A novel N staging system for NPC based on IMRT and RTOG guidelines for lymph node levels: Results of a prospective multicentric clinical study

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Abstract. The present study aimed to investigate the cervical lymph node metastasis of nasopharyngeal carcinoma (NPC) and to establish a novel N staging standard for NPC, based on intensity modulated radiation therapy (IMRT) via a prospective multicenter clinical trial. Between January 2006 and December 2009, a total of 492 patients with NPC without distant metastasis were included in the present study. All patients were treated with IMRT. According to Radiation Therapy Oncology Group division standards, the present study proposed a novel N staging system following the review of magnetic resonance images in comparison with the 7th edition of Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system. Retropharyngeal lymph nodes, cervical lymph node level and cervical lymph node laterality were independent prognostic factors used in multivariate analyses. According to the results of the risk variety, the present study suggested that the novel N staging system included: N0 (no lymph node metastasis), N1 [retropharyngeal or/and unilateral upper cervical (I, II, III, Va, VIIb, VIII, IX and X regions) lymph node metastasis], N2 [bilateral upper cervical (I, II, III, Va, VIIb, VIII, IX and X regions) lymph node metastasis] and N3 (lymph node metastasis in IVa and Vb regions and their lower regions). The novel N staging system proposed in the present study performs better in risk difference and distribution balance. Furthermore, the differences of 5-year curves of distant metastasis-free survival and overall survival had greater statistically significant differences compared with the 7th edition of the UICC/AJCC staging system. The present study suggested a novel N staging system for cervical lymph node metastasis of NPC, which may predict the prognosis of patients with NPC in a more objective and accurate way.

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Introduction

Cervical lymph node metastasis of nasopharyngeal carcinoma (NPC) has an incidence as high as 70% (1), and is a key factor that affects the clinical staging of NPC, treatment plan and prognosis (2). The current existing international standards for NPC staging originated from the 7th edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system that is primarily based on palpation (3,4). Palpation of lymph nodes usually depends on the subjectivity of doctors, which may interfere with the accuracy of staging and the development of individualized treatment plans. In previous years, intensity modulated radiation therapy (IMRT) has become an important therapy for NPC (5-12). As a type of precision radiotherapy, IMRT requires precise anatomical locations; however, the 7th edition of the UICC/AJCC staging system has included body surface positions that are used for the determination of cervical lymph node metastasis (13). For example, in this staging system, supraclavicular fossa (SCF) is defined as a triangle area formed by the upper edge of the sternal end of the clavicle, the upper edge of the outer end of the clavicle and the neck-shoulder intersection; however, this area may include the IV region and the tail of V region in the international cervical lymph node partition system (14). Therefore, SCF, a position that does not have accurate positioning in cross sections in imaging, cannot satisfy the requirements by IMRT. Thus, the 7th edition of UICC/AJCC staging system

has certain limitations regarding the outline of NPC target areas, the definition of treatment plans and the evaluation of prognosis (15).

Initially, the Radiation Therapy Oncology Group (RTOG) divides cervical lymph nodes into retropharyngeal region, I (Ia, Ib) region, II (IIa, IIb) region, III region, IV region, V region and VI region (16). Subsequently, retrostyloid space and supraclavicular region are included in a modified version of RTOG division standards (17). In 2013, RTOG division standards further defined IVb, Vc, VII, VIII, IX and X regions (18). The internationally recognized cervical lymph node imaging division standards are widely used among the radiation oncology research community. The present study used RTOG division standards and magnetic resonance imaging (MRI) to investigate cervical lymph node metastasis of NPC and to establish a novel N staging standard for NPC based on IMRT via a prospective multicenter clinical trial.

Materials and methods

Patients. Between January 2006 and December 2009, 492 patients with NPC without distant metastasis from six hospitals (The First Affiliated Hospital of Guangxi Medical University, Nanning; Liuzhou Worker Hospital, Liuzhou; First People's Hospital of Yulin City, Yulin; People's Hospital of Guangxi Zhuang Autonomous Region, Nanning; Affiliated Hospital of Guilin Medical University, Guilin; Wuzhou Red Cross Hospital, Wuzhou, Guangxi, China) were included in the present study. Among them, 338 were male and 154 were female. The median age of the group was 45 years old (range, 18-81 years old). All patients received IMRT. Patients with a Karnofsky performance status of ≥70, who met criteria for blood counts and other tests (i.e., serum creatinine ≤1.6 mg/dl and serum bilirubin ≤1.5 mg/dl; white blood cell ≥3,600/mm^3, platelet ≥100,000/mm^3 and hemoglobin ≥12.0 g/dl for males, ≥11.0 g/dl for females) were eligible. Prior to treatment, all patients received detailed physical examination, general situation appraisal, blood routine examination, nasopharyngeal fiberscope examination, chest X-ray or computed tomography (CT), abdominal ultrasound and MRI of areas including the nasopharynx and neck. Patients with N2-N3 stage received additional bone scanning. All procedures were approved by the Ethics Committee of Guangxi Medical University (Nanning, China). Written informed consent was obtained from all patients or their families prior to enrolment in the present study.

MRI. MR images were obtained using a 1.5-T MRI scanner (GE Healthcare Life Sciences, Little Chalfont, UK). All patients received routing and enhanced scanning. Scanning directions were cross sectional, sagittal, coronal, T2-weighted (TR 3,000-4,000 ms, TE 102-110 ms), T1-weighted (TR 2,200-2,400 ms, TE 77-109 ms, TI 750 ms) and enhanced T1-weighted scanning. Head quadrature coil was adopted, with a thickness of 6 mm, interlayer space of 1 mm and matrix of 256x192. Cross-sectional scanning ranged from suprasellar cistern to the lower edge of the clavicle. The contrast medium was gadopentetate dimeglumine-diethylenetriaminepentacetate, with a dose of 15 ml.

Clinical staging. All MR images were independently reviewed using a picture archiving and communication system by two physicians. The stage of this research group was defined according to the 7th edition of UICC/AJCC clinical staging standard, taking into account patient symptoms and physical examination information. Lymph node metastasis was diagnosed by MRI, but not by palpation, according to the guidelines of RTOG 2013 edition (19,20).

Therapeutic method. A total of 492 patients with NPC received IMRT during the whole process. Computed tomography contrast-enhanced scanning was applied from the skull cap to 3 cm below the clavicle, with a layer distance of 3 mm and layer thickness of 3 mm. Under the guidance of Report 50 and Report 62 of International Commission on Radiation Units and Measurements, gross tumor volume (GTV) included primary tumor sites, and their invasion range (GTVnx), retropharyngeal metastatic lymph nodes (GTVrpn) and cervical metastatic lymph node (GTVnd) (21). The clinical target volume (CTV) range may be adjusted according to involvement degrees. For example, CTV1 should include GTVnx, GTVrpn, the whole nasopharyngeal mucosa and submucosal 5 mm region; CTV2 should include CTV1, as well as some of the following: Posterior nasal cavity, pterygopalatine fossa, posterior maxillary sinus, part of the posterior ethmoid sinus, lateral pharyngeal space, skull base, part of cervical vertebra and slope. Planning target volume (PTV) included position errors and organ movements during treatments, which are usually externally expanded for 3-5 mm based on GTVs and CTVs. The prescription doses were as follows: PGTVnx and PTVrpn (68-74 Gy), PTVnd (66-70 Gy), PTV1 (60-66 Gy) and PTV2 (50-56 Gy; 5 fractions/week for a total of 30-33 fractions). The setting of restricted dosages for critical organs followed international consensus (21,22).

All stages were defined according to the 7th edition of the UICC/AJCC staging standards. Of the 477 patients with Stage II-IVB disease, 93.70% patients (461/492) received chemotherapy, including 51.0% (235/461) with concurrent chemotherapy, 37.09% (171/461) with induction + concurrent chemotherapy, 7.59% (35/461) with concurrent + adjuvant chemotherapy, 4.12% (19/461) with induction + concurrent + adjuvant chemotherapy, and 0.22% (1/461) with induction chemotherapy. The chemotherapy drugs were primarily platinum-based. All centers used identical chemotherapy protocols.

Follow-ups. Regular follow-ups commenced from 3 months after the patients ended their treatment. The follow-up period was defined as the period starting from the commencement date of treatment to the last date of regular follow-up or to the time of mortality of patients. By December 31st 2014, the last date of regular follow-up, the median follow-up period was 64.1 months (6-92 months). A percentage of 96.3% of patients had complete follow-up data of 5 years. The main analysis factors included overall survival (OS), disease-free survival (DFS), relapse-free survival (RFS) and distant metastasis-free survival (DMFS).

Statistical analysis. All results were analyzed using SPSS v19.0 statistical software (IBM Corp., Armonk, NY, USA). The

Kaplan-Meier method was used to calculate various survival rates. The log-rank test was used to examine the significance of differences in survival rate. Analyses of prognosis were performed using univariate analysis or multivariate analysis. P<0.05 was considered to indicate a statistically significant difference. Data are presented as the mean ± standard error of the mean.

Results

Rate of lymph node metastasis of NPC is high, with retropharyngeal and II regional lymph nodes being the most likely to have metastasis. To determine the distribution of metastatic lymph nodes, the locations of the metastasis were recorded for all 492 patients with NPC. Among the 492 patients, 428 (87%) had cervical lymph node metastasis, including 82 (19.2%) cases with left cervical metastasis only, 77 (18.0%) cases with right cervical metastasis only and 269 (62.9%) cases with cervical metastasis on both sides. The number of patients with retropharyngeal lymph node metastasis was 339 (79.2%), including 128 cases of bilateral metastasis (38.1%) and 210 cases of unilateral metastasis (61.9%). The number of patients with II regional lymph node metastasis was 351 (82.0%), including 189 cases of bilateral metastasis (44.2%; Table I). Among the 428 patients with lymph node metastasis, only 4 patients without II regional metastasis had III regional metastasis (0.9%), including 1 case that demonstrated IV, Va and Vb regional metastasis. Among patients without II and III regional metastasis, no IV regional metastasis was observed. These results suggested that the rate of lymph node metastasis of NPC was high, with retropharyngeal and II regional lymph nodes being the most likely to have metastasis.

Table I. Percentage and distribution of the metastatic lymph nodes in 428 patients with NPC.

	No. of patients (%)			
Level	Left	Right	Bilateral	Total
Ia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ib	3 (0.7)	6 (1.4)	1 (0.2)	8 (1.9)
II	254 (59.3)	286 (66.8)	189 (44.2)	351 (82.0)
III	104 (24.3)	99 (23.1)	35 (8.2)	168 (47.4)
IVa	21 (4.9)	15 (3.5)	4 (0.9)	32 (7.5)
IVb	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Va	10 (2.3)	8 (1.9)	1 (0.2)	17 (4.0)
Vb	4 (0.9)	5 (1.2)	0 (0.0)	9 (2.1)
Vc	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.5)
VI	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
VIIa	239 (55.8)	228 (53.3)	129 (38.1)	339 (79.2)
VIIb	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
VIII	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IX	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Xa	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Xb	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

NPC, nasopharyngeal carcinoma.

Retropharyngeal lymph nodes, cervical lymph node level and cervical lymph node laterality are associated with the prognosis of patients. To investigate the association between lymph node characteristics and prognosis, univariate analysis and multivariate analysis were performed. According to the 7th edition of the UICC/AJCC staging system, patients at I, II, III, IVa, and IVb stages accounted for 3.0% (15/492), 14.4% (71/492), 35.8% (176/492), 38.0% (187/492) and 8.7% (43/492), respectively. In addition, patients at T1, T2, T3 and T4 stages accounted for 6.7% (33/492), 18.5% (91/492), 33.7% (166/492) and 41.1% (202/492), respectively. Furthermore, patients at N0, N1, N2, N3a and N3b stages accounted for 13.0% (64/492), 32.3% (159/492), 45.9% (226/492), 2.2% (11/492) and 6.5% (32/492), respectively (data not shown). The OS rate after 5 years was 80.5%, the DFS rate was 78.6%, the RFS rate was 94.1% and the DMFS rate was 84.3%. Univariate analysis of 428 patients with cervical lymph node metastasis demonstrated that lymph nodal level, sizes [measured as the maximum diameter (D_{max})] had a statistically significant effect on OS, DFS and DMFS, cervical lymph node laterality and retropharyngeal region had a statistically significant effect on OS, DFS, RFS and DMFS, and extracapsular spread had a statistically significant effect on OS, whereas liquefaction necrosis had no significant effect (Table II). In addition, distant metastasis survival and overall survival in Ib, retropharyngeal (VIIa), III and Va regions were not significantly different from II region, whereas those in IVa, Vb and lower regions were significantly different from the II region. Therefore, lymph node levels were divided into two groups: Level 1 (L1), retropharyngeal (VIIa), Ib, II, III and Va regions; and level 2 (L2), IVa, IVb, Vb and Vc regions (Table III). Multivariate analysis of all 492 patients revealed that D_{max} of cervical lymph nodes, extracapsular spread and liquefaction necrosis did not have independent prognostic significance. Of note, retropharyngeal lymph nodes, cervical lymph node level and cervical lymph node laterality were independent prognostic factors (Table IV). These results indicated that retropharyngeal lymph nodes, cervical lymph node level and cervical lymph node laterality are associated with the prognosis of patients.

Novel N staging system proposed in the present study is more suitable for IMRT compared with the 7th edition of the UICC/AJCC staging system. According to univariate and multivariate analysis results, the 492 patients included in the present study were classified into six subgroups, including the N0 group (no lymph node metastasis), retropharyngeal lymph nodes (Nrp) group, L1Lu group (unilateral upper cervical lymph node metastasis), L1Lb group (bilateral upper cervical lymph node metastasis), L2Lu group (unilateral lower cervical lymph node metastasis) and L2Lb group (bilateral lower cervical lymph node metastasis). Compared with the L1Lu group (hazard ratio=1), the hazard ratio for the risk of distant metastasis survival and overall survival in the N0 group was 0. Thus, N0 group was classified as N0 stage. Compared with the L1Lu group (hazard ratio=1), the hazard ratio for the risk of distant metastasis survival in the Nrp group was 1.367 and the risk of overall survival was 1.857. Statistically, the L1Lu and

Table II. Univariate analysis of the association between various cervical lymph node variables and patient prognosis.

Variables	OS	χ^2	P-value	DFS	χ^2	P-value	RFS	χ^2	P-value	DMFS	χ^2	P-value
Level		30.003	<0.001		22.774	0.001		1.170	0.978		31.184	<0.001
Level IB	-			-			-			-		
Level II	82.7			81.9			94.4			87.7		
Level III	75.2			73.6			93.3			79.9		
Level IVa	67.0			65.6			93.3			71.9		
Level Va	92.3			65.9			91.7			74.0		
Level Vb	37.0			44.4			100			44.4		
Level (IVb+Vc)	33.3			33.3			100			33.3		
Level VIIa	78.9			86.5			91.7			85.9		
Group		12.109	0.001		10.682	0.001		0.062	0.803		13.792	<0.001
Level 1	79.8			78.0			93.6			83.9		
Level 2	39.2			59.1			95.0			63.6		
D_{max}, cm		14.566	0.001		15.728	<0.001		0.575	0.750		14.068	0.001
≤3	81.0			77.3			93.6			83.3		
>3 and ≥6	78.1			76.4			94.8			81.3		
>6	45.5			36.4			90.9			45.5		
Laterality		12.640	<0.001		11.866	0.001		4.645	0.031		6.682	0.010
Unilateral	89.2			86.3			97.6			88.5		
Bilateral	71.2			70.3			92.0			77.7		
RLN		17.872	0.046		14.199	<0.001		4.710	0.030		8.970	0.003
No	96.2			91.9			98.9			93.0		
Yes	73.3			71.9			92.3			78.9		
Extracapsular spread		6.071	0.014		1.700	0.192		0.001	0.976		1.921	0.166
No	86.0			79.4			93.7			85.4		
Yes	73.8			74.5			93.9			80.2		
Necrosis		0.426	0.514		1.754	0.185		2.636	0.104		0.315	0.574
No	78.2			77.2			94.7			82.2		
Yes	72.7			70.2			89.0			80.2		

OS, overall survival; DFS, disease-free survival; RFS, relapse-free survival; DMFS, distant metastasis-free survival; D_{max}, maximum diameter; RLN, retropharyngeal lymph nodes.

Nrp groups had no significant difference. Thus, the L1Lu and Nrp group were classified as N1 stage. However, the hazard ratio for the risk of distant metastasis survival and overall survival in the L1Lb group was 2.142 and 2.755, respectively, significantly compared with that in the L1Lu group (P<0.05). Thus, the L1Lb group was classified as N2 stage. Compared with the L1Lu group, the hazard ratio for the risk of distant metastasis survival and overall survival in the L2Lu group (3.825 and 3.835, respectively), and in the L2Lb group (4.785 and 5.415, respectively) was also significantly higher (P<0.05). Thus, the L2Lu and L2Lb groups were classified as N3 stage (Table V). According to the effects of different factors on prognosis, the present study proposed novel N staging standards: N0 (no lymph node metastasis), N1 [retropharyngeal or/and unilateral upper cervical (I, II, III, Va, VIIb, VIII, IX and X regions) lymph node metastasis], N2 [bilateral upper cervical (I, II, III, Va, VIIb, VIII, IX and X regions) lymph node metastasis] and N3 (lymph node metastasis in IVa and Vb regions and their lower regions). To evaluate the novel N staging, differences in the survival prediction value, the distribution balance and the risk ratio were compared between the novel N staging and the 7th edition of the UICC/AJCC staging system. In the proposed novel N staging system, the OS curves were significantly different among all stages: N0:N1 (χ^2=5.198, P<0.05), N0:N2 (χ^2=14.663, P<0.01), N0:N3 (χ^2=29.990, P<0.01), N1:N2 (χ^2=9.215, P<0.01), N1:N3 (χ^2=22.592, P<0.01) and N2:N3 (χ^2=9.305, P<0.01). In addition, the DMFS curves were significantly different among all stages: N0:N1 (χ^2=5.528, P<0.05), N0:N2 (χ^2=11.748, P<0.01), N0:N3 (χ^2=25.172, P<0.01), N1:N2 (χ^2=8.525, P<0.01), N1:N3 (χ^2=18.934, P<0.01) and N2:N3 (χ^2=7.315, P<0.01; Fig. 1, Table VI). Conversely, OS and DMFS curves were not significantly different between N3a and N3b stages according to the 7th edition of the UICC/AJCC staging system (Fig. 1, Table VI). Furthermore, the ratio of distribution in N3a and N3b stages in the 7th edition of the UICC/AJCC staging system accounted for 2.2 and 6.5%, respectively, whereas the N3 stage in the proposed novel N staging system accounted for 8.9%, being more balanced compared with the

Table III. Comparison of distant metastasis survival and OS of various lymph node levels.

		Risk ratio (95% CI)	
Nodal variables	No.	Distant metastasis survival	OS
Level II	196	1	1
Level VIIa	37	0.998 (0.382-2.607)	1.080 (0.475-2.452)
Level III	138	1.565 (0.909-2.697)	1.520 (0.934-2.474)
Level IVa	32	2.357 (1.100-5.050)[a]	2.124 (1.041-4.335)[a]
Level Va	13	1.779 (0.537-5.893)	0.462 (0.063-3.381)
Level Vb	9	6.318 (2.415-16.532)[a]	5.302 (2.057-13.667)[a]
Level (IVb+Vc)	3	10.559 (2.492-44.750)[a]	10.491 (2.483-44.318)[a]
Level Ib	0	-	-

[a]P<0.05. OS, overall survival; CI, confidence interval.

Table IV. Multivariate analysis of cervical lymph node variables associated with prognosis.

Variables	OS	DFS	RFS	DMFS
Levels 1 and 2	0.007	0.003	0.006	0.003
D_{max}	0.918	0.764	0.793	0.945
Laterality	0.006	0.006	0.004	0.007
RLN	<0.001	<0.001	<0.001	0.001
Extracapsular spread	0.909	0.999	0.962	0.925
Necrosis	0.242	0.424	0.232	0.193

OS, overall survival; DFS, disease-free survival; RFS, relapse-free survival; DMFS, distant metastasis-free survival; D_{max}, maximum diameter; RLN, retropharyngeal lymph nodes.

Table V. Distribution patterns and failure hazards of different N subsets.

	Hazard ratio (95% CI)	
Group	Distant metastasis survival	OS
L1Lu	1	1
N0	0.152 (0.020-1.166)	0.271 (0.061-1.201)
Nrp	1.367 (0.481-3.879)	1.857 (0.071-4.657)
L1Lb	2.142 (1.129-4.064)[b]	2.755 (1.499-5.065)[a]
L2Lu	3.825 (1.079-13.556)[b]	3.835 (1.092-13.471)[a]
L2Lb	4.785 (2.181-10.497)[b]	5.415 (2.537-11.562)[a]

[a]P<0.05. OS, overall survival; CI, confidence interval.

7th edition of the UICC/AJCC staging system (Table VII). In addition, the risk ratio for each stage in the proposed novel N staging system was significantly different compared with the N0 stage (P<0.05), whereas the risk ratio for the N1 stage in the 7th edition of the UICC/AJCC staging system was not significantly different compared with the N0 stage (P>0.05; Table VII). These results suggested that the novel N staging system proposed in the present study was more suitable for IMRT compared with the 7th edition of the UICC/AJCC staging system.

Discussion

NPC has a high rate of cervical lymph node metastasis and ~70% of patients were diagnosed with cervical lymph node metastasis at their preliminary diagnosis (1,23). The MRI data in the present study demonstrated that 87.0% of 492 patients had lymph node metastasis, which was consistent with the results reported by Wang *et al* (24) and Ho *et al* (25). The metastatic rates for retropharyngeal, II, III, IV, Va, Vb and Vc regions were 79.2, 82.0, 47.4, 7.7, 4.0, 2.1 and 0.5%, respectively. Consistent with a previous study, the metastatic rates of each region decreased from the upper region to the lower region, and the skipping metastatic rate was 0.9% (26). However, it has not been confirmed whether the retropharyngeal or II region lymph node is the sentinel lymph node (1,27-30). Lv *et al* (31) revealed that the metastatic rates of retropharyngeal and II region lymph nodes were 74.5 and 75.3%, respectively, suggesting that both are sentinel lymph nodes. Consistent with this observation, the present study demonstrated that the metastatic rates of retropharyngeal and II region lymph nodes in 428 patients were 351 cases (82.0%) and 339 cases (79.2%), respectively. This observation may be associated with lymph node drainage via retropharyngeal

Table VI. OS rate and distant failure-free rates of various N stages between the proposed system and the 7th edition of the UICC/AJCC system.

	OS		DMFS	
	X2	P	X2	P
Proposed system				
N0:N1	5.198	0.039	5.528	0.042
N0:N2	14.663	<0.001	11.748	<0.001
N0:N3	29.990	<0.001	25.172	<0.001
N1:N2	9.215	0.001	8.525	0.002
N1:N3	22.592	<0.001	18.934	<0.001
N2:N3	9.305	<0.001	7.315	<0.001
UICC/AJCC system				
N0:N1	4.203	0.040	4.325	0.038
N0:N2	14.104	<0.001	11.197	0.001
N0:N3a	39.270	<0.001	39.328	<0.001
N0:N3b	34.506	<0.001	31.973	<0.001
N1:N2	11.438	0.001	6.491	0.011
N1:N3a	35.277	<0.001	28.276	<0.001
N1:N3b	34.218	<0.001	31.427	<0.001
N2:N3a	6.544	0.011	9.797	0.002
N2:N3b	9.510	0.002	12.721	<0.001
N3a:N3b	0.121	0.728	0.070	0.792

OS, overall survival; DMFS, distant metastasis-free survival; UICC/AJCC, Union for International Cancer Control/American Joint Committee on Cancer.

and II regions. In the 7th edition of the UICC/AJCC staging system, retropharyngeal lymph node metastasis was classified as N1 (32). Tang *et al* (33) recommended classifying retropharyngeal lymph node metastasis as N1. The results of the present study revealed that retropharyngeal lymph node metastasis (regardless of sides and sizes) is an independent prognostic factor that affects OS, DFS, RFS and DMFS of patients with NPC. Due to various N staging standards of NPC that have distinct lymph node parameters (15,20,29,34,35), the present study suggested setting a unified standard based on objective MRI data and international lymph node imaging division method.

Supraclavicular fossa defined in the 7th edition of the UICC/AJCC staging system has been demonstrated to have high risk of distant metastasis. According to the RTOG for Lymph Node criteria, supraclavicular fossa is located at IV region, the lower part of V region and the whole supraclavicular region (13). Cervical lymph nodes are an ordered defense system. Once supraclavicular lymph nodes are affected, tumor cells may further invade thoracic ducts and possibly the whole body. Mao *et al* (34) suggested that lymph node metastasis regions may be categorized into retropharyngeal, Ib, II, III, V and IV regions, as well as the supraclavicular region, when using the N staging based on MRI and RTOG to evaluate distant metastasis risks. Ng *et al* (15) and Yue *et al* (36) suggested replacing supraclavicular fossae in UICC/AJCC standards with IV and Vb regions. Li *et al* (37) revealed that lower cervical lymph node metastasis (IV, Vb and supraclavicular regions) is an independent prognostic factor that affects survival (37). Consistent with these reports, the present study divided the lymph node level into Level 1 (retropharyngeal, Ib, II, III and Va regions) and Level 2 (IVa, IVb, Vb and Vc regions), and univariate and multivariate analyses confirmed the significant differences in prognosis between the two.

NPC usually metastasizes according to the direction of lymphatic drainage (38). As it is different from other malignant tumors in the head and neck, NPC usually has lymph node metastasis (bilateral or unilateral) during its early stage, with a 40% rate of bilateral lymph node metastasis (39). The primary difference between N1 and N2 stages in the 7th edition of the UICC/AJCC staging system is unilateral or bilateral lymph node metastasis. The present study demonstrated that OS, DFS, RFS and DMFS rates were significantly different between unilateral and bilateral metastases, suggesting that cervical lymph node laterality is an independent prognostic factor for NPC.

A previous literature review investigating the data for the N-staging system for NPC revealed that the prognostic significance attributed to size was controversial (40-44). Lee *et al* (4) demonstrated that the largest lymph node size was independently significant in predicting survival. However, certain reports revealed that lymph node size was not an independent prognostic factor (40-43). The multivariate analysis of present study indicated that lymph node size was not an independent prognostic factor. According to the 7th edition of the UICC/AJCC staging system, the diagnosis of lymph nodes >6 cm was primarily based on palpation, which is subjective. Few lymph nodes >6 cm may be diagnosed by MRI or CT. Therefore, it is still controversial whether lymph node size should be included in the N staging standards.

The prognostic significance of extracapsular spread in the treatment of NPC remains unclear. Mao *et al* (34) suggested that lymph node extracapsular spread should be classified into N2 stage as a staging factor. The results of the univariate analysis of the present study demonstrated that extracapsular spread does not significantly affect RFS, DMFS and DFS rates. In addition, multivariate analysis indicated that cervical lymph node extracapsular spread was not an independent prognostic factor. This may be due to the lack of pathological evidence and diagnostic standard. Therefore, extracapsular spread is not included in the proposed novel N staging system.

The tumor-node-metastasis staging system is the comprehensive manifestation of all types of prognosis factors revealed by the investigation of clinical epidemiology, and the identification of novel prognostic factors depends on the improvement of diagnosis and therapy. Due to the continuous improvement of diagnosis and therapy, prognostic factors are also changing, and staging system should also be continuously improved. The staging standard of the 7th edition of the UICC/AJCC published in 2009 is primarily based on the data of regular two-dimensional radiotherapy. As the progress of accurate radiotherapy, IMRT has been more frequently applied in the treatment of NPC than regular two-dimensional radiotherapy (44-46). In addition, the

Table VII. Distribution and differences in risk ratios between the 7th edition of the UICC/AJCC staging system and the proposed novel N staging system.

N stage	No.	Risk ratio (95% CI)	
		Distant metastasis survival	OS
Proposed system			
N0	64 (13.0)	1	1
N1	161 (32.7)	7.557 (1.009-56.613)[a]	4.596 (1.077-19.609)[a]
N2	223 (45.3)	13.827 (1.903-100.486)[a]	10.000 (2.431-41.132)[a]
N3	44 (8.9)	30.123 (3.993-227.251)[a]	18.584 (4.282-80.651)[a]
UICC/AJCC system			
N0	64 (13.0)	1	1
N1	159 (32.3)	6.316 (0.834-47.812)	3.955 (0.917-17.050)
N2	226 (45.9)	13.288 (1.827-96.612)[a]	9.719 (2.361-40.006)[a]
N3a	11 (2.2)	51.936 (6.243-432.084)[a]	36.384 (7.268-182.153)[a]
N3b	32 (6.5)	38.744 (5.091-294.830)[a]	23.544 (5.369-103.245)[a]

[a]P<0.05 compared with N0. OS, overall survival; UICC/AJCC, Union for International Cancer Control/American Joint Committee on Cancer; CI, confidence interval.

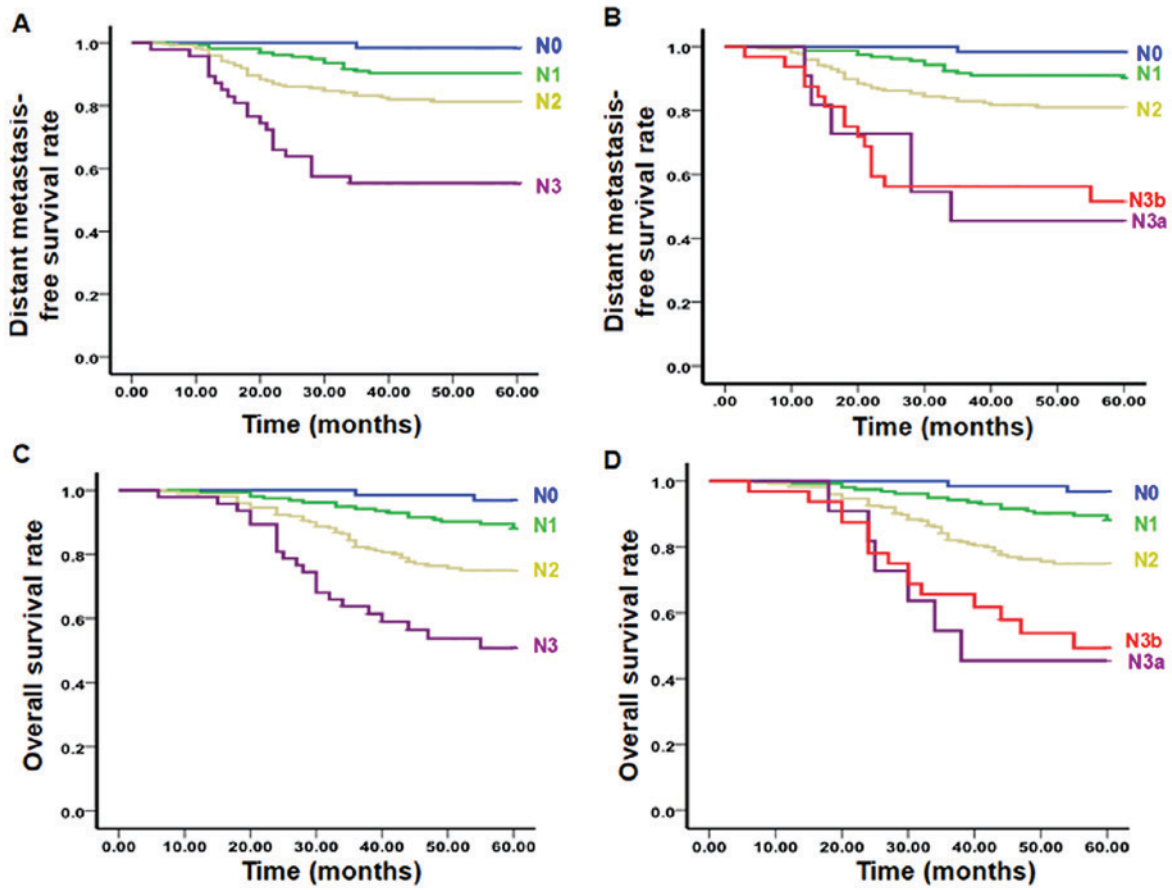

Figure 1. Distant failure-free rates of various N stages as defined by the (A) proposed system and (B) the 7th UICC/AJCC system. Overall survival rate of various N stages as defined by the (C) proposed system and the (D) 7th UICC/AJCC system. UICC/AJCC, Union for International Cancer Control/American Joint Committee on Cancer.

7th edition of UICC/AJCC is primarily based on palpation (3,4). Palpation of lymph nodes usually depends on the subjectivity of doctors, which may interfere with the accuracy of staging and the development of individualized treatment plans (34). Previous

studies have demonstrated that there were no significant differences in DMFS between N3a and N3b, and suggested that N3a and N3b may be combined as N3 in the novel N stage (47,48). The present study used RTOG division standards and MRI to investigate cervical lymph node metastasis of NPC, and to establish a novel N staging standard for NPC based on IMRT in a prospective multicenter clinical trial. It was proposed that the novel N staging system include: N0 (no lymph node metastasis), N1 [retropharyngeal or/and unilateral upper cervical (I, II, III, Va, VIIb, VIII, IX and X regions) lymph node metastasis], N2 [bilateral upper cervical (I, II, III, Va, VIIb, VIII, IX and X regions) lymph node metastasis] and N3 (lymph node metastasis in IVa and Vb regions and their lower regions). Compared with the 7th edition of the UICC/AJCC staging system, the novel N staging system has improved risk difference and distribution balance, as well as distinct DMFS rate and OS rate between stages. In conclusion, the novel N staging system is more suitable for IMRT and more accurately predicts the prognosis of patients with NPC.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

MK and RW designed the research and assigned the tasks to teams. PZ, TW, TZ and JL collected and analyzed data. MK accessed the relevant information. GL and HY helped with MRI examination. ML and GF participated in image analysis. JZ was involved in statistical analysis. RW, GL, HY, GF, ML and JZ critically revised the manuscript for important intellectual content. RW approved the final version of the manuscript to be submitted.

Ethics approval and consent to participate

All procedures were approved by the Ethics Committee of Guangxi Medical University (Nanning, China). Written informed consent was obtained from all patients or their families prior to enrolment in the present study.

Consent for publication

Not applicable.

Competing interests

The authors declared that they have no competing interests.

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