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Optimal Cut-Off Values of Lymph Node Ratio Predicting Recurrence in Papillary Thyroid Cancer

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Abstract: Regional lymph node (LN) metastasis has a significant impact for prediction of recurrence in patients with papillary thyroid cancers (PTC); however, the prognostic value of the lymph node ratio (LNR), which is defined as the ratio of the number of metastatic LNs to the total number of investigated LNs, is controversial. In this study, we determined the optimal cut-off values of LNRs for the prediction of recurrence in PTC patients.

This large cohort study retrospectively evaluated 2294 patients who had undergone total thyroidectomy for PTC at a single institution from October 1985 to June 2009. The prediction probability of central LNR (cLNR, level VI) and total LNR (tLNR, levels II–VI) were estimated by binominal logistic regression analysis. Hazard ratios of the cut-off LNR values for cancer recurrence were calculated for relevant covariates using multivariate Cox regression analyses. Kaplan–Meier analyses were also utilized to assess the effects of estimated LNR cut-off values on recurrence-free survival (RFS).

Of the 2294 patients, 138 (6.0%) presented cancer recurrence during the follow-up period (median duration = 107.1 months). The prediction probability indicated that LNRs of 0.4 and 0.5 for central LN and total LN, respectively, are optimal cut-off values for precise prediction with minimization of outliers. Multivariate Cox regression analyses revealed that cLNR $\geq$0.4 was independently predictive of recurrence in patients with N0 and N1a PTCs (hazard ratio [HR]: 7.016, 95% confidence interval [CI]: 3.72–12.986, $P < 0.001$) and that tLNR $\geq$0.5 indicated a significantly increased risk of recurrence in patients with N1b PTCs (HR: 2.372, 95% CI: 1.458–3.860, $P < 0.001$). In addition, Kaplan–Meier analyses clearly demonstrated that these LNR cut-off values are precisely operational in RFS estimation.

The cut-off LNR values of 0.4 and 0.5 for cLNR and tLNR, respectively, were identified. Risk stratification combined with these LNR cut-off values may prove useful to determine treatment and follow-up strategies for PTC patients.

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Abbreviations: AJCC = American Joint Committee on Cancer, CCND = central compartment node dissection, CI = confidence interval, cLNR = central lymph node ratio, CT = computed tomography, FNAB = fine needle aspiration biopsy, HR = hazard ratio, LN = lymph node, LNR = lymph node ratio, MRND = modified radical neck dissection, pN0 = positron emission tomography-computed tomography, PTC = papillary thyroid cancer, RAI = radioactive iodine, RFS = recurrence-free survival, Tg = thyroglobulin, TgAb = anti-Tg antibody, tLNR = total lymph node ratio, TT = total thyroidectomy, US = ultrasonography.

INTRODUCTION

Papillary thyroid cancer (PTC) is the most common endocrine malignancy worldwide and elicits good therapeutic response to surgery and/or radioiodine therapy; however, a significant proportion of PTC patients experience recurrence especially in neck lymph nodes (LNs).[1–3] In fact, to predict the clinical outcome of PTC, most clinicians utilize the international American Joint Committee on Cancer (AJCC) tumor, node, metastases (TNM) staging system, but this classical classification system cannot precisely predict nodal recurrence of patients with PTC, as this system was designed to predict patient mortality.[4–6]

Recently, the American Thyroid Association (ATA) proposed that the number and the size of metastatic LNs in the neck can be an important predictor for recurrence of PTC.[7,8] Therefore, complete evaluation including the number and the size of metastatic LNs in PTC has become more important for the determination of exact tumor stage, direction of appropriate adjuvant treatment plans, and prediction of long-term prognosis, including nodal recurrence. In addition to the number and the size of metastatic LNs, the ratio of metastatic LNs to examined LNs (lymph node ratio, LNR) has been suggested by several groups to be useful to predict PTC recurrence.[9–12]

Creation of a personalized treatment plan is primarily based on individualized risk estimation of recurrence and disease-specific mortality. Thus, a better refinement of LN metastasis using the LNR would be influential in creating such a treatment plan; however, previous studies have been unable to eliminate confounding factors caused by inhomogeneous central and/or lateral LN dissection yield.[10,13] Furthermore, the

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optimal LNR cut-off value that will predict tumor recurrence remains undetermined.[12,14,15] In this study, we analyzed clinicopathological parameters in a large cohort of PTC patients who underwent total thyroidectomy (TT) and central compartment node dissection (CCND) with or without modified radical neck dissection (MRND) in a single tertiary referral hospital. To determine the optimal LNR cut-off value for PTC, we also performed statistical analyses to estimate the prediction probabilities of LNRs and to calculate recurrence-free survival (RFS) using the defined optimal LNR cut-off value.

MATERIALS AND METHODS

Study Subjects

The medical records of 2750 PTC patients who underwent TT with CCND or MRND between October 1985 and June 2009 were retrospectively analyzed. Clinico-pathological parameters, including number of metastatic LNs and LN dissection yield at the initial operation, were collected from the database of our institution. To investigate the long-term effects of LNRs on PTC recurrence in a homogenous patient cohort, we designed the study protocol as shown in Figure 1. Of the 2750 patients, 176 (6.4%) were excluded as a result of inadequate follow-up duration (<5 years) and 25 (0.9%) were excluded because they were too young or too old (aged ≤13 years or ≥76 years) at baseline. Of the remaining 2549 patients, 1829 (71.8%) with tumors classified as N0 or N1a underwent TT with CCND, whereas the remaining 720 (28.2%) with tumors classified as N1b underwent TT with MRND. To ensure adequate cervical LN dissection yield, patients with <6 central LNs harvested by CCND (n=175, 9.6%) and <18 total LNs harvested by MRND (n=80, 11.1%) were excluded. Therefore, 2294 patients were eligible for analysis. The study protocol was approved by the local institutional review board, which waived the requirement for informed consent due to the retrospective nature of this study.

Management Protocol

Following complete radiologic and histologic examinations, the extent of thyroidectomy in all patients with PTC was determined using ATA guidelines[13]. Cervical LNs in levels II–VI were evaluated preoperatively by neck ultrasonography (US) and computed tomography (CT). Patients underwent CCND (level VI; pretracheal, prelaryngeal, and paraesophageal LNs) prophylactically for accurate staging of PTC and for management of subclinical LN metastasis or therapeutically for clinically suspicious LNs. For the lateral (levels II-V) neck compartment, patients preoperatively presenting with clinical LN metastasis underwent therapeutic MRND.

Excluding those with T1N0M0 tumors, patients who underwent TT received low-dose (1.1 GBq) radioactive iodine (RAI) for remnant ablation at 4 to 8 weeks after surgery. At 5 to 7 days after RAI treatment with T4 withdrawal or rhTSH injection, serum thyroglobulin (Tg) and anti-thyroglobulin antibody (TgAb) concentrations were measured, and post-ablation whole body scans (WBS) were performed. High-dose RAI (3.7–5.5 GBq) was recommended to patients with more aggressive tumor histology (T4 or N1b stage) or initial distant metastasis as well as to selected patients with high serum thyroglobulin (Tg) levels yet without definite metastatic lesions, after RAI WBS.

Follow-Up Protocol

Patients underwent radioactive iodine (RAI) ablation about 1 to 3 months after surgery using a dose based on ATA guidelines.[16] Patients were then examined by physical examination, neck US, and measurement of serum Tg and anti-Tg antibody (TgAb) concentrations at 3 and 6 months and annually thereafter. Patients with evidence of recurrence or distant metastasis were assessed by additional imaging modalities, including neck CT and/or positron emission tomography-computed tomography (PET-CT). Structural disease recurrence was

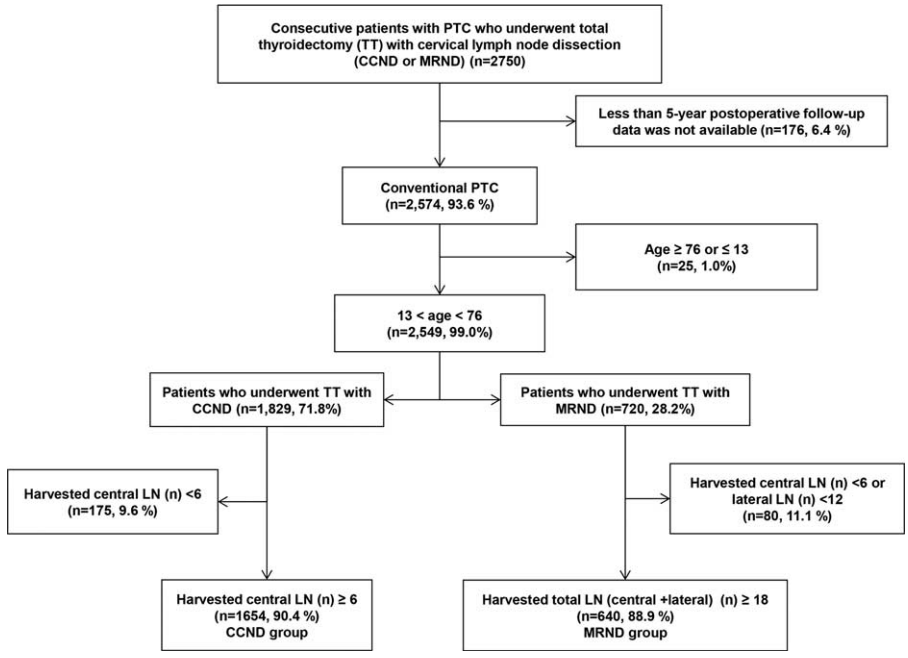

FIGURE 1. Flow diagram outlining the study protocol.

confirmed by imaging modalities and/or by pathological diagnosis using US-guided fine needle aspiration biopsy (FNAB).

Measurement of LNR

Whole surgical specimens were analyzed histologically to determine tumor characteristics and to assess the presence of LN metastasis. The pathologic LN status of these specimens was reassessed independently by 2 experienced pathologists. Pathologic N0 (pN0) was defined as the absence of metastatic foci in the harvested cervical LN, whereas pN1a and pN1b were defined as the presence of metastatic LNs among any retrieved central and lateral LNs, respectively. LNR was defined as the total number of metastatic LNs divided by the total number of LNs retrieved from the central compartment (level VI) alone (cLNR = number of metastatic LNs/number of dissected LNs in level VI) and from the central and lateral compartments (levels II–VI; tLNR = number of metastatic LNs/number of dissected node in LNs in level II–VI).

Statistical Analysis

Rates and proportions were calculated for categorical data, whereas means ± SDs were calculated for continuous data. Groups were compared using Student's *t* test, chi-square test, or Wilcoxon rank sum test as appropriate. RFS was defined as the time from the date of surgery to the date of first detection of structural recurrent disease. Binominal logistic regression analysis was used to calculate the predicted probability function of recurrence for each LNR, and threshold cLNR and tLNR were selected. Univariate analyses were utilized to determine factors significantly associated with recurrence; factors analyzed included patient age and gender; tumor size; extrathyroidal extension; pathologic T-, N-, M-, and TNM-stages; and predicted LNR. Factors that proved significant by univariate analysis were entered into multivariate analysis by logistic regression to determine factors independently associated with tumor recurrence. Survival curves were calculated according to the Kaplan–Meier method and compared by the log-rank test. All *P* values <0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS statistics 20.0 (SPSS Inc., Chicago, IL).

RESULTS

Characteristics of the Study Patients

Of the 2294 patients who fulfilled the selection criteria, 1654 (72.1%) underwent TT with CCND and 640 (27.9%) underwent TT with MRND. The baseline characteristics of these patients are shown in Supplementary Table 1, http://links.lww.com/MD/A668. Study patients were mostly women (87.5%). The mean age at time of surgery was 44.6 ± 12.0 years (range, 13–76 years), and mean tumor size was 14.8 ± 9.5 mm (range, 6.0–80.0 mm). The ablation success rate parameters of study patients at low- or high-dose RAI ablation after surgery are presented in Supplementary Table 2, http://links.lww.com/MD/A668.

Median follow-up duration was 107.1 months (range, 72–289 months) at the time of the last clinic visit. At the time of last follow-up, 17 patients (0.7%) had died due to disease-specific causes. Structural recurrence was observed in 138 (6.0%) patients, and 133 (5.8%) showed locoregional recurrence with 128 (5.6%) in regional LNs and 5 (0.2%) in the operative bed. All of these local recurrences were confirmed by cytological reports. Five patients (0.2%) developed distant spreading during the follow-up period.

Estimation of the Optimal LNR Cut-Off Values

Based on the presence of metastatic LNs, 787 patients (34.3%) were classified as pN0, 867 (37.8%) as pN1a, and 640 (27.9%) as pN1b. The 10-year RFS rates for these groups were 99.3%, 92.6%, and 81.8%, respectively ($P < 0.001$). LNRs were calculated for the total number of central LNs in the CCND group (cLNR) and the total number of central and lateral LNs (levels II-VI) in the MRND group (tLNR). The mean cLNR and tLNR were 0.20 ± 0.27 and 0.31 ± 0.17, respectively (Supplementary Table 3, http://links.lww.com/MD/A668). The probability function displayed an exponential pattern, indicating that the probability of an event increases exponentially with increasing LNR. The threshold LNRs of 0.4 and 0.5 were at the inflection points of the curves without outliers (Figure 2). When we excluded the pN0 patients, the probability function also indicated an exponential pattern, and the inflection points of the curves were ~0.2 and 0.8 (Supplementary Figure 1, http://links.lww.com/MD/A668). However, as our study goal was to find the optimal cut-off value for a clinical setting and we had performed CCND for prophylactic and therapeutic purposes, we decided to include the pN0 patients in the analysis of the CCND group.

Relationship Between LNRs and RFS

In the Kaplan–Meier analysis, RFS rates were significantly decreased in the higher cLNR or tLNR categories. In the CCND group, patients with cLNR ≥0.4 had significantly lower 5-year (93.9% vs 99.2%, $P < 0.001$) and 10-year (86.8% vs 98.7%, $P < 0.001$) RFS rates than patients with cLNR < 0.4 (Figure 3A). In addition, in the MRND group, patients with tLNR ≥0.5 had significantly lower 5-year (73.8% vs 93.9%,

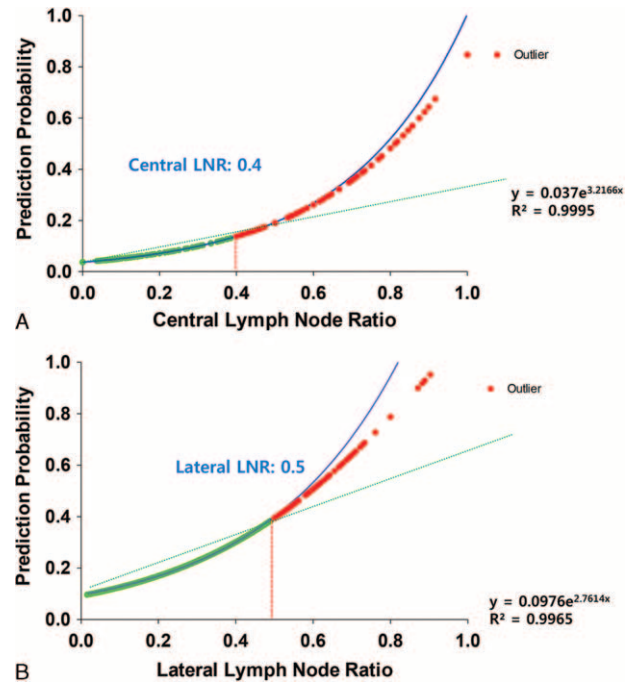

FIGURE 2. Prediction probability of lymph node ratio (LNR) using binominal logistic regression analysis. The optimal cutoffs were determined to be 0.4 for cLNR (A) and 0.5 for tLNR (B). cLNR = central lymph node ratio, LNR = lymph node ratio, tLNR = total lymph node ratio.

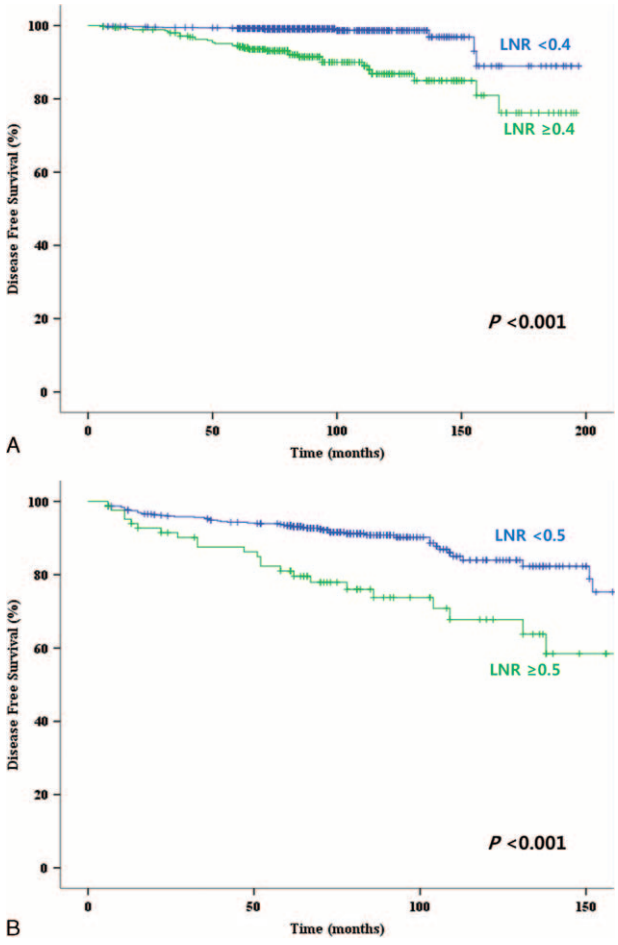

FIGURE 3. Comparison of 5-year and 10-year RFS between LN ratio <0.4 and ≥0.4 in CCND group (A) and LN ratio <0.5 and ≥0.5 in MRND group (B). CCND = central compartment node dissection, LN ratio = lymph node ratio, MRND = modified radical neck dissection, RFS = recurrence-free survival.

$P < 0.001$) and 10-year (58.4% vs 93.2%, $P < 0.001$) RFS rates than patients with tLNR < 0.5 (Figure 3B).

Univariate analyses were performed to identify clinical and pathological factors that are predictive of 5- and 10-year RFS. In the CCND group, larger tumor size; extrathyroidal invasion; higher pT-, pN-, pM- and TNM-stages; and cLNR (≥0.4) were significantly associated with recurrence (Table 1). In the MRND group, male gender, larger tumor size, pM1-stage, and tLNR (≥0.5) were significantly associated with recurrence (Table 2). Multivariate Cox's regression analyses revealed that all clinicopathologic parameters correlated significantly with RFS in univariate analysis were independent prognostic factors in both the CCND and MRND groups. Interestingly, log-rank tests indicated that the hazard ratio (HR) of high cLNR (HR: 7.016, 95% confidence interval [CI]: 3.792–12.983, $P < 0.001$) was higher than that of pN stage (HR: 4.796, 95% CI: 2.146–10.719, $P < 0.001$) in the CCND group (Table 3). In the MRND group, high tLNR (≥0.5) significantly increased the risk of PTC recurrence (HR: 2.372, 95% CI: 1.458–3.860), whereas pN classification had no statistically significant impact, indicating that LNRs may be a more useful predictor for recurrence than the pN designation (Table 4).

DISCUSSION

LN metastases are frequently observed in patients with PTC and occur in anyway from 20% to 70% of patients depending on the definition of LN metastases, due to the high prevalence of subclinical metastases.[17–19] Although many investigators propose that clinically detectable metastatic LNs are associated with tumor recurrence, the role of prophylactic CCND to completely remove all potentially subclinical disease remains unclear. Prophylactic CCND, however, has been reported to reduce the likelihood of central neck recurrence, because neck US has a limited ability to evaluate these central compartment LNs preoperatively and micrometastatic LNs are detected in up to 90% of these patients.[2,19–22] Prophylactic CCND may, however, increase complications, while simultaneously imparting questionable therapeutic impacts on patients without clinically apparent disease in LNs.[2,16,18,19,22] As controversy regarding the role of prophylactic CCND continues, finding an optimal approach to determine detailed LN status in patients with PTC has been regarded as a critical step to enhance the staging accuracy, to choose appropriate adjuvant treatments, and finally to predict long-term patient prognosis. Based on this information, all patients who underwent TT according to ATA guidelines have also undergone routine prophylactic CCND at our institution. As a result, our surgical treatment policy provides complete removal of all potential metastatic lesions in level VI LNs.

The number of LNs examined has been regarded as a surrogate measure of the extent of dissection in different nodal basins.[9,12,23–26] Maximizing the number of LNs retrieved during thyroid cancer surgery has been reported to increase the likelihood of complete remission and reduce the incidence of recurrence;[12,24] however, LNR is influenced not only by the disease burden but also by the extent of the neck dissection and pathologic examination. Therefore, it is important to determine whether a minimum number of LNs should be harvested during cervical LN dissection to achieve an adequate operative yield and decrease the risk of recurrence. Several previous studies evaluated the LNR of cases of thyroid cancer from which >3 LNs were harvested.[10,13] However, many variations have been reported in the minimum number of LNs required to determine proper LNR criteria in thyroid cancer surgery. For example, 1 previous study included patients with >4 LNs, whereas another included those with >6 LNs.[12,14,15] These confusing results have demonstrated the difficulty in suggesting the proper criteria for determining the minimum number of LNs to be removed in thyroid cancer surgery. As the lymph node yield (LNY) is an indicator for adequate staging, we can expect that the smaller the number of LNs harvested, the higher the probability that metastatic nodal disease would be left unresected. It is reasonable to assume that such unresected disease may contribute not only to local recurrence but to long-term prognosis as well. Several studies have found that the risk of recurrence is positively associated with a higher number of LN metastases at initial presentation. Leboulleux et al reported that the 10-year risk of recurrence was significantly higher in patients with >10 metastatic LNs (21%) than in patients with < 5 LN metastases (3%).[27] Likewise, Sugitani et al demonstrated that the risk of recurrence was significantly higher in patients with >5 LN metastases (19%) that in those with < 5 LN metastases (8%).[28] According to these results, the ATA Surgical Affairs Committee's Taskforce concluded via meta-analysis that the median risk

TABLE 1. Univariate Analysis of Prognostic Factors for Recurrence-Free Survival in PTC Patients who Underwent Total Thyroidectomy with CCND (N = 1654)

Variable	Number	Percentage of 5-year RFS	*P* Value*	Percentage of 10-Year RFS	*P* Value*
Age, y					
<45	755	98.2	0.612	95.1	0.554
≥45	899	98.1		93.0	
Gender					
Female	1492	98.3	0.185	98.2	0.299
Male	162	97.5		91.9	
Tumor size (mm)					
≤10	895	98.9	0.106	98.9	<0.001
>10	759	97.3		92.7	
Histologic subtype					
Conventional PTC	1289	97.9		97.8	0.257
Follicular variant PTC	319	99.0	0.390	99.0	
Other variants of PTC**	46	87.5		61.2	
Multifocality					
Absent	954	98.6	0.318	98.5	0.284
Present	700	97.6		97.6	
Bilaterality					
Absent	1128	98.5	0.394	95.4	0.267
Present	526	97.5		95.3	
Extrathyroidal extension					
Absent	644	98.9	0.075	96.9	0.001
Present	1010	97.7		90.6	
pT classification					
T1	596	99.0		99.0	0.001
T2	43	99.0	0.015	98.1	
T3	968	97.8		95.5	
T4a	46	78.1		67.0	
T4b	1	0		0	
pN classification					
N0	780	99.5	0.003	99.5	<0.001
N1a	825	96.9		92.6	
LNR (0.4)					
<0.4	1301	99.2	<0.001	98.7	<0.001
≥0.4	353	93.9		86.8	
pM classification					
M0	1651	98.4	<0.001	95.6	<0.001
M1	3	0		0	
TNM stage					
I	944	98.5		97.0	
II	4	75.0		62.0	
III	647	98.3	<0.001	95.1	<0.001
IVa	34	70.4		26.1	
IVb	1	0		0	
IVc	2	0		0	

CCND = central compartment node dissection, LNR = ratio of metastatic to examined lymph nodes, PTC = papillary thyroid cancer, RFS = re-recurrence-free survival.

* *P* value: log-rank test.

** Other variants of PTC: tall cell variant, diffuse sclerosing variant, columnar variant, and solid variant of PTC.

of recurrence in papillary thyroid cancer patients varies markedly according to the number of positive nodes (<5 nodes: 4% [range 3%–8%] vs >5 nodes: 19%, [range 7%–21%]).[29] Taken together, we decided on a cut-off of at least 6 central LNs in the CCND group based on the criteria of recurrence risk determined by the ATA Taskforce. This cut-off range of LNs may provide the proper LNY and thus minimize the variations in surgical and pathologic factors used to determine LNR.

Several staging systems have been developed to identify reliable clinico-pathological factors that can be used to stratify patients relative to outcomes and to propose proper long-term management for patients with PTC.[1,4–6,16] The staging accuracy of these systems has profound variations that originate from practical issues, such as completeness of potential metastatic LNs removal, or from the characteristics of the staging system itself, such as oversimplification of metastatic cervical LNs. In the case of the AJCC TNM staging system, cervical LN

TABLE 2. Univariate Analysis of Prognostic Factors for Recurrence-Free Survival in PTC Patients who Underwent Total Thyroidectomy with MRND (N = 720)

Variable	Number	Percentage of 5-Year RFS	*P* Value*	Percentage of 10-Year RFS	*P* Value*
Age, y					
<45	377	92.4	0.219	91.0	0.667
≥45	263	98.1		85.6	
Gender					
Female	515	93.4	0.412	92.8	0.004
Male	125	91.9		84.4	
Tumor size, mm					
≤10	895	98.9	0.328	97.5	<0.001
>10	759	97.3		90.7	
Histologic subtype					
Conventional PTC	468	91.9	0.146	90.3	0.078
Follicular variant PTC	149	94.9		90.5	
Other variants of PTC**	23	87.0		62.7	
Multifocality					
Absent	316	98.1	0.904	92.8	0.518
Present	324	97.6		90.7	
Bilaterality					
Absent	399	93.5	0.315	92.6	0.102
Present	241	88.5		87.8	
Extrathyroidal extension					
Absent	117	94.8	0.472	66.8	0.099
Present	526	93.2		90.1	
pT classification					
T1	91	91.5	0.348	87.6	0.176
T2	24	82.0		72.1	
T3	464	91.8		90.4	
T4a	52	78.1		20.8	
T4b	9	44.4		0	
LNR (0.5)					
<0.5	555	93.9	<0.001	93.2	<0.001
≥0.5	85	73.8		58.4	
pM classification					
M0	626	94.7	<0.001	92.7	<0.001
M1	14	35.7		0	
TNM stage					
I	351	93.8	0.104	45.7	0.067
II	9	66.7		65.6	
III	2	92.0		90.6	
IVa	269	78.1		50.4	
IVb	3	44.4		0	
IVc	6	16.7		0	

LNR = ratio of metastatic to examined lymph nodes, MRND = modified radical neck dissection, PTC = papillary thyroid cancer, RFS = recur-recurrence-free survival.

* *P* value: log-rank test

** Other variants of PTC: tall cell variant, diffuse sclerosing variant, columnar variant, and solid variant of PTC.

metastases are categorized into only 2 groups: N1a (level VI) or N1b (levels II–V and VII).[5,6] Actually, the AJCC TNM staging system classifies the metastatic LNs based on cervical anatomical compartment, but this system does not reflect the extent of LN involvement, as the number of metastatic LNs has no impact on pN stage.

To improve the predictive ability of LN status, the LNR has been assessed in patients with PTC, and most studies indicated that the LNR category is independently prognostic, more so than the conventional AJCC TNM staging system.[4,9–11,23,30] Whether LNR is a better predictor than the AJCC pN category alone, however, remains unknown. Thus, we sought to determine the optimal cut-off LNRs for long-term (5 and 10 year) prediction of RFS in a large number of patients with PTC. We found that a cLNR of 0.4 was the optimal cut-off value in patients who underwent CCND of at least 6 dissected central LNs. Furthermore, a tLNR of 0.5 was also optimal in patients who underwent MRND with at least 18 total harvested LNs. Using these cut-off values, we found that even after adjusting for other significant prognostic factors of RFS, these cLNR and tLNR values predicted the risk of recurrence of PTC and exhibited an independent association with RFS.

TABLE 3. Multivariate Analysis (Cox Proportional Hazard Model) of Prognostic Factors for RFS in PTC Patients who Underwent Total Thyroidectomy with CCND (N = 1654)

Variable	HR	CI	*P* Value
Tumor size	3.751	1.852–7.596	<0.001
Extrathyroidal extension	3.691	1.656–8.225	0.001
pT classification			
T1	0.537	1.234–3.226	0.004
T2	1.168	1.514–3.691	
T3	2.685	2.541–4.534	
T4a	15.470	1.425–18.214	
pN classification	4.796	2.146–10.719	<0.001
LNR (≥0.4)	7.016	3.792–12.983	<0.001
pM classification	16.650	1.012–17.807	<0.001
TNM stage			
I	1.027	0.601–1.102	<0.001
II	1.343	1.102–1.514	
III	1.754	1.257–1.942	
IVa	2.212	1.322–2.215	
IVb	9.615	1.512–15.812	
IVc	13.125	1.814–19.512	

CCND = central compartment node dissection, CI = confidence interval, HR = hazard ratio, LNR = ratio of metastatic to examined lymph nodes, PTC = papillary thyroid cancer, RFS = recurrence-free survival.

Recently, as our understanding of the molecular biological aspect of thyroid carcinogenesis has markedly improved, targeted agents such as sorafenib (Nexavar®), vemurafenib, trametinib, and dabrafenib have been investigated and developed for the purpose of treating recurrent or persistent PTC.[31] In addition to the discoveries of new drugs, molecular markers to support precise diagnosis and predict poor prognosis have also been studied, such as the BRAFV600E mutation and TERT promoter mutation.[32–34] Coupling with these new advances in molecular markers, the assessment of LNR after surgical treatment could improve the predictability of PTC prognosis in future studies.

Although this study revealed numerous important positive findings, this study had several limitations, including its retrospective design and performance at a single center. Even within a single institution, surgical skills and pathologic assessments may vary. This study attempted to minimize these drawbacks by adjusting LNR and LN yield for the extent of neck dissection. Furthermore, we included only those patients from whom at least 6 central LNs or 18 central and lateral LNs were harvested. The median follow-up period in this study was only 107 months, which was likely not long enough to completely determine RFS rates in patients with PTC, a cancer that can recur decades after initial treatment. Another unresolved issue in the present work was whether patient ablation using high-dose RAI (3.7–5.5 GBq) would have an impact on long-term outcomes, compared with patients who did not undergo high-dose RAI ablation. Our results indicate that further clinical trials are needed to define the effectiveness of RAI ablation. Finally, this study included patients who underwent prophylactic CCND. Due to the insufficient data for patients without prophylactic CCND, the potential role of prophylactic CCND in PTC patients remains a subject of debate. In the future, large multicenter studies may provide further evidence of the ability of threshold LNR values to predict recurrence and influence postoperative treatment in patients with PTC.

TABLE 4. Multivariate Analysis (Cox Proportional Hazard Model) of Prognostic Factors for RFS in PTC Patients who Underwent Total Thyroidectomy with MRND (N = 720)

Variable	HR	CI	*P* Value
Gender	2.016	1.241–3.275	0.005
Tumor size	1.665	0.935–2.965	0.083
LNR (≥0.5)	2.372	1.458–3.860	0.001
pM classification	13.680	6.776–27.620	<0.001

CI = confidence interval, HR = hazard ratio, LNR = ratio of metastatic to examined lymph nodes, MRND = modified radical neck dissection, PTC = papillary thyroid cancer, RFS = recurrence-free survival.

In conclusion, our study assessed the ability of LNR to predict RFS in patients with PTC. A cut-off LNR of 0.4 in CCND patients and 0.5 in MRND patients were significant independent predictors of disease recurrence and may be superior to using known risk factors, including pN stage, as predictors. These findings suggest that assessment of proper cut-off LNRs, combined with existing staging systems and prognostic variables, will aid the determination of further treatment and follow-up strategies in patients with PTC.

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REFERENCES

1. Adam MA, Pura J, Gu L, et al. Extent of surgery for papillary thyroid cancer is not associated with survival: an analysis of 61 775 patients. *Ann Surg*. 2014;260:601–605.
2. Hartl DM, Leboulleux S, Al Ghuzlan A, et al. Optimization of staging of the neck with prophylactic central and lateral neck dissection for papillary thyroid carcinoma. *Ann Surg*. 2012;255:777–783.
3. Yu XM, Wan Y, Sippel RS, et al. Should all papillary thyroid microcarcinomas be aggressively treated? An analysis of 18 445 cases. *Ann Surg*. 2011;254:653–660.
4. Mankarios D, Baade P, Youl P, et al. Validation of the QTNM staging system for cancer-specific survival in patients with differentiated thyroid cancer. *Endocrine*. 2014;46:300–308.
5. Shaha AR. TNM classification of thyroid carcinoma. *World J Surg*. 2007;31:879–887.
6. Tanase K, Thies ED, Mader U, et al. The TNM system (version 7) is the most accurate staging system for the prediction of loss of life expectancy in differentiated thyroid cancer. *Clin Endocrinol (Oxf)*. 2016;84:284–291.
7. Jeon MJ, Kim WG, Jang EK, et al. Sub-classification of lateral cervical lymph node metastasis in papillary thyroid carcinoma by pathologic criteria. *PLoS One*. 2015;10:e0133625.
8. Jeon MJ, Kim WG, Choi YM, et al. Recent changes in the clinical outcome of papillary thyroid carcinoma with cervical lymph node metastasis. *J Clin Endocrinol Metab*. 2015;100:3470–3477.
9. Lango M, Flieder D, Arrangoiz R, et al. Extranodal extension of metastatic papillary thyroid carcinoma: correlation with biochemical endpoints, nodal persistence, and systemic disease progression. *Thyroid*. 2013;23:1099–1105.

10. Schneider DF, Chen H, Sippel RS. Impact of lymph node ratio on survival in papillary thyroid cancer. *Ann Surg Oncol.* 2013;20: 1906–1911.
11. Schneider DF, Mazeh H, Chen H, et al. Lymph node ratio predicts recurrence in papillary thyroid cancer. *Oncologist.* 2013;18:157–162.
12. Vas Nunes JH, Clark JR, Gao K, et al. Prognostic implications of lymph node yield and lymph node ratio in papillary thyroid carcinoma. *Thyroid.* 2013;23:811–816.
13. Lang BH, Wong KP, Wan KY, et al. Significance of metastatic lymph node ratio on stimulated thyroglobulin levels in papillary thyroid carcinoma after prophylactic unilateral central neck dissection. *Ann Surg Oncol.* 2012;19:1257–1263.
14. Takada H, Kikumori T, Imai T, et al. Patterns of lymph node metastases in papillary thyroid carcinoma: results from consecutive bilateral cervical lymph node dissection. *World J Surg.* 2011;35:1560–1566.
15. Jeon MJ, Yoon JH, Han JM, et al. The prognostic value of the metastatic lymph node ratio and maximal metastatic tumor size in pathological N1a papillary thyroid carcinoma. *Eur J Endocrinol.* 2013;168:219–225.
16. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2009;19:1167–1214.
17. Noguchi S, Noguchi A, Murakami N. Papillary carcinoma of the thyroid. I. Developing pattern of metastasis. *Cancer.* 1970;26: 1053–1060.
18. Grubbs EG, Evans DB. Role of lymph node dissection in primary surgery for thyroid cancer. *J Natl Compr Canc Netw.* 2007;5: 623–630.
19. Lang BH, Ng SH, Lau LL, et al. A systematic review and meta-analysis of prophylactic central neck dissection on short-term locoregional recurrence in papillary thyroid carcinoma after total thyroidectomy. *Thyroid.* 2013;23:1087–1098.
20. Son YI, Jeong HS, Baek CH, et al. Extent of prophylactic lymph node dissection in the central neck area of the patients with papillary thyroid carcinoma: comparison of limited versus comprehensive lymph node dissection in a 2-year safety study. *Ann Surg Oncol.* 2008;15:2020–2026.
21. Caliskan M, Park JH, Jeong JS, et al. Role of prophylactic ipsilateral central compartment lymph node dissection in papillary thyroid microcarcinoma. *Endocr J.* 2012;59:305–311.
22. McHenry CR, Stulberg JJ. Prophylactic central compartment neck dissection for papillary thyroid cancer. *Surg Clin North Am.* 2014;94:529–540.
23. Adam MA, Pura J, Goffredo P, et al. Presence and number of lymph node metastases are associated with compromised survival for patients younger than age 45 years with papillary thyroid cancer. *J Clin Oncol.* 2015;33:2370–2375.
24. Esfandiari NH, Hughes DT, Yin H, et al. The effect of extent of surgery and number of lymph node metastases on overall survival in patients with medullary thyroid cancer. *J Clin Endocrinol Metab.* 2014;99:448–454.
25. Jeon MJ, Kim WG, Choi YM, et al. Recent changes in the clinical outcome of papillary thyroid carcinoma with cervical lymph node metastasis. *J Clin Endocrinol Metab.* 2015;100:3470–3477.
26. Machens A, Dralle H. Correlation between the number of lymph node metastases and lung metastasis in papillary thyroid cancer. *J Clin Endocrinol Metab.* 2012;97:4375–4382.
27. Leboulleux S, Rubino C, Baudin E, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. *J Clin Endocrinol Metab.* 2005;90:5723–5729.
28. Sugitani I, Kasai N, Fujimoto Y, et al. A novel classification system for patients with PTC: addition of the new variables of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. *Surgery.* 2004;135:139–148.
29. Randolph GW, Duh QY, Heller KS, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid.* 2012;22:1144–1152.
30. Sterpetti AV. Optimization of staging of the neck with prophylactic central and lateral neck dissection for papillary thyroid carcinoma. *Ann Surg.* 2015;261:e30.
31. Mandal R, Becker S, Strebhardt K. Stamping out RAF and MEK1/2 to inhibit the ERK1/2 pathway: an emerging threat to anticancer therapy. *Oncogene.* 2015; doi: 10.1038/onc.2015.329.
32. Xing M, Alzahrani AS, Carson KA, et al. Association between BRAF V600E mutation and recurrence of papillary thyroid cancer. *J Clin Oncol.* 2015;33:42–50.
33. Shi X, Liu R, Qu S, et al. Association of TERT promoter mutation 1 295 228 C>T with BRAF V600E mutation, older patient age, and distant metastasis in anaplastic thyroid cancer. *J Clin Endocrinol Metab.* 2015;100:E632–E637.
34. Xing M, Liu R, Liu X, et al. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. *J Clin Oncol.* 2014;32:2718–2726.