

# Pattern of Nodal Metastasis in Papillary Thyroid Carcinoma among Filipinos

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## ABSTRACT

**Objective.** The objective of the study is to describe the pattern of nodal metastasis in papillary thyroid carcinoma (PTC) among Filipinos and to determine the possible clinicopathologic factors associated with level V involvement.

**Methods.** This study included patients >18 years old with PTC with clinically positive neck node (cN1b) who underwent total thyroidectomy with lateral neck dissection (levels II-IV) or posterolateral neck dissection (II-V) from 2011-2016 at the Department of Otorhinolaryngology-Head and Neck Surgery, Philippine General Hospital. Histopathology reports were reviewed for the presence of nodal metastasis per level, tumor size, tumor location, gross extrathyroidal involvement and subtype. Univariate analysis utilized Pearson Chi-square test or the Fischer exact test. Multivariate analysis utilized logistic regression.

**Results.** Lymph node involvement in the lateral neck was highest in level III (87.04%), followed by level IV (81.48%), IIa (66.67%), V (60.00%) and IIb (42.59%). No clinicopathologic factor was found to be associated with level V involvement.

**Conclusion.** The pattern of lymph node metastasis among Filipinos is similar but higher than that reported in the literature. Level V involvement is high and thus, this study suggests including level II-V in the neck dissection among Filipinos with cN1b papillary thyroid carcinoma.

**Key Words:** *papillary thyroid carcinoma, neck dissection, nodal metastasis*

## Introduction

Lymph node metastasis in papillary thyroid cancer (PTC) is associated with recurrence and poor survival outcomes.<sup>1,2</sup> Thus, adequate therapeutic lateral neck dissection is necessary.

The extent of the neck dissection of clinically positive lateral neck has some controversies. The American Thyroid Association recommended therapeutic selective neck dissection of levels IIa, III, IV and Vb among patients with

biopsy-proven metastatic papillary thyroid carcinoma (PTC) to the lateral neck node.<sup>3</sup> Local guideline recommended therapeutic ipsilateral selective neck dissection of levels II, III, IV and/or V.<sup>4</sup> The indications when to include level V nodes is not yet standardized.

Compared to American counterparts, Filipinos have a higher incidence of thyroid cancer. Filipino men and women have 2.6 and 3.2 times greater risk to develop thyroid cancer, respectively, compared to American men and women. Filipinos also have greater risk for a negative outcome.<sup>5</sup> A recent study by Kus et al. reported a higher recurrence rate of thyroid cancer among Filipinos compared to non-Filipinos (25.0% vs 9.5%). In this study, five of the six patients with PTC had regional recurrence, while the other case had a distant recurrence.<sup>6</sup>

Given the higher prevalence and greater risk of recurrence of papillary thyroid cancer among Filipinos, the possibility of a more aggressive nodal metastasis pattern compared to those reported in the foreign literature merits further investigation. This study aims to describe the pattern of nodal metastasis in PTC among Filipinos and to determine the possible clinicopathologic factors associated with level V involvement. Data from this study will guide physicians in the appropriate extent of neck dissection of clinically positive lateral neck PTC.

## Materials and Methods

This study was approved by the University of the Philippines Manila Research Ethics Board (UPMRB) Panel. All patient information were kept confidential. Forty five patients more than 18 years old, diagnosed with papillary thyroid carcinoma with clinically positive neck node who underwent total thyroidectomy with lateral neck dissection (levels II-IV) or posterolateral neck dissection (II-V) from 2011-2016 at the Department of Otorhinolaryngology-Head and Neck Surgery, Philippine General Hospital were included in this study. The indication for neck dissection in all patients was the presence of neck mass diagnosed on physical examination or computed tomography (CT) scans. In our institution, levels II-IV are routinely included in the neck dissection of cN1b patients. Levels I, V and VI were included if noted to be involved via physical examination, CT scan or intraoperative findings. Papillary thyroid carcinoma was diagnosed through fine needle aspiration biopsy or intraoperative frozen section. Specimens from the neck dissection were separated per level for histopathology

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**Table 1.** Association of Clinicopathologic Factors to Level V Involvement

Clinicopathologic factors	Level V involvement		p-value
	Absent	Present	
Age			
<45	7	14	0.29
≥45	11	13	
Sex			
Male	9	13	0.57
Female	9	14	
Tumor subtype			
Conventional	13	25	0.21
Follicular	1	1	
Tall Cell	2	0	
Conventional and Follicular	2	1	
Multilevel involvement			
Absent	2	4	0.54
Present	16	23	
Involvement of level IIa			
Absent	7	7	0.28
Present	11	20	
Involvement of level IIb			
Absent	8	18	0.12
Present	10	9	
Involvement of level III			
Absent	3	2	0.31
Present	15	25	
Involvement of level IV			
Absent	4	4	0.40
Present	14	23	

analysis. Histopathology reports were reviewed for the presence of nodal metastasis per level, tumor size, tumor location, gross extrathyroidal involvement and subtype. Statistical analysis was computed using STATA version 13. Fischer exact test was used to test for the association of Level V nodal metastasis and the clinicopathologic factors. A p-value of less than 0.05 was considered statistically significant.

**Results**

Of the 45 patients with papillary thyroid carcinoma with lateral neck node metastasis, 22 (48.89%) were female while 23 (51.11%) were male. The mean age was 45.04 years old ± 16.94 (range: 19-84 years old), 23 patients were younger than 45 years old. Thirty six (80%) underwent unilateral selective neck dissection while 9 (20%) underwent bilateral neck dissection. The mean primary tumor size was 4.01 cm ± 2.03. Forty percent (10 out of 25) of the primary tumors were 2-4 cm, 26% (13) were more than 4 cm while 8% (2) were less than 2cm. The tumor size was not reported in 20 of the cases. The primary tumor was located in one lobe in 19 cases, in

the isthmus in 2 cases and in multiple locations in 22 cases, and was not reported in 2 cases. The status of gross extrathyroidal extension was reported only in 10 cases, eight of these were positive. With regards subtype, 84.44% (38/45) were conventional. Each of the follicular and tall cell variant comprise 4.44% (2/45) of the cases while the rest were combined conventional and follicular subtype.

Lymph node involvement in the lateral neck was highest in level III (87.04%, 47/54), followed by level IV (81.48%, 44/54), IIa (66.67%, 36/54), V (60.00%, 27/45) and IIb (42.59%, 23/54). Level Ib and Ia were involved in 2/6 (33.33%) and 2/7 (28.57%), respectively. Level VI involvement was noted in 30/37 (81.08%). Of the three neck dissection specimens involving single level only, two involved level IV and one involved level IIb.

There were no statistically significant association between level V involvement and the clinicopathologic factors studied (Table 1).

**Discussion**

The predominant site of lateral nodal metastasis was level III, followed by level IV, IIa, V and IIb. This pattern is similar to foreign literature (Table 2).<sup>7-11</sup> In comparison to level III and IV, Level IIb and level V lymph nodes have lower proportion of metastatic lymph nodes. This can be explained by its remote location from the thyroid gland compared to levels III and IV.

Compared to foreign data, our results showed a higher proportion of lymph node involvement in all levels (Table 2). Our study concurs with several studies that showed that PTC among Filipinos behaves in a more aggressive manner.<sup>5,12</sup>

Surgical management should achieve the balance between complete eradication of the disease and minimizing the complications associated with surgery. Thus, the optimal management of levels IIb and V has some controversies. In dissection of levels IIb and V, the spinal accessory nerve (SAN) may be stretched, may have microtrauma and compromised vascular supply leading to neuropraxia. SAN dysfunction usually manifests as “shoulder syndrome” comprised of shoulder droop, trapezius atrophy, limited shoulder abduction, and shoulder and neck pain.

In a review by Vayisoglu et al., positive Level IIa lymph node metastasis and multilevel involvement were associated with level IIb positivity in PTC.<sup>13</sup> The authors concluded that dissection of level IIb might not be needed in the absence of

**Table 2.** Comparison of Studies on the Prevalence of Neck Node Metastasis in Clinically Positive Lateral Neck Node (Cn1b) Papillary Thyroid Carcinoma

Authors (Country,Year)	Total patients (Neck Dissection)	Metastasis rates (%)							
		Ia	Ib	IIa	IIb	III	IV	V	VI
Zhang et al. (China, 2013) <sup>8</sup>	330			65.30		74.80	70.60	28.80	
Keum et al. (2012) <sup>9</sup>	72 (79)			56.90		69.40	75.00	20.80	87.50
Lim et al. (Korea, 2012) <sup>10</sup>	90			47.00	10.00	76.00	68.00	17.00	81.00
Kliseska et al. (Croatia, 2011) <sup>11</sup>	42			20.27	0.00	32.63	11.84	4.08	
Eskander et al. (meta-analysis, 2013) <sup>7</sup>	1145 (1298)			53.10	15.50	70.50	66.30	25.30	
Grullo et al. (Philippines, 2016)	45 (57)	28.57	33.33	66.67	42.59	87.04	81.48	60.00	81.08

these factors. In addition, Roh et al. stated that all level IIb involvement in their series was always accompanied by level IIa positivity.<sup>14</sup> This is in contrast with our study wherein 9 of the 23 positive level IIb has uninvolved level IIa. Koo et al. reported 19.2% of occult metastasis to level II in patients with clinically positive lateral neck node.<sup>15</sup> They recommended inclusion of level II lymph nodes only in the presence of simultaneous involvement of levels III and IV. Our study reported 42.59% involvement of level IIb that is above the range reported in the literature.<sup>7-11</sup> In our institution, level IIb is routinely included in the selective lateral neck dissection of cN1b PTC.

Inclusion of level V in the neck dissection of cN1b remains to be debated.<sup>7-11</sup> Lim et al. reported a 16% rate of occult metastasis to level V and suggested that routine neck dissection of level V is not necessary.<sup>10</sup> On the other hand, Zhang et al. and Kupferman et al. reported 28.8% and 53% rate of level V involvement.<sup>8,16</sup> In a systematic review by Eskander et al. of eighteen studies, they reported 25.3% level V involvement.<sup>7</sup> These authors suggested including level V in the neck dissection of cN1b PTC. In this study, level V involvement is higher than the previous three studies. In addition, preoperative imaging using CT and ultrasound was not sensitive in identifying positive level V nodes.<sup>16</sup> Thus, inclusion in the neck dissection or at least an intraoperative assessment of level V is suggested.

Several studies reported on the possible clinicopathologic factors associated with level V involvement. Similar to this study, age and sex were not significantly associated with level V involvement.<sup>16</sup> Single level involvement of level II, III, or IV as well as multilevel involvement of levels II, III, and IV was associated with nodal metastases in level V.<sup>8,10,16</sup> In a study by Lim et al., level V involvement was always accompanied by simultaneous level IV lymph node metastases. They suggested that dissection of level V only when level IV is also involved.<sup>10</sup> Although level V involvement was not found to be statistically associated with single level or multilevel involvement (II-IV) in this study, there were no cases of isolated level V involvement in our series.

Other pathologic factors were reported to be associated with lateral neck node metastasis. Tumor size, extrathyroid extension and lymphovascular invasion were reported to increase the frequency of lateral nodal metastasis but the results were not stratified according to levels.<sup>17,18</sup> Zhang et al. reported that whole thyroid involvement and gross extrathyroidal extension were associated with level V positivity.<sup>8</sup> In contrast, Kupferman et al. reported that primary tumor size, extrathyroidal extension, multifocal disease and lymphovascular invasion were not associated with level V involvement.<sup>16</sup>

In conclusion, the pattern of lymph node metastasis among Filipinos is similar to that reported in the literature. However, the proportion of lymph nodes harboring metastatic PTC is higher compared to foreign data. Level V

involvement is high and thus, this study suggests including level II-V in the neck dissection among Filipinos. Level V lymph nodes should be routinely dissected or at least inspected among Filipinos with cN1b PTC.

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