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Suggestions for Lymph Node Classification of UICC/AJCC Staging System: A Retrospective Study Based on 1197 Nasopharyngeal Carcinoma Patients Treated With Intensity-Modulated Radiation Therapy

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Abstract: This article provides suggestions for N classification of Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system of nasopharyngeal carcinoma (NPC), purely based on magnetic resonance imaging (MRI) in intensity-modulated radiation therapy (IMRT) era.

A total of 1197 nonmetastatic NPC patients treated with IMRT were enrolled, and all were scanned by MRI at nasopharynx and neck before treatment. MRI-based nodal variables including level, laterality, maximal axial diameter (MAD), extracapsular spread (ECS), and necrosis were analyzed as potential prognostic factors. Modifications of N classification were then proposed and verified.

Only nodal level and laterality were considered to be significant variables affecting the treatment outcome. N classification was thus proposed accordingly: N0, no regional lymph node (LN) metastasis; N1, retropharyngeal LNs involvement (regardless of laterality), and/or unilateral levels I, II, III, and/or Va involvement; N2, bilateral levels I, II, III, and/or Va involvement; and N3, levels IV, Vb, and Vc involvement. This proposal showed significant predicting value in multivariate analysis. N3 patients indicated relatively inferior overall survival (OS) and distant metastasis-free survival (DMFS) than N2 patients; however, the difference showed no statistical significance ($P = 0.673$ and 0.265 for OS and DMFS, respectively), and this was considered to be correlated with the small sample sizes of N3 patients (79 patients, 6.6%).

Nodal level and laterality, but not MAD, ECS, and necrosis, were considered to be significant predicting factors for NPC. The proposed N classification was proved to be powerfully predictive in our cohort; however, treatment outcome of the proposed N2 and N3 patients could not differ significantly from each other. This insignificance may be because of the small sample sizes of N3 patients. Our results are based on a single-center data, to develop a new N classification that is universally acceptable; further verification by data from multicenter is warranted.

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Abbreviations: CLN = cervical lymph node, DMFS = distant metastasis-free survival, ECS = extracapsular spread, IMRT = intensity-modulated radiation therapy, LN = lymph node, MAD = maximal axial diameter, MID = minimal axial diameter, MRI = magnetic resonance imaging, NPC = nasopharyngeal carcinoma, OS = overall survival, RLN = retropharyngeal lymph node, RRFS = regional relapse-free survival, SCF = supraclavicular fossa, TNM = tumor nodal metastasis, TNMc2008 = the Chinese 2008 Staging System, UICC/AJCC = Union for International Cancer Control/American Joint Committee on Cancer.

INTRODUCTION

Intensity-modulated radiation therapy (IMRT) and its combination with chemotherapy have improved the locoregional control of nasopharyngeal carcinoma (NPC), whereas distant metastasis remains as the main failure pattern after treatment.[1] Tumor-nodal-metastasis (TNM) system for NPC is critical in predicting prognosis, facilitating treatment planning, and exchanging experiences between different institutions, and N categories have been reported to be the most crucial predictor for distant control.[2,3]

The current 7th edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) TNM Classification for NPC is a staging system purely based on the anatomical extent of the disease, and is now internationally recommended.[4] However, its N classification does have limitations. First, magnetic resonance imaging (MRI) was designated by AJCC as the main diagnostic modality for NPC; however, its N-staging criteria was defined mainly depending on clinical palpation, but not image information, which might contain the fusion of multiple nodes, and could not reflect the true size of nodes detected by MRI.[5] In addition, the definition of the supraclavicular fossa (SCF), originally described by Ho, is primarily based on clinical landmarks, and there is no reliable way to describe it on cross-sectional imaging.[6]

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The N classification of the Chinese 2008 Staging System for NPC (TNMc2008),[7] which was released by the Chinese Committee for Staging of NPC, has been reported to be superior to the 7th UICC/AJCC system.[8,9] All the N descriptors adopted in TNMc2008 were based on MRI, including nodal level that was defined by the 2006 International Consensus Guidelines.[10] TNMc2008 also replaced SCF involvement with levels IV and Vb, with the rationality that had been verified by Ng et al.[5] Although TNMc2008 was based on data from 2-dimensional radiation therapy and has its inherent limitations, their experience on the N category could be used as reference for the modification of the UICC/AJCC system.

Several studies have reported their proposals of new N classifications based on MRI lymph node (LN) variables for the UICC/AJCC system.[6,9,11,12] However, not all the patients enrolled were treated by IMRT, and these N classifications differed from each other, in terms of the enrolment of LN variables. Fujian Province is another endemic area in China; here, we attempt to reevaluate the prognostic value of different MRI-determined nodal variables based on data from our institution, and aim to propose a more practical and simplified N classification for NPC staging in IMRT era.

MATERIALS AND METHODS

Patient Characteristics

Between June 2005 and December 2010, a total of 1197 histologically diagnosed nonmetastatic NPC patients treated with IMRT in our institution were enrolled; all were scanned by MRI at nasopharynx and neck and treated according to an Institutional Review Board (IRB)-approved institutional treatment protocol.[13] This study has been approved by the IRB of Fujian Provincial Cancer Hospital. Although patients' consents were not specifically obtained for this analysis, all information had been anonymized and deidentified prior to its analysis. All patients completed a pretreatment evaluation according to our institutional protocol[2] and restaged according to the 7th edition of the UICC/AJCC staging system.[4] Clinical characteristics of the patients were shown in Table 1.

TABLE 1. Demographic and Clinical Characteristics of Cohort (n = 1197)

Characteristic	No. of Patients (%)
Sex	
Male	905 (75.6)
Female	292 (24.4)
Age, y (median = 46 y)	
≤50	754 (63)
>50	443 (37)
T category	
T1	295 (24.6)
T2	225 (18.8)
T3	441 (36.8)
T4	236 (19.7)
N category	
N0	170 (14.2)
N1	675 (56.4)
N2	290 (24.2)
N3a	26 (2.2)
N3b	36 (3.0)
Clinical stage	
I	57 (4.8)
II	314 (26.2)
III	541 (45.2)
IVa	223 (18.6)
IVb	62 (5.2)
Chemotherapy	
Yes	1030 (86.0)
No	167 (14.0)

Imaging Protocol, Assessment, and Diagnostic Criteria

The imaging protocol of MRI has been indicated in our previous report.[14] MRI images were reviewed independently by 2 radiologists with >10 years of experience and disagreements were resolved by consensus. Nodal levels were defined according to the 2013 International Consensus Guidelines[15]; nodal maximal axial diameter (MAD) was the largest nodal diameter measured in all the 3 planes, including the longitudinal, sagittal, and coronal planes. The diagnostic criteria for retropharyngeal lymph node (RLN) and cervical lymph node (CLN) metastases included lateral RLN with a minimal axial diameter (MID) of ≥5 mm in the largest plane or any node in the median retropharyngeal group, CLN in the digastric region with an MID ≥11 mm, or any other CLN ≥10 mm; LNs of any size with central necrosis or a contrast-enhanced rim; nodal grouping, the presence of ≥3 contiguous and confluent LNs, each with an MID of 8–10 mm; and LNs of any size with extracapsular spread (ECS).[16,17]

Treatment

All patients were initially treated with definitive IMRT. A detailed description of the IMRT had been published previously.[2] Of the 1015 patients with Stages II–IVB disease, 84.8% were given platinum-based chemotherapy, the sequence used was induction in 247 (24.3%), concurrent 69 (6.8%), adjuvant 16 (1.6%), concurrent-adjuvant 22 (2.2%), induction-concurrent 210 (20.7%), induction-adjuvant 291 (28.7%), and induction-concurrent-adjuvant 160 (15.8%). Whenever possible, salvage treatments (including intracavitary brachytherapy, surgery, and chemotherapy) were provided for patients who developed relapse or persistent disease.

Follow-Up and Statistical Analyses

The median follow-up period for the entire cohort was 57 months (range, 2–105 months). The overall survival (OS), regional relapse-free survival (RRFS), and distant metastasis-free survival (DMFS) rates were measured and calculated from the first day of diagnosis to death, the first regional failure, and the distant failure, respectively. The survival data were analyzed with SPSS software, version 18.0 (SPSS, Inc., Chicago, IL). Survival curves were created with the Kaplan–Meier method and compared with the log-rank test. Multivariate analyses by Cox proportional hazards model were performed to test the independent prognostic significance of the staging factors. Two-tailed P values <0.05 were considered statistically significant.

RESULTS

Treatment Outcome and the Characteristics of Nodal Spread

The 5-year OS, RRFS, and DMFS rates for the entire cohort were 81.5%, 95.3%, and 82.5%, respectively. Of the whole cohort, 85.8% (1027/1197) patients presented with LNs involvement. The most commonly involved regions include

TABLE 2. Characteristics of Nodal Spread in the 1027 Node-Positive Patients

Characteristic	No. of Patients (%)
Level	
Retropharyngeal region	886 (86.3)
Level I	23 (2.2)
Level IIa	543 (52.9)
Level IIb	687 (66.9)
Level III	217 (21.1)
Level IV	59 (5.7)
Level Va	86 (8.4)
Level Vb, Vc	31 (3.0)
Laterality	
Unilateral RLN	526 (59.4)
Bilateral RLNs	360 (40.6)
Unilateral I, II, III, Va	493 (63.9)
Bilateral I, II, III, Va	279 (36.1)
Unilateral IV, Vb, Vc	67 (84.8)
Bilateral IV, Vb, Vc	12 (15.2)
Necrosis	
Yes	527 (51.3)
No	500 (48.7)
Extracapsular spread	
Yes	776 (75.6)
No	251 (24.4)

RLN = retropharyngeal lymph node.

retropharyngeal and level II LNs, and no LN metastasis was found in level VI. Information of other variables including laterality, ECS, and necrosis were also showed in Table 2.

Prognostic Value of Nodal Level in the Whole Group (Step 1)

Of the 1197 patients, age, sex, T classification, chemotherapy, and nodal level (ie, N0 vs RLN, and levels I, II, III, Va vs levels IV, Vb, Vc) were included in the univariate and multivariate analysis to find their prognostic value. Nodal level showed significant predicting value for DMFS, RRFS, and OS (DMFS hazard ratio [HR] 1.316, 95% confidence interval [CI] 1.035–1.674, $P = 0.025$; RRFS HR 1.803, 95% CI 1.031–3.151, $P = 0.039$; OS HR 1.295, 95% CI 1.047–1.602, $P = 0.017$), and therefore was considered as the first nodal variable to be enrolled in N classification.

Prognostic Value of ECS and Necrosis in 1027 Patients With Lymphadenopathy (Step 2)

In this step, we try to found out whether ECS and necrosis have significant prognostic value for NPC patients. Besides ECS and necrosis, nodal level (RLN, and levels I, II, III, Va vs levels IV, Vb, Vc), age, sex, T classification, and chemotherapy were enrolled. Multivariate analysis showed nodal level remained as a significant predicting factor for DMFS, RRFS, and OS ($P = 0.002$, 0.004, and 0.005, respectively), and no significant prognostic value for ECS were found, in terms of DMFS, RRFS, and OS ($P = 0.264$, 0.931, and 0.629, respectively). Necrosis was only found to be significant in RRFS predicting ($P = 0.012$), but not for OS and DMFS ($P = 0.130$ and 0.190 for OS and DMFS, respectively). Since distant failure was the main failure pattern that impact overall survival, but not regional failure, and necrosis, as well as ECS, was found to be strongly correlated with nodal level ($P = 0.000$ for both), these 2 nodal variables were excluded in subsequent analysis.

Prognostic Value of Laterality and MAD in 772 Patients With Levels I, II, III, and Va Involvement (Step 3)

Of the 772 patients, 279 (36.1%) patients presented with bilateral involvement, only 4.5% had a nodal MAD >6 cm, 45.3% of them presented with a nodal MAD of ≤3 cm, and 50.1% of them was in the 3 to 6 cm group. Cox regression model indicated that both laterality and nodal MAD cannot well predict RRFS. For OS and DMFS, nodal laterality was found to be the independent prognostic factor for both, regardless of the cutoff value of nodal MAD (Table 3). Thus, the second variable that should be included in the staging system was nodal laterality.

Nodal MAD failed to show any significant prognostic value for all the endpoint censorship when the cutoff point was set at 6 or 3 cm (Table 3). However, when we divided the patients into 3 subgroups by 3 and 6 cm (ie, ≤3 vs 3–6 vs >6 cm), clear trends demonstrated that larger nodal MAD was associated with inferior DMFS and OS ($P = 0.061$ for DMFS, $P = 0.054$ for OS) (Table 3). Hence, we considered nodal MAD (ie, ≤3 vs 3–6 vs >6 cm) was another nodal variable maybe considered in the proposed N classification.

Suggestions and Verification for a New N Classification

According to the results we analyzed in the previous subsection, we supposed that N classification may be modified as follows (Proposal A): N0, no regional LN metastasis; N1, RLN involvement, and/or unilateral levels I, II, III, and/or Va, and ≤3 cm; N2, 3–6 cm, and/or bilateral levels I, II, III, and/or Va; N3, >6 cm, and/or levels IV, Vb, and Vc (Figure 1A). Multivariate analysis indicated that Proposal A was a significant predicting factor for DMFS ($P = 0.000$), but not for OS ($P = 0.460$) and RRFS ($P = 0.295$). Pairwise comparison in log-rank analysis showed that DMFS and OS had no significant difference between N1 and N2, and N2 and N3 (Figure 1B and D). For RRFS, all the adjacent N categories could not differ significantly from each other (Figure 1C).

We considered that Proposal A, which enrolled nodal MAD, cannot well predict the prognosis of NPC. Thus, we proposed that nodal MAD should be excluded, and N classification may be modified as follows (Proposal B): N0, no regional LN metastasis; N1, RLN involvement, and/or unilateral levels I, II, III, and/or Va; N2, bilateral levels I, II, III, and/or Va; and N3, levels IV, Vb, Vc. The 1197 patients were then classified into 4 groups accordingly (Figure 2A). Cox regression analysis indicated a significant prognostic value of our Proposal B for OS, RRFS, and DMFS (Table 4).

In log-rank analysis, N2 patients showed higher 5-year DMFS than N3 disease, but their difference showed no statistically significant in pairwise comparison ($P = 0.265$), as shown in Figure 2B. For 5-year RRFS, there were 98.8%, 96.0%, 91.8%, and 93.9% for N0, N1, N2, and N3, respectively (Figure 2C). The 5-year RRFS of N3 disease could not differ significantly from N1 and N2 patients in pairwise comparisons ($P = 0.526$ for N1 and N3, $P = 0.514$ for N2 and N3). Interestingly, we found that N3 patients had relatively higher 5-year RRFS than N2 group (93.9% vs 91.8%). For OS, N3 patients indicated relatively inferior survival than N2 patients, but also showed no statistically significance ($P = 0.673$, Figure 2D).

TABLE 3. Multivariate Analysis of Prognostic Value of Laterality and Nodal MAD for 722 Patients With Levels I, II, III, and Va Involvement

	DMFS		RRFS		OS	
Factor	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Laterality	1.572 (1.131–2.184)	0.007	1.808 (0.954–3.427)	0.069	1.663 (1.200–2.304)	0.002
Nodal MAD (≤6 vs >6 cm)	1.578 (0.821–3.033)	0.172	2.585 (0.894–7.474)	0.079	1.398 (0.725–2.695)	0.317
Laterality	1.479 (1.055–2.075)	0.023	1.668 (0.867–3.208)	0.125	1.536 (1.094–2.155)	0.013
Nodal MAD (≤3 vs 3–6 vs >6 cm)	1.321 (0.987–1.769)	0.061	1.610 (0.914–2.834)	0.099	1.326 (0.995–1.767)	0.054
Laterality	1.502 (1.072–2.104)	0.018	1.743 (0.908–3.347)	0.095	1.554 (1.110–2.175)	0.010
Nodal MAD (≤3 vs >3 cm)	1.320 (0.931–1.872)	0.119	1.481 (0.744–2.951)	0.264	1.373 (0.969–1.944)	0.074

CI = confidence interval, DMFS = distant metastasis-free survival, HR = hazard ratio, MAD = maximal axial diameter, OS = overall survival, RRFS = regional relapse-free survival.

DISCUSSION

The N classification of the 7th UICC/AJCC staging system of NPC was defined mainly depending on clinical palpation and landmarks, but not image information, which could not be suitable in precise radiotherapy era (ie, IMRT). In this study, we evaluated the prognostic value of different MRI-based nodal variables and proposed an N category purely based on MRI. Nodal level and laterality were found to be the only 2 variables that affect the prognosis significantly. Thus, we suggested that the N classification can be modified as follows: N0, no regional LN metastasis; N1, RLN involvement, and/or unilateral levels I,

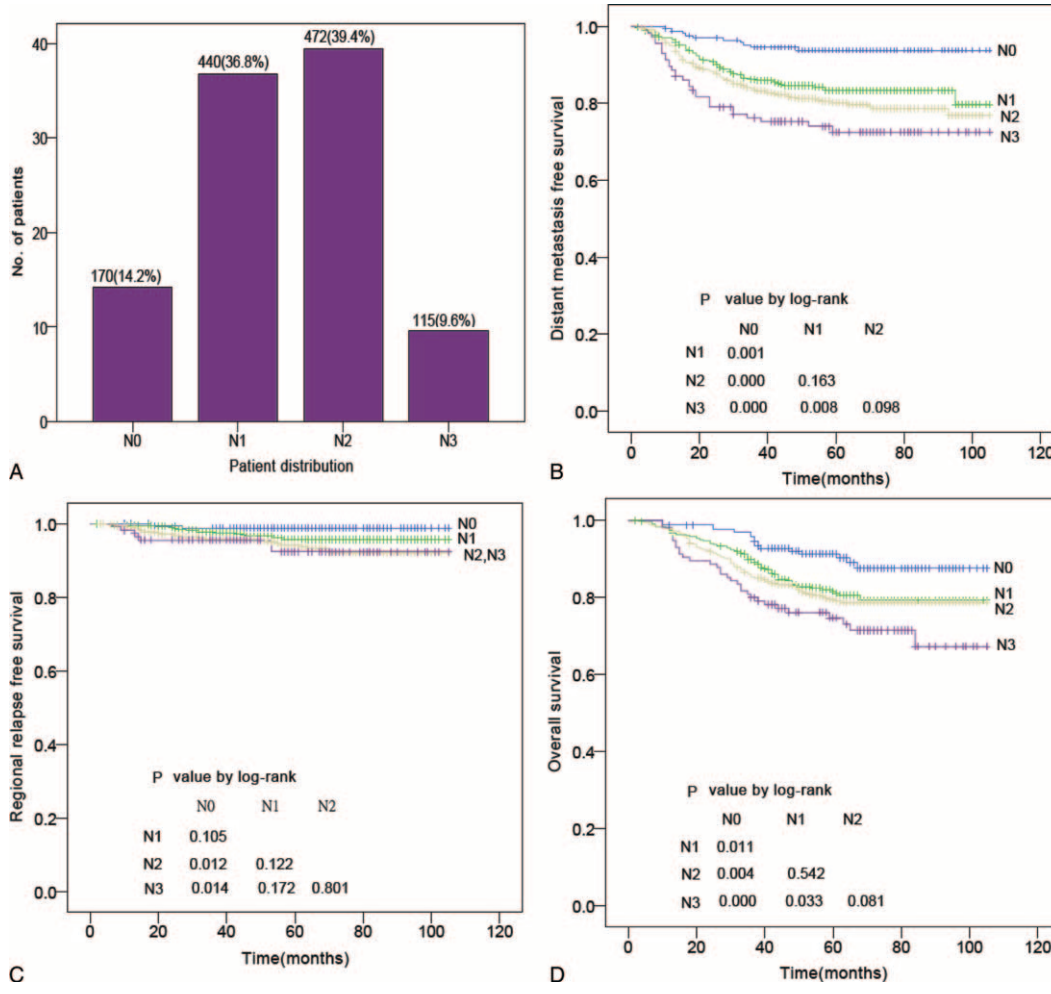

FIGURE 1. Proposal A. (A) N distribution. (B) Distant metastasis-free survival. (C) Regional relapse-free survival. (D) Overall survival.

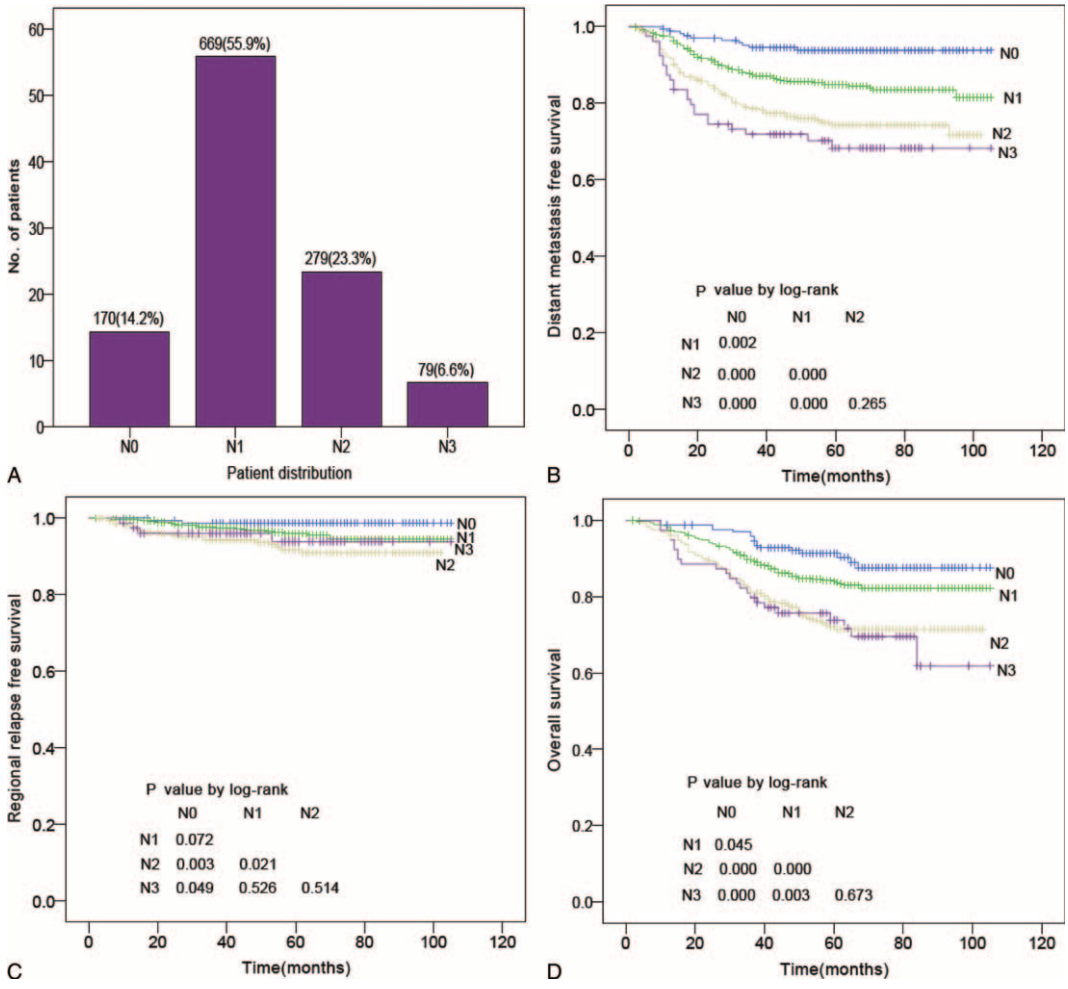

FIGURE 2. Proposal B. (A) N distribution. (B) Distant metastasis-free survival. (C) Regional relapse-free survival. (D) Overall survival.

II, III, and/or Va; N2, bilateral levels I, II, III, and/or Va; and N3, levels IV, Vb, Vc. Representative MRI imaging pictures depicting each N classification are shown in Figure 3; our proposal showed good predicting value, however, the difference of DMFS, RRFS, and OS between N2 and N3 patients showed no statistical significance, which may be because of the small sample sizes of N3 patients. Our results are of particular importance that we analyzed a relatively large cohort of patients treated by IMRT in endemic area, the proposed N classification is simple and practical and can be accomplished using MRI imaging in IMRT era.

Lymphatic spread in cervical nodal chain from NPC primary follows an orderly fashion, with a very low risk of 0.5% in skip nodal metastasis.[18,19] Nodal level was considered as the first important LN variables in the N classification in our series, as have been reported in other literatures.[6,11,12,20–23] Nodal level as depicted by MRI was highly predictive and may provide a more objective method for staging and treatment

TABLE 4. Multivariate Analysis of Potential Prognostic Factors for 1197 Patients

	DMFS		RRFS		OS	
Factor	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Sex	0.734 (0.513–1.050)	0.091	1.074 (0.571–2.021)	0.825	0.731 (0.515–1.039)	0.081
Age	1.384 (1.041–1.838)	0.025	0.844 (0.461–1.546)	0.583	2.587 (1.971–3.396)	0.000
T category	1.377 (1.194–1.588)	0.000	1.496 (1.118–2.001)	0.007	1.570 (1.363–1.809)	0.000
Chemotherapy	1.104 (1.902–3.013)	1.649	0.563 (0.239–1.329)	0.190	0.810 (0.525–1.248)	0.339
Proposed N category	1.680 (1.414–1.996)	0.000	1.705 (1.214–2.394)	0.002	1.595 (1.354–1.879)	0.000

CI = confidence interval, DMFS = distant metastasis-free survival, HR = hazard ratio, OS = overall survival, RRFS = regional relapse-free survival.

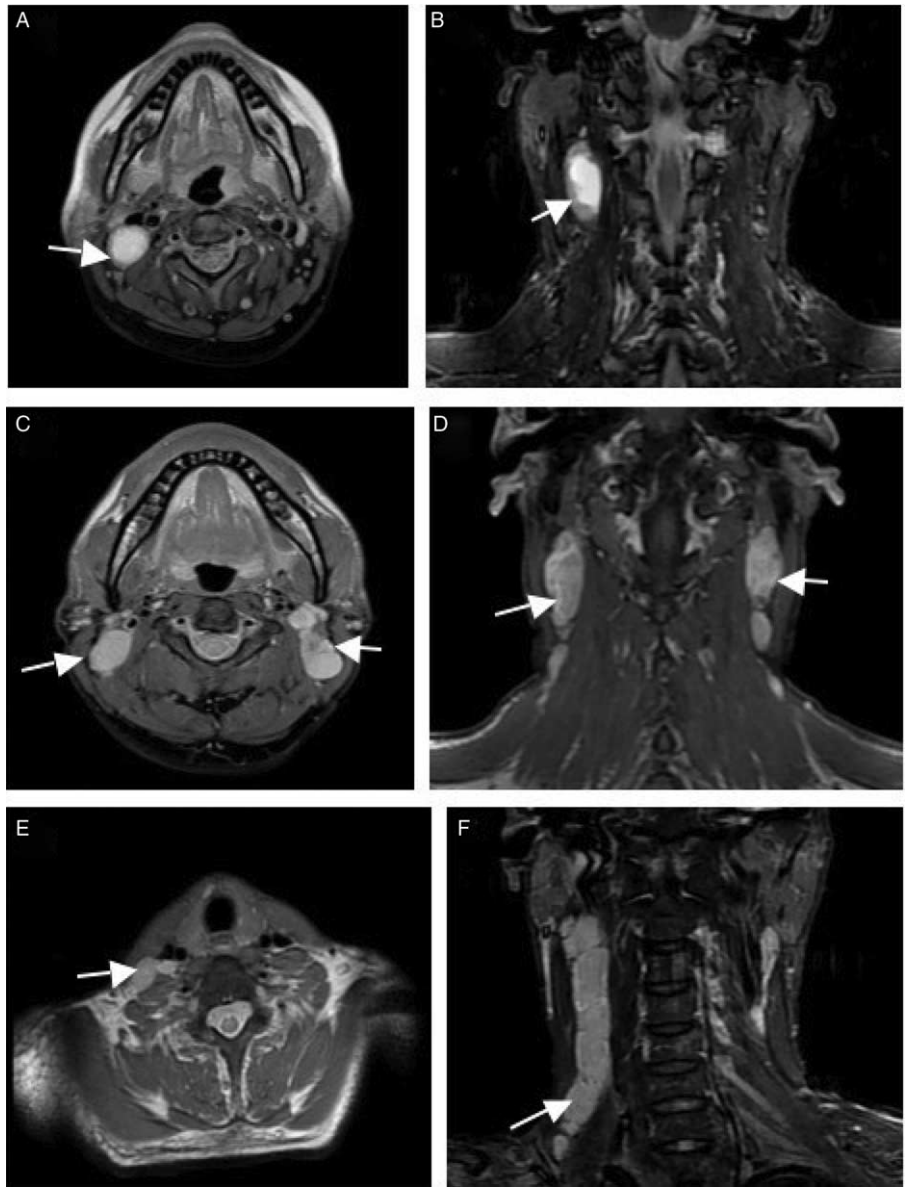

FIGURE 3. Representative MRI imaging pictures of three patients with N1 (A and B), N2 (C and D), and N3 (E and F). (A), (C), and (E) applied T2-weighted axial MRI scan; (B), (D), and (F) used coronal T2-weighted STIR scan. (A) and (B) showed lymph node involvement in right level III, with central necrosis; (C) and (D) demonstrated bilateral lymph nodes involvement in levels II (bilateral) and III (left); and (E) and (F) illustrated lymph nodes involvement in right levels II–IV. MRI = magnetic resonance imaging, STIR = short time inversion recovery.

planning.[7] The replacement of SCF by levels IV and Vb, which was defined by Som et al,[24] has been reported by Ng et al[5] as they described that the nodal areas of the lower neck (Ho's triangle) are actually the same as level IV and Vb regions. To be more accurate, the current study defined nodal level according to the 2013 International Consensus Guidelines[15] and replaced the lower neck (Ho's triangle) with levels IV, Vb, and Vc; we found this level classification to be very predictive, as has been reported by Yue et al.[12]

NPC is a nonsurgically treated tumor with frequent infiltration across the midline. Laterality was the second LN variables to be enrolled in the N classification in our series. The role to distinguish patients with different prognosis has been reported in many studies.[6,11,12,20–22] Our data demonstrated that patients with bilateral levels I, II, III, and Va involvement had a significant lower DMFS than unilateral involvement and, thus, was classified into 2 different N categories. Laterality of RLNs was not considered, since evidence from retrospective studies indicated that patients with RLNs alone have a risk of distant failure similar to N1 disease, regardless of its laterality.[17,25] Laterality of those with levels IV, Vb, and Vc involvement was not considered as well, since the proportion of this subgroup of patients was as low as no $>1\%$.

Nodal size was considered to be an important prognostic factor and be included in the UICC/AJCC staging system and the Chinese 2008 staging system. However, the significance attributed to size was most confusing with clinical palpation and the prognostic significance was controversial. Lee et al[20] found

that maximum LN size was independently significant in predicting survival, but other investigators could not confirm this finding.[21,22] Nodal MAD measured on MRI imaging is more accurate than palpation-based greatest dimension, since it might involve subcutaneous tissue and aggregated nodes.[11] However, as reported by Li et al,[11] nodal MAD failed to show any independent prognostic value in multivariate analysis. The authors explained that no measurements of longitudinal nodal diameter were made in the coronal or sagittal planes and the small number of patients with large LNs (ie, diameter >6 cm) may be the reasons of its insignificance. The present series measured nodal diameter of the upper LNs in all the 3 planes, including the longitudinal, sagittal, and coronal planes, with only 4.5% patients having a MAD larger than 6 cm; the predicting role of nodal MAD could not be confirmed as well. The results suggested that nodal MAD might not be a useful indicator in predicting the spread potential of NPC patients, whereas nodal level and laterality were the most important variables that should be considered. In view of this finding, our study suggested to reject nodal dimension from the N stage, and thus created a more simple and objective staging system.

ECS was defined as the presence of indistinct nodal margins, irregular nodal capsular enhancement, or infiltration into the adjacent fat or muscle.[16] The significance of ECS on prognosis and treatment has been reported in other head and neck cancers, including laryngeal and oral tongue cancer,[26,27] since the presence of ECS often leads to more extensive resection during surgical management and more radical postoperative external beam radiotherapy and adjuvant chemotherapy.[28] For NPC, MRI-identified ECS has been reported by Mao et al[23] to be an independent prognostic factor. However, NPC is a malignance that is mainly treated by radiotherapy; the identification of ECS for NPC was based on imaging but not pathology and therefore was more subjective than identification of other features of malignancy, and resulted in a wider variation in interpretation between different centers. The present series indicated a ECS incidence of 75.6%, which was much higher than that reported by Mao et al[23] and Li et al,[11] suggesting that the incidence of ECS varied between different centers. Moreover, MRI has a poor ability to detect ECS objectively; radiologic–pathologic studies reported a sensitivity of 74% to 80%, specificity of 72% to 78%, and accuracy of 76% to 86% for MRI.[29,30] Multivariate analysis showed that ECS failed to show any independent prognostic value after stratification by nodal level, age, sex, T classification, chemotherapy, and necrosis, and was excluded from the proposed N category, in agreement with the study by Li et al.[11]

The last LN variable demonstrated was central necrosis of LN, which is considered to be a late event in the biological evolution of tumor metastases within LNs, and represent the endpoint of severe, chronic hypoxia in tissues distal to functional blood vessels.[31] Although IMRT offers improved tumor target coverage, hypoxia in tumor not only makes the tissues less sensitive to radiotherapy but also induces the transcription of a variety of genes that increase tumor aggressiveness and promote tumor progression, when compared to nonhypoxic tumors.[32,33] However, the only 2 studies that evaluated the prognostic value of LN necrosis of NPC found no significant difference of treatment outcome between patients with and without LN necrosis.[11,23] The present studies showed that LN necrosis had no significant predicting value for DMFS, OS, and DFS, but for RRFS, those with LN necrosis had significant higher rate of regional failure. Considering that the prognostic significance of LN necrosis may mostly be attributed to the nodal level, since LN necrosis and nodal level had strong correlation (Table 3), LN necrosis was not considered in our proposed N classification.

Several literatures have proposed new N classifications based on MRI images for the upcoming 8th UICC/AJCC system.[6,9,11,12] The one reported by OuYang et al[9] was modified slightly based on TNMc2008; the only one revision they made was the classification of positive RLN as N1. ECS and nodal MAD remained as staging criteria in their proposal. The 2 studies reported by Ng et al[5] and Yue et al[12] both considered nodal MAD as a significant predicting variable, with the cutoff value be set at 6 cm; unfortunately, the significance of nodal MAD could not be proved in our series. The last literature reported by Li et al[11] proposed a new classification that is remarkably similar to Proposal B in our series. Both the 2 N category models disregard ECS and nodal MAD, only nodal level and laterality of the upper neck were included. The only difference existed between our proposal and Li et al's proposal was the classification of SCF; however, the replacement of SCF with levels IV, Vb, and Vc has been proved to be reasonable by Yue et al.[12] According to our data, N2 had higher DMFS than N3 patients, but the difference showed no significance, since N3 patients only accounted for 6.6% in our group; we considered this insignificance might be because of the small sample sizes of this subgroup of patients.

Several limitations should be addressed for our series. First, the retrospective nature of the study certainly served as an inherited and fundamental pitfall. Second, only 84.8% of patients with stages II to IVb received chemotherapy, and the choice of chemotherapy plans (ie, concurrent, neoadjuvant, adjuvant, or any combination) was at the discretion of the attending physicians. However, in IMRT era, the role of chemotherapy in terms of regimens and number of cycles has not been clearly demonstrated yet. Finally, our results are based on a single-center data, to develop a new staging system that is universally acceptable, and further verification by data from multicenter is warranted.

CONCLUSIONS

The information presented herein, with a large number of patients at a single institution receiving combined treatment, and the systemic staging workup by MRI offered valuable data for evaluating the prognostic value of different nodal variables. Nodal level and laterality, but not MAD, ECS, and necrosis, were considered to be significant predicting factors for NPC. The proposed N classification was proved to be powerfully predictive.

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