Significance of micrometastases in the calculation of the lymph node ratio for papillary thyroid cancer

Young Woo Chang, Hwan Soo Kim, Seung Pil Jung, Hoon Yub Kim, Jae Bok Lee, Jeoung Won Bae, Gil Soo Son

Department of Breast Endocrine Surgery, Korea University College of Medicine, Seoul, Korea

Purpose: The lymph node ratio (LNR) is an important prognostic factor in papillary thyroid carcinoma (PTC), but micrometastases in cervical lymph nodes (LNs) are not of great clinical importance. In this study, we analyzed the accuracy of prediction of the prognosis depending on whether micrometastases were included in the number of metastatic LNs when calculating LNR.
Methods: The study included 353 PTC patients who underwent total thyroidectomy with neck LN dissection, and calculated LNR by 2 methods according to whether micrometastases were included in the number of metastatic LNs: Method 1 did not and method 2 did include. To compare the predictive values of LNR by the 2 methods, correlation coefficients and receiver operating characteristic (ROC) curves were analyzed.
Results: Positive correlations were found between LNR and preablation stimulated thyroglobulin (sTg) levels in both methods, but the correlation between method 1 LNR and preablation sTg level was significantly stronger than that for method 2 (Fisher z = 1.7, P = 0.045). The areas under these 2 independent ROC curves were analyzed; the prognostic efficacy of method 1 LNR was more accurate than that of method 2 LNR, and the difference was statistically significant (P = 0.0001).
Conclusion: Regional recurrence of PTC can be predicted more accurately by not including micrometastases in the number of metastatic LNs when calculating LNR.
[Ann Surg Treat Res 2017;92(3):117-122]

Key Words: Papillary thyroid carcinoma, Lymph nodes

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common histologic type of differentiated thyroid cancer and has a 10-year survival rate of greater than 90% [1-3]. Despite its excellent prognosis, regional recurrence in cervical lymph nodes (LNs) occurs in 5.4%–13% of PTC patients who undergo surgery [4,5]. The presence of neck LN metastases is an independent risk factor for recurrence, and regional neck LN metastases are found in approximately 30%–65% of PTC patients [6-8]. According to the pathological TNM classification for PTC of the American Joint Committee on Cancer (AJCC), the nodal status for PTC is categorized into N1a and N1b, based on the neck compartment location of the metastatic LNs. However, the prognoses of patients with the same nodal status are quite variable, and it is difficult to predict the prognosis using the traditional TNM classification.

Recent studies have suggested that a higher lymph node ratio (LNR), the ratio of the number of metastatic LNs to the total number of LNs retrieved, was strongly associated with recurrence of PTC after initial surgery, and LNR has emerged as an alternative nodal staging system [9-11]. Metastatic LN size is also an important prognostic factor in PTC [11-13], and several studies showed that micrometastases in the cervical

LNs were not of great clinical importance [14-16]. To our knowledge, no studies have analyzed the accuracy of prediction of the prognosis depending on whether micrometastases were included in the number of metastatic LNs when calculating LNR.

In this study, we calculated LNR by 2 methods according to whether micrometastases were included in the number of metastatic LNs, and evaluated to determine which method could predict the prognosis more accurately.

METHODS

Study population

Between January 2003 and December 2012, records of 733 PTC patients who underwent total thyroidectomy with neck LN dissection were retrieved. Among these, only patients who underwent radioactive iodine (RAI) ablation after surgery were included. Patients with distant metastases or an intraoperative finding of gross tumor invasion to the surrounding structures were excluded; those with a serum thyroglobulin (Tg) autoantibody level of ≥100 U/mL were also excluded to avoid interference with preablation stimulated Tg (sTg) levels. Finally, 353 patients were eligible for analysis. This retrospective study was approved by the Institutional Review Board of Korea University Medical Center, Ansan University (registration number: AS16037–001).

Surgery and pathologic examination

All 353 patients underwent total thyroidectomy with neck LN dissection. Patients with clinically negative neck nodal findings underwent ipsilateral central neck dissection, and bilateral central neck dissection was performed in patients with clinically suspicious node metastases or bilateral PTC. Central neck dissection had the following boundaries: the hyoid bone superiorly, the carotid sheath laterally, the manubrium inferiorly, and the prevertebral fascia dorsally. Lateral neck dissection was performed in patients with evidence of lateral neck LN metastases through preoperative imaging or fine needle aspiration biopsy. Regional level IIa, III, and IV LNs were routinely included in the extent of lateral neck dissection, and level Vb LN dissection was performed only in patients with evidence of level Vb LN metastases. The entire surgical specimen was sent for pathologic examination. Histologic findings of primary tumors and LNs were recorded and analyzed.

Postoperative management and follow-up

RAI ablation therapy was administered after surgery. The dose of RAI ablation therapy was 3.7–5.6 GBq depending on risk factors such as tumor diameter, extrathyroidal extension, residual microscopic disease, or LN metastases. After RAI ablation therapy, thyroid stimulating hormone (TSH) suppressive therapy was initiated in all patients. Serum TSH was maintained at a level of ≤0.1 μU/mL. Physical examination, neck ultrasonography, and sTg levels were examined every 6 months during the follow-up period. Diagnostic RAI whole body scan, computed tomography, or whole-body fluorodeoxyglucose-PET were also performed in some patients. Clinical recurrence was defined as pathologically confirmed structural disease with fine needle aspiration biopsy, but an elevated Tg level in the absence of structural disease was not considered recurrence in this study.

Definitions

LNR was defined as the number of metastatic LNs divided by the number of removed LNs. Micrometastasis in neck LNs was defined as the presence of metastatic deposits ≤2 mm in diameter, and macrometastasis was defined as deposits >2 mm

Table 1. Clinicopathologic characteristics of the study population (n = 353)

Characteristic	Value
Age at operation (yr)	47 (16–76)
Sex	
Women	320 (90.7)
Men	33 (9.3)
Tumor size (cm)	1.1 (0.1–7.0)
Extrathyroidal extension	130 (36.8)
Extent of neck lymph node dissection	
Unilateral central compartment	173 (49.0)
Bilateral central compartments	141 (39.9)
Central and lateral compartments	39 (11.0)
Retrieved lymph nodes	6 (1–42)
Metastatic lymph nodes	
Method 1	2 (0–25)
Method 2	2 (0–26)
LNR	
Method 1	0.33 (0–1.00)
Method 2	0.38 (0–1.00)
TNM staging	
I	175 (49.6)
II	1 (0.3)
III	159 (45.0)
IVa	18 (5.1)
Radioiodine therapy	
3.7 GBq	146 (41.4)
5.6 GBq	207 (58.6)
Follow-up period (mo)	64 (2–155)
Preablation sTg level (ng/mL)	1.2 (0.3–3,102.5)
First site of recurrence	
Locoregional	26 (7.4)
Distant	0 (0)

Values are presented as median (range) or number (%).
LNR, lymph node ratio; sTg, stimulated thyroglobulin.

in maximal diameter. This is a commonly accepted pathological definition [16,17]. LNR was calculated by 2 methods according to whether micrometastases were included in the number of metastatic LNs: method 1 did not and method 2 did include.

Statistical analysis

Statistics were calculated using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA), and MedCalc ver. 16.2.1 (MedCalc Software, Oostende, Belgium) was also used for analyzing data and plotting graphs. Continuous variables were presented as medians with range, and categorical variables were presented as numbers with percentages. The relationship between 2 variables was calculated using correlation coefficients, and Fisher transformation was used to analyze the difference between 2 correlation coefficients. Receiver operating characteristic (ROC) curve analysis was performed to calculate the difference between the areas under the curves (AUCs). Differences were considered statistically significant at a P-value of <0.05.

RESULTS

Patient characteristics and pathology

Of 353 patients included in this study, 320 (90.7%) were women and 33 (9.3%) were men, with a median age of 47 years (range, 16–76 years). The median tumor size was 1.1 cm (range, 0.1–7.0 cm), and extrathyroidal extension was observed in 130 patients (36.8%). A total of 314 patients (89.0%) underwent central neck dissection, and 39 (11.0%) with evidence of lateral neck LN metastases underwent central and lateral neck dissection. The median number of retrieved LNs was 6 (range, 1–42). The median number of metastatic LNs in methods 1 and 2 was 2 (range, 0–25) and 2 (range, 0–26), respectively. The median LNRs of methods 1 and 2 were 0.33 and 0.38, respectively. Using the TNM classification system, 175 patients (49.6%) had stage I disease, 1 (0.3%) had stage II disease, 159 (45.0%) had stage III disease, and 18 (5.1%) had stage IVa disease. All patients received RAI therapy; 146 (41.4%) received 3.7 GBq and 207 (58.6%) received 5.6 GBq. During a median follow-up of 64 months (range, 2–155 months), 26 events (7.4%) of locoregional recurrence occurred, but there were no cases of distant recurrence. Clinicopathologic characteristics of the
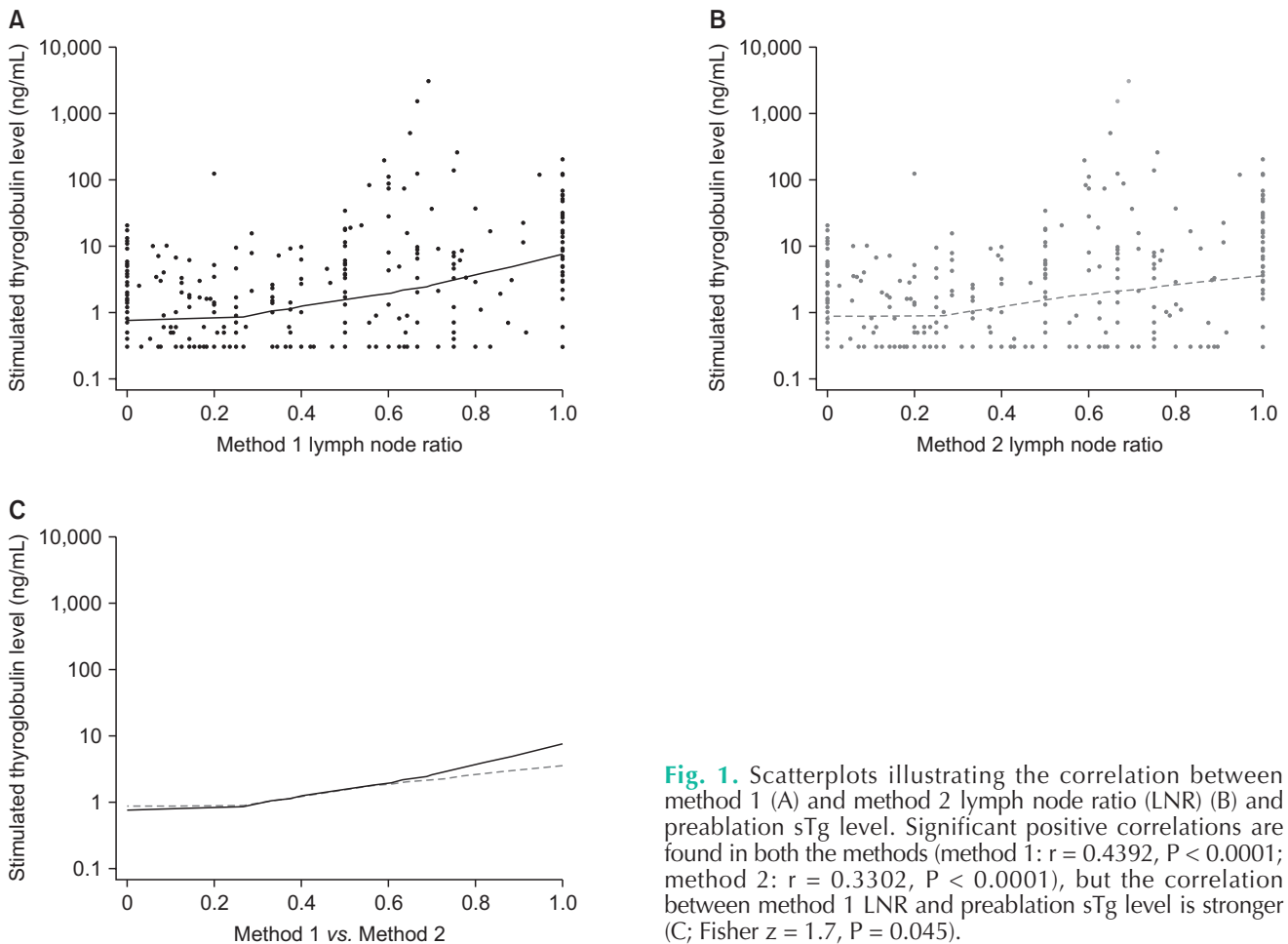

Fig. 1. Scatterplots illustrating the correlation between method 1 (A) and method 2 lymph node ratio (LNR) (B) and preablation sTg level. Significant positive correlations are found in both the methods (method 1: r = 0.4392, P < 0.0001; method 2: r = 0.3302, P < 0.0001), but the correlation between method 1 LNR and preablation sTg level is stronger (C; Fisher z = 1.7, P = 0.045).

study population are summarized in Table 1.

Comparison of correlation coefficients in both methods

We analyzed correlation coefficients in both methods. Positive correlations were found between LNR and preablation sTg level in both methods. The correlation covariants between LNR and preablation sTg levels in methods 1 and 2 were r = 0.4392 (P < 0.001) and r = 0.3302 (P < 0.001), respectively. The Fisher r-to-z transformation was used to assess the significance of the difference between correlation coefficients of the 2 methods, and the correlation between method 1 LNR and preablation sTg level was significantly stronger than for method 2 (Fisher z = 1.7, P = 0.045). The results are illustrated as a scatterplot in Fig. 1.

Comparison of ROC curves of both methods

ROC curves were used to examine prognostic efficacy of LNR in both methods. Examination of the coordinates of the curve indicates that the best cutoff point for both methods was 0.4706. At this value, the sensitivity for methods 1 and 2 was 84.6%

and 84.6%, with a specificity of 63.3% and 58.1%, respectively. The AUC values for the 2 methods were 0.749 (95% confidence interval [CI], 0.700–0.793) and 0.710 (95% CI, 0.660–0.757), respectively. DeLong test was used to analyze the significance of the difference between these 2 independent AUCs. The prognostic accuracy of the method 1 LNR was greater than that for method 2, and the difference was statistically significant (P = 0.0001). The ROC curves are represented in Fig. 2.

DISCUSSION

In PTC patients who undergo surgery, LNR is an independent predictor of recurrence, according to recent studies [9-11,18-21]. LNR is better at predicting prognosis than the AJCC TNM staging system, because the latter was developed for predicting mortality in PTC patients, not recurrence. The prognosis for patients with PTC is excellent. However, patients with recurrence may require additional surgery, and may have complications that are likely to affect the quality of life [22]. Thus, predicting recurrence is as important as predicting mortality, and LNR is useful for predicting recurrence.
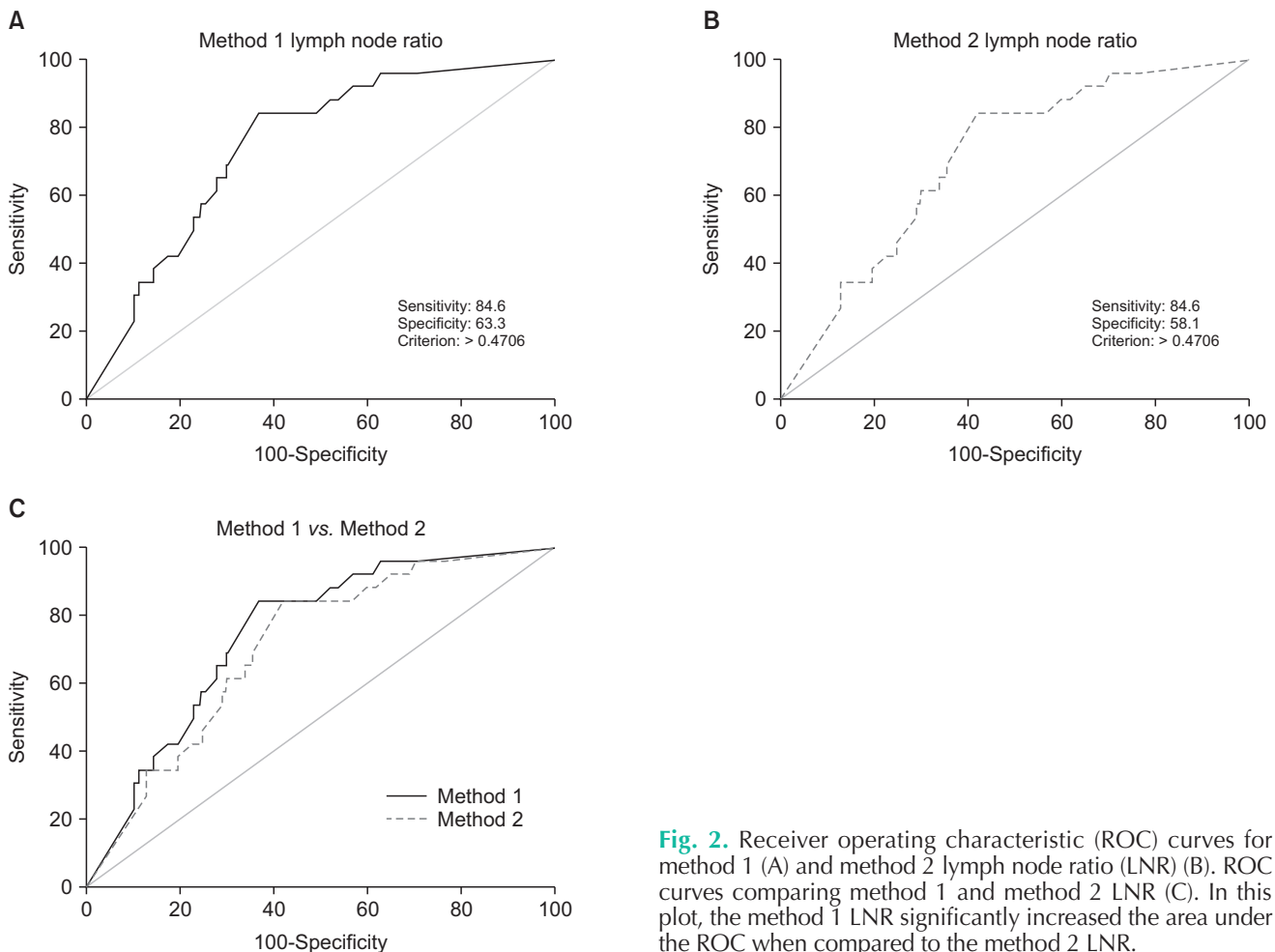

Fig. 2. Receiver operating characteristic (ROC) curves for method 1 (A) and method 2 lymph node ratio (LNR) (B). ROC curves comparing method 1 and method 2 LNR (C). In this plot, the method 1 LNR significantly increased the area under the ROC when compared to the method 2 LNR.

A study on the relationship between maximal tumor size of metastatic LNs and prognosis was initiated for breast cancer in 1971 [17]. A recent study showed that micrometastases 2 mm or less in size in sentinel LNs did not influence the prognosis in early breast cancer [23]. In PTC patients, several studies used a similar concept, and reported that micrometastases in neck LNs did not lead to higher rates of recurrence [11,14-16]. LNR was defined as the number of metastatic LNs divided by the number of removed LNs. Thus, the predictive ability of LNR could be influenced by whether micrometastases are included in the number of metastatic LNs, the numerator in the LNR.

The serum Tg level is used for surveillance for recurrence of PTC and is more accurate when the serum TSH level is high [24]. The LNR and preablation sTg level have a strong positive relationship [25]; therefore, the predictive ability for recurrence in the 2 methods could be compared using r values of the correlation coefficient. We found that the correlation between the LNR and preablation sTg level is significantly stronger when micrometastases are not included in the number of metastatic LNs ($R = 0.4392$ *vs.* $R = 0.3302$), i.e., the predictive ability is more accurate when micrometastases are excluded from the LNR.

We also analyzed the ROC curves of the 2 methods. Method 2 had the same optimal cutoff point for LNR, 0.4706, as method 1. This cutoff point was comparable to that of other reports using various methods such as quantiles, ROC curves, and predicted probability [10,11,26]. However, whether micrometastases were included in the number of metastatic LNs did not influence changes in the cutoff value. Method 2 also had the same sensitivity at this cutoff point as method 1, but the specificity of the optimal cutoff point was lower than that for method 1. This means that inclusion of micrometastases in the LNR does not predict more patients who will have recurrence of PTC, but instead could increase the probability of predicted recurrence in patients who will not actually have a recurrence. The AUCs were compared to determine whether LNR had greater efficacy for predicting recurrence in method 1 or method 2. As expected, the AUC of method 1 was larger than that of method 2; this suggests that inclusion of micrometastases in the LNR would decrease its efficacy for predicting recurrence.

In a previous study on the prognostic value of micrometastases [14], enrolled patients were divided into 3 PTC groups: those with only micrometastatic LNs, those with only macrometastatic LNs, and those without metastasis; the recurrence rate in each group was examined. This was a good method for assessment of the prognostic value of micrometastases, but the number of PTC patients with only micrometastatic LNs was small, and the PTC patients with micrometastatic and macrometastatic LNs could not be analyzed. In contrast to the previous study, we did not divide enrolled patients into groups, but calculated LNR by 2 methods in the patients and assessed the prognostic value by comparing correlation coefficients and ROC curves. Accordingly, we could include even the PTC patients with micrometastatic and macrometastatic LNs in this study and assess the prognostic value of micrometastases in more patients with micrometastatic LNs than the previous study.

Several limitations of this study should be considered, including its retrospective design, which has potential bias. The median follow-up period was 64 months, which was relatively short to completely determine recurrence in patients with PTC. Furthermore, there was no analysis according to the dose of RAI, which could influence the long–term outcome; we excluded patients who did not undergo RAI ablation in order to avoid variables due to the effectiveness of RAI. Finally, recurrence was defined as only pathologically confirmed structural disease. Biochemical recurrence was not considered, because the relationship between LNR and preablation sTg level requires analysis in this study. Accordingly, the results must be interpreted with caution, and further studies with a longer follow-up period would have to be conducted.

In conclusion, regional recurrence of PTC can be predicted more accurately by not including micrometastases in the number of metastatic LNs when calculating LNR.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 1990;71:414-24.
2. Tubiana M, Schlumberger M, Rougier P, Laplanche A, Benhamou E, Gardet P, et al. Long-term results and prognostic factors in patients with differentiated thyroid carcinoma. Cancer 1985;55:794-804.
3. Samaan NA, Maheshwari YK, Nader S, Hill CS Jr, Schultz PN, Haynie TP, et al. Impact of therapy for differentiated carcinoma of the thyroid: an analysis of 706 cases. J Clin Endocrinol Metab 1983; 56:1131-8.

4. Sivanandan R, Soo KC. Pattern of cervical lymph node metastases from papillary carcinoma of the thyroid. Br J Surg 2001; 88:1241-4.

5. Grant CS, Hay ID, Gough IR, Bergstralh EJ, Goellner JR, McConahey WM. Local recurrence in papillary thyroid carcinoma: is extent of surgical resection important? Surgery 1988;104:954-62.

6. Wada N, Duh QY, Sugino K, Iwasaki H, Kameyama K, Mimura T, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. Ann Surg 2003;237:399-407.

7. Roh JL, Park JY, Park CI. Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and postoperative levels of serum parathyroid hormone. Ann Surg 2007;245:604-10.

8. Chang YW, Kim HS, Kim HY, Lee JB, Bae JW, Son GS. Should central lymph node dissection be considered for all papillary thyroid microcarcinoma? Asian J Surg 2016;39:197-201.

9. Ryu IS, Song CI, Choi SH, Roh JL, Nam SY, Kim SY. Lymph node ratio of the central compartment is a significant predictor for locoregional recurrence after prophylactic central neck dissection in patients with thyroid papillary carcinoma. Ann Surg Oncol 2014;21:277-83.

10. Lang BH, Wong KP, Wan KY, Lo CY. Significance of metastatic lymph node ratio on stimulated thyroglobulin levels in papillary thyroid carcinoma after prophylactic unilateral central neck dissection. Ann Surg Oncol 2012;19:1257-63.

11. Jeon MJ, Yoon JH, Han JM, Yim JH, Hong SJ, Song DE, 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;168:219-25.

12. Ito Y, Fukushima M, Kihara M, Takamura Y, Kobayashi K, Miya A, et al. Investigation of the prognosis of patients with papillary thyroid carcinoma by tumor size. Endocr J 2012;59:457-64.

13. Lee YS, Lim YS, Lee JC, Wang SG, Kim IJ, Lee BJ. Clinical implication of the number of central lymph node metastasis in papillary thyroid carcinoma: preliminary report. World J Surg 2010;34:2558-63.

14. Cranshaw IM, Carnaille B. Micrometastases in thyroid cancer. An important finding? Surg Oncol 2008;17:253-8.

15. Teixeira G, Teixeira T, Gubert F, Chikota H, Tufano R. The incidence of central neck micrometastatic disease in patients with papillary thyroid cancer staged preoperatively and intraoperatively as N0. Surgery 2011;150:1161-7.

16. Qubain SW, Nakano S, Baba M, Takao S, Aikou T. Distribution of lymph node micrometastasis in pN0 well-differentiated thyroid carcinoma. Surgery 2002; 131:249-56.

17. Huvos AG, Hutter RV, Berg JW. Significance of axillary macrometastases and micrometastases in mammary cancer. Ann Surg 1971;173:44-6.

18. Beal SH, Chen SL, Schneider PD, Martinez SR. An evaluation of lymph node yield and lymph node ratio in well-differentiated thyroid carcinoma. Am Surg 2010;76:28-32.

19. Schneider DF, Chen H, Sippel RS. Impact of lymph node ratio on survival in papillary thyroid cancer. Ann Surg Oncol 2013;20:1906-11.

20. Yip J, Orlov S, Orlov D, Vaisman A, Hernandez KG, Etarsky D, et al. Predictive value of metastatic cervical lymph node ratio in papillary thyroid carcinoma recurrence. Head Neck 2013;35:592-8.

21. Schneider DF, Mazeh H, Chen H, Sippel RS. Lymph node ratio predicts recurrence in papillary thyroid cancer. Oncologist 2013;18:157-62.

22. Lee YS, Kim SW, Kim SW, Kim SK, Kang HS, Lee ES, et al. Extent of routine central lymph node dissection with small papillary thyroid carcinoma. World J Surg 2007;31:1954-9.

23. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol 2013;14:297-305.

24. Pacini F, Lari R, Mazzeo S, Grasso L, Taddei D, Pinchera A. Diagnostic value of a single serum thyroglobulin determination on and off thyroid suppressive therapy in the follow-up of patients with differentiated thyroid cancer. Clin Endocrinol (Oxf) 1985;23:405-11.

25. Chang YW, Kim HS, Jung SP, Kim HY, Lee JB, Bae JW, et al. Pre-ablation stimulated thyroglobulin is a better predictor of recurrence in pathological N1a papillary thyroid carcinoma than the lymph node ratio. Int J Clin Oncol 2016;21:862-8.

26. Lee SG, Ho J, Choi JB, Kim TH, Kim MJ, Ban EJ, et al. Optimal cut-off values of lymph node ratio predicting recurrence in papillary thyroid cancer. Medicine (Baltimore) 2016;95:e2692.