

## Significance of Metastatic Lymph Node Ratio on Stimulated Thyroglobulin Levels in Papillary Thyroid Carcinoma after Prophylactic Unilateral Central Neck Dissection

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### ABSTRACT

**Background.** Prognostic significance of metastatic central lymph node ratio (CLNR) in papillary thyroid carcinoma (PTC) remains unknown. Because postsurgical detectable stimulated thyroglobulin (DsTg) after radioiodine ablation may imply persistent or recurrent disease, we evaluated the association between CLNR and rate of DsTg in patients with PTC who underwent unilateral prophylactic central neck dissection.

**Methods.** To be eligible for analysis, the prophylactic central neck dissection specimen had to contain  $\geq 3$  central lymph nodes (CLNs) with  $\geq 1$  harboring metastasis. Of 129 specimens, 51 (39.5%) were eligible. CLNR was calculated as follows: (number of metastatic CLNs/number of CLNs retrieved)  $\times$  100. They were categorized into group 1 (CLNR  $< 33.34\%$ ) ( $n = 14$ ), group 2 (CLNR 33.34–66.67%) ( $n = 15$ ), and group 3 (CLNR  $> 66.67\%$ ) ( $n = 22$ ). Postablation sTg level was measured 6 months after radioiodine ablation. A multivariate analysis was conducted to identify factors for postablation DsTg.

**Results.** Young age, palpable neck swelling, large tumor size, advanced tumor, node, metastasis system (TNM) stage, and large number of metastatic CLNs were significantly associated with high CLNR ( $P < 0.05$ ). Compared to groups 1 and 2, group 3 had significantly higher DsTg rate ( $P = 0.018$ ). Those who developed subsequent recurrence had significantly higher DsTg rate than those who did not (100% vs. 39.1%,  $P = 0.013$ ). In the

multivariate analysis for postablation DsTg, after adjusting for age, palpable neck swelling, tumor size, TNM stage, and number of metastatic CLNs, CLNR was the only independent factor (odds ratio 1.15, 95% confidence interval 1.01–1.31,  $P = 0.036$ ).

**Conclusions.** A higher CLNR was associated with a higher rate of postablation DsTg; this may imply higher future recurrence rate.

Papillary thyroid carcinoma (PTC) is the most common type of differentiated thyroid carcinoma, and its age-adjusted incidence has doubled in the last 25 years.<sup>1</sup> Despite its relatively good prognosis with a 10-year cancer-specific survival above 90%, locoregional recurrence is common.<sup>2</sup> With recognition of the concept of stepwise progression of lymph node metastasis originating from the central (level VI) to the lateral compartment (levels II–V), a growing number of surgeons are advocating routine prophylactic central neck dissection (pCND) at the time of the total thyroidectomy for PTC.<sup>3</sup> Although the role of pCND remains controversial because there is still no good evidence to show that it improves long-term outcomes such as cancer-specific or disease-free survival when compared to without pCND, the analysis of short-term markers for recurrence (e.g., postsurgical stimulated thyroglobulin level, sTg) seems to indicate that pCND may improve short-term outcomes.<sup>4–6</sup>

Metastatic lymph node ratio (LNR) (defined as number of metastatic lymph nodes divided by number of lymph nodes examined) after prophylactic lymphadenectomy has been shown to be a promising prognostic variable in a variety of nonthyroidal primary cancers (e.g., colorectal, gastric, and pancreatic cancers).<sup>7–9</sup> The concept of LNR is based on the assumption that it indirectly reflects the extent

or stage of the initial cancer, with a higher ratio implying a more advanced cancer stage. In addition to the tumor, node, metastasis system (TNM), LNR has been shown to be an independent predictor of tumor biology and has been used to guide adjuvant treatment in select patient groups.<sup>7,8,10</sup> However, the prognostic value of LNR in PTC has not been as well studied. To our knowledge, two studies have specifically looked at the prognostic significance of LNR in PTC.<sup>11,12</sup> Although both studies suggested that a higher LNR may be associated with poorer survival outcomes and more advanced disease, they analyzed patients who underwent prophylactic or therapeutic lymphadenectomy. Because pCND has increasingly been advocated at the time of total thyroidectomy for PTC, our study aim was to evaluate the impact of metastatic central lymph node ratio (CLNR) on short-term outcomes (with sTg used as a surrogate marker) in patients who underwent unilateral pCND after total thyroidectomy for PTC.<sup>13</sup>

## PATIENTS AND METHODS

### Patients

From June 2004 to February 2011, a total of 267 consecutive patients with PTC underwent surgery at our institution. All were managed by the same surgical team. Of these, 129 (48.3%) underwent a routine unilateral pCND at the time of the total thyroidectomy. None had evidence of central lymph node (CLN) metastases preoperatively on ultrasound (US) or intraoperatively, and those with concomitant clinical lymph node metastases (N1b) or distant metastases (M1) were excluded. To calculate CLNR (%), the number of metastatic CLNs was divided by the total number of CLNs retrieved in the excised pCND specimen and multiplied by 100. During the study period, all resected specimens were examined by the same group of pathologists in our institution by using a standardized technique. For this study, specimens containing <3 CLNs retrieved during pCND ( $n = 38$ ) were excluded. This was to avoid falsely exaggerating the CLNR when only one or two CLNs were available.<sup>11,12</sup> Also because the study aimed to assess the effect of CLNR rather than the impact of metastatic CLNs on sTg, specimens containing no metastatic CLN (pN0) were excluded ( $n = 40$ ). Therefore, a total of 51 patients were eligible for analysis. In terms of patient characteristics, most were women (84.3%) and ethnic Chinese (96.1%). The median age at operation was 45.0 (range 17.7–71.9) years, and the median follow-up period was 31.2 (range 7.3–77.1) months. The median number of metastatic CLNs was 4 (range 1–16) and the median number of CLNs collected was 8 (range 3–26); therefore, the median CLNR was 64.1% (range 12.5–100.0%). To evaluate the association between

CLNR and other patient characteristics, patients were categorized into group 1 (CLNR <33.34%) ( $n = 14$ ), group 2 (CLNR = 33.34–66.67%) ( $n = 15$ ), and group 3 (CLNR > 66.67%) ( $n = 22$ ).

### Methods

All relevant clinical, laboratory, radiologic, and perioperative data were collected prospectively, and follow-up data were regularly updated in a computerized database. The present study protocol was approved by the local institutional review board. Patient clinicopathologic features, sTg, and postoperative outcomes were compared between the three groups.

### Management of PTC

Details of surgical treatment, criteria for radioactive iodine (RAI) ablation, postoperative care, and follow-up protocol had been described previously.<sup>6,14</sup> In brief, total thyroidectomy was the preferred procedure for all patients with a preoperative diagnosis of PTC. A similar extent of unilateral pCND was performed for all patients regardless of tumor size or extent.<sup>6</sup> The pCND consisted of the removal of all nodes and fibro-fatty tissue extending vertically from the hyoid bone to the thoracic inlet and laterally from the medial border of common carotid artery to the midline of the trachea. The ipsilateral recurrent laryngeal nerve was mobilized and skeletonized along its entire cervical course. An intraoperative nerve stimulator was used to confirm its functional integrity.<sup>15</sup> Parathyroid autotransplantation was readily performed. sTg was defined as a thyroglobulin (Tg) level measured in the presence of thyroid-stimulating hormone (TSH) at a level of >30 mIU/L either by 4-week thyroxine withdrawal or recombinant TSH injections. The preablation sTg levels were taken approximately 2 months after surgery (at the time of RAI ablation), while the postablation levels were taken approximately 9 months after surgery (6–7 months after RAI ablation or at the time of the whole-body scan). Tg autoantibodies were measured at the same time. The decision for RAI ablation was based on the presence of at least one or more risk factors, such as tumor size >1 cm, lymph node metastasis, age of >45 years, extrathyroidal extension, macroscopic postoperative residual disease in the neck, and distant metastasis; the decision did not depend on the preablative sTg level. Three gigabecquerels or 80 mCi of <sup>131</sup>I was the standard fixed ablative dose, while subsequent <sup>131</sup>I therapy was performed with 5.5 GBq (or 150 mCi). TSH suppression to below <0.1 µg/L was recommended for high- and intermediate-risk patients.

### Postoperative and Follow-up Protocol

Serum calcium and phosphate levels were measured postoperatively. Calcium with or without vitamin D supplements were prescribed if symptomatic or if calcium was  $<1.70$  mmol/L. Those who discontinued supplements in the presence of normocalcemia within 6 months were considered to have temporary hypoparathyroidism, and those who needed supplements for  $>6$  months were considered to have permanent hypoparathyroidism. Perioperative direct laryngoscopy was performed to assess vocal cord function. Vocal cord palsy lasting  $>6$  months was regarded as permanent. All postsurgical patients were followed up within 4 weeks at a specialized combined oncology clinic. A follow-up visit was conducted at 3-month intervals in the first 2 years, 6-month intervals in the next 3 years, and annually thereafter. Clinical examination, neck US, and nonstimulated Tg level were assessed during follow-up visits. Locoregional recurrence was defined as macroscopic disease at clinical examination or US that was not initially present.

### Laboratory Methods

All postoperative sTg levels were measured at the same laboratory by the same immunometric assay. The assay used was the Immulite 2000 (Diagnostic Products, Roche, Los Angeles, CA). This was calibrated against the CRM-457 standard. A sTg level of  $>0.5$   $\mu\text{g/L}$  was considered a detectable stimulated thyroglobulin (DsTg). Normal reference range was  $<0.5$ – $55$   $\mu\text{g/L}$ , and sensitivity was  $<0.2$   $\mu\text{g/L}$ .

### Statistical Analysis

Statistical analysis was performed by the chi-square test or Fisher's exact test to compare categorical variables, and the Mann-Whitney *U*-test or the Kruskal–Wallis test was used to compare continuous variables between groups. To evaluate the correlation between two continuous variables, the Spearman rank correlation test was performed. Continuous variables were expressed as medians with ranges. Variables that were statistically significant in the univariate analysis were entered into multivariate analysis. To improve clinical utility, before entering into the multivariate analysis, some potentially significant continuous variables such as age and CLNR were converted into categorical variables. Binary logistic regression analysis with a variable entrance criterion of 0.05 or less was conducted to identify factors associated with detectable postablative after surgery. All statistical analyses were performed by SPSS software, version 18.0 (SPSS, Chicago, IL).

## RESULTS

Table 1 shows a comparison of patient clinicopathologic features, TNM tumor stages, CLNR and metastases, age, completeness of surgery, invasion, and size (MACIS) score between groups 1, 2, and 3. The median age at operation was significantly different between the three groups ( $P < 0.001$ ), with group 3 having the youngest median age. There was an inverse correlation between age and CLNR ( $\rho = -0.399$ ,  $P = 0.004$ ). Group 3 was significantly more likely to present with a palpable swelling than groups 1 and 2 ( $P = 0.031$ ). There was a direct association between tumor size and CLNR, with group 3 having the largest median size relative to groups 1 and 2 (2.8 cm vs. 0.8 cm and 1.7 cm, respectively,  $P < 0.001$ ). Other tumor characteristics like multifocality, capsular invasion, extrathyroidal extension, and coexistent thyroiditis were similar between the groups. Regarding TNM staging, group 1 had highest proportion of stage I tumors ( $P = 0.001$ ) and the lowest proportion of stage III and IV tumors ( $P = 0.001$ ). There were no stage II tumors because patients aged  $<45$  years with distant metastases and aged  $\geq 45$  years with no lymph node metastases were already excluded.

Figure 1 shows the distribution of number of CLNs collected during pCND in the cohort. The median number of CLNs retrieved was similar between the three groups ( $P = 0.351$ ), but the number of metastatic CLNs excised was significantly higher in group 3 ( $P < 0.001$ ). The number of CLNs collected was not different between those aged  $<45$  years and aged  $\geq 45$  years ( $P = 0.396$ ). The median number of metastatic CLNs excised in groups 1, 2, and 3 was 1, 4, and 7, respectively. The MACIS score in the three groups was not significantly different ( $P = 0.068$ ). In terms of postoperative cord palsy, 2 patients (14.3%) in group 1 developed temporary palsy, and patient 1 (4.5%) in group 3 developed permanent palsy. The rate of cord palsy was similar between the 3 groups ( $P = 0.209$ ). For hypoparathyroidism, no patient developed permanent hypoparathyroidism. The rate of temporary hypoparathyroidism in groups 1, 2, and 3 were 14.3%, 42.9% and 36.6%, respectively, and were similar between the three groups ( $P = 0.227$ ).

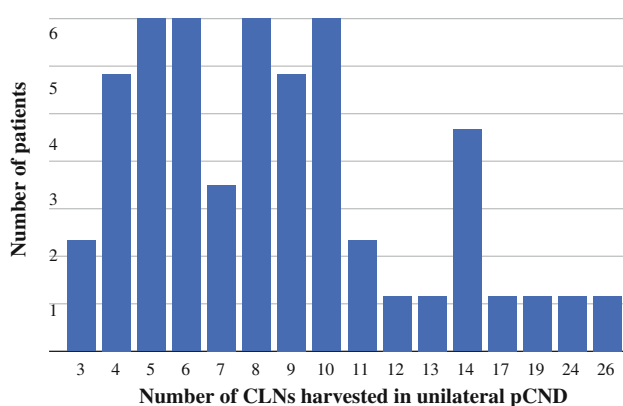
Table 2 shows a comparison of postoperative sTg levels, follow-up period, and recurrence between groups 1, 2, and 3. All patients received RAI ablation 2–3 months after surgery. In the preablation period, median TSH, sTg, and the rate of DsTg were similar between the three groups, while in the postablation period, the median sTg level and the rate of DsTg were statistically significantly different. Relative to groups 1 and 2, group 3 had the highest median postablation sTg level (3.8  $\mu\text{g/L}$  vs.  $<0.5$  and  $<0.5$   $\mu\text{g/L}$ , respectively,  $P = 0.031$ ) and rate of DsTg (72.7% vs.

**TABLE 1** Patient clinicopathologic features, tumor stage, and MACIS score

Characteristic	Group 1 ( <i>n</i> = 14)	Group 2 ( <i>n</i> = 15)	Group 3 ( <i>n</i> = 22)	<i>P</i> -value
Age at operation, years	49.0 (47.0–71.9)	45.0 (29.1–70.8)	38.2 (17.7–59.4)	<0.001
Sex				0.933
Male	2 (14.3)	2 (13.3)	4 (18.2)	
Female	12 (85.7)	13 (86.7)	18 (81.8)	
Presented as a palpable neck swelling	8 (57.1)	9 (60.0)	20 (90.9)	<b>0.031</b>
Tumor characteristics				
Tumor size, mm	0.8 (0.6–2.2)	1.7 (1.3–3.5)	2.8 (1.0–5.5)	<0.001
Multifocality	4 (28.6)	4 (26.7)	6 (27.3)	0.995
Capsular invasion	2 (14.3)	2 (13.3)	6 (27.3)	0.522
Extrathyroidal extension	2 (14.3)	5 (33.3)	6 (27.3)	0.614
Coexisting thyroiditis	4 (28.6)	4 (26.7)	4 (18.2)	0.225
Stage of PTC by TNM				<b>0.001</b>
I	6 (42.9)	2 (13.3)	6 (27.3)	
II	0 (0.0)	0 (0.0)	0 (0.0)	
III	6 (42.9)	10 (66.7)	9 (40.9)	
IV	2 (14.3)	3 (20.0)	7 (31.8)	
No. of CLNs retrieved	5 (4–16)	9 (3–26)	9 (3–14)	0.351
No. of metastatic CLNs excised	1 (1–2)	4 (2–16)	7 (3–14)	<0.001
Metastatic CLNR, %	20.0 (12.5–25.0)	44.4 (36.4–66.67)	80.0 (70.0–100.0)	<0.001
MACIS score	3.84 (3.3–6.3)	4.7 (4.2–7.9)	4.1 (3.2–7.1)	0.068

Continuous variables are expressed as median (range); categorical variables are expressed as *n* (%)

PTC papillary thyroid carcinoma, TNM 6th edition tumor, node and metastasis staging system, MACIS metastases, age, completeness of surgery, invasion and size



**FIG. 1** Histogram showing the distribution of total number of CLNs collected in unilateral pCND

21.4% and 26.7%, respectively,  $P = 0.018$ ). Similarly, although the proportion of preablation DsTg was similar ( $P = 0.793$ ), the postablative DsTg was significantly lower in group 2 than in group 3 (26.7% vs. 72.7%,  $P = 0.032$ ). The median follow-up duration and recurrence rate were similar between the three groups. At the time of analysis, all patients were alive. In group 1, one patient experienced bilateral lateral compartment recurrence 32.9 months after

surgery, while in group 2, there was no patient who developed recurrence. In group 3, four patients developed ipsilateral lateral compartment. These four recurrences developed at 13.5, 16.3, 18.5, and 20.9 months, respectively, after surgery. All five of these recurrences had postablation DsTg 9 months after surgery, and their median sTg level was 9.7  $\mu\text{g/L}$  (range 2.5–481.0  $\mu\text{g/L}$ ). The patient with the recurrence and a detectable stimulated Tg of 2.5 had an abnormal US 5 months later. The rate of DsTg was significantly different between those who developed recurrence and those who did not (100% vs. 39.1%,  $P = 0.013$ ). Those with recurrence ( $n = 5$ ) had similar number of LNs collected as those without recurrence ( $n = 46$ ) ( $P = 0.317$ ).

Figure 2 shows the cumulative disease-free survivals for groups 1, 2, and 3. No differences were observed between the groups ( $P = 0.385$ ).

Table 3 shows the results of the multivariable analysis of clinicopathologic factors for postablation DsTg level 9 months after surgery. Variables that were statistically significant in the univariate analysis were entered into the multivariate analysis, except for a palpable neck swelling and tumor size, because they were interrelated. Therefore, only one of these two variables was entered into the

**TABLE 2** Postoperative sTg levels, follow-up period, and recurrence rate

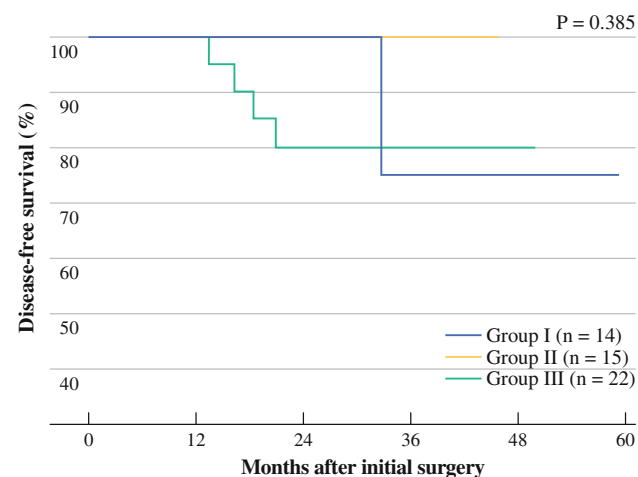
Characteristic	Group 1 (n = 14)	Group 2 (n = 15)	Group 3 (n = 22)	P-value
Preablation period <sup>a</sup>				
TSH level (mIU/L)	47 (35–99)	43 (30–73)	48 (32–182)	0.679
sTg level (µg/L)	1.5 (<0.5–56.0)	1.5 (<0.5–108.0)	5.4 (<0.5–324.0)	0.543
No. of DsTg	7 (50.0)	10 (66.7)	16 (72.7)	0.505
Postablation period <sup>b</sup>				
TSH level (mIU/L)	91 (48–146)	52.5 (40–85)	65.5 (30–146)	0.076
sTg level (g/L)	<0.5 (<0.5–9.7)	<0.5 (<0.5–17.0)	3.8 (<0.5–481.0)	<b>0.031</b>
No. of DsTg	3 (21.4)	4 (26.7)	16 (72.7)	<b>0.018</b>
Follow-up period, mo	22.7 (6.4–65.9)	25.5 (6.1–59.2)	24.6 (6.3–73.7)	0.298
First site of recurrence				
Locoregional	1 (7.1)	0 (0.0)	4 (18.2)	0.190
Distant	0 (0.0)	0 (0.0)	0 (0.0)	

Continuous variables are expressed as median (range); categorical variables are expressed as n (%)

<sup>a</sup> Two months after surgery

<sup>b</sup> Nine months after surgery

TSH thyroid stimulating hormone, sTg stimulated thyroglobulin, DsTg detectable stimulated thyroglobulin (or stimulated thyroglobulin >0.5 µg/L)



**FIG. 2** Cumulative disease-free survival curves of PTC with a metastatic CLNR of <33.34% (group 1), 33.34–66.67% (group 2), and >66.67% (group 3) after unilateral pCND

multivariate analysis at a time. However, regardless of whether tumor size or a palpable neck swelling was entered, CLNR (expressed as a continuous variable) remained the only independent factor for detectable postablation sTg level (odds ratio 1.15, 95% confidence interval 1.01–1.31,  $P = 0.036$ ), after adjusting for TNM stage, age at operation, and number of metastatic CLNs excised. When CLNR was entered into the multivariate analysis as a categorical variable (i.e., <33.34%, 33.34–66.67%, >66.67%), a CLNR of >66.67% remained the only independent risk factor for detectable postablation sTg ( $\beta$  coefficient 3.60, odds ratio 36.64, 95% confidence interval 1.10–1217.53,  $P = 0.044$ ).

**TABLE 3** Multivariable analysis of clinicopathologic risk factors for postablative DsTg 9 months after surgery

Covariate	$\beta$ coefficient	Odds ratio (95% confidence interval)	P-value
Presented as a palpable swelling			
No		1	
Yes	1.13	3.10 (0.16–59.89)	0.495
Age at operation	0.101	1.107 (0.90–1.36)	0.338
Metastatic CLNR	0.138	1.15 (1.01–1.31)	<b>0.036</b>
No. of metastatic CLNs	0.672	1.958 (0.85–4.52)	0.115
Stage of PTC by TNM			
I		1	
II		–	
III	3.53	34.21 (0.42–2777.84)	0.115
IV	6.43	617.01 (0.31–1235019)	0.098

PTC papillary thyroid carcinoma, TNM 6th edition tumor, node and metastasis staging system

## DISCUSSION

Although LNR carries prognostic significance in several nonthyroidal cancers, its significance in PTC remains unclear. Two recent studies reported that a higher LNR in PTC might be associated with worse outcomes, but they included patients who underwent prophylactic or therapeutic lymphadenectomy. Furthermore, their LNRs were calculated based on lymph nodes retrieved from both the

central and lateral compartments. Our study aimed specifically to evaluate the significance of CLNR because pCND has been increasingly advocated in PTC.<sup>6,13</sup> However, because PTC is an indolent tumor with an excellent prognosis, it is difficult to adequately evaluate the prognostic significance of CLNR unless a large patient population followed for a long period is available for analysis. Because postoperative DsTg after RAI is a surrogate for persistent or recurrent disease, our study aimed to evaluate the association between CLNR and rate of DsTg in patients who underwent an unilateral pCND.<sup>13,16–18</sup>

In terms of the association between CLNR and clinicopathologic characteristics, our data showed there was a marked inverse association between age and CLNR with group 1 having the oldest median age when compared to groups 2 and 3. However, because this association has not been previously evaluated, this finding requires further validation. Nevertheless, some studies found that young age was an independent risk factor of CLN metastases, and so this could possibly account for the higher CLNR in this age group, assuming that the number of CLNs retrieved was similar across all ages.<sup>19</sup> In our analysis, the number of CLNs retrieved was not different between those aged <45 years and those aged  $\geq 45$  years ( $P = 0.396$ ). Similar to a recent study, our data showed that tumor size was directly correlated with CLNR, with larger tumors associated with higher CLNR.<sup>12</sup> However, because both age and tumor size are important variables in the TNM staging system, it was surprising that groups 2 and 3 still had a far greater proportion of stage III and IV tumors than group 1.

In terms of outcomes, our data found there was no statistically significant association between preablative sTg and CLNR. However, this would be consistent with our previous analysis because we previously reported that preablative sTg level was only dependent on pCND and not on other clinicopathologic variables, and in our cohort, all patients underwent pCND.<sup>6</sup> On the other hand, our data found an association between postablative sTg and CLNR as well as postablative DsTg and CLNR. To further validate this association, a multivariate analysis was performed. In the multivariate analysis, after adjusting for factors like age, palpable neck swelling, number of metastatic CLNs, and TNM stage, CLNR turned out to be the only independent factor for postablation DsTg. When entered as a categorical variable, we found that if the CLNR in the excised pCND specimen was  $>66.67\%$ , the chance of having postablative DsTg was 36.64 times higher than if the CLNR was  $<33.34\%$ . Because the number of metastatic CLNs was adjusted, theoretically a pCND specimen containing 1 of 3 metastatic CLNs would have a similar rate of DsTg as a specimen containing 2 of 6 metastatic CLNs. However, this needs to be further validated.

Although DsTg does not always imply higher recurrence and worse prognosis, all 5 patients who developed recurrences in our cohort had DsTg with sTg levels ranging 2.5–481.0  $\mu\text{g/L}$ . Furthermore, the rate of DsTg was significantly different between those who subsequently developed recurrence and those who did not (100% vs. 39.1%,  $P = 0.013$ ). On the basis of these, perhaps a higher CLNR implies a higher chance of residual microscopic disease which may in turn lead to higher recurrences. In our cohort, we believe that some of these “early recurrences” may actually represent persistent microscopic disease that was too small to be detected by US in early postoperative period. Because a unilateral pCND was performed, the likely site for these residual microscopic diseases included the contralateral central and/or lateral compartments. However, because we did not perform contralateral pCND in cases of lateral recurrence, we could not confirm this.

We believe that these findings may have important implications. First, a high CLNR might be a parameter for administering a higher RAI ablation dose after pCND, as this has not been widely adopted in many institutions. Of note, despite the 3 GBq ablative dose, none of the remaining 16 patients in group 3 became athyroglobulinemic, and this differed from group 2, where 6 of 10 remaining patients became athyroglobulinemic. Second, for surgeons who are contemplating prophylactic lateral neck dissection in PTC, group 3 would be the group that might benefit most, although this would mean a second operation. Regarding whether the contralateral central neck should be explored in this situation, we could not evaluate this because none of the 5 locoregional recurrences had the contralateral central neck explored; however, this would be an interesting aspect to evaluate in future studies.

Despite these findings, it is important to note that lymph node status probably has little survival significance in PTC in patients younger than 45. We also acknowledge certain shortcomings with our study, including the small number of patients within each group, potential biases in the selection for pCND, and subtle variation in histopathologic findings between pathologists. Some clinicians would argue that a sTg cutoff of 0.5  $\mu\text{g/L}$  would be too low and a sTg level taken at 9 months after surgery might be too soon as an outcome measurement. However, a sTg of  $<0.5 \mu\text{g/L}$  at 1 year has been shown to have a  $>98\%$  likelihood of identifying patients completely free of disease at follow-up, and a stimulated Tg level assessed at 1 year after surgery has been shown to be as good as a level assessed at 2–3 years after surgery.<sup>20,21</sup> Therefore, we believe that sTg of  $<0.5 \mu\text{g/L}$  at 9 months after surgery would serve as a good surrogate for future recurrences. Interestingly, one of the recurrences did have a low sTg level of 2.5  $\mu\text{g/L}$ , but this may be explained by the small volume of recurrent disease, which was only detected by US 5 months later.

We postulate that perhaps the recurrent disease might have been present at the time of sTg testing. Therefore, although sTg might be a good surrogate, it should be interpreted in the context of normal imaging findings. The clinical significance of mildly elevated Tg remains unknown, and some detectable levels may occasionally decrease with time.<sup>13,20,22</sup> Perhaps with a larger-sized cohort, recurrence might be a better study end point.

In conclusion, young age, a palpable neck swelling, large tumor size, advanced TNM stage, and large number of metastatic CLNs were statistically significantly associated with a high CLNR. CLNR was the only independent determinant of DsTg 9 months after surgery. A higher CLNR was associated with a higher rate of postablative DsTg, and this may imply higher recurrences in the future.

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