Retropharyngeal Lymph Node Metastasis in Nasopharyngeal Carcinoma: Prognostic Value and Staging Categories

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Abstract

Purpose: To investigate the incidence, prognostic value, and staging categories of retropharyngeal lymph node (RLN) metastasis in nasopharyngeal carcinoma (NPC).

Experimental Design: We did a retrospective review of the data from 749 biopsy-proved non-metastatic NPC patients. All patients had undergone contrast-enhanced computed tomography and had radiotherapy as their primary treatment.

Results: The incidence of RLN metastasis was 51.5%. After adjusting for tumor (T) and node (N) classifications, a borderline significant difference of distant metastasis-free survival (DMFS) rates was observed between patients with or without RLN metastasis. In N_0 disease, the presence of RLN metastasis was a significant independent predictor for overall survival (OS), loco-regional relapse-free survival, and DMFS in multivariate Cox modeling analysis. No significant difference was observed in all end points between patients with unilateral and bilateral RLN metastasis. The hazard ratios of death and distant failure for N_0 with RLN metastasis were similar to N_1. The survival curve of OS and DMFS for N_0 disease with RLN metastasis had approximated that of N_1 disease. The survival curve of OS for T_1 disease with RLN metastasis was approximately the same as T_2 disease. However, the survival curve of DMFS for T_1 disease with RLN metastasis was approximately the same as in T_3 disease.

Conclusions: RLN metastasis has a tendency to affect the DMFS rates of patients with NPC. Retropharyngeal node involvement has a negative effect on the prognosis of N_0 disease. RLN metastasis should be classified as N_1.

Nasopharyngeal carcinoma (NPC) is endemic in certain regions, especially in Southeast Asia. The incidence is 30 to 80 of 100,000 people per year in Southern China (1).

NPC has a higher incidence of cervical lymph node metastasis compared with other head and neck cancers. There is a well-developed network of lymphatics in the nasopharynx (2). The retropharyngeal lymph node (RLN) is regarded as the most common lymph node involved in NPC (3); RLNs are not amenable to evaluation using manual palpation. Consequently, the diagnosis of enlarged RLNs in patients with NPC is made on the basis of imaging examinations, such as X-ray computed tomography (CT), positron emission tomography PET, and magnetic resonance imaging (MRI). According to several recent studies, the frequency of RLN metastasis is high (4–6), but the prognostic value of RLN metastasis in patients with NPC is controversial (7–9).

The fifth edition of the tumor-node-metastasis (TNM) classification published by the Unio Internationale Contra Cancrum (UICC) and American Joint Committee on Cancer (AJCC) in 1997 is a universally accepted staging system (10, 11). No additional changes (except addition of the term masticator space as a synonym for infratemporal fossa) have been introduced to the current UICC/AJCC sixth edition (12). Because the RLN involvement criteria are ambiguous in the published staging systems, classification of RLN varies among different centers (13). The goal of this study was to evaluate the prognostic value of RLN involvement in NPC based on a large sample and to provide references for defining the categories of RLN involvement in the future UICC/AJCC staging system.

Materials and Methods

Patient characteristics. This was a retrospective study of patients with biopsy-proved NPC without metastasis referred to the authors' hospital from January 1999 to December 1999. A total of 749 patients were included in this study. There were 543 male patients and 206 female patients, with a male-female ratio of 2.6:1, and the median age was 46 years (range, 13–74 years). Histologically, 10% of the patients

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Table 1. Relationship between RLN metastasis and T and N classification and overall stage

RLN	No. patients (column %)			
T classification	T_1	T_2	T_3	T_4
Negative	77 (77)	132 (41.5)	82 (55.0)	72 (39.6)
Positive	23 (23)	186 (58.5)	67 (45.0)	110 (60.4)
N classification	N_0	N_1	N_2	N_3
Negative	141 (65.9)	141 (47.3)	48 (30.8)	33 (40.7)
Positive	73 (34.1)	157 (52.7)	108 (69.2)	48 (59.3)
Overall stage	Stage I	Stage II	Stage III	Stage IV
Negative	30 (90.9)	136 (52.3)	103 (46.2)	94 (40.3)
Positive	3 (9.1)	124 (47.7)	120 (53.8)	139 (57.9)

NOTE: Using χ^2 test: $P < 0.001$ for RLN versus T_1 and T_2; $P = 0.006$ for RLN versus T_2 and T_3; $P = 0.005$ for RLN versus T_3 and T_4; $P < 0.001$ for RLN versus T_1 and $T_{2\text{-}4}$; $P < 0.001$ for RLN versus N_0 and N_1; $P = 0.001$ for RLN versus N_1 and N_2; $P = 0.125$ for RLN versus N_2 and N_3; $P < 0.001$ for RLN versus N_0 and $N_{1\text{-}3}$; $P < 0.001$ for RLN versus stage I and stages II-IV.
Abbreviation: RLN, RLN metastasis.

had WHO type II disease, 89% had WHO type III disease, and the rest (1%) had WHO type I disease.

Patients were grouped according to the UICC/AJCC 1997 staging system. RLN involvement was disregarded in determining N and T category. All patients had undergone fiber optic endoscopic biopsy of the nasopharynx and contrast-enhanced CT of the nasopharynx and neck during staging work-up. Regional disease was assessed by clinical examination combined with the CT findings, and in the case of a discrepancy between the CT and initial clinical findings, upgrading was allowed. Cranial nerve palsy was assessed clinically.

CT technique and criteria for RLN metastasis and other cervical lymph node. All patients underwent contrast-enhanced CT. The CT studies were done with an Elscint Twin Flash helical scanner (Haifa, Israel) before treatment. Contiguous axial CT scans at 5-mm intervals were obtained in a plane parallel to the hard palate from the supracellar cistern to the C3 vertebra, followed by axial scans at 8-mm intervals to the supraclavicular fossa. CT scans were done after an i.v. injection (100 mL bolus at 2 mL/s) of contrast agents (Ultravist, Schering, Guangzhou, China; or Omnipaque, Nycomed Amersham, Shanghai, China). The images were taken using soft tissue and bone algorithms and filmed in the respective window settings.

Two radiologists specializing in head and neck cancers separately evaluated all scans. Any disagreements were resolved by consensus. In this study, the RLN group included the medial and lateral RLNs. Diagnostic CT criteria for metastatic lymphadenopathy includes (*a*) lateral retropharyngeal nodes with a minimal axial dimension of ≥5 mm and any node seen in the median retropharyngeal group, lymph nodes with a minimal axial diameter of ≥11 mm in the diagastric region and 10 mm for all other cervical nodes, except the retropharyngeal group; (*b*) lymph nodes of any size with central necrosis or a contrast-enhancing rim; and (*c*) nodal grouping, the presence of three or more contiguous and confluent lymph nodes, each of which should have a minimal axial diameter of 8 to 10 mm (6, 14–16). Furthermore, the parapharyngeal space involvement was delineated according to the degree of extension by the Sham line (17). Grade 1, grade 2, and grade 3 denoted extensions beyond the Sham line I, Sham line II, and Sham line III, respectively.

Treatment. All patients were treated by definitive intent radiation therapy. A total of 708 patients were treated with two lateral-opposing faciocervical portals to irradiate the nasopharynx and the upper neck in one volume followed by the shrinking-field technique (two lateral-opposed facial fields) to avoid excessive irradiation of the spinal cord. The remaining 41 patients with small tumors confined to the nasopharynx underwent a technique consisting of two lateral-opposed facial fields in the whole course of treatment. An anterior cervical field was used to treat the whole neck with a laryngeal block. The accumulated radiation doses were 68 to 70 Gy to the primary tumor, 60 to 62 Gy to the involved areas of the neck, and 50 Gy to the uninvolved areas.

Booster portal was done if necessary. Different radiation energies, including megavoltage photons (6 MV or cobalt-60) and electrons, were used. In cases with nasal or ethmoidal involvement, an anterior facial electron field was added. Patients with bulky parapharyngeal disease were boosted with a "parapharyngeal boost technique," as described by Tsao (18). A boost dose of 10 to 14 Gy per five to seven fractions was delivered to the skull base in patients with involvement of the skull base and intracranial extension. Intracavitary afterloading treatment with iridium-192 was done for local persistence 2 to 3 weeks after external radiotherapy (20–24 Gy per four to five fractions per 2 weeks to 1 cm above the midpoint of the iridium-192 source). Any palpable residual nodes after external radiotherapy were boosted to 70 Gy at the 90% isodose level with an electron field of 9 to 12 MeV. Whenever possible, salvage treatments were given to patients after documented relapse or when disease was persistent.

A total of 160 patients with local or regional advanced disease (classified as T_3-T_4 or N_2-N_3) received neoadjuvant, concomitant, or adjuvant chemotherapy, in conjunction with a platinum-based therapeutic clinical trial.

Follow-up and statistical analysis. A total of 97%, 94%, and 90% of patients had a complete follow up at 1 year, 3 years, and 5 years, respectively. The follow-up duration was calculated from the first day of radiation therapy to either the day of death or the day of last examination. The median follow up for the whole group was 62 months (range, 3-73 months).

SPSS 11.0 statistical software was used to determine statistical significance. The incidences of RLN metastasis in patients with different T and N classifications and overall stages were compared and analyzed using the χ^2 test.

All events were measured from the date of commencement of radiotherapy. The actuarial rates were calculated by the Kaplan-Meier

Table 2. Survival by RLN metastasis

	RLN (+)	RLN (−)	*P* value	*P* value (adjusting for T and N classification)
5-y OS	58.7%	72.2%	<0.001	0.118
5-y FDMS	75.0%	84.6%	<0.001	0.079
5-y LRRFS	77.9%	82.4%	0.173	

Table 3. Summary of multivariate analysis of prognostic factors in NPC patients

End point	Variable	*B*	*P* value	Exp(*B*)	95% CI for Exp(*B*)
OS	Gender	0.609	<0.001	1.921	1.5010-2.459
	Age (>50 y)	0.653	<0.001	1.839	1.322-2.557
	Grade 2/3 PPS	0.511	<0.001	1.667	1.266-2.194
	Intracranial extension	0.560	0.004	1.751	1.200-2.553
	Paranasal sinuses	0.329	0.055	1.389	0.993-1.942
	Laterality of LN	0.383	<0.001	1.466	1.197-1.796
	Location of LN	0.208	0.002	1.231	1.076-1.409
	Cranial nerve	0.233	0.041	1.262	1.009-1.578
	RLN			NS	
	Chemotherapy			NS	
Distant failure	Gender	0.887	<0.001	2.429	1.476-3.997
	Age (>50 y)	0.373	0.032	1.452	1.033-2.041
	Grade 2/3 PPS	0.428	0.020	1.534	1.070-2.197
	Intracranial extension	0.684	0.001	1.981	1.318-2.997
	Laterality of LN	0.333	0.024	1.395	1.047-1.862
	Location of LN	0.360	<0.001	1.433	1.211-1.696
	RLN	0.353	0.053	1.424	0.995-2.036
	Chemotherapy			NS	

Abbreviations: PPS, parapharyngeal extension; 95% CI, 95% confidence interval; LN, lymph node.

method (19), and the differences were compared with the log-rank test. The following end points (time to the first defining event) were assessed: overall survival (OS), the loco-regional relapse-free survival (LRRFS), and distant metastasis-free survival (DMFS). These end points were analyzed and compared in patients with and without RLN metastasis.

Multivariate analyses with the Cox proportional hazards model were used to test the independent significance by backward elimination of insignificant explanatory variables (20). The Cox proportional hazards model was also used to test the hazard consistency and hazard discrimination. Host factors (age and sex) were included as covariates in all tests. In addition, the T classification was included as a covariable in the analysis of N classification.

The hazard consistency and hazard discrimination were compared when RLN metastasis was classified as N_1 and T_{2b}.

A two-tailed P value of <0.05 was considered statistically significant.

Results

Incidence of RLN metastasis. In patients, RLN metastasis includes the medial and lateral nodes; however, only the lateral RLNs were detected in the current study. The incidence of RLN metastasis in this study was 51.5% (386 of 749 patients). The mean values of the minimal axial diameter of the positive nodes were 11.53 $\pm$ 4.01 mm (range, 5-25 mm). A higher incidence of metastatic RLNs was found when cervical lymph node metastasis was present (χ^2 = 36.414, P < 0.001). The incidence of metastatic RLNs in patients with unilateral cervical lymph node metastasis was lower than in patients with bilateral cervical lymph node metastasis (52.5% versus 67.9%, χ^2 = 11.581, P = 0.001).

The incidences of RLN metastasis in different T and N classifications are summarized in Table 1. A higher incidence of RLN involvement was found in the 1997 UICC/AJCC staging system designated categories: T_2 to T_4 disease compared with T_1 disease and N_1 to N_3 disease compared with N_0 disease, and in stages II to IV compared with stage I. These differences are statistically significant (χ^2 = 15.869, P < 0.001; χ^2 = 36.414, P < 0.001; χ^2 = 24.900, P < 0.001, respectively). The incidence of metastatic RLNs in N_1 patients is lower than in N_2 patients (χ^2 = 11.537, P = 0.001).

Table 4. Summary of multivariate analysis of prognostic factors in patients with N_0 disease

Endpoint	Factor	*B*	*P* value	Exp(*B*)	95%CI for Exp(*B*)
Death	Sex	0.609	0.097	1.838	0.896-3.773
	Age (>50 y)	1.021	0.001	2.777	1.518-5.078
	Grade 2/3 PPS	0.718	0.048	2.050	1.006-4.178
	Intracranial extension	1.069	0.002	2.913	1.477-5.745
	Cranial base	0.902	0.035	2.464	1.067-5.687
	RLN	0.853	0.007	2.347	1.264-4.356
Distant failure	Sex	1.352	0.072	3.867	0.885-16.902
	Cranial base	1.526	0.007	1.424	0.995-2.036
	RLN	1.104	0.023	3.015	1.161-7.833
Local failure	Age (>50 y)	0.950	0.015	2.586	1.201-5.570
	Cranial base	0.954	0.046	2.597	1.019-6.618
	Intracranial extension	1.164	0.009	3.202	1.340-7.653
	RLN	1.007	0.008	2.736	1.302-5.570

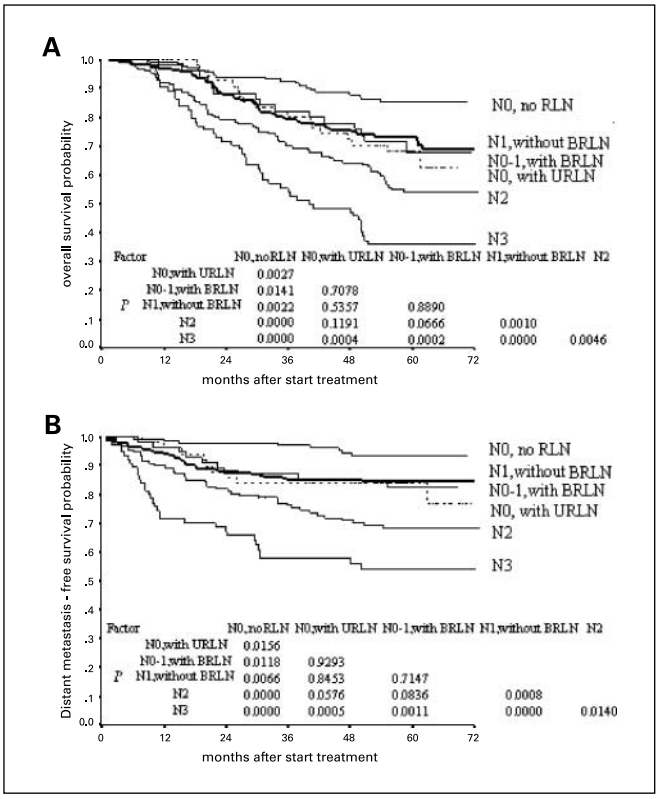

Fig. 1. OS probability (*A*) and DMFS probability (*B*) according to AJCC/UICC N classification. N_0 and N_1 patients were divided into four groups: N_0 disease without RLN metastasis, N_0 disease with URLN metastasis, N_1 disease without BRLN metastasis, and N_{0-1} patients with BRLN metastasis.

Prognosis. The treatment outcome of patients with and without RLN metastasis is compared in Table 2. Significant differences were observed in OS (58.7% versus 72.2%, $P < 0.001$) and DMFS (75.0% versus 84.6%, $P < 0.001$), with better rates occurring in patients without RLN metastasis. No significant difference was observed in LRRFS (77.9% versus 82.4%, $P = 0.173$). After adjusting for T and N classification, a marginal significant difference in DMFS was observed ($P = 0.079$). Multivariate analysis was done to adjust for various prognostic factors. The following variables were included in the Cox proportional hazards model by backward elimination of insignificant explanatory variables: age (≤50 years versus >50 years), gender, nasal fossa, paranasopharyngeal space (grade 0/1 versus grade 2/3; ref. 17), oropharyngeal extension, hypopharyngeal extension, infratemporal fossa extension, RLN metastasis, base of skull erosion, pterygoprocess zone, paranasal sinus extension, cranial nerve palsy/intracranial extension, laterality of cervical lymph node, greatest diameter of cervical lymph node (≤60 mm versus >60 mm), Ho's location (21) of cervical lymph nodes, and chemotherapy. The variables in the equation are summarized in Table 3.

RLN metastases was not of prognostic significance in OS but were marginally significant in DMFS. Chemotherapy was not significant for OS or DMFS. In N_0 disease, significant differences were observed in OS, DMFS, and LRRFS ($P = 0.002$, $P = 0.02$, and $P = 0.01$, respectively), and better rates were observed in patients without RLN metastasis. The presence of RLN metastases was a significant independent predictor for OS, LRRFS, and DMFS, as shown by multivariate analysis ($P = 0.007$, $P = 0.023$, and $P = 0.008$, respectively; Table 4). No significant differences were observed in OS, DMFS, and LRRFS between patients with unilateral RLN (URLN) and bilateral RLN (BRLN) metastasis ($P = 0.511$, $P = 0.190$, and $P = 0.132$, respectively).

Hazard consistency and hazard discrimination. We divided N_0 and N_1 patients into four groups: N_0 disease without RLN metastasis, N_0 disease with URLN metastasis, N_1 disease without BRLN metastasis, and N_{0-1} patients with BRLN metastasis. The survival curves for the different N subsets are shown in Fig. 1. We found no significant differences in OS and DMFS between N_1 patients without BRLN and N_0 patients with URLN ($P = 0.536$ and $P = 0.845$), N_1 patients without BRLN and N_{0-1} patients with BRLN ($P = 0.889$ and $P = 0.715$), and N_0 patients with URLN and N_{0-1} patients with BRLN ($P = 0.708$ and $P = 0.924$). Conversely, the difference in OS and DMFS between N_{0-1} patients with BRLN and N_2 patients was very close to statistical significance ($P = 0.067$ and $P = 0.084$). Hence, N_1 patients with BRLN metastasis should not be classified as N_2.

The risk of distant metastasis and death is shown in Table 5 by the different N subsets (N_0 disease without RLN metastasis, N_0 disease with RLN metastasis, N_1 disease, N_2 disease, and N_3 disease). The hazard ratios (HR) of death and distant failure for patients with N_0 disease and RLN metastasis were 0.596 and 0.433, respectively, which is similar to patients with N_1 disease (HR = 0.633, HR = 0.531, respectively). These results suggest that there is no difference in HRs of OS and DMFS between patients with N_0 disease and RLN metastasis and patients with N_1 disease. Kaplan-Meier plots are shown in Fig. 2. The survival curve for patients with N_0 disease and RLN metastasis was approximately the same as that of patients with N_1 disease, and the log-rank test for OS and DMFS shows that the difference is insignificant ($P = 0.6096$ and $P = 0.8995$, respectively). However, the difference in OS and DMFS between patients with N_0 disease without RLN metastasis and patients with N_0 disease and RLN metastasis turned out to be significant ($P = 0.0021$ and $P = 0.0187$, respectively).

Table 5. Effect of N classification and stage group on risk of death and distant failure

Category	HR (95% confidence interval)	
	Death	Distant failure
RLN was unclassified		
N_0 without RLN	0.272 (0.163-0.453)	0.177 (0.083-0.378)
N_0 with RLN	0.596 (0.369-0.961)	0.433 (0.223-0.848)
N_1	0.633 (0.454-0.883)	0.531 (0.347-0.813)
N_2	1	1
N_3	1.585 (1.086-2.312)	1.620 (1.020-2.571)
RLN was classified to N_1 category		
N_0	0.272 (0.163-0.453)	0.177 (0.083-0.378)
N_1	0.624 (0.456-0.854)	0.509 (0.340-0.762)
N_2	1	1
N_3	1.585 (1.086-2.312)	1.620 (1.021-2.571)
RLN was classified to T_2 category		
N_0	0.387 (0.157-0.464)	0.270 (0.157-0.464)
N_1	0.633 (0.450-0.883)	0.531 (0.347-0.813)
N_2	1	1
N_3	1.589 (1.089-2.318)	1.621 (1.020-2.571)

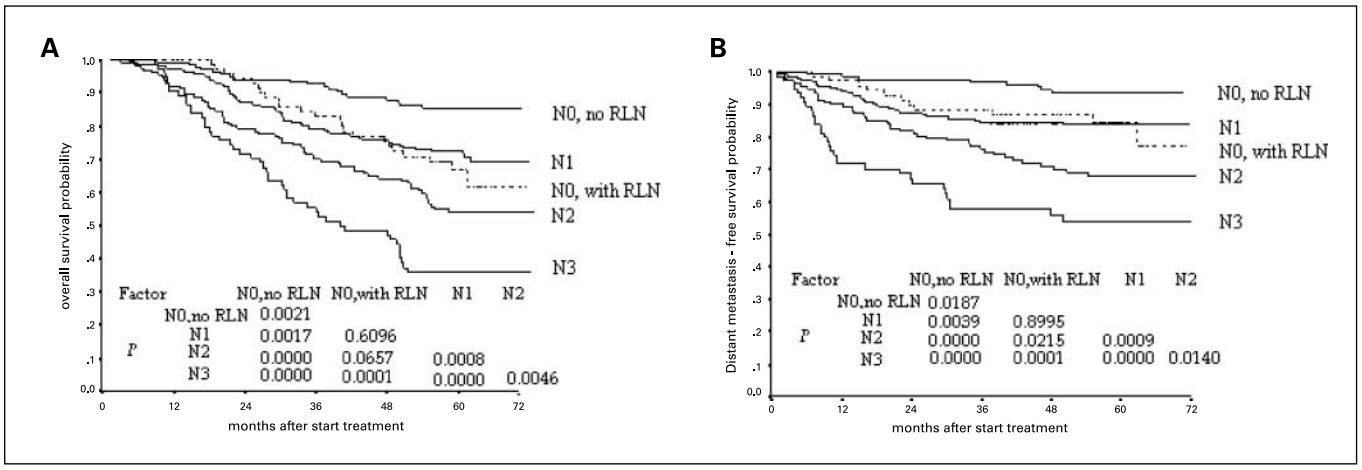

Fig. 2. OS probability (*A*) and DMFS probability (*B*) according to AJCC/UICC N classification. N_0, with RLN, N_0 disease with RLN metastasis.

We also found that the survival curve of OS for patients with T_1 disease and RLN metastasis was approximately the same as patients with T_2 disease ($P = 0.9501$; Fig. 3). The survival curve of DMFS for patients with T_1 disease and RLN metastasis was approximately the same as patients with T_3 disease ($P = 0.8869$; Fig. 3).

Comparing staging categories of RLN metastasis. When RLN metastasis is classified as T_{2b} and N_1, an even and orderly increase in the HRs of OS and DMFS in different N subsets is observed in the two situations (Table 5). The survival curves of OS and DMFS for the N subsets were both split evenly (Figs. 4 and 5), but there was a better segregation of different N stage diseases in terms of OS and DMFS curves when RLN metastasis was classified as N_1. When RLN metastasis was classified as N_1 and stage I patients with RLN metastasis were upstaged to stage II, the survival curves of OS and DMFS for the overall stage were also evenly distributed (Fig. 6).

If RLN involvement is classified as T_2, a total of 23 T_1 patients with RLN involvement would be upgraded to T_2. The distribution of patients according to T classification was as follows: T_1, 77 (10.3%); T_2, 341 (45.5%); T_3, 149 (19.9%); T_4, 182 (24.3%). If RLN involvement is classified as N_1, a total of 73 N_0 patients would be upgraded to N_1. The distribution of patients according to N classification was as follows: N_0, 141 (18.8%); N_1, 371 (49.5%); N_2, 156 (20.8%); N_3, 81 (10.8%). Regardless of whether RLN metastasis is classified as T_2 or N_1, a total of three stage-I patients would be upgraded to stage II and the distribution of patients in each stage group would be as follows: stage I, 30 (4.0%); stage II, 263 (35.1%); stage III, 223 (29.8%); stage IV, 233 (31.1%).

Discussion

According to Rouviere, the retropharyngeal nodes are divided into medial and lateral groups (22). In this study, all RLN metastases were located in the lateral group. The incidence of RLN metastasis in our study was 51.5%, which is less frequent than other MRI studies (3–6). Our results are probably an underestimation of the true incidence of RLN disease due to the limitations of CT imaging.

A higher incidence of RLN involvement was found in the 1997 UICC/AJCC staging system T_2 to T_4 disease compared with T_1 disease. The pharyngobasilar fascia is an effective barrier to tumor invasion. Tumor invasion beyond the confinement of the pharyngobasilar fascia may be related to increased risk of RLN metastasis (9).

The efferent vessels of the RLNs drain to the upper jugular chain and to the posterior triangle (23). A higher incidence of

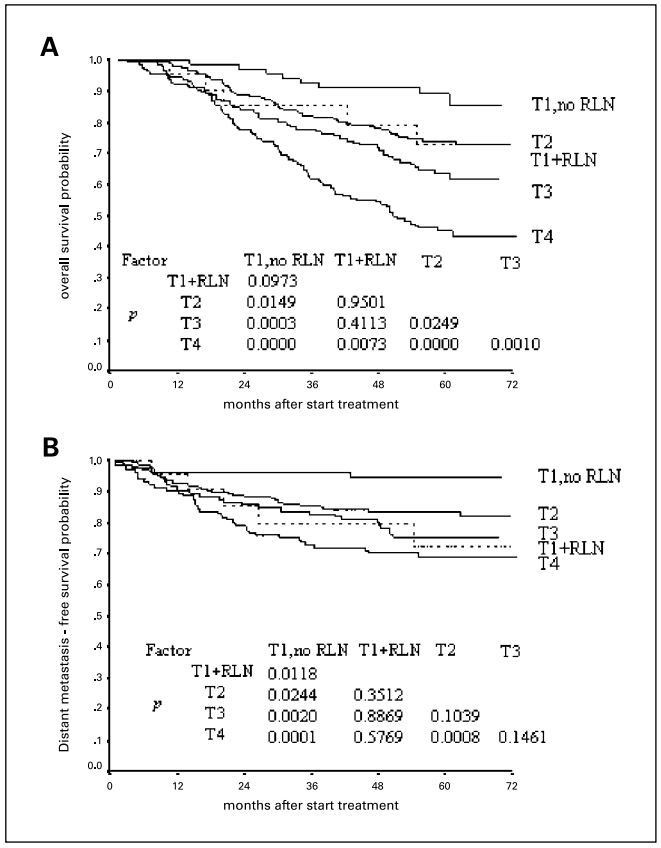

Fig. 3. OS probability (*A*) and DMFS probability (*B*) according to AJCC/UICC T classification. T_1 + *RLN*, T_1 disease with RLN metastasis.

metastatic RLNs was found in patients with cervical lymph node metastases (patients classified as N_1 to N_3). We also found that the incidence of metastatic RLNs in patients with unilateral cervical lymph node metastases was lower than in patients with bilateral cervical lymph node metastases. Patients with bilateral cervical lymph nodes measuring <6 cm above the supraclavicular fossa were classified as N_2. Therefore, the incidence of metastatic RLNs in N_1 patients is lower than in N_2 patients.

In our study, a low incidence of metastatic RLNs was observed in patients with stage I disease. A higher incidence of metastatic RLNs was associated with primary involvement beyond the nasopharynx mucosa (T_2-T_4 patients) and cervical lymph node metastasis. The implication is that RLN involvement might affect the treatment outcome. However, the prognosis of RLN metastasis is controversial. Some studies report that higher distant metastasis rates are observed in patients with NPC with RLN metastasis (7, 8, 24), but those studies are based on univariate analysis. The study by Chua (9) shows no significant effect on outcome and prognosis after adjusting for T and N classifications and suggests that there is insufficient evidence for upgrading N_0 patients with RLN lymph node metastasis to N_1, regardless of the node size. These observations are based on a relatively small number of patients, and the criteria for RLN involvement is the same as for the cervical lymph nodes. The results should, therefore, be interpreted with caution. In our study using univariate analysis, a significant difference was found in the OS and DMFS rates. RLN metastasis was not of prognostic significance in LRRFS, and a likely explanation is related to the cancer treatment. All patients in our study received lymph node irradiation, regardless of clinical lymph node status and CT finding, and the upper neck and nasopharynx were treated in one volume in 94.7% of patients. A boost treatment was also given for patients with significant disease in the paranasopharyngeal space, whether it was a direct tumor extension or RLN involvement. Thus, adequate control of RLN disease was not unexpected.

Using multivariate analysis, we found that RLN metastasis is not an independent significant prognostic factor in OS. A marginal significant difference was observed in DMFS. The effect of RLN metastasis on prognosis may have been shielded by the advanced T and N classification. RLN metastasis may contribute to DMFS. In our study, only 21.4% (160 of 749) of patients received chemoradiotherapy. The North American Intergroup study (0099) reported that chemoradiotherapy improves the 5-year OS for advanced NPC patients in 1998 (25). However, there is controversy over whether the results were applicable to patients in endemic regions (26–28). In our study, chemotherapy was not an independent prognostic factor in multivariate analysis.

In contrast with Chua et al.'s study (9), our data show a significant difference in all end points using multivariate analysis between N0 patients with or without RLN metastasis. These differences may be explained by a difference of RLN size criteria. A minimal axial diameter of ≥5 mm for metastatic RLNs was used as the size criteria in our study, based on the recommendation of published reports (3, 4). In Chua et al.'s study, lymph nodes with a maximum dimension of ≥10 mm were used as the size criteria for RLN metastasis, and a decreased incidence (29.1%) of RLN metastasis was observed (9). Chua et al.'s report was based on a relatively small sample, with 21 metastatic RLN patients of 134 patients with clinical N_0 disease. In this study, N classification was determined solely by palpation, which may result in N_1 patients being misdiagnosed as N_0. This may reduce the prognostic difference of N_0 disease with or without RLN metastasis.

An ideal staging classification has several characteristics. First, the subgroups defined by T, N, and M should have similar survival rates (hazard consistency). Second, the survival rates should differ among the groups (hazard discrimination). Third, the distribution of patients among the groups should be balanced (29).

Because RLN criteria in the published staging systems are ambiguous, RLN involvement had been classified as T_2 (29) or N_1 (13) in different studies. According to the general principle used by the AJCC staging system, RLN should be classified as N_1 if unilateral and N_2 if bilateral. However, in our series, no significant differences were observed in all end points between patients with URLN or BRLN metastasis. We also observed that there is no difference in OS and DMFS among N_0 patients with URLN, $N_{0\text{-}1}$ patients without BRLN, and $N_{0\text{-}1}$ patients with

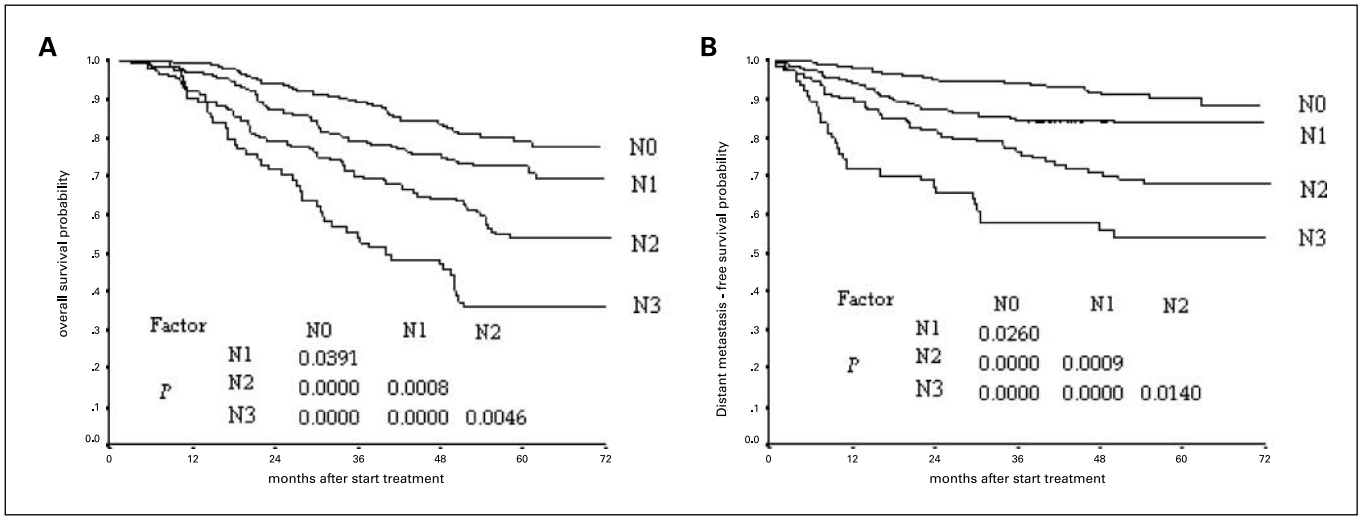

Fig. 4. OS probability (*A*) and DMFS probability (*B*) according to AJCC/UICC N classification. RLN metastasis was classified as T_2.

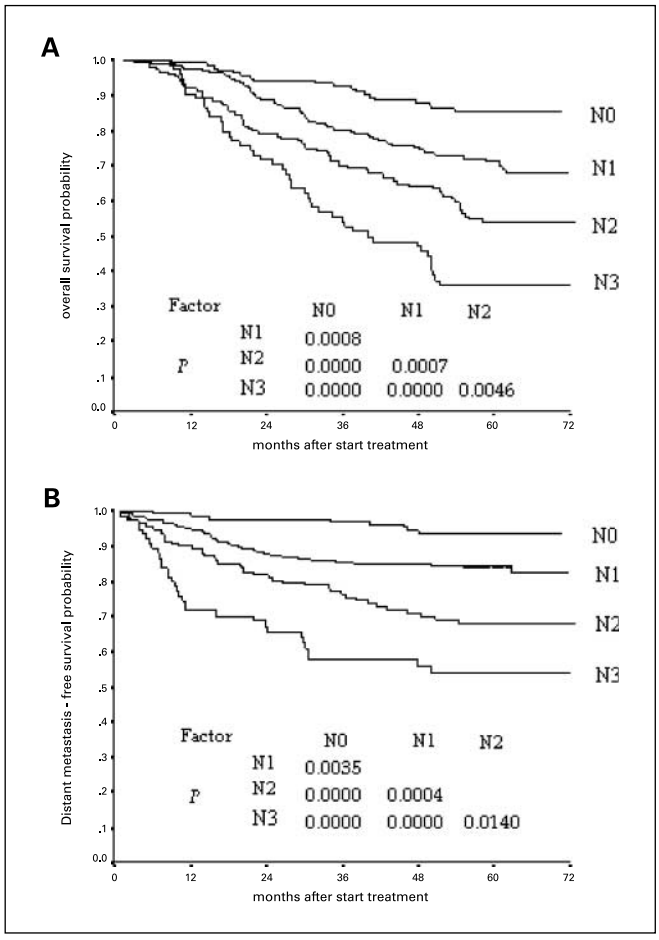

Fig. 5. OS probability (*A*) and DMFS probability (*B*) according to AJCC/UICC N classification. RLN metastasis was classified as N_1.

BRLN. However, the difference in OS and DMFS between N_2 patients and $N_{0\text{-}1}$ patients with BRLN turned out to be close to statistically significant. There is no evidence to upgrade N_0 and N_1 patients with BRLN metastasis to N_2.

In this study, the difference of the HRs between N_0 disease and N_0 disease with RLN metastasis is significant. The survival curve of OS and DMFS for patients with N_0 disease with RLN metastasis was approximately the same as N_1 disease. The survival curve of OS for patients with T_1 disease with RLN metastasis was approximately the same as patients with T_2 disease. However, the survival curve of DMFS for patients with T_1 disease with RLN metastasis was approximately the same as patients with T_3 disease. Thus, it seems that RLN metastasis has a tendency to affect the DMFS. Hazard discrimination was in good order when RLN metastasis was classified as N_1 or T_2, but there was a better segregation of different N stage diseases in terms of OS and DMFS curves when the RLN metastasis was classified as N_1. It is well known that RLNs are the first echelon nodes of NPC. In most cases, RLNs can be discriminated from the primary tumor on CT or magnetic resonance images. According to the principle of hazard consistency and hazard discrimination, it seems more reasonable to classify RLNs as N_1 and stage I patients with RLN involvement should be upstaged to stage II. However, when the RLN metastasis was regarded as N_1, the percentage of N_1 patients was 49.7%, which creates an uneven distribution for N classification. Furthermore, due to the current and widely accepted treatment protocol, the identification of RLN metastasis, probably, has limited effect on treatment decision making. In our series, only 3 of 749 patients with RLNs were upstaged from stage I to stage II; thus, the actual effect on the current staging system is likely to be small. The incidence of RLN metastasis in stage I patients was 10%, and the effect of RLN involvement should not be ignored in stage I diseases.

The imaging modality also has an effect on the staging. The superior soft tissue contrast of MRI could be of paramount importance in discriminating individual lymph nodes from direct tumor extension and oropharyngeal involvement (30, 31). In contrast, CT is unable to depict the small soft tissue structure and might lead to diagnoses with a higher incidence of parapharyngeal and oropharyngeal involvement and lesser incidence of bony structures involvement than MRI (22, 30, 32). It is likely that the percentage of T_2 patients in our series is overestimated. The staging categories of RLN metastasis should be further investigated using MRI, and more explicit recommendations might be included in a future staging system. Our study comprises the largest amount of data with the longest follow-up time (median, 62 months) for investigating the prognostic value and staging categories of RLN metastasis in NPC patients. Our study provides an important reference for the further MRI study.

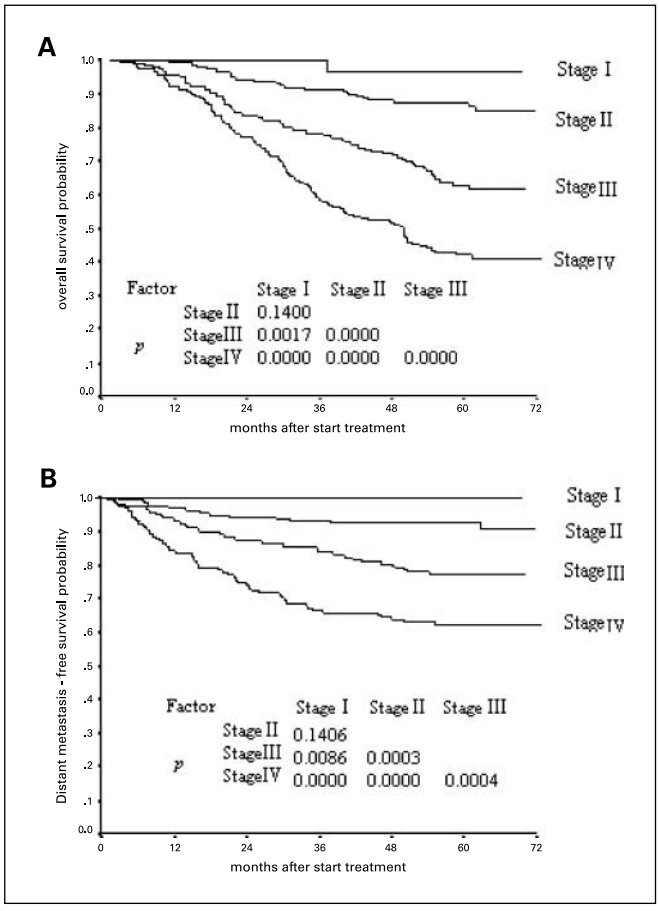

Fig. 6. OS probability (*A*) and DMFS probability (*B*) according to AJCC/UICC overall stage. Stage I patients with RLN metastasis were upgraded to stage II.

It should be stressed that only traditional radiotherapy techniques were used in our series. With conformal radiation therapy and intensity-modulated radiation therapy techniques, the gross tumor volume includes the nasopharyngeal primary and the retropharyngeal lymphadenopathy, so that a high dose can be delivered to RLNs. It has been shown that local control is directly related to the tumor dose (33, 34). Intensity-modulated radiation therapy may improve the local control in patients with RLN involvement. The influence of intensity-modulated radiation therapy on treatment outcome in patients with RLNs should be evaluated in the future.

In conclusion, a high incidence of RLN involvement is present in patients with NPC. RLN metastasis has a tendency to affect the DMFS. The RLN involvement affects OS, loco-regional relapse, and distant metastasis in N_0 disease. Thus, it is our opinion that RLN metastasis should be classified as N_1, and stage I patients with RLN involvement should be upstaged to stage II.

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