs, bilateral RLN metastasis was associated with poorer outcomes than unilateral RLN metastasis considering 5-year OS (79.2% vs. 86.5%, $p = 0.014$), PFS (67.9% vs. 77.9%, $p = 0.006$), and DMFS (79.2% vs. 88.8%, $p = 0.003$) (Supplementary Fig. 2).

A proposed N classification system

Based on the results, we proposed a revised N classification system that re-assigns cases of N1 disease and upstage bilateral RLN metastasis to N2 disease. The proposed N classification system of NPC: N0, no regional lymph node metastasis; N1, retropharyngeal (unilateral), cervical: unilateral, ≤ 6 cm, and above caudal border of cricoid cartilage; N2, retropharyngeal(bilateral), cervical: bilateral, ≤ 6 cm, and above caudal border of cricoid cartilage. For cases of N1 disease based on the revised N classification system, the 5-year rates were 90.1% for OS, 81.3% for PFS, and 91.2% for DMFS. For cases of N2 disease, the new N classification system provided 5-year rates of 79.5% for OS, 69.4% for PFS, and 80.4% for DMFS. These changes broadened the differences in OS, DMFS, and PFS between N1 and N2 disease, although no significant differences were observed between N0 and N1 disease. The HR values for distinguishing N1 and N2 disease were also noticeably improved (Table 4 and Fig. 2). Finally, the new system provided a more balanced distribution between N1 and N2 disease (39.2% vs. 32.3%), relative to the 8th edition of the AJCC system (N1: 55.4%, N2: 16.1%).

Table 3

Multivariate analyses of factors that influenced overall, distant metastasis-free, and progression-free survival.

Outcome	Variable	B	P	EXP (B)	95% CI for exp (B)
OS	Age	0.671	<0.001	1.955	1.420–2.693
	T classification	1.369	<0.001	3.931	2.356–6.558
	Regional lymph node	−0.601	0.012	0.549	0.344–0.875
	Bilateral RLN metastasis	0.487	0.003	1.628	1.178–2.250
	Bilateral CLN metastasis	1.326	<0.001	3.766	2.165–6.551
DMFS	T classification	1.094	<0.001	2.987	1.777–5.020
	Regional lymph node	−0.512	0.044	0.599	0.364–0.986
	Bilateral RLN metastasis	0.500	0.004	1.649	1.170–2.323
	Bilateral CLN metastasis	1.499	<0.001	4.477	2.412–8.312
PFS	Age	0.332	0.008	1.394	1.089–1.783
	T classification	0.959	<0.001	2.608	1.796–3.788
	Regional lymph node	−0.474	0.020	0.623	0.418–0.927
	Bilateral RLN metastasis	0.414	0.002	1.513	1.163–1.969
	Bilateral CLN metastasis	1.235	<0.001	3.437	2.154–5.484

The multivariable models were adjusted for AJCC T classification, age, induction chemotherapy, regional lymph node, RLN metastasis, and CLN metastasis.

CI: confidence interval, OS: overall survival, DMFS: distant metastasis-free survival, PFS: progression-free survival, RLN: retropharyngeal lymph node, CLN: cervical lymph node.

Table 4

Hazard Discrimination of Different N Classification Subsets by the Risk of overall, progression-free, and distant metastasis-free survival.

N status	Current 8th edition						Proposed system					
	OS		DMFS		PFS		OS		DMFS		PFS	
	HR	P	HR	P	HR	P	HR	P	HR	P	HR	P
N0	1	ref	1	ref	1	ref	1	ref	1	ref	1	ref
N1	1.645 (0.998–2.712)	0.051	2.004 (1.131–3.553)	0.017	1.911 (1.281–2.851)	0.002	1.355 (0.798–2.301)	0.261	1.59 (0.869–2.912)	0.133	1.639 (1.078–2.494)	0.021
N2	3.401 (1.985–5.826)	<0.001	4.373 (2.384–8.023)	<0.001	3.233 (2.078–5.032)	<0.001	2.921 (1.766–4.829)	<0.001	3.758 (2.118–6.666)	<0.001	2.952 (1.962–4.441)	<0.001
N3	5.091 (2.829–9.16)	<0.001	5.963 (3.084–11.531)	<0.001	4.461 (2.735–7.278)	<0.001	5.089 (2.828–9.156)	<0.001	5.962 (3.083–11.529)	<0.001	4.461 (2.735–7.278)	<0.001

OS: overall survival, DMFS: distant metastasis-free survival, PFS: progression-free survival, HR: hazard ratio, ref: reference.

C-index analysis results

The C-index analysis results revealed that the new system for classifying N1 and N2 disease provided higher C-index values than the 8th edition of the AJCC system for OS (0.680 vs. 0.665), DMFS (0.660 vs. 0.647), and PFS (0.634 vs. 0.625) (all $p < 0.05$). Among all disease stages, the new system provided C-index values similar to those in the 8th edition of the AJCC system for OS (0.710 vs. 0.703), DMFS (0.697 vs. 0.690), and PFS (0.661 vs. 0.657) (all $p > 0.05$). These results indicate that the new system was not inferior to the AJCC system for all disease stages, and that the new system improve value for predicting OS, DMFS, and PFS among cases with N1 and N2 disease.

Prognostic value of RLN metastasis laterality based on a MID of ≥ 6 mm

Some researchers have recommended using a MID of ≥ 6 mm to identify RLN metastasis. When we applied this criterion to the study sample, we found that 493 patients (40.2%) had no RLN involvement, 489 (39.9%) had unilateral RLN metastasis, and 243 (19.9%) had bilateral RLN metastasis.

When we compared patients with unilateral or bilateral RLN metastasis based on the 6-mm cut-off, we detected significant differences in the 5-year rates of DMFS (90.3% vs. 82.1%, $p = 0.017$) and PFS (79.5% vs. 70.0%, $p = 0.025$), but not OS ($p = 0.172$). Multivariate analyses revealed that DMFS and PFS were independently predicted by T classification, regional lymph node, and bilateral CLN metastasis, but not bilateral RLN metastasis.

Discussion

NPC has a tendency to produce bilateral LN metastases [16], and 47% of patients with nasopharyngeal midline tumors had bilateral nodal involvement [17]. RLNs, being classified as lateral or medial, and lateral RLNs having the possibility of being present bilaterally or unilaterally [6]. Our findings (consistent with those of other studies and the 8th edition of the AJCC system) confirm that bilateral CLN metastasis was an independent prognostic factor in this setting [18,19]. Moreover, we found that bilateral RLN metastasis was an independent prognostic factor, although this finding disagrees with some reported results and the 8th AJCC system, which do not distinguish between bilateral or unilateral RLN metastasis. There are two lymphatic pathways can be involved in NPC, with one leading to direct lymphatic spread from the RLNs (first-echelon nodes for NPC) to the CLNs [20]. The second pathway allows direct lymphatic spread to the level II nodes without RLN involvement [17], which may explain the anatomical independence of RLN and CLN metastasis, as our matched pair analyses eliminated the confounding effects of various factors.

Relative to the 7th edition, the 8th edition of the AJCC staging system involved some changes regarding N classification [10,21]. Both Ma et al. [7] and Tang et al. [8] have used the UICC/AJCC 7th staging system or 6th edition of the AJCC system, while our study used the 8th edition, possibly explaining some of the discrepancies in our findings. Furthermore, Ma et al. identified RLN metastasis were identified from NPC using contrast-enhanced CT with a MID of ≥ 5 mm, although MRI has been used

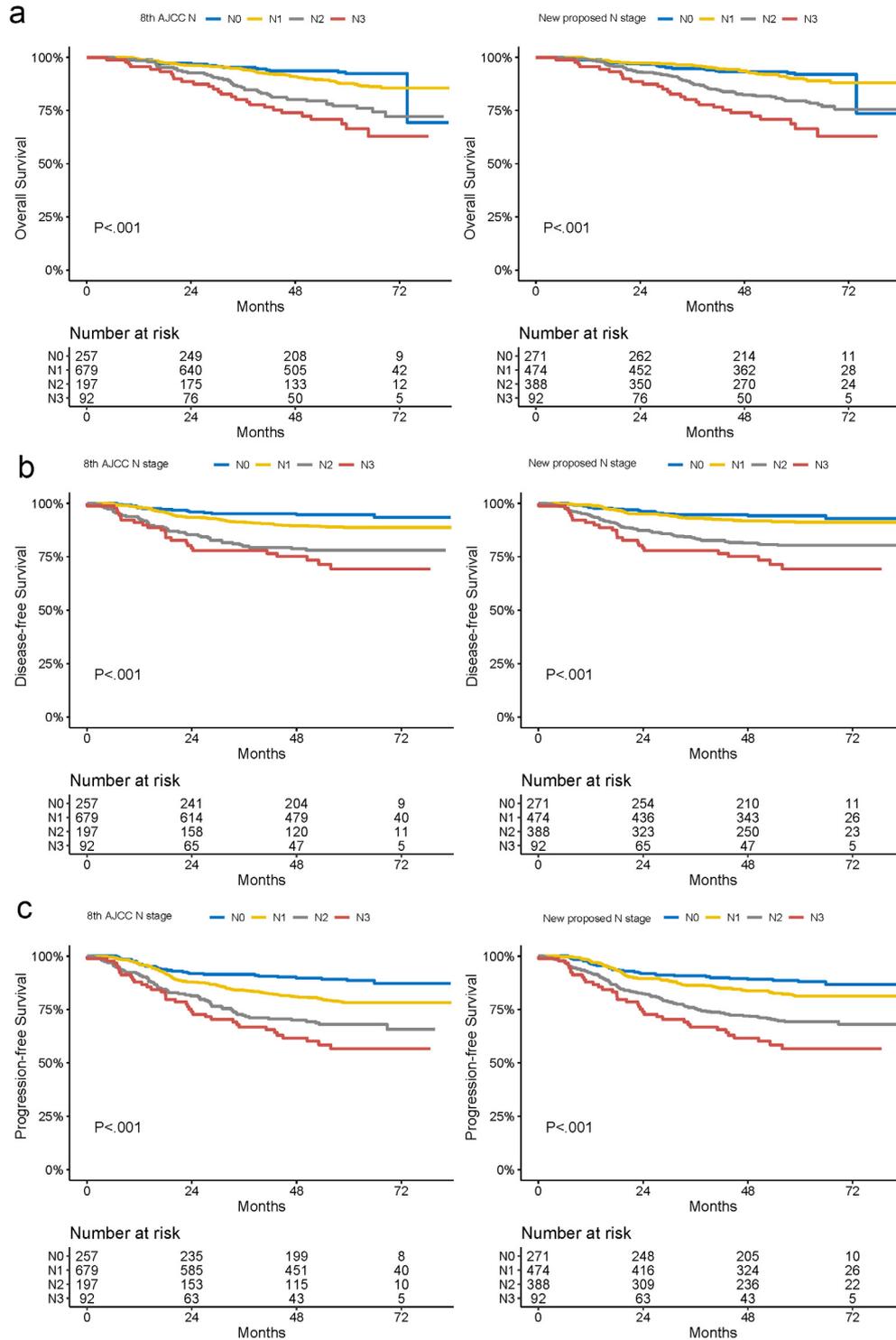


Fig. 2. Kaplan-Meier curves for overall (a), distant metastasis-free (b), and progression-free survival (c) according to our new N classification system and the 8th AJCC system. OS: overall survival, PFS: progression-free survival, DMFS: distant metastasis-free survival.

because contrast-enhanced CT may not be able to identify small lymph nodes with inconspicuous soft-tissue contrast [4]. Moreover, the patients from Ma et al.'s study received definitive radiation therapy, while our patients received IMRT, possibly resulting in differences in the survival outcomes, as IMRT provides a significantly higher survival rate for patients with NPC. Finally, the present study had a larger sample than those in the previous studies, thereby providing additional data for validation. Moreover, those studies failed to consider the potential

confounding related to CLN and T classification, which we adjusted for.

The present study revealed that bilateral RLN metastasis was associated with poorer survival, which may help guide prognostication and treatment. Using the new N classification system based on our results resulted in a more even distribution of N1 and N2 cases, thereby improving the prognosis of N1 and N2 cases, although no significant difference was observed between N0 and N1 cases. This lack of a significant difference may be related to

an insufficient sample size, although it also may not be clinically relevant, as early-stage disease can be managed using radiotherapy alone [22]. Furthermore, distant metastasis is the predominant pattern in NPC treatment failure owing to the substantial improvement in locoregional control [23,24]. Moreover, a higher N classification is a strong predictor of distant metastasis from NPC [25,26], making it crucial to distinguish between N1 and N2 disease, as the treatments differ for stage I/II and stage III/IV NPC. Finally, downgrading locoregional advanced NPC from N2 to N1 is associated with poor survival related to inadequate treatment [27,28].

To evaluate our proposed N classification system, we compared the C-index values for our revised system and the 8th AJCC staging system. When we evaluated cases of N1 and N2 disease, our revised N classification system provided significantly higher C-index values for OS, DMFS, and PFS.

There are inconsistencies in the clinical cut-off for identifying metastatic RLNs [29]. King et al. [20] and Lam et al. [14] proposed a radiologic MID of ≥ 5 mm has also been suggested. However, later research by Zhang et al. [3] and Li et al. [12] have recommended a radiologic MID of ≥ 6 mm, although this recommendation may have been influenced by some of Zhang et al.'s patients not receiving IMRT. Thus, the present study evaluated the effects of using MID of ≥ 5 mm and ≥ 6 mm. Nevertheless, a radiologic MID of ≥ 5 mm is suitable for evaluating the prognostic value of RLN metastasis laterality.

The present study has three important limitations. First, we only considered whether prognosis was influenced by RLN metastasis laterality; further studies are needed to examine the effects of RLN number, CLN number, nodal size, central necrosis, and lymph node clustering. Second, we failed to detect significant differences in survival when we compared cases of N0 or N1 disease. Third, while a MID of ≥ 5 mm was sufficient for prognostication in this setting, there is no consensus regarding the optimal cut-off value for radiological diagnosis of RLN metastasis.

In conclusion, among patients with NPC, unilateral RLN metastasis was associated with better survival than bilateral RLN metastasis. Thus, we propose a revised N classification system that assigns N2 status to cases with bilateral RLN metastasis. This revised system may help improve the predictive ability of the N classification used in the 8th edition of the AJCC staging system.

Financial support

This work was supported by grants from the National Natural Science Foundation of China (No. 81572652); Health & Medical Collaborative Innovation Project of Guangzhou City, China (No. 201604020003); Science and Technology Planning Project of Guangdong Province (No. 2017B020226004); Health & Medical Collaborative Innovation Project of Guangzhou City (No. 201803010021); Guangdong Provincial Medical Research Fund Directive Project (No. C2016072); Science and Technology Planning Project of Guangzhou, China (No.201907010043) and Guangdong Medical Research Fund Project (No. A2016320).

Declaration of Competing Interest

There is no conflicts of interest regarding the publication of this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2019.04.024>.

References

- [1] Wei WI, Sham JS. Nasopharyngeal carcinoma. *Lancet* (London, England) 2005;365:2041–54.
- [2] Chen C, Wu JB, Jiang H, Gao J, Chen JX, Pan CC, et al. A prognostic score for nasopharyngeal carcinoma with bone metastasis: development and validation from multicenter. *J Cancer* 2018;9:797–806.
- [3] Zhang GY, Liu LZ, Wei WH, Deng YM, Li YZ, Liu XW. Radiologic criteria of retropharyngeal lymph node metastasis in nasopharyngeal carcinoma treated with radiation therapy. *Radiology* 2010;255:605–12.
- [4] Tang L, Li L, Mao Y, Liu L, Liang S, Chen Y, et al. Retropharyngeal lymph node metastasis in nasopharyngeal carcinoma detected by magnetic resonance imaging : prognostic value and staging categories. *Cancer* 2008;113:347–54.
- [5] Chen KW, Wang WY, Liang WM, Twu CW, Chao JY, Liang KL, et al. The volume of retropharyngeal nodes predicts distant metastasis in patients with advanced nasopharyngeal carcinoma. *Oral Oncol* 2011;47:1171–5.
- [6] Coskun HH, Ferlito A, Medina JE, Robbins KT, Rodrigo JP, Strojjan P, et al. Retropharyngeal lymph node metastases in head and neck malignancies. *Head Neck* 2011;33:1520–9.
- [7] Ma J, Liu L, Tang L, Zong J, Lin A, Lu T, et al. Retropharyngeal lymph node metastasis in nasopharyngeal carcinoma: prognostic value and staging categories. *Clin Cancer Res* 2007;13:1445–52.
- [8] Tang LL, Guo R, Zhou G, Sun Y, Liu LZ, Lin AH, 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:e108375.
- [9] Chen M, Tang LL, Sun Y, Mao YP, Li WF, Guo R, et al. Treatment outcomes and feasibility of partial neck irradiation for patients with nasopharyngeal carcinoma with only retropharyngeal lymph node metastasis after intensity-modulated radiotherapy. *Head Neck* 2014;36:468–73.
- [10] Pan JJ, Ng WT, Zong JF, Chan LL, OSullivan B, Lin SJ, et al. Proposal for the 8th edition of the AJCC/UICC staging system for nasopharyngeal cancer in the era of intensity-modulated radiotherapy. *Cancer* 2016;122:546–58.
- [11] OuYang PY, Xiao Y, You KY, Zhang LN, Lan XW, Zhang XM, et al. Validation and comparison of the 7th and 8th edition of AJCC staging systems for non-metastatic nasopharyngeal carcinoma, and proposed staging systems from Hong Kong, Guangzhou, and Guangxi. *Oral Oncol* 2017;72:65–72.
- [12] Li YZ, Xie CM, Wu YP, Cui CY, Huang ZL, Lu CY, et al. Nasopharyngeal carcinoma patients with retropharyngeal lymph node metastases: a minimum axial diameter of 6 mm is a more accurate prognostic predictor than 5 mm. *AJR Am J Roentgenol* 2015;204:20–3.
- [13] van den Brekel MW, Stel HV, Castelijns JA, Nauta JJ, van der Waal I, Valk J, et al. Cervical lymph node metastasis: assessment of radiologic criteria. *Radiology* 1990;177:379–84.
- [14] Lam WW, Chan YL, Leung SF, Metreweli C. Retropharyngeal lymphadenopathy in nasopharyngeal carcinoma. *Head Neck* 1997;19:176–81.
- [15] King AD, Tse GM, Ahuja AT, Yuen EH, Vlantis AC, To EW, et al. Necrosis in metastatic neck nodes: diagnostic accuracy of CT, MR imaging, and US. *Radiology* 2004;230:720–6.
- [16] Tang L, Mao Y, Liu L, Liang S, Chen Y, Sun Y, et al. The volume to be irradiated during selective neck irradiation in nasopharyngeal carcinoma: analysis of the spread patterns in lymph nodes by magnetic resonance imaging. *Cancer* 2009;115:680–8.
- [17] Ng SH, Chang JT, Chan SC, Ko SF, Wang HM, Liao CT, et al. Nodal metastases of nasopharyngeal carcinoma: patterns of disease on MRI and FDG PET. *Eur J Nucl Med Mol Imaging* 2004;31:1073–80.
- [18] Lan M, Huang Y, Chen CY, Han F, Wu SX, Tian L, 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;276:536–44.
- [19] 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.
- [20] King AD, Ahuja AT, Leung SF, Lam WW, Teo P, Chan YL, et al. Neck node metastases from nasopharyngeal carcinoma: MR imaging of patterns of disease. *Head Neck* 2000;22:275–81.
- [21] Yang XL, Wang Y, Liang SB, He SS, Chen DM, Chen HY, et al. Comparison of the seventh and eighth editions of the UICC/AJCC staging system for nasopharyngeal carcinoma: analysis of 1317 patients treated with intensity-modulated radiotherapy at two centers. *BMC Cancer* 2018;18:606.
- [22] Lu H, Yao M. The current status of intensity-modulated radiation therapy in the treatment of nasopharyngeal carcinoma. *Cancer Treat Rev* 2008;34:27–36.
- [23] Wee CW, Keam B, Heo DS, Sung MW, Won TB, Wu HG. Locoregionally advanced nasopharyngeal carcinoma treated with intensity-modulated radiotherapy plus concurrent weekly cisplatin with or without neoadjuvant chemotherapy. *Radiat Oncol J* 2015;33:98–108.
- [24] Peng H, Chen L, Li WF, Guo R, Mao YP, Zhang Y, et al. Tumor response to neoadjuvant chemotherapy predicts long-term survival outcomes in patients with locoregionally advanced nasopharyngeal carcinoma: a secondary analysis of a randomized phase 3 clinical trial. *Cancer* 2017;123:1643–52.
- [25] Leung TW, Tung SY, Sze WK, Wong FC, Yuen KK, Lui CM, et al. Treatment results of 1070 patients with nasopharyngeal carcinoma: an analysis of survival and failure patterns. *Head Neck* 2005;27:555–65.

- [26] Li JX, Huang SM, Wen BX, Lu TX. Prognostic factors on overall survival of newly diagnosed metastatic nasopharyngeal carcinoma. *Asian Pac J Cancer Prev: APJCP* 2014;15:3169–73.
- [27] Zong J, Lin S, Lin J, Tang L, Chen B, Zhang M, et al. Impact of intensity-modulated radiotherapy on nasopharyngeal carcinoma: Validation of the 7th edition AJCC staging system. *Oral Oncol* 2015;51:254–9.
- [28] Sun X, Zeng L, Chen C, Huang Y, Han F, Xiao W, et al. Comparing treatment outcomes of different chemotherapy sequences during intensity modulated radiotherapy for advanced N-stage nasopharyngeal carcinoma patients. *Radiat Oncol (London, England)* 2013;8:265.
- [29] Mao YP, Liang SB, Liu LZ, Chen Y, Sun Y, Tang LL, 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;14:7497–503.