

The N Staging System in Nasopharyngeal Carcinoma with Radiation Therapy Oncology Group Guidelines for Lymph Node Levels Based on Magnetic Resonance Imaging

Yan-Ping Mao,^{1,3} Shao-Bo Liang,^{1,3} Li-Zhi Liu,^{1,2} Yong Chen,^{1,3} Ying Sun,^{1,3} Ling-Long Tang,^{1,3} Li Tian,^{1,2} Ai-Hua Lin,⁴ Meng-Zhong Liu,^{1,3} Li Li,^{1,2} and Jun Ma^{1,3}

Abstract Purpose: To evaluate the prognostic value of variables including nodal size, level, laterality, extra-nodal neoplastic spread (ENS), and necrosis in patients with nasopharyngeal carcinoma (NPC) and further explore the feasibility of an N-staging system using Radiation Therapy Oncology Group (RTOG) guidelines for lymph node levels based on magnetic resonance imaging (MRI). **Experimental Design:** The MRI scans of 924 patients with histologically diagnosed nondisseminated NPC were reviewed retrospectively. The distribution of the tumors was mapped using RTOG guidelines and laterality. The multiplicity of each tumor was calculated, as well as the size and status of ENS and the necrosis of individual nodes. **Results:** Nodal level, cervical lymph node laterality, and ENS were independent prognostic factors for disease failure and distant failure in multivariate analyses. There was no significant difference in the hazard ratios (HR) for distant failure between level II and retropharyngeal, level Ib, level V, or level III involvement, whereas patients with level IV and supraclavicular fossa involvement had a significant increase in HRs. The subsets that made up a given N stage group had similar HRs for distant failure. Both the HRs for disease failure and distant failure by the proposed N staging system between one stage and the next were statistically significant ($P < 0.05$). The survival curves of disease-free survival and distant metastasis-free survival for all subclassifications of N stage showed significant difference from the adjacent stage ($P < 0.05$). The overall distribution pattern of the proposed N staging was more equitable than that of the 6th American Joint Committee on Cancer N staging. **Conclusions:** Nodal variables including level, cervical lymph node laterality, and ENS are independent prognostic factors for NPC. The proposed N staging system of NPC using RTOG guidelines based on MRI is highly predictive and may provide a more objective method for staging NPCs.

Nasopharyngeal carcinoma (NPC) occurs with much greater frequency in southern China, northern Africa, and Alaska (1), and the incidence remains high among Chinese people who have immigrated to southeast Asia or North America (2). The

reported yearly incidence rate is 30 to 80 per 100,000 in southern China (3).

The tumor-node-metastasis staging system is crucial for predicting prognosis, guiding treatment strategy for different risk groups, and facilitating exchange of experience between oncology centers (4). However, a variety of N staging systems for NPC have been used in the past. The two most widely used systems, Ho's system and the International Union Against Cancer/American Joint Committee on Cancer (AJCC) system, each have their own merits in predicting outcome and guiding treatment (5). The 5th edition of the AJCC system for NPC, which merged the two, has been reported to be superior over the previous systems in terms of improved prognostication and a more balanced distribution between stages (6, 7). No further changes have been introduced into the current 6th edition of the AJCC N staging system (4).

However, N staging by the 6th edition of the AJCC system for NPC does have limitations. First, the N staging criteria mainly depend on clinical examination, which is by no means perfect (8). For example, palpation-determined nodal size differs among clinicians. In addition, the definition of the supraclavicular fossa (SCF), originally described by Ho, is based primarily on clinical landmarks, and there is no reliable way to

Authors' Affiliations: ¹State Key Laboratory of Oncology in Southern China; ²Imaging Diagnosis and Interventional Center, Cancer Center, ³Department of Radiation Oncology, Cancer Center, and ⁴Department of Medical Statistics and Epidemiology, School of Public Health, Sun Yat-Sen University, Guangzhou, Guangdong, People's Republic of China

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Note: Y-P. Mao and S-B. Liang contributed equally to this work.

Requests for reprints: Jun Ma, Department of Radiation Oncology, Cancer Center, Sun Yat-Sen University, 651 Dongfeng Road East, Guangzhou 510060, People's Republic of China. Phone: 86-20-87343469; Fax: 86-20-87343295; E-mail: majun2@mail.sysu.edu.cn.

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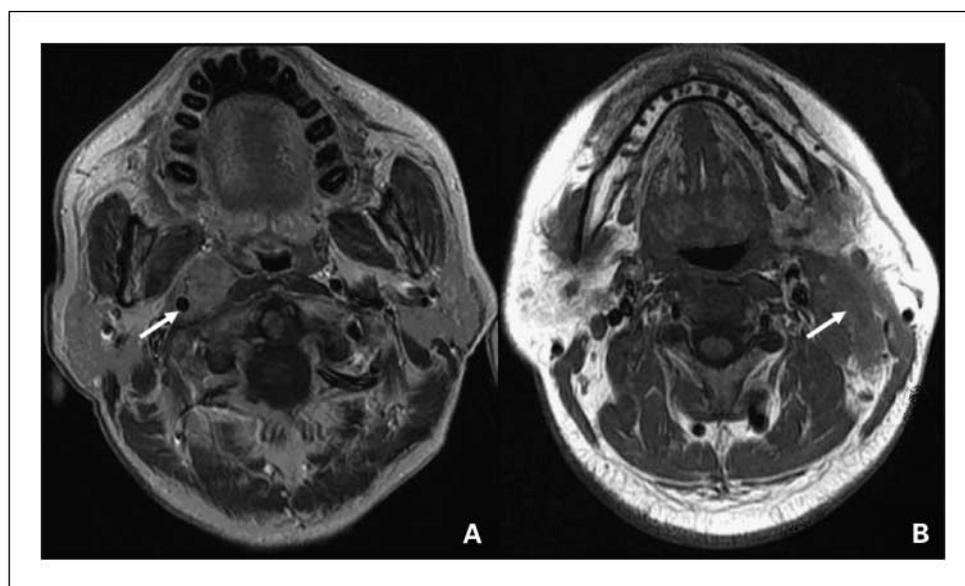


Fig. 1. MRI of patients with NPC shows nodal extracapsular spread. *A*, axial T1-weighted spin-echo contrast-enhanced MRI illustrates the lymph node with an irregular border and infiltration into the adjacent fat and the carotid sheath (*arrow*) in the right RP space. *B*, axial T1-weighted MRI illustrates the lymph node with an irregular border and infiltration into the adjacent fat and muscle (*arrow*) in the left level II.

define the SCF radiologically (9). In addition, the N categories used in patients with NPC are not in line with those used for other head and neck cancers, in which surgical regional lymph node levels are used to describe the location of lymph node metastases (4).

The development of diagnostic and therapeutic techniques revolutionized the management of NPC and improved its 5-year relative survival rates from 50% to 75%, approximately, over the past 10 years (7, 10–12). The higher sensitivity of magnetic resonance imaging (MRI) allows more accurate evaluation of the local tumor extension and the nodal spread pattern than computerized tomography (CT), thereby improving the accuracy of the classification and changing the treatment strategies for NPC (13, 14). Furthermore, the implementation of three-dimensional conformal radiotherapy (3-DCRT) and, particularly, intensity-modulated radiation therapy (IMRT) requires the delineation of the target volume in cross-sectional imaging and the standardization of the terminology and procedures for neck irradiation. Within this framework, a common set of recommendations, known as Radiation Therapy Oncology Group (RTOG) guidelines, for delineation of neck node levels was proposed by the major international cooperative groups in Europe and in North America (9, 15). The RTOG guidelines, translating as accurately as possible the surgical guidelines into radiologic guidelines, facilitate uniform delineation of the target volumes in the neck among radiation oncologists.

The present study evaluated the prognostic value of MRI-determined variables of neck nodes in patients with NPC to determine whether MRI of the neck can provide a more predictive scheme for nodal staging in NPC than the traditional AJCC criteria.

Materials and Methods

Patient characteristics. Between January 2003 and December 2004, 924 patients, with newly diagnosed, biopsy-proven, and nonmetastatic NPC presented at the Department of Radiation Oncology, Cancer Center, Sun Yat-Sen University, were entered into our study. There were

685 male patients and 239 female patients, with a male to female ratio of 2.9:1, and the median age was 45 y (range, 11–78 y). Histologically, 99% (915 of 924) of the patients had WHO type II or type III disease, 0.8% (7 of 924) had WHO type I disease, and the rest 0.2% (2 of 924) had adenocarcinoma. All patients were investigated by physical examination, fiber optic examination, chest X-ray, abdominal ultrasound, and imaging studies by magnetic resonance. All patients with N2–N3 disease underwent emission computed tomography, and 6.1% (56 of 924) patients underwent positron emission tomography-computed tomography (PET-CT). Medical records and imaging studies were analyzed retrospectively, and the patients were staged according to the 6th edition of the AJCC staging system. Retropharyngeal lymph node (RP-LN) involvement was assigned to N1 regardless of laterality (16). The distribution of stage group for the whole series was 4.9% (45 of 924) stage I, 27.1% (250 of 924) stage IIA–B, 39.2% (363 of 924) stage III, and 28.8% (266 of 924) stage IVA–B.

Imaging protocol. All patients underwent MRI with a 1.5-T system (Signa CV/i, General Electric Healthcare). The area from the suprasellar cistern to the inferior margin of the sternal end of clavicle was examined with a head and neck combined coil. According to the advice of reviewer, we had provided more variables for our MR sequences and prescribed as follow: T1-weighted fast spin-echo images in the axial, coronal, and sagittal planes (repetition time of 500–600 ms and echo time of 10–20 ms, two excitations, a 22-cm field of view, and a 320 × 224 frequency matrix) and T2-weighted fast spin-echo MR images in the axial plane (repetition time of 4,000–6,000 ms and echo time of 95–110 ms, one excitation, a 22-cm field of view, and a 320 × 224 frequency matrix) were obtained before injection of contrast material. After i.v. gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) injection at a dose of 0.1 mmol/kg of body weight, spin-echo T1-weighted axial and sagittal sequences and spin-echo T1-weighted fat-suppressed coronal sequences were done sequentially, with variables similar to those used before Gd-DTPA injection. Section thickness was 5 mm with a 1-mm interslice gap for the axial plane and 6 mm with a 1-mm interslice gap for the coronal and sagittal planes.

PET-CT integrates a four-slice helical CT scanner (Light Speed Plus, GE Medical System) and PET scanner (Advance Nxi, GE Medical System). The imaging and data acquisition were done on a combined PET-CT system (Discovery LS, GE Medical System). Single-photon emission computed tomography is equipped with high-resolution low-energy collimator (Sophia DSX).

Image assessment and criteria for lymph node metastasis. Two experienced radiologists separately evaluated the MR images. Any

Table 1. Correlation between size and other nodal variables

Variables	Size (cm)					P
	≤2	>2 to ≤3	>3 to ≤4	>4 to ≤5	>5	
Level						
RP, Ib, II, III, V	374 (95.7%)	236 (88.7%)	88 (85.4%)	11 (55.0%)	2 (33.3%)	<0.001
IV, SCF	17 (4.3%)	30 (11.3%)	15 (14.6%)	9 (45.0%)	4 (66.7%)	
Laterality						
Unilateral	205 (57.8%)	101 (44.0%)	39 (44.7%)	5 (25.0%)	1 (33.3%)	<0.001
Bilateral	186 (42.2%)	165 (56.0%)	64 (55.3%)	15 (75.0%)	5 (66.7%)	
Multiplicity						
Single	177 (45.3%)	36 (13.5%)	15 (14.6%)	0	0	<0.001
Multiple	214 (54.7%)	230 (86.5%)	88 (85.4%)	20 (100.0%)	6 (100.0%)	
ENS						
No	293 (74.9%)	133 (50.0%)	40 (38.8%)	5 (25.0%)	0	<0.001
Yes	98 (25.1%)	133 (50.0%)	63 (61.2%)	15 (75.0%)	6 (100.0%)	
Necrosis						
No	320 (81.8%)	187 (70.3%)	59 (57.3%)	8 (40.0%)	3 (50.0%)	<0.001
Yes	71 (18.2%)	79 (29.7%)	44 (42.7%)	12 (60.0%)	3 (50.0%)	

disagreements were resolved by consensus every 2 wk. Diagnostic criteria for metastatic lymphadenopathy include (a) lateral RP-LN with a minimal axial diameter (MID) in the largest plane of an individual node at least 5 mm and any node seen in the median RP group, lymph nodes with a MID of at least 11 mm in the jugulodigastric region and 10 mm for all other cervical nodes, except the RP group; (b) lymph nodes of any size with central necrosis or a contrast-enhancing rim; (c) nodal grouping, the presence of three or more contiguous and confluent lymph nodes, each of which should have a MID of 8 to 10 mm; and (d) lymph nodes of any size with extracapsular spread, the presence of indistinct nodal margins, irregular nodal capsular enhancement or infiltration into the adjacent fat or muscle (Fig. 1; ref. 17). In this study, the interobserver variation for the detection of extranodal neoplastic spread (ENS) showed a κ coefficient of 0.6087 (95% lower and upper confidence limit of 0.3906 and 0.8297, respectively).

The assignment of lymph node location was determined according to RTOG guidelines (8, 14). The following 11 nodal groups were assessed: RP, level Ia, level Ib, level IIa, level IIb, level III, level IV, level V, level VI, SCF, and retrostyloid. When nodes located in the border of two regions crossed different axial planes, the status of the nodes was recorded in both regions. When overlaps happened in the same axial plane, the assignment was done according to the main body of the node.

Treatment. All patients were treated with radiation therapy. Our policy was to cover the nasopharynx and the RP-LNs within the primary target in every radical attempt and to treat patients with gross lymphadenopathy with whole-neck irradiation. Most patients (773 of 924, 83.7%) were treated with conventional techniques, 12.7% (118 of 924) with IMRT, and 3.6% (33 of 924) with 3-DCRT. Details about the radiotherapy techniques carried out at the Cancer Center of Sun Yat-Sen University have been reported previously (16, 18, 19).

Most of the patients (517 of 629, 82.2%) with stage III or IV (classified as T3-T4 or N2-N3) received neoadjuvant, concomitant, or adjuvant chemotherapy, in conjunction with a platinum-based therapeutic clinical trial. When possible, salvage treatments (including afterloading, surgery, and chemotherapy) were provided in the event of documented relapse or when the disease persisted despite therapy.

Follow-up and statistical analysis. The follow-up duration was calculated from the first day of therapy to either the day of death or the day of last examination. The median follow-up for the whole group was 43 mo (range, 2-59 mo).

The Statistical Package for the Social Sciences version 11.0 (SPSS) was used. The actuarial rates were calculated by the Kaplan-Meier method, and the differences were compared with the log-rank test (20). All events were measured from the date of commencement of treatment. The

following end points (time to the first defining event) were assessed: overall survival, local relapse-free survival rate, nodal relapse-free survival rate, distant metastasis-free survival rate, and disease-free survival rate.

Multivariate analyses with the Cox proportional hazards model (21) were used as described previously (16). The Cox proportional hazards model was also used to test hazard consistency and hazard discrimination. Host factors (age and sex) and T classification were included as covariates in all tests. A two-tailed *P* value of <0.05 was considered statistically significant.

Results

Pattern and characteristic of nodal spread. The frequency of MRI-positive node was 85.1% (786 of 924). Of the 786 patients, RP and level IIb were the most frequently involved regions followed by level IIa, level III, level V, level IV, SCF, and level Ib, with the incidences of 86.4% (679 of 786), 65.0% (511 of 786), 42.7% (336 of 786), 28.8% (226 of 786), 11.1% (87 of 786), 7.1% (56 of 786), 3.9% (31 of 786), and 3.1% (24 of 786), respectively. No lymph node metastasis was found in level Ia, level VI, or the retrostyloid.

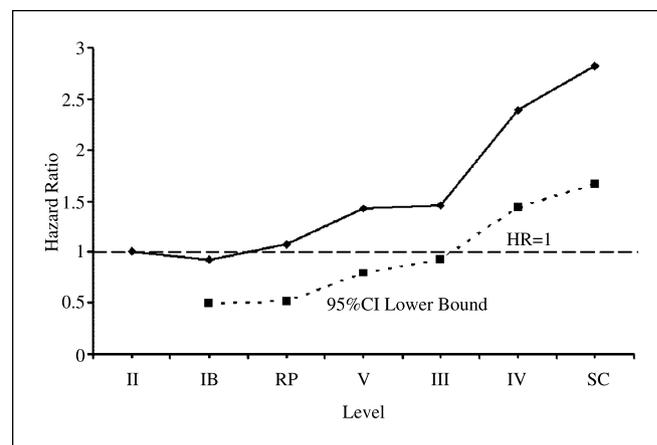


Fig. 2. HR of distant failure for different lymph node levels by RTOG guidelines (HR adjusted for age, gender, CLN laterality, ENS, and T-category by 6th AJCC system).

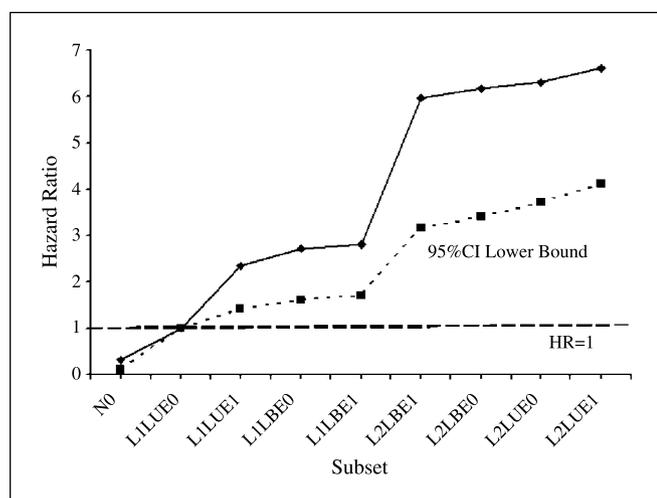


Fig. 3. HR of distant failure for different subsets (HR adjusted for age, gender, and T-category by 6th AJCC system).

Of the 786 patients whose nodes tested positive for NPC, bilateral node involvement was observed in 49.6% (390 of 786). Of these, 19.5% (153 of 786) were confined to the RP region and 55.3% (435 of 786) had lymphatic spread to bilateral cervical nodes. Multiple nodes were present in 71.0% (558 of 786) and necrosis was seen in 22.5% (208 of 786). ENS occurred in 39.8% (313 of 786). Of these, 9.8% (77 of 786) occurred in the RP-LN only, with 30.0% (236 of 786) in cervical nodes.

The mean values of the MID and maximal axial diameters (MAD) of the positive nodes were 14.5 ± 6.0 mm (range, 4-40 mm) and 21.1 ± 9.5 mm (range, 5-62 mm), respectively. Nodal size was statistically correlated with other variables, including level, laterality, multiplicity, ENS, and necrosis ($P < 0.001$; Table 1).

Prognostic value of different nodal variables. Altogether, 225 patients (24.4%) had experienced local-regional failure or distant metastases and 164 patients (17.7%) had died. The 3-year result for all patients was local relapse-free survival rate of 92.7%, nodal relapse-free survival rate of 97.2%, distant metastasis-free survival rate of 85.0%, and overall survival rate of 85.5%.

All MRI-determined nodal variables were analyzed by univariate analyses and multivariate analyses. The categorization criteria of nodal variables were defined as follows: size (1, ≤ 2 cm; 2, >2 cm to ≤ 3 cm; 3, >3 cm to ≤ 4 cm; 4, >4 cm to ≤ 5 cm; 5, >5 cm MAD), level (1, RP; 2, level Ib; 3, level II; 4, level III; 5, level V; 6, level IV; 7, SCF), cervical lymph node metastases (CLN)/RP-LN laterality (1, unilateral; 2, bilateral), multiplicity (1, single; 2, multiple), and ENS (1, no; 2, yes).

Univariate analysis revealed that all MRI-determined nodal variables, including size, level, multiplicity, ENS, necrosis, CLN laterality, and RLN laterality, were significant for distant failure and disease failure ($P < 0.01$) but insignificant for local failure and nodal failure.

Multivariate analysis was done to adjust for various prognostic factors. The following known important prognostic variables were included in the Cox proportional hazards model: age, gender, T-category, chemotherapy, radiation technique, and all nodal variables listed in univariate analysis above. Level, CLN laterality, and ENS all had such significant prognostic value for distant failure and disease failure in this model that they all should be included as categories in the proposed N staging system. The rest had no significant effect on any of the two end points.

Categorization criteria for the level of lymph node. The prognostic value of different lymph node levels was further analyzed to explore the optimal categorization criteria. There was no significant difference in hazards between level II [hazard ratio (HR), 1] and the RP region [HR, 1.07; 95% confidence interval (95% CI), 0.51-1.56] and level Ib (HR, 0.92; 95% CI, 0.49-1.44) and level V (HR, 1.37; 95% CI, 0.67-2.81) and level III (HR, 1.45; 95% CI, 0.87-3.08) involvement, whereas patients with level IV (HR, 2.06; 95% CI, 1.20-3.87) and SCF (HR, 2.82; 95% CI, 1.49-4.34) involvement had a significant increase in the HR (Fig. 2). Hence, the categorization criteria for lymph node level might be defined as RP region, level Ib, level II, level III, and level V versus level IV and SCF involvement.

Hazard consistency for different combinations of independent prognostic variables. The different combinations of independent prognostic variables, specifically the categorization criteria for level, CLN laterality, and ENS, were further analyzed to explore the proper subsets that comprise the N staging system. Any involvement in the RP region or levels Ib, II, III, or V was abbreviated as L₁, whereas SCF or level IV involvement was

Table 2. Effect of N stage classification and stage group on risk of distant failure and death

N stage	Distant failure		Death	
	HR* (95% CI)	P	HR* (95% CI)	P
Proposed system				
N0	1		1	
N1	1.523 (0.770-3.009)	0.226	1.556 (0.759-3.190)	0.228
N2	2.364 (1.208-4.626)	0.012	3.124 (1.552-6.286)	0.001
N3	5.834 (2.862-11.893)	0.000	7.193 (3.409-15.178)	0.000
6th AJCC system				
N0	1		1	
N1	1.496 (0.767-2.916)	0.237	1.667 (0.827-3.362)	0.153
N2	2.833 (1.417-5.664)	0.003	3.783 (1.851-7.732)	0.000
N3	5.560 (2.695-11.471)	0.000	6.820 (3.242-14.348)	0.000

*HR adjusted for age, gender, and T-category by 6th AJCC system.

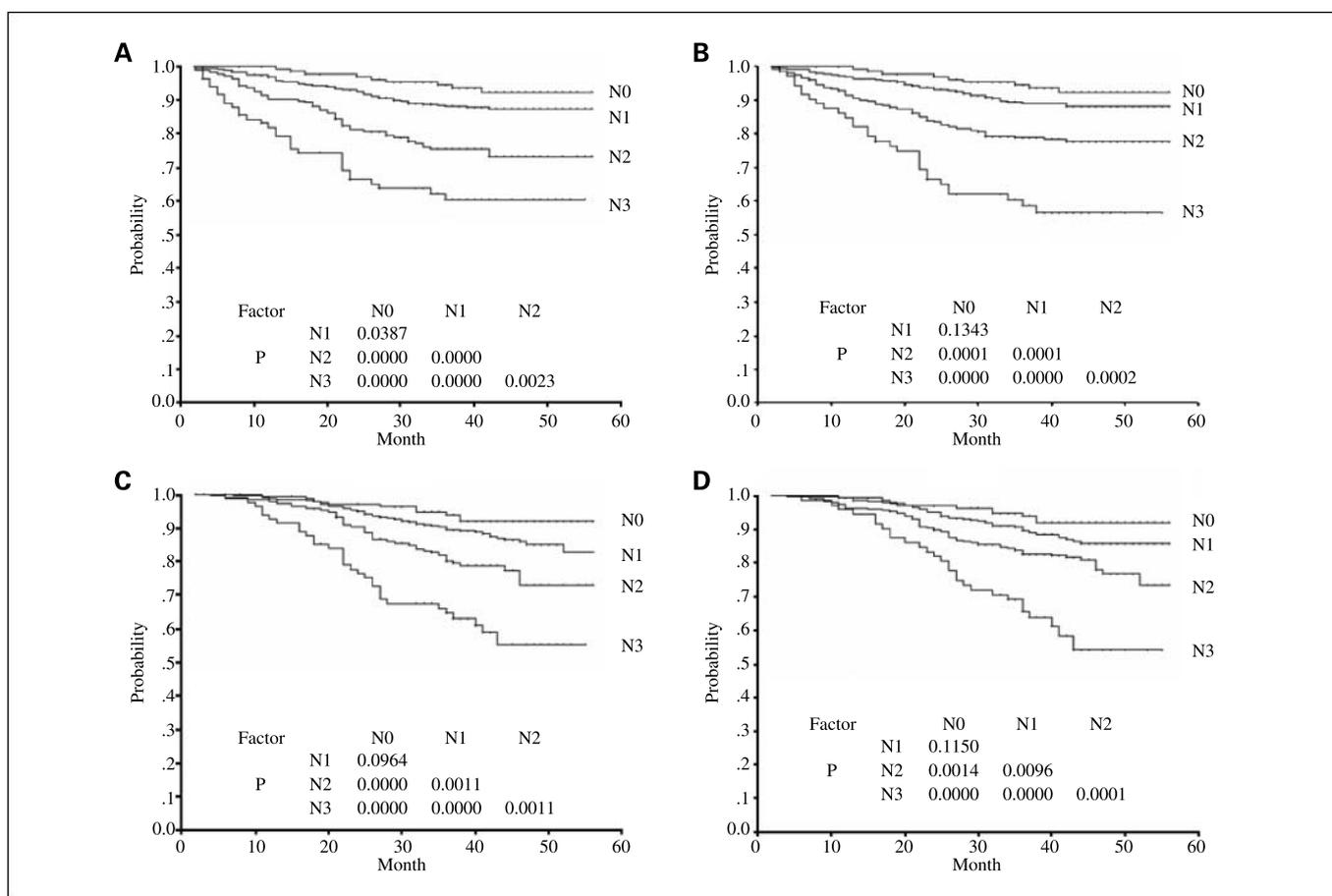


Fig. 4. Distant failure-free rate for different N stages as defined by the proposed system (A) and the 6th AJCC system (B). Overall survival rate for different N stages as defined by the proposed system (C) and the 6th AJCC system (D).

abbreviated as L_2 . CLN laterality, either unilateral or bilateral, was abbreviated as L_U or L_B , respectively. Nodes with or without ENS were classified as E_1 or E_0 , respectively.

All of the patients were divided into nine groups as follows: N0 (lymph node negative), $L_1L_U E_0$, $L_1L_U E_1$, $L_1L_B E_0$, $L_1L_B E_1$, $L_2L_U E_0$, $L_2L_U E_1$, $L_2L_B E_0$, and $L_2L_B E_1$. There were significant differences in HRs for distant failure between $L_1L_U E_0$ (HR, 1) and other subsets, with the lower boundary of the 95% CI at the baseline and upper boundary of the 95% CI for the N0 subset at 0.11. Interestingly, the HRs of $L_1L_U E_1$ (HR, 2.34), $L_1L_B E_0$ (HR, 2.72), and $L_1L_B E_1$ (HR, 2.81) were similar to each other, whereas those of $L_2L_U E_0$ (HR, 6.29), $L_2L_U E_1$ (HR, 6.78), $L_2L_B E_0$ (HR, 6.43), and $L_2L_B E_1$ (HR, 5.96) were similar to one another but significantly different from the others (Fig. 3). Therefore, we propose that the $L_1L_U E_0$ subset be defined as N1, the $L_1L_U E_1$, $L_1L_B E_0$, and $L_1L_B E_1$ subsets as N2, and the $L_2L_U E_0$, $L_2L_U E_1$, $L_2L_B E_0$, and $L_2L_B E_1$ subsets as N3.

The proposed N staging system. Our data therefore suggested that N staging system could be optimized by adopting the following set of variables and categorization criteria: N0, no regional lymph node metastasis; N1, unilateral level Ib, II, III, and V involvement, or RP-LN involvement, but without ENS; N2, bilateral level Ib, II, III, and V involvement, or with ENS; and N3, level IV, SCF involvement.

Hazard discrimination and balance for the proposed N staging system. The corresponding trends of HR for failures in

different groups are shown in Table 2. Correlation with distant failure and death was significant. Although the increases in risk between adjacent N stages were consistent in both of the systems, the total difference between N0 and N3 was slightly wider with the proposed system. This trend was further verified by plotting the long-term distant failure-free survival rate and overall survival rate for different N stages, as defined by the two different systems (Fig. 4).

By our system, 14.9% (138 of 924) of the patients in this study would have NPCs classified as N0, with 39.3% (363 of 924) as N1, 37.7% (348 of 924) as N2, and 8.1% (75 of 924) as N3. By the 6th AJCC N staging system, 14.9% (138 of 924) would be classified as N0, 55.4% (512 of 924) as N1, 20.6% (190 of 924) as N2, and 9.1% (84 of 924) as N3, with the largest portion of patients (55.4%) as N1. We could conclude that our proposed pattern is obviously less skewed than that of the 6th AJCC N staging system.

Discussion

Since the first classification system was described by Geist and Portman in 1952, different systems have been proposed for NPC (4, 22–27). Variables used for N staging include clinically palpable nodal size, level, multiplicity, laterality, and fixity. Several studies have focused on the correlation between the N staging criteria and the prognosis of NPC based on clinical

palpation; unfortunately, differences in clinicians and their characterization of palpated tumors have resulted in a chaotic diversity in prognosis (5, 10, 28). The introduction of new types of therapeutic interventions or new technologies may require modification of the classification and staging systems (4). Because MRI is such an important tool for pretreatment staging assignment and treatment program determination (4), it is urgent to reevaluate the prognostic value of MRI-determined nodal variables for NPC.

Size. The significance attributed to size was most confusing with clinical palpation. Lee and coworkers (5) found that maximum lymph node size was independently significant in predicting survival, but both Heng et al. (10) and Teo et al. (28) found that maximum lymph node size was not a significant prognostic factor. In our study, MAD was measured more accurately than palpation-based greatest dimension, which might contain the fusion of multiple nodes. In addition, the MAD of the lymph node was significantly interrelated with not only level but also ENS. It has been reported that 23% of metastatic nodes measuring <2 cm, ~50% of those measuring 2 to 3 cm, and 75% of those measuring >3 cm have ENS in patients with primary squamous cell carcinoma of the head and neck (29). Our data showed that ENS presented in 27.2% of patients with nodes measuring <2 cm, 55.8% of those measuring more than 3 to 4 cm, and 100% of those measuring >5 cm. Therefore, the significant effect of nodal size in predicting survival seen in univariate, but not in multivariate analysis, could be accounted for by differences in level and ENS, rather than size.

Extranodal neoplastic spread. The importance of ENS is not only as a diagnostic criterion for a malignant node but also because of its effect on prognosis and treatment in head and neck cancers (30, 31). The presence of ENS often leads to more extensive resection during surgical management and more radical postoperative external beam radiotherapy and adjuvant chemotherapy (4). However, the prognostic value of ENS for NPC has not been reported yet. One reason may be that the identification of ENS for NPC was based on imaging but not pathology and therefore was more subjective than identification of other features of malignancy, such as nodal necrosis, and resulted in a wider variation in interpretation. However, interobserver variation showed no significant difference for the identification of ENS using MRI (32). In the present study, a moderate agreement also was found between observers for the diagnosis of ENS (κ coefficient of 0.6077). Another reason for not using ENS in NPC prognosis may have been worries about the overall accuracy of MRI for detecting ENS. Objectively, radiologic-pathologic studies reported a sensitivity of 74% to 80%, specificity of 72% to 78%, and accuracy of 76% to 86% for MRI (32, 33). Although the sensitivity and specificity for the detection of ENS should be improved in the future, our data strongly suggested that it is feasible to identify ENS using MRI for NPC and that ignoring ENS results in a significant loss of predictive power.

Level. For any tumor, accurate evaluation of the extent of intrusion into the surrounding tissue improves the prognostic accuracy of the N staging system. Although Ho's level was based primarily on clinical landmarks, SCF involvement was strongly significant in predicting survival for NPC (5, 10, 28). RTOG guidelines, defining less ambiguous boundaries than previously described (15), may be important in the standardi-

zation of both delineation of target volume and staging. According to the HRs for distant failure, our study found that the optimal categorization criteria were involvement in the RP region, level Ib, level II, level III, and level V versus level IV and SCF involvement. Actually, the level IV and SCF involvement determined by RTOG guidelines is very similar to the SCF involvement described by Ho, but the RTOG guidelines are more objective (9).

Retropharyngeal lymph node. As RP-LN is well documented to be one of the first nodal stations for regional spread of NPC (34), it should be included in the N staging system. With a MID of at least 5 mm and nodal feature of necrosis as the criteria for RP-LN metastasis (16) based on MRI, our study showed that there is no significant difference in prognosis between bilateral RP-LN and unilateral RP-LN involvement, which differs from what is seen for cervical nodes. The HR of distant failure for RP-LN metastasis was similar to level II involvement. Hence, it is reasonable to classify a node as depending on the ENS status. Compared with the 6th N staging system, 16.1% (149 of 924) patients were classified as N2 by the proposed system because of ENS. Of those, 2.4% (22 of 924) had ENS in the RP-LN only, which shows the balanced overall distribution pattern of the proposed N staging system.

A good staging classification system should meet the following criteria (35): (a) survival rates should differ among the groups (hazard discrimination); (b) the subsets defined by T, N, and M that make up a given group should have similar survival rates (hazard consistency); (c) the patient distribution across the groups should be balanced; and (d) the cure prediction should be high (outcome prediction). Based on solid data with full statistical justification, and all analyses being duly adjusted for related variables to minimize potential biases, the proposed N staging system was proved to be powerfully predictive. More importantly, it meets the requirement of diagnostic development, introducing the MRI-determined prognostic variables to an N staging system for NPC for the first time.

Curtin et al. (36) assume that technology will continue to evolve and thus have an influence on the effect of assessment. For example, fast spin-echo imaging and fat suppression represented important advances in MRI of the head and neck. Findings in a separate study indicate that the visibility of nodes was improved with fast spin-echo T2-weighted imaging (37). It is therefore important to discuss MRI technology. In our imaging protocol, MR sequences were done on T1-weighted fast spin-echo images in the axial, coronal, and sagittal planes; T2-weighted fast spin-echo MR images in the axial plane; and spin-echo T1-weighted axial and sagittal sequences, as well as spin-echo fat-suppressed coronal sequences, after injection of Gd-DTPA. Thus, our data provide accurate information for evaluating nodal metastasis and the N staging of NPC.

The information presented herein, with a large number of patients at a single institution receiving combined treatment, and the systemic staging workup by more sensitive and specific imaging technologies offered valuable data for evaluating the prognostic value of different nodal variables. However, it should be noted that only 12.7% (118 of 924) of patients were treated with IMRT and 3.6% (33 of 924) with 3-DCRT because of resource limitations. However, included as a covariate, radiation technique was not an independent prognostic factor for both distant failure and disease failure in multivariate

analyses. Although 3-DCRT/IMRT techniques were reported to provide excellent local-regional control for NPC, distant metastases are still the main cause of failure (19, 38). Furthermore, there is a very close correlation between N staging and distant failure. The positive effect of 3-DCRT/IMRT on prognosis might have been shielded by the N staging, which might account for this result. Thus, inaccuracy due to radiation techniques was minimal in our investigation.

Conclusion

MRI-determined nodal variables, including level, CLN laterality, and ENS, are independent prognostic factors for NPC. The proposed N staging system with RTOG guidelines

based on MRI is powerfully predictive. Although we await large-scale validation from other centers, this proposed system is attractive for several reasons: our data, with a large number of patients at a single institution, are fairly representative of those treated currently; the definition of N staging criteria with RTOG guidelines for lymph node levels based on MRI avoids the ambiguity in determining level, thereby leading to a more consistent assessment; and incorporating ENS into the N staging system for NPC increases the predictive power.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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