

Imaging in NPC

N-staging by magnetic resonance imaging for patients with nasopharyngeal carcinoma: Pattern of nodal involvement by radiological levels[☆]

Wai T. Ng^{a,*}, Anne W.M. Lee^a, Wai K. Kan^b, John Chan^b,
Ellie S.Y. Pang^c, Tsz K. Yau^a, Kam Y. Lau^b

^aDepartment of Clinical Oncology, and, ^bDepartment of Radiology, Pamela Youde Nethersole Eastern Hospital, Hong Kong, ^cHong Kong Cancer Fund, Hong Kong

Abstract

Background and purpose: To study the pattern of lymphatic spread for patients with nasopharyngeal carcinoma (NPC), the significance of retropharyngeal node (RP-LN) involvement, and the possibility of replacing the supraclavicular fossa (SCF) by Levels IV and Vb (LL) as a demarcating criterion for N3-category.

Patients and methods: The magnetic resonance imaging (MRI) of 202 consecutive patients with NPC treated during 2001–2002 were retrospectively reviewed. Distribution in terms of radiological level (using the same criteria as other head and neck cancers) was mapped, and the size of individual node measured. Prognostic significance of RP-LN and LL was analyzed.

Results: Only 4% of patients were node-negative on presentation. The nodal involvement occurred predominately at II (94%), III (85%) and RP-LN (80%). The presence of RP-LN affected the N-category in 3.5% of patients, and had no significant impact on tumor control. Replacing SCF by LL as one of the criteria for defining N3 is predictive for both distant control and overall survival.

Conclusions: With sensitive detection by MRI, the incidence of nodal involvement was very high for patients with NPC. It was difficult to isolate the prognostic significance of RP-LN. The current criterion for defining N3-category by extension into SCF or nodal size >6 cm is the recommended standard, however replacing SCF with LL could be potentially useful and further validation is warranted.

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An accurate staging system for nasopharyngeal carcinoma (NPC) is crucial for predicting prognosis and guiding treatment strategy for different risk groups. However, previous studies on the pattern of nodal spread were based mostly on clinical and computed tomography (CT) findings, hence, the actual incidence of lymphatic spread may well be underestimated. With the higher sensitivity of magnetic resonance imaging (MRI) as staging investigation [1,2], the pattern of nodal spread can be more accurately assessed, and it would be interesting to see how this influences the staging and disease prognosis.

Lymphatic spread for other head and neck cancers is often described according to the level of neck node involvement. Past studies clearly demonstrated that extension to

the supraclavicular fossa (SCF) is an important prognostic factor [3]. The anatomical boundary of SCF, originally described by Ho [4,5], is the triangular region defined by the superior margin of the sternal end of the clavicle, the superior margin of the lateral end of the clavicle, and the point where the neck meets the shoulder. However, this definition of SCF involvement is based primarily on clinical examination and there is no reliable way to define SCF radiologically using the above clinical landmarks [6–8]. One of the objectives in the current analysis is to explore the feasibility of replacing SCF involvement by lower level (LL) that includes Levels IV and Vb.

Another problem in the current N-staging system is the uncertainty regarding the significance of retropharyngeal lymph node (RP-LN). Our center considers RP-LN as equivalent to other cervical LN, and patients are classified as N1 if unilateral and N2 if bilateral involvement. However, other centers may classify all patients with RP-LN as N1 irrespec-

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tive of the laterality, or T2b as it is difficult to distinguish from soft tissue involvement by CT [9–11], or even totally ignoring its presence because it was believed to have little impact on outcome [10]. Hence, another objective of the current analysis is to assess the independent significance of RP-LN.

Patients and methods

Patient characteristics

This is a retrospective study of 202 consecutive patients with NPC treated with radical intent at the Pamela Youde Nethersole Eastern Hospital (Hong Kong) from January 2001 to December 2002. All had non-keratinizing or undifferentiated carcinoma of the nasopharynx. The median age was 48 years (range: 27–84) and 76% of patients were men. The performance status by the Eastern Cooperative Oncology Group (ECOG) scale was 0–1 in all patients. All patients were evaluated by complete physical examination, fiberoptic nasopharyngoscopy, chest radiograph and MRI of the nasopharyngeal and cervical region. Additional metastatic workup by bone scan and ultrasonography of the liver was performed for those with clinical symptoms or biochemical abnormalities. No patient had gross distant metastasis at presentation or serious co-morbidities. The AJCC/UICC staging system, 5th edition, was initially used. The T-category distribution was 3% T1, 29% T2, 38% T3, and 30% T4. Clinical involvement of SCF was found in 31 patients (15%). Basing on SCF involvement and/or nodal size >6 cm, 43 (21.3%) patients were classified as N3; the distribution of the other N-category was 4.5% N0, 5.4% N1, and 68.8% N2 (Table 3A).

Radiological assessment and re-staging by a modified 'Level' system

All images were obtained by 1.5 T MRI systems. A head coil was used in all the sequences. In addition, a neck coil was used in NE coronal T1 and CE FS coronal T1 of the nasopharynx and CE FS axial T1-images of the neck. Baseline MRI of all patients in the study period were retrospectively reviewed by diagnostic radiologists. Nodal involvement was based on the following features: presence of necrosis, extracapsular spread, shortest axial diameter ≥ 10 mm (11 mm for jugulo-digastric node and 5 mm for retropharyngeal node), or group of ≥ 3 LN that were borderline in size [12]. Retropharyngeal lymph node (RP-LN), defined as the node located within 2 cm of skull base and medial to internal carotid artery, was considered the same as other cervical node in staging classification.

Distributions in terms of radiological level as defined by Som [13] were mapped, and the size of individual node was measured. Lymph node level is defined by extension to particular level, that is, if an enlarged LN extends from level II to level III, both levels are considered to be positive regardless of the epicenter of the node.

Using radiological LL (Levels IV and Vb) instead of SCF as the demarcating criterion for N3, a modified 'Level' system for classification of N-category was applied retrospectively:

- N0 – no neck node involvement;
- N1 – unilateral neck node involvement, less than or equal to 6 cm in size and not involved LL;
- N2 – bilateral neck node involvement, less than or equal to 6 cm in size and not involved LL;
- N3 – neck node more than 6 cm, or extension into LL.

Treatment

All patients were irradiated with 6 MV photons using three-dimensional conformal techniques throughout the whole course. Chemotherapy had been added in 41% of patients. Various regimens of concurrent cisplatin-based chemotherapy (together with either induction chemotherapy or adjuvant chemotherapy) that had been used as prospective randomised trials were being conducted during this period to assess the benefit of chemotherapy in Asian population with stage III and IV diseases. Details of the radiotherapy techniques and chemotherapy scheme have been described in our previous reports [14–16].

Statistical methods

All events were measured from the date of commencement of RT. The time to the first defining event was assessed for the following end-points: nodal failure-free rate (N-FFR – persistence /recurrence at cervical lymphatics), distant failure-free rate (D-FFR – disease recurrence at distant sites), and overall survival (OS – death due to any cause). Diagnosis of failure is based on signs of progressive disease on clinical and/or radiological examinations. The actuarial rates were calculated with the Kaplan–Meier method [17], the differences compared with the log rank test [18], and Cox's proportional hazards model was used to analyze the significance of RP-LN. All statistical tests used two-sided *p* values with α level 0.05 as significant. SPSS computer program, version 12.0 (SPSS Inc.), was used for all statistical analysis.

Results

Pattern of nodal spread

The pattern of nodal spread based on MRI is summarized in Fig. 1. The frequency of neck node involvement at presentation was as high as 95.5%. Nodal metastases occurred predominantly in levels II (94%), III (85%) and retropharyngeal space (80%). No skip metastasis was identified in the present series. As only 5% of patients presented with N0 and another 5% with N1 disease, they were grouped together in the subsequent analyses of treatment outcomes.

Overall tumor control

With a median follow-up of 3.4 years (range: 0.3–4.8), 54 patients had failed at one or more sites; and 57 patients had died. The 3-year result for the whole series: N-FFR was 96%, D-FFR 80%, and OS 78%. As there were too few events of nodal failure for further analysis, the following assessment will focus on D-FFR and OS.

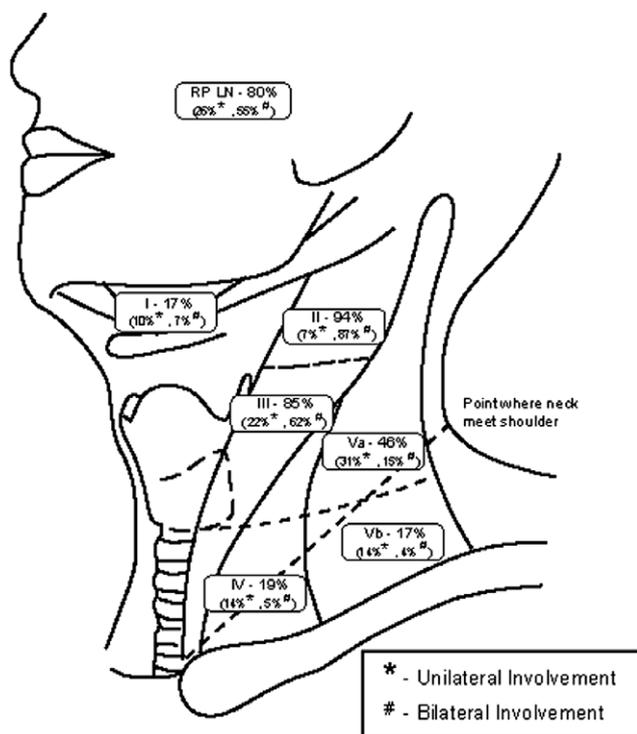


Fig. 1. Distribution of lymphadenopathy.

Significance of retropharyngeal nodes

Only 1% patients had nodal involvement confined to the RP-LN, while 15% had lymphatic spread to other cervical nodes without RP-LN involvement. Presence of RP-LN only affected the N-category in 3.5% of patients (with 1% up-staged from N0 to N1 and 2% from N1 to N2) (Table 1). To study the independent effect of RP-LN involvement, patients were staged by AJCC criteria based on involvement of other nodes alone, and RP-LN involvement was analyzed as a separate co-variate by multivariate analyses (Table 2). No significant impact was shown for any end-points.

Pattern of N-staging

The stage distribution by the AJCC/UICC system and the modified 'Level' system is shown in Table 3. Ten patients initially staged as N2 were classified as N3 by the 'Level' system, resulting in decreased proportion of N2 from 69% to 64%, and increased proportion of N3 from 21% to 26%.

Table 1

Difference in distribution of N-category by AJCC/UICC staging: inclusion vs. exclusion of retropharyngeal lymph node as a regional node in staging consideration

	N0 (+)	N1 (+)	N2 (+)	N3 (+)
N0 (-)	9	3		
N1 (-)		8	4	
N2 (-)			135	
N3 (-)				43

(+) N-category based on involvement of both cervical and retropharyngeal nodes.

(-) N-category based on involvement of cervical nodes alone.

Significance of N-category based on AJCC/UICC classification and the modified 'Level' system

N-category based on the AJCC/UICC classification (N_A) was a significant factor for all end-points (Fig. 2). The 3-year OS was 94% for N0/1, 84% for N2 and 53% for N3 patients ($p < 0.01$). The N-category based on the modified 'Level' system (N_L) was also a significant factor for OS and D-FFS (Fig. 2). The 3-year OS was 94% for N0/1, 80% for N2 and 67% for N3 patients ($p = 0.04$); and the corresponding D-FFR were 94%, 82% and 70%, respectively ($p = 0.04$).

Discussion

Due to its central location of occurrence, NPC is treated primarily by radiotherapy with or without chemotherapy. As surgico-pathological data in neck node involvement are lacking, staging of nodal disease relies heavily on accurate radiological information.

With better sensitivity of MRI compared with CT, a very high incidence of nodal involvement at presentation (60–88%) was noted in recent series [19–21]. The incidence shown in the current study was as high as 96%, and bilateral involvement is extremely common. Similar to the pattern observed by Ng et al. from Taiwan using similar radiological approach [19], nodal involvement showed an orderly spread from upper neck node downward towards the clavicle. The nodal metastases predominantly involved Level II (94%), followed by Level III (85%) and RP-LN (80%).

Recent studies on other head and neck cancers suggest that RP-LN involvement was associated with unfavorable outcome, particularly for oropharyngeal and hypopharyngeal carcinoma [22–25]. Specific studies on NPC are very limited. In a small series, Xiao et al. [11] reported higher distant metastasis rate among those patients with positive RPLN. On the contrary, Chua et al., based on 364 CT-staged patients [10], showed that the outcome of patients with RP-LN alone was not significantly different from those who were otherwise node negative. Both studies were limited by the inferior sensitivity of CT and the incidences of RP-LN reported were only 11% and 29%, respectively. The issue is further complicated by the policy of classifying RP-LN involvement as Stage T2 parapharyngeal involvement by some centers as it is very difficult to differentiate local infiltration to parapharyngeal space from nodal deposit in RP-LN by CT [9,26].

With more accurate detection by MRI, the current study provides more reliable data for assessing the prognostic significance of RP-LN. We attempt to assess the independent significance of RP-LN by putting its involvement (presence vs. absence) and N-category based on other cervical nodes as separate covariates in multivariate analyses. The presence of RP-LN did not show significant impact on tumor control or survival (Table 2). The lack of significance, in contrast to other head and neck cancers, might be attributed to the small number of patients with absence of RP-LN involvement, leading to gross under-power in statistical analyses. Furthermore, as adequate coverage of RP-LN (and parapharyngeal space) to 70 Gy can generally be attained with conformal technique, the presence of RP-LN involvement rarely affects locoregional control.

Table 2
Significance of retropharyngeal node involvement on treatment outcome by multivariate analysis

End-point		Hazard Ratio	95% CI	p value
Nodal failure	RP-LN, without vs. with N-category ^a	0.00		0.94
	N2 vs. N0/1	0.22	0.02–2.25	0.04
	N3 vs. N0/1	1.41	0.15–12.86	0.20
	T-category (Non-convergence)			0.76
	Age, per year increase	1.00	0.94–1.07	0.80
	Sex, male vs. female	1.17	0.23–5.90	0.92
				0.85
Distant failure	RP-LN, without vs. with N-category ^a	1.75	0.74–4.14	0.20
	N2 vs. N0/1	1.36	0.30–6.24	<0.01
	N3 vs. N0/1	6.06	1.27–29.02	0.68
	T-category			0.02
	T2b vs. T1/2a	2.20	0.22–21.90	0.05
	T3 vs. T1/2a	7.35	0.98–55.42	0.50
	T4 vs. T1/2a	7.96	1.04–60.89	0.05
	Age, per year increase	1.02	0.99–1.04	0.05
	Sex, male vs. female	3.30	0.99–10.90	0.31
				0.05
Overall survival	RP-LN, without vs. with N-category ^a	1.86	0.90–3.82	0.09
	N2 vs. N0/1	2.05	0.46–9.07	<0.01
	N3 vs. N0/1	6.86	1.48–31.78	0.35
	T-category			0.01
	T2b vs. T1/2a	3.55	0.39–32.45	0.01
	T3 vs. T1/2a	10.56	1.42–78.59	0.26
	T4 vs. T1/2a	13.35	1.79–99.66	0.02
	Age, per year increase	1.03	1.01–1.06	0.01
	Sex, male vs. female	2.51	0.98–6.46	0.01

Abbreviation: RP-LN, retropharyngeal lymph node involvement; CI, confidence interval.

^a N-category: N-staging based on other cervical lymph nodes (i.e. exclusion of retropharyngeal node) using the AJCC/UICC criteria.

As RP-LN is well documented to be one of the first nodal stations for the spread of NPC, there is no good reason to ignore it as part of the lymphatic system of the head and neck region. Hence, despite the lack of proven prognostic value, we believe that this should be included as a regional node in the N-staging for NPC.

Concerning the N3 criterion, there is little controversy that patients with lymphatic spread down to the SCF, as originally defined by Ho [3], have the poorest prognosis due to high incidence of distant failure [27–29]. However, while the demarcating boundaries for SCF can be easily

defined on clinical examination, these cannot be consistently defined by radiological imaging. Som et al. [13] suggested to define SCF as the region at or caudal to the level of clavicle as seen on each axial scan, lateral to carotid artery on each side of the neck, above and medial to the ribs. Gregoire et al. [8] proposed another criteria for defining the borders: lower border of level IV/Vb cranially, the sterno-clavicular joints caudally, and the lateral edge of the posterior scalenus muscle laterally. Unfortunately, these radiological definitions are confusing and did not correlate well with the exact clinical

Table 3
Distribution of T- and N-categories

	T1	T2a	T2b	T3	T4	Total (%)
<i>(A) Original staging based on AJCC/UICC classification</i>						
N0 _A	1	0	3	3	2	9 (4.5)
N1 _A	1	2	6	2	0	11 (5.4)
N2 _A	3	8	30	52	46	139 (68.8)
N3 _A	1	2	7	20	13	43 (21.3)
<i>(B) Re-staging by the modified 'Level' system</i>						
N0 _L	1	0	3	3	2	9 (4.5)
N1 _L	1	2	6	2	0	11 (5.4)
N2 _L	3	7	24	52	43	129 (63.9)
N3 _L	1	3	13	20	16	53 (26.2)

Note: Retropharyngeal nodes included as regional node in classification of N-category.

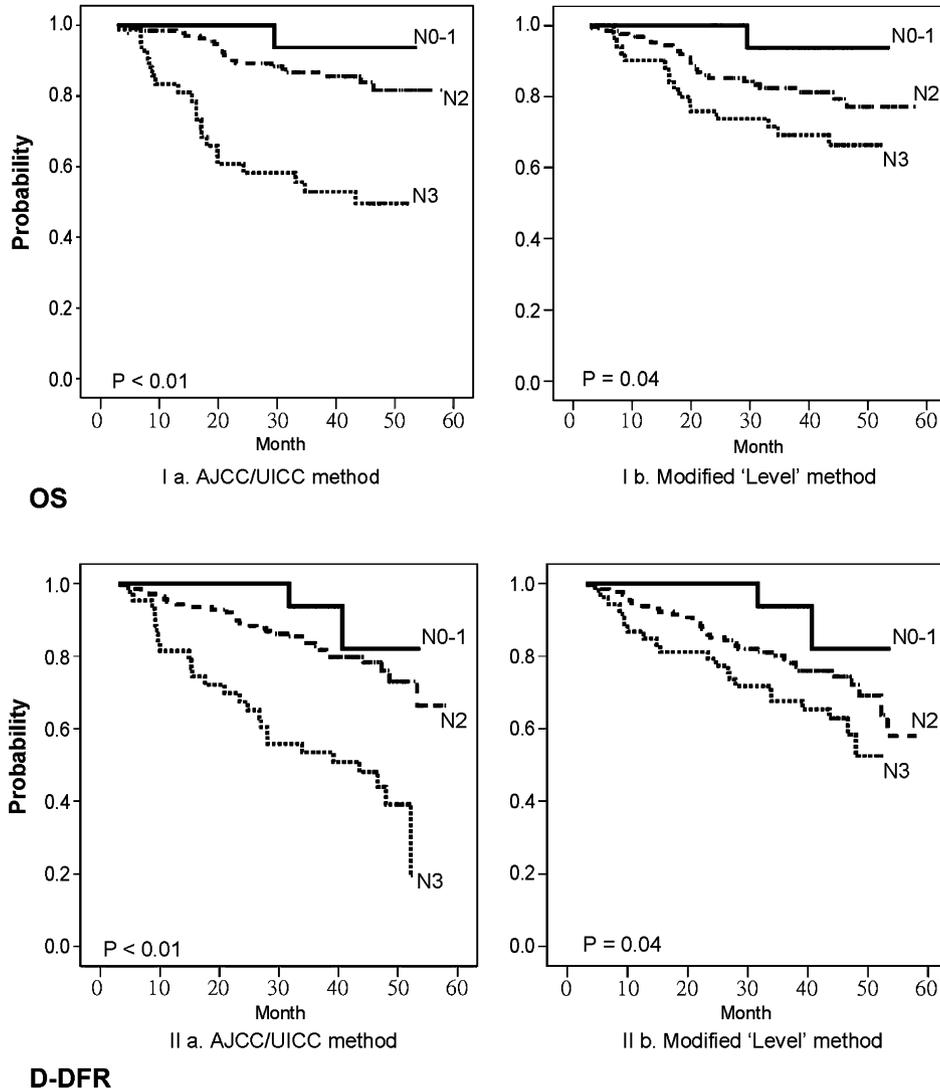


Fig. 2. OS and D-DFR according to nodal status based on AJCC/UICC method and modified 'Level' method.

definition of SCF. In addition, there is increasing need to clearly understand the nodal distribution by radiological level for conformal/intensity-modulated RT planning [30–32]. The current study hypothesizes to use MRI defined Levels IV and Vb, instead of the radiological ambiguity of SCF, as one of the criteria in defining N3-category. Our preliminary data support that this modified 'Level' system could be potentially useful. Therefore, prospective validation is warranted.

* **Corresponding author.** Wai T. Ng, Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, 3 Lok Man Road, Chai Wan, Hong Kong. *E-mail address:* ngwt1@ha.org.hk

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