Original Article

Added value of metastatic cervical lymph node group V in nodal staging of nasopharyngeal cancer

Jiraporn Setakornnukul MD | Kullathorn Thephamongkhol MD | Panid Chaysiri MD

Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Correspondence
Panid Chaysiri, 2 Prannok Road, Siriraj District, Bangkoknoi, Bangkok 10700, Thailand. Email: pcanime44@gmail.com

Section Editor: Kai-Ping Chang

Abstract

Background: Prognostic significance of posterior cervical lymph node metastasis in nasopharyngeal cancer is largely unknown. This study aims to determine the added prognostic significance of cervical lymph node group V to the standard American Joint Committee on Cancer (AJCC) staging system (eighth edition AJCC) of nasopharyngeal patients with cancer treated with intensity-modulated radiation therapy (IMRT) in terms of overall survival (OS), distant metastatic-free survival (DMFS), and disease-free survival (DFS).

Methods and Materials: A retrospective cohort of 199 consecutively diagnosed nasopharyngeal patients with cancer treated with definitive radiotherapy (RT) or concurrent chemoradiotherapy (CCRT) in the era of IMRT in a large university hospital in endemic area of Southeast Asia. Pre-treatment imaging studies were thoroughly re-evaluated and re-staged by a board-certified radiologist using radiographic criteria for cervical lymph node metastasis. T and N classifications were reclassified according to the eighth AJCC staging system. Group V (Va and Vb) cervical node was evaluated for its added prognostic significance. Cox's proportional hazard model was used to retrieve hazard ratio (HR), 95% confidence interval and $P$ value for N classification. Harrell's C-statistic (concordance index) was used for test of discrimination and internal validation was calculated by bootstrap method.

Results: This study demonstrated greater separation of OS with HR of 6.75 (95%CI 1.94-23.51, $P = .003$) by using group Vb only as N3 compared to HR of 4.70 (95%CI 1.37-16.13, $P = .014$) by using current standard N3 disease (groups IV and Vb). Similarly, N2 with presence of Va shows worsened DFS with HR of 8.70 (95%CI 1.08-69.67, $P = .042$) compared to N2 without Va with HR of 5.93 (95%CI 0.76-46.00, $P = .089$). After incorporating cervical group V into nodal staging, the HR and 95%CI among each group was better separated than the eighth AJCC staging system but without significant improvement in C-index.

Conclusion: Cervical lymph node group V is a potentially added prognostic factor to standard TNM staging.
INTRODUCTION

Nasopharyngeal cancer is a leading form of cancer in Southeast Asia, Southern China, and the middle east/north Africa. Radiation therapy either alone or given concurrently with chemotherapy with or without adjuvant chemotherapy has been a standard treatment. Several literatures and staging systems have been proposed to better classify the prognostic groups and guide for an appropriate treatment for each group of patients. In 2017, the eighth edition American Joint Committee on Cancer (AJCC) staging system has provided changes in both tumor (T) and nodal (N) classification for nasopharyngeal carcinoma. The definition of N3 disease has been specifically described based on the basis of cross-sectional imaging. Nevertheless, prognostic significance of each cervical lymph node regarding risk of distant metastasis and survival, though widely studied, but to our knowledge, none has ever paid significant attention to sequential echelon drainage in association with the increment in micrometastasis risk, especially the sequential drainage to posterior cervical group V which consists of Va and Vb, radiographically separated by caudal end of cricoid cartilage. In the current eighth AJCC staging system, cervical lymph node group Vb combined with cervical node group IVa is considered as a replacement for supraclavicular fossa.

Cervical node group V was previously proposed as a second echelon receiving lymphatic drainage from occipital, and retroauricular nodes, and as a second lymphatic collector via lateral retropharyngeal node from the nasopharynx, however, its anatomical proximity to the anterior cervical groups lead to our hypothesis that the cervical lymph node group Va could receive direct drainage from cervical lymph nodes groups II and III, and thus should be considered as the third echelon group equal to cervical lymph node group IVa by mean of comparable regional lymph node extent. The additional value of cervical lymph node group V incorporated into the current eighth AJCC staging system would prove our hypothesis and support further study to improve prognostic assessment in these groups of patients.

PATIENTS AND METHODS

Single center retrospective study of consecutively newly diagnosed nasopharyngeal patients with carcinoma treated with definite radiation therapy (RT) or concurrent chemo-radiation (CCRT) with or without induction or adjuvant chemotherapy using IMRT technique in Siriraj hospital since 2007. The inclusion criteria include histologically proven nasopharyngeal carcinoma, age $\geq$ 18 years old, ECOG performance status of 0-1, pre-treatment CT or MRI of nasopharynx and neck. Complete metastatic work up prior to treatment including chest X-ray, CT scan of the chest, ultrasonography or CT of upper abdomen, and bone scan are required prior to definitive treatment.

Exclusion criteria are patients with evidence of distant metastasis at any site, secondary primary cancer or synchronous malignancy, unachievable pretreatment imaging, pathologically proven adenocarcinoma, salivary gland tumor, lymphoma, or metastasis.

Radiographic criteria of pathological nodes including size criteria and suspicious characteristic features, and radiographic mapping of image-based nodal station are described in Data S1. All pre-treatment imaging was recorded, reviewed and re-staged by a single board-certified radiologist.

Primary endpoint is overall survival (OS) and secondary endpoints are distant metastatic-free survival (DMFS) and disease-free survival (DFS) according to the presence or absence of cervical lymph node groups Va and Vb involvement in addition to eighth edition AJCC staging system.

STATISTICAL ANALYSIS

Sample size was calculated based on expected overall survival using type I alpha error of 5%, power 80%, HR 2.74. Univariate and multivariate Cox proportional hazard regression was used for calculating hazard ratio (HR) for survival analysis. The cox proportional hazard was also used for hazard consistency and hazard discrimination tests. T classification was used as covariate in all tests. All P-values are resulted from two-sided statistical tests, and the level of significance was 0.05. Harrell’s C-statistic (concordance index) was also calculated for test of discrimination. Bootstrap method was used for internal validation.

Categorical variables compared using the Chi-square or Exact fisher test.
RESULTS

4.1 Data collection and patients’ characteristics

From January, 2007 to March, 2011, 270 consecutive eligible patients were included for the study. Seventy-one patients were subsequently excluded as shown in Figure 1. A total of 199 patients were re-evaluated and re-staged according to eighth edition AJCC system. Median follow up time was 77.8 months with 38 of 199 (19.1%) patients were lost to follow up.

The patients’ characteristics, demographic data are shown in Table 1. T and N classifications according to eighth AJCC system and cervical group V involvement is shown in Table 2. Radiotherapy technique for IMRT is described in Data S1.

4.2 Cervical lymph node metastasis distributions

The incidences of cervical lymph node metastasis are level II (66.6%), retropharyngeal LN (60.1%), level III (31.9%), Va (7.5%), IV (12.6%), and Vb (7.5%).

Nodal stations are compared using Chi-square test or Exact Fisher test and show significant correlation between groups in an orderly pattern. The presence of retropharyngeal lymph node (RPN) metastasis is correlated with the incidence of groups II, III, and Va. The incidence of group Va is significantly increased while there are co-existing nodal metastases in RPN, II, and III, up to 61% as compared to combination of RPN and group II only (40.7%). No skipped metastasis is found.

4.3 Overall survival

OS for N classification categorized according to eighth edition AJCC system are presented in Figure 2. Cox regression model adjusted by T classification shows trends toward decreased survival in N2 compared to N0, HR 1.64 (95%CI 0.47-5.68, \( P = .435 \)), and significantly reduced survival in N3 as compared to N0 disease, HR 4.70 (95%CI 1.37-16.13, \( P = .014 \)). Whereas, N classification categorized regarding the presence or absence of cervical lymph node group V added into each standard N classification, adjusted cox regression survival analysis demonstrates non-statistically significant trends of diminished survival in all nodal classification (without V and with V) as compared to N0 disease except for N1 disease without cervical group Va as shown in Figure 3.

Furthermore, comparing survival of N3 disease to N0 by using subgroup of lower cervical group V (Vb) only or the combination of cervical groups IV and Vb (replacement of supraclavicular fossa), there is greater separation of survival by using group Vb only, HR 6.75 (95%CI 1.94-23.51, \( P = .003 \)) compared to HR of 4.69 (95%CI 1.37-16.13, \( P = .014 \)) by using standard eighth AJCC staging. Interestingly, the OS in N1 disease with presence of cervical group Va is resembling those of N2 disease without cervical group Va, and likewise, the OS in N2 disease with cervical group Va is comparable to N3 disease without cervical lymph node group Vb. The added value of cervical lymph node group V to standard nodal staging system is shown in Table 3.

When adjusting N classification with age, sex, pathology, T classification and type of primary treatment, no statistical difference is observed except for T classification and primary treatment type.

On multivariate analysis according to age, sex, pathology, T classification and type of primary treatment, CCRT alone as primary treatment modality is the only significant factor associated with survival outcome. In fact, patients who received CCRT alone were never intended for CCRT alone but were also planned for adjuvant chemotherapy. Most of these patients failed to receive adjuvant chemotherapy due to toxicity during CCRT and some were lost to follow up after the completion of CCRT. Therefore, primary treatment association with survival outcomes cannot be concluded as a significant factor but rather a confounding result. Multivariate analysis is shown in Table 4.
Incorporating cervical lymph node group V into the eighth AJCC staging system yields better separation of survival plots, adjusted HR, and 95%CI among each group than standard staging alone. Proposed nodal staging:

### TABLE 1 Demographic data of 199 patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>144 (72.4)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>55 (27.6)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>57.5 ± 12.89</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>59.0 ± 12.73</td>
<td></td>
</tr>
<tr>
<td>Histology (WHO classification)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratinizing squamous cell carcinoma</td>
<td>1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Nonkeratinizing carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differentiated</td>
<td>104 (52.3)</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>92 (46.2)</td>
<td></td>
</tr>
<tr>
<td>Basaloid squamous cell carcinoma</td>
<td>1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td>1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR) follow up time (months)</td>
<td>77.8 (35.1-90.5)</td>
<td></td>
</tr>
<tr>
<td>Type of definite treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT alone</td>
<td>21 (10.6)</td>
<td></td>
</tr>
<tr>
<td>Induction chemotherapy followed by CCRT</td>
<td>29 (14.6)</td>
<td></td>
</tr>
<tr>
<td>CCRT followed by adjuvant chemotherapy</td>
<td>136 (68.3)</td>
<td></td>
</tr>
<tr>
<td>CCRT alone</td>
<td>13 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Type of concurrent chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>147 (82.6)</td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>19 (10.7)</td>
<td></td>
</tr>
<tr>
<td>Cisplatin switched to Carboplatin</td>
<td>9 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Unknown (records from other hospital)</td>
<td>3 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Radiation dose (Gy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥66 Gy</td>
<td>192(96.5)</td>
<td></td>
</tr>
<tr>
<td>60-65.9 Gy</td>
<td>5(2.5)</td>
<td></td>
</tr>
<tr>
<td>&lt;60 Gy</td>
<td>2(1)</td>
<td></td>
</tr>
<tr>
<td>Radiation interruption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>186 (93.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Overall treatment time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤56 days</td>
<td>175 (87.9)</td>
<td>49 ± 4.48</td>
</tr>
<tr>
<td>&gt;56 days</td>
<td>24 (12.1)</td>
<td>63 ± 4.41</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; RT, radiation therapy; CCRT, concurrent chemoradiotherapy; Gy, gray.

### TABLE 2 T and N staging according to 8th AJCC system and cervical group V involvement

<table>
<thead>
<tr>
<th>Eighth AJCC staging</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T classification</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>25 (12.6)</td>
</tr>
<tr>
<td>T2</td>
<td>86 (43.2)</td>
</tr>
<tr>
<td>T3</td>
<td>39 (19.6)</td>
</tr>
<tr>
<td>T4</td>
<td>49 (24.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N classification</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>14 (7.0)</td>
</tr>
<tr>
<td>N1</td>
<td></td>
</tr>
<tr>
<td>Without Va</td>
<td>54 (27.1)</td>
</tr>
<tr>
<td>With Va</td>
<td>19 (9.5)</td>
</tr>
<tr>
<td>N2</td>
<td></td>
</tr>
<tr>
<td>Without Va</td>
<td>40 (20.1)</td>
</tr>
<tr>
<td>With Va</td>
<td>23 (11.6)</td>
</tr>
<tr>
<td>N3</td>
<td></td>
</tr>
<tr>
<td>Without Vb</td>
<td>21 (10.6)</td>
</tr>
<tr>
<td>With Vb</td>
<td>28 (14.1)</td>
</tr>
</tbody>
</table>

Abbreviations: T classification, tumor classification; N classification, lymph node classification.

### FIGURE 2 Overall survival according to eight edition AJCC system [Color figure can be viewed at wileyonlinelibrary.com]

Incorporating cervical lymph node group V into the eighth AJCC staging system yields better separation of survival plots, adjusted HR, and 95%CI among each group than standard staging alone. Proposed nodal staging.
staging system using additional value of cervical lymph node group V is shown in Table 5.

Further analysis using Harrell’s C concordance statistic reveals Harrell’s C index of 0.733 for the proposed staging system. This indicates non-significant improvement in concordance index as compared to eighth AJCC staging system (C index of 0.721) and could lead to suggestion that cervical lymph node group V could only add small prognostic value in an already good prognostic predicting staging system.

Internal validation to determine the reproducibility of the proposed prediction model is performed and also shown in Table 5 with reduction of Harrell’s C index to 0.703.

For N3 to truly represent the survival outcome of the involvement of cervical node group IV or Vb, we exclude 4 of 199 patients with large cervical node of greater than 6 cm in diameter and reanalyze for survival outcome which still show significant detrimental effect of N3 with Vb (Data S1; Table 7).

### 4.4 | Distant metastatic-free survival

Significantly reduced DMFS is demonstrated only in N3 disease whose cervical lymph node group Vb is also seen, HR 16.13 (95%CI 2.10-123.73, \( P = .007 \)). Trend of decreased survival is also seen in N3 disease without group Vb with HR of 7.0 (95%CI 0.82-59.50, \( P = .075 \)) as shown in Figure 4.

### 5 | DISEASE-FREE SURVIVAL

DFS under Cox regression analysis shows separation of survival plots with significantly decreased survival for N2 disease with presence of cervical group Va (N2 + Va), HR 8.67 (95%CI 1.08-69.67, \( P = .042 \)), N3 disease without cervical group Vb, HR 11.91 (95%CI 1.47-96.16, \( P = .02 \)) and N3 with Vb, HR 20.94 (95%CI 2.75-159.36, \( P = .003 \)). There is non-statistically significant trend toward decreased survival of N2 disease without Va, HR 5.93 (95%CI 0.76-45.99, \( P = .089 \)). No significant difference in DFS for N1 disease regardless of the presence or absence of cervical node group V is demonstrated. DFS of each N classification with or without cervical group V is shown is Figure 5. Table 6 shows DFS comparison between eighth AJCC staging system and proposed new nodal staging.

**FIGURE 3** Overall survival for N staging with or without group V [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 3** Added value of cervical lymph node group V to standard nodal staging system

<table>
<thead>
<tr>
<th>N classification</th>
<th>Eight AJCC system HR (95%CI; ( P ) value)</th>
<th>Cervical node gr V</th>
<th>Eight AJCC system ± cervical gr V HR (95%CI; ( P ) value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>N1</td>
<td>0.90 (0.25-3.18; .864)</td>
<td>Without Va*</td>
<td>0.76 (0.20-2.84; .682)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With Va</td>
<td>1.23 (0.27-5.58; .787)</td>
</tr>
<tr>
<td>N2</td>
<td>1.64 (0.47-5.68; .435)</td>
<td>Without Va</td>
<td>1.39 (0.39-5.04; .613)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With Va</td>
<td>2.00 (0.49-8.16; .336)</td>
</tr>
<tr>
<td>N3</td>
<td>4.7 (1.37–16.13; .014)</td>
<td>Without Vb**</td>
<td>2.33 (0.56-9.66; .244)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With Vb</td>
<td>6.75 (1.94–23.51; .003)</td>
</tr>
</tbody>
</table>

Abbreviations: N classification, lymph node classification; AJCC, American joint committee on cancer; HR, hazard ratio; CI, confidence interval.

*Va, upper cervical lymph node group V.

**Vb, lower cervical lymph node group V.
11 of 199 patients had regional relapses, 8 of 11 patients had both regional and distant recurrences, 2 of 11 with concomitant local and regional relapse, and 1 of 11 with regional relapse alone.

In-field recurrence was observed in 8 of 11 patients, 6 of 8 patients had cervical and 2 of 8 patients had retropharyngeal node recurrences.

There were three parotid node relapses, 2 of 3 patients had intra-parotid lymph node relapse at superficial lobe of parotid gland not included in high or intermediate risk CTV at the time of RT. One patient had cervical group II relapse (In-field) with direct extension to involve ipsilateral parotid gland.

42 of 199 patients developed distant relapse. Sites of metastases were bone in 18 of 42 patients (42.8%), lung in 15/42 (35.7%), and liver in 11/42 (26.2%).

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>OS</th>
<th>DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>112</td>
<td>1.307</td>
<td>0.75-2.27</td>
</tr>
<tr>
<td>≥60</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>142</td>
<td>0.77</td>
<td>0.39-1.49</td>
</tr>
<tr>
<td>Women</td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differentiated</td>
<td>105</td>
<td>0.80</td>
<td>0.45-1.41</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>24</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>T2</td>
<td>86</td>
<td>1.06</td>
<td>0.39-2.89</td>
</tr>
<tr>
<td>T3</td>
<td>38</td>
<td>1.30</td>
<td>0.41-4.13</td>
</tr>
<tr>
<td>T4</td>
<td>49</td>
<td>3.25</td>
<td>1.17-9.09</td>
</tr>
<tr>
<td>N classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>13</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>N1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without Va</td>
<td>53</td>
<td>0.93</td>
<td>0.24-3.59</td>
</tr>
<tr>
<td>With Va</td>
<td>19</td>
<td>1.57</td>
<td>0.33-7.46</td>
</tr>
<tr>
<td>N2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without Va</td>
<td>40</td>
<td>1.85</td>
<td>0.49-7.04</td>
</tr>
<tr>
<td>With Va</td>
<td>23</td>
<td>2.44</td>
<td>0.57-10.45</td>
</tr>
<tr>
<td>N3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without Vb</td>
<td>21</td>
<td>2.80</td>
<td>0.65-11.92</td>
</tr>
<tr>
<td>With Vb</td>
<td>28</td>
<td>8.45</td>
<td>2.35-30.41</td>
</tr>
<tr>
<td>Primary treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCRT+Adj</td>
<td>135</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>RT alone</td>
<td>20</td>
<td>1.47</td>
<td>0.56-3.82</td>
</tr>
<tr>
<td>CCRT alone</td>
<td>13</td>
<td>3.28</td>
<td>1.06-10.14</td>
</tr>
<tr>
<td>Neo + CCRT</td>
<td>29</td>
<td>1.30</td>
<td>0.65-2.61</td>
</tr>
</tbody>
</table>

Abbreviations: OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; T classification, tumor classification; N classification, lymph node classification; CCRT, concurrent chemoradiotherapy; Adj, adjuvant chemotherapy; RT, radiation therapy; Neo, neoadjuvant chemotherapy.

### 5.1 Pattern of recurrence

11 of 199 patients had regional relapses, 8 of 11 patients had both regional and distant recurrences, 2 of 11 with concomitant local and regional relapse, and 1 of 11 with regional relapse alone.

In-field recurrence was observed in 8 of 11 patients, 6 of 8 patients had cervical and 2 of 8 patients had retropharyngeal node recurrences.
For the subgroup of patient with Vb, 16 of 28 patients (57.1%) developed distant metastases. The most common sites of distant metastases are bone (10 of 16 patients; 62.5%) and lung (4 of 16 patients; 25.0%). Other sites include liver, and axillary lymph node metastasis. 2 of 28 patients (7.1%), both of which had concomitant distant failures also showed regional relapses, one at cervical lymph node group Ib and another at parotid lymph node. 2 of 28 patients (7.1%) developed local recurrence, one of which had direct intracranial progression.

### TABLE 5 Overall survival for the proposed new nodal staging system

<table>
<thead>
<tr>
<th>N classification</th>
<th>8th AJCC staging system HR (95%CI; P value)</th>
<th>Proposed N classification</th>
<th>Proposed nodal staging system HR (95%CI; P value)</th>
<th>Proposed nodal staging system (internal validation) Corrected HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>Reference</td>
<td>Proposed N0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>N1</td>
<td>0.90 (0.25–3.18; .864)</td>
<td>Proposed N1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.86 (0.24-3.05; .82)</td>
<td>0.88</td>
</tr>
<tr>
<td>N2</td>
<td>1.64 (0.47-5.68; .435)</td>
<td>Proposed N2a&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.40 (0.39-5.08; .06)</td>
<td>1.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proposed N2b&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.15 (0.59-7.86; .25)</td>
<td>1.90</td>
</tr>
<tr>
<td>N3</td>
<td>4.69 (1.37-16.13; .014)</td>
<td>Proposed N3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.73 (1.92-23.43; .003)</td>
<td>4.94</td>
</tr>
</tbody>
</table>

Abbreviations: N classification, lymph node classification; AJCC, American joint committee on cancer; HR, hazard ratio; CI, confidence interval.

<sup>a</sup>Proposed N1: N1; Proposed N2a: N2 without Va; Proposed N2b: N2 with Va or N3 without Vb; Proposed N3: N3 with Vb.

### FIGURE 4 Distant metastatic-free survival with or without group V [Color figure can be viewed at wileyonlinelibrary.com]

For the subgroup of patient with Vb, 16 of 28 patients (57.1%) developed distant metastases. The most common sites of distant metastases are bone (10 of 16 patients; 62.5%) and lung (4 of 16 patients; 25.0%). Other sites include liver, and axillary lymph node metastasis. 2 of 28 patients (7.1%), both of which had concomitant distant failures also showed regional relapses, one at cervical lymph node group Ib and another at parotid lymph node. 2 of 28 patients (7.1%) developed local recurrence, one of which had direct intracranial progression.

### FIGURE 5 Disease-free survival with or without group V [Color figure can be viewed at wileyonlinelibrary.com]

6 | DISCUSSION

Our study aimed to determine the added prognostic significance of the posterior cervical node group beyond the standard eighth AJCC staging system. This study demonstrated that by adding cervical node group V into the proposed staging system, there was better survival separation between each N classification and N3 with Vb (proposed N3) demonstrated the worst survival outcome. The results showed that nodal burden in the posterior cervical neck could, in some degree, result in decreased survival, owing to higher rates of disease recurrence and death.

To best of our knowledge, our study is the first to identify the value of cervical lymph node group V by mean of OS, DMFS, and DFS. A previous study by Thephamongkhol et al<sup>12</sup> has indicated that posterior cervical nodal involvement is an independent prognostic factor for nasopharyngeal cancer stages IVA and IVB.
treated with induction chemotherapy in prediction of DMFS with effects seen on PFS and OS.

Mao et al\textsuperscript{11} had evaluated the prognostic values of nodal variables and found that node level, laterality, and extranodal spreading were independent factors for disease failure and distant failure, in this study, node locations were classified according to Som et al\textsuperscript{13} radiographic nodal classification. No statistically significant difference in hazards (HR) between cervical node level II, RP, Ib, III, and V is observed but significantly increased HR in level IV and supraclavicular fossa (SPC) is evident leading to adoption of the Chinese 2008 classification\textsuperscript{14} for nodal classification.

Subsequent analysis by Pan et al\textsuperscript{2} showed greater separation of the Chinese 2008 nodal classification among nodal subgroup in DMFS as compared to the seventh AJCC system, hence, it has been incorporated in the development of the latest eighth edition AJCC system which has considered replacing supraclavicular fossa with a more reliable anatomical nodal levels of cervical groups IV and Vb.

Our results show that, other than cranio-caudal nodal involvement that could significantly diminish survival, nodal burdens in the mesh lymphatic networking of the patients might play a role. Unquestionably, the involvement of lower cervical group V (Vb) in replacement of supraclavicular fossa would result in such a worsened prognosis in terms of DFS, DMFS and OS. The other remaining question is whether the presence of upper cervical group V (Va) involvement would also reflect a poorer outcome. In this study, there was significantly worsened DFS in N2 disease with the presence of Va involvement even though its presence in N1 disease did not showed any difference in terms of disease recurrence or death. This could possibly be explained by the nature of lymphatic drainage in which group Va could serve as either a second echelon node receiving direct lymphatic drainage or as a third echelon from its neighboring anterior cervical groups II-III. The finding of a possible added prognostic significance of cervical lymph node group V could support our hypothesis in a way that one could be aware of and recognize its presence and take into consideration for the treatment selection in addition to other clinical prognostic factors, especially if de-escalation of treatment is considered. Nevertheless, our study needs to be verified and validated in a larger cohort before its significance could be adopted in clinical use.

The role of adjuvant or neoadjuvant chemotherapy following concurrent chemo-radiotherapy is still debating with conflicting results across the studies. A meta-analysis\textsuperscript{15} of five randomized studies in 2012 by Liang et al demonstrates no survival benefit of adjuvant chemotherapy in terms of OS, PFS, and DMFS. On the contrary, a small retrospective series\textsuperscript{16} in locally advanced nasopharyngeal carcinoma stages II-IV demonstrates a borderline significant OS benefit in N2-N3 subgroups. Another retrospective analysis\textsuperscript{17} of 523 patients have shown OS benefits of adjuvant chemotherapy in high risk group of two or more high risk factors including T classification, N classification, age, and serum albumin level. Recent studies on the benefit of induction chemotherapy in loco-regionally advanced nasopharyngeal carcinoma by Sun et al and Zhang et al\textsuperscript{18,19} demonstrated significantly improved failure-free survival and ultimately overall survival, of note, both were using seventh AJCC for staging categorization and were consisted of approximately 50%-60% N2-3 disease. The advancement and improvement in disease control with the use of various duet or triplet chemotherapeutic regimens leads to consideration of how to appropriately choose a specific group of patients who would benefit the most from the intensified regimens given that chemotherapy toxicity would be higher altogether.

Several limitations of our study include retrospective nature of our study with several patients were lost to follow up over time period up to 19.1% and some missing

<table>
<thead>
<tr>
<th><strong>TABLE 6</strong> Disease-free survival for the proposed new nodal staging system</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N classification</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>N3</td>
</tr>
</tbody>
</table>

Abbreviations: N classification, lymph node classification; AJCC, American joint committee on cancer; HR, hazard ratio; CI, confidence interval.

\textsuperscript{a}Proposed N1: N1; Proposed N2a: N2 without Va; Proposed N2b: N2 with Va or N3 without Vb; Proposed N3: N3 with Vb.
data collection regarding chemotherapeutic regimen that had been used along with the reasons of incomplete treatment. Since the study is retrospective, lack of EBV DNA data is our major limitation in which current clinical study has shown its prognostic value in correlation with disease outcome. Another limitation is that the majority of our imaging modality was CT scan with contrast and only few cases of MRI which would cause lower detection rate for medial retropharyngeal group, however, due to low incidence of the medial retropharyngeal group and much higher incidence of lateral retropharyngeal group, review of image was thoroughly done for any suspicious nodal involvement in such a group. The presence of selection bias in our study is also evident for treatment selection of clinician preference regarding patients' disease stages and performance status during treatment period which inarguably could strongly affect survival outcome. Another major limitation of our study is the lack of a concurrent external validation cohort which is deemed necessary for prognostic study.

In conclusion, our study depicts trends of additional value of cervical lymph node group V in addition to the eighth AJCC staging system, especially cervical lymph node group Vb which results in poorer outcome compared to N3 without Vb. Further studies in a prospective cohort is needed to better demonstrate the probable significances of the presence of cervical lymph node group V and its burden reflecting survival outcomes.

7 CONCLUSION

Cervical lymph node group V is likely a small but one of the added prognostic factor to standard TNM staging. Further validation is warranted for added prognostic value confirmation and potential benefit in clinical use as another guidance to treatment intensification.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Panid Chaysiri
https://orcid.org/0000-0002-1250-544X

REFERENCES


SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Setakornnukul J, Thephamongkhol K, Chaysiri P. Added value of metastatic cervical lymph node group V in nodal staging of nasopharyngeal cancer. Head & Neck. 2020;42:2801–2810. https://doi.org/10.1002/hed.26325