



Ultrasonographic Indeterminate Lymph Nodes in Preoperative Thyroid Cancer Patients: Malignancy Risk and Ultrasonographic Findings Predictive of Malignancy

Roh-Eul Yoo, MD^{1,2}, Ji-hoon Kim, MD, PhD^{1,2}, Jeong Mo Bae, MD, PhD³, Inpyeong Hwang, MD^{1,2}, Koug Mi Kang, MD^{1,2}, Tae Jin Yun, MD, PhD^{1,2}, Seung Hong Choi, MD, PhD^{1,2}, Chul-Ho Sohn, MD, PhD^{1,2}, Jung Hyo Rhim, MD⁴, Sun-Won Park, MD, PhD^{2,4}

Departments of ¹Radiology and ³Pathology, Seoul National University Hospital, Seoul, Korea; ²Department of Radiology, Seoul National University College of Medicine, Seoul, Korea; ⁴Department of Radiology, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Korea

Objective: Proper management of lymph nodes (LNs) with ultrasonographic (US) indeterminate features in thyroid cancer patients remains elusive. We aimed to evaluate the malignancy risk and US findings predictive of malignancy for US indeterminate LNs in preoperative thyroid cancer patients through node-by-node correlation.

Materials and Methods: A total of 348 LNs in 284 thyroid cancer patients, who underwent fine-needle aspiration or core-needle biopsy between December 2006 and June 2015, were included. We determined the malignancy risks for US probably benign, indeterminate, and suspicious categories. For US indeterminate LNs, which had neither echogenic hilum nor hilar vascularity in the absence of any suspicious finding, US findings were compared between benign and metastatic LNs using Mann-Whitney U test and Fisher's exact test.

Results: US imaging diagnoses were probably benign in 20.7% (n = 72) cases, indeterminate in 23.6% (n = 82), and suspicious in 55.7% (n = 194). Malignancy risk of US indeterminate LNs (19.5% [16/82]) differed from those of the US probably benign (2.8% [2/72]) ($p = 0.002$) and US suspicious LNs (78.4% [152/194]) ($p < 0.001$). Among US indeterminate LNs, there were no significant differences in short, long, and long-to-short diameter (L/S) ratios between benign and metastatic LNs (3.9 vs. 3.8 mm, $p = 0.619$; 7.3 vs. 7.3 mm, $p = 0.590$; 1.9 vs. 1.9, $p = 0.652$).

Conclusion: US indeterminate LNs were frequently encountered during preoperative evaluation and had intermediate malignancy risk. Given the lack of discriminative power of size criteria and L/S ratio, clinical factors such as surgical strategy and node size should be considered for proper triage of US indeterminate LNs in thyroid cancer.

Keywords: Lymph nodes; Risk; Thyroid neoplasms; Triage; Ultrasonography

INTRODUCTION

Despite the low mortality rate of approximately 0.5 deaths per 100000 population, previous reports on differentiated thyroid carcinoma show a long-term recurrence rate as high as 30% (1, 2). In most studies, differentiated thyroid

carcinoma—particularly papillary thyroid carcinoma (PTC)—is known to accompany cervical lymph node (LN) metastases in 20–50% of patients (3, 4). Residual metastatic LNs are reported as the most common site of disease persistence/recurrence following incomplete surgical resection (5). Therefore, complete surgical resection of clinically apparent

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Corresponding author: Ji-hoon Kim, MD, PhD, Department of Radiology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.

• Tel: (822) 2072-3280 • Fax: (822) 747-7418 • E-mail: jihnkim@gmail.com

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LN metastasis based on accurate preoperative diagnosis of LN metastasis at the initial presentation is necessary to reduce the chance of repetitive surgery, which accompanies a higher risk of postoperative complications.

At present, ultrasonography (US) is considered the imaging modality of choice for preoperative diagnosis of LN metastases in thyroid cancer patients. Several studies have investigated the diagnostic performance of US for predicting LN metastases and have identified a number of individual US imaging features for the differential diagnosis of benign and metastatic LNs (6-9). However, the overall diagnostic accuracy of US for LN metastases is limited, although there have been some specific US features reported for suspicious LN metastases.

In routine clinical practice, when LNs with either echogenic hilum or hilar vascularity in the absence of suspicious features are regarded as probably benign, a non-negligible number of LNs that belong to neither a probably benign nor a suspicious category are encountered. Until now, LNs with so-called round shapes among those had been variably included (7-12) or not included (13-15) as suspicious LNs for metastasis in the literature and guidelines because their features had not been regarded as highly specific to metastasis. Recently, they have been termed "indeterminate LNs" in some guidelines (14, 15) and are likely to be one of the important reasons for the limited diagnostic accuracy of US for LN metastasis.

Notably, no studies have focused on the analysis of US indeterminate LNs, and proper management of LNs with US indeterminate features in thyroid cancer patients remains elusive. Thus, the aim of this study was to evaluate the malignancy risk and US findings predictive of malignancy for US indeterminate LNs in thyroid cancer patients through node-by-node correlation.

MATERIALS AND METHODS

The Institutional Review Board of our hospital approved this retrospective study, and the requirement for informed consent was waived due to its retrospective nature.

Patient Selection

A radiology report database search uncovered 55276 patients who had undergone fine-needle aspiration (FNA) or core-needle biopsy (CNB) for neck lesions at our institution between December 2006 and June 2015. The inclusion criteria selected patients with primary thyroid cancer who

underwent either FNA or CNB of neck LNs. The patient exclusion criteria were as follows: 1) FNA or CNB at sites other than LNs (n = 47427), 2) history of head and neck or other malignancy (n = 6768), and 3) history of previous surgery for thyroid cancer (n = 793), or non-diagnostic results on biopsy (n = 4).

As a result, a total of 348 LNs in 284 consecutive preoperative thyroid cancer patients (76 men and 208 women; mean age, 47 years; age range, 18-82 years), with a final diagnosis based on either FNA or CNB, were included in this study (Table 1). Biopsy results were used as the reference standard for the final diagnosis for the following reasons: 1) A level-by-level correlation based on operative findings has intrinsic limitations because it is not certain that the metastatic tumor identified in the operative field corresponds precisely to the biopsied LN. 2) There is no established threshold for tissue thyroglobulin levels in preoperative patients with thyroid cancer, and the final diagnosis based on tissue thyroglobulin levels may inevitably lead to false positive or false negative results in some cases.

US Image Acquisition and US-Guided Biopsy for Neck LNs

All US scanning was performed by faculty radiologists, residents, or board-certified radiologists who participated in head and neck radiology fellowship training under faculty supervision using linear transducers (7.5-15.0 MHz). Grayscale and color Doppler images were examined for thyroid nodules and cervical LNs in their most representative slices.

US-guided biopsies in our hospital were primarily conducted for US indeterminate or suspicious LNs at the

Table 1. Demographic Data of Final Diagnoses of LNs Based on Each Diagnostic Criterion

Diagnostic Criteria	No. of LNs (n = 348)	Final Diagnosis
FNA	292	
Benign	154	Benign
Metastatic	138	Metastatic
CNB	40	
Benign	21	Benign
Metastatic	19	Metastatic
Both FNA and CNB	16	
Benign	3	Benign
Metastatic	13	Metastatic

CNB = core-needle biopsy, FNA = fine-needle aspiration, LN = lymph node

operator's discretion, and sometimes for benign-looking LNs according to the requests of referring physicians. Specifically, FNA with thyroglobulin measurement was performed in most cases, and CNB was selectively performed to diagnose metastatic LNs. One to three needle passes with a 23-gauge needle were made during FNA under US-guidance, and the aspiration technique with applied negative pressure was used for sampling. Following the sample acquisition, two or three direct smears were prepared with the conventional method. CNB was performed under US-guidance with a disposable 1.1-cm excursion 18-gauge, double-action spring-activated needle (TSK Ace-cut, Create Medic, Yokohama, Japan).

Image Analysis

All US images were independently analyzed by two radiologists (with 8 and 17 years of experience performing thyroid US imaging, respectively), and discrepant cases were determined by consensus of two reviewers. The nodal classification scheme of the American Joint Committee on Cancer level system was adopted to denote the LN compartment and level (central [level 6] vs. lateral [level 1 to 5]) (13, 16, 17). In addition, we assessed LN laterality (ipsilateral or contralateral) with respect to index tumors defined as pathologically proven thyroid cancer on preoperative FNA or CNB. The short- (SD) and long-diameters (LD) were both measured in the most representative longitudinal nodal plane showing the LN maximum and minimum diameters, and the long-to-short diameter (L/S) ratio was calculated afterwards (7). The LN echogenicity was classified as hyperechoic (diffuse or focal), isoechoic, or hypoechoic using the anterior neck muscles (the strap or sternocleidomastoid muscles) as the reference standard. The presence or absence of echogenic hilum within LNs was evaluated on grayscale images. Vascular LN configurations were categorized into three patterns (none, hilar pattern, or peripheral or diffuse) on color Doppler images (if available). Based on the US findings, all LNs were categorized as probably benign, indeterminate, or suspicious (15). US probably benign LNs were defined by the presence of either echogenic hilum or hilar vascularity in the absence of any suspicious finding. LNs were interpreted as US suspicious if any one of the following features was present: 1) calcification, 2) cystic change (anechoic portion with the echogenicity similar to that of the common carotid artery), 3) hyperechogenicity, or 4) peripheral or diffuse color Doppler pattern. US indeterminate LNs did not have

US probably benign or suspicious LN imaging features (had neither echogenic hilum nor hilar vascularity in the absence of any suspicious finding), in accordance with the Korean Society of Thyroid Radiology guidelines (15).

Statistical Analysis

All statistical analyses were performed with MedCalc software, version 11.1.1.0 (MedCalc, Mariakerke, Belgium). Numerical data were assessed for normality with the Kolmogorov-Smirnov test. A *p*-value of < 0.05 was considered statistically significant for all tests. Malignancy risks of US categories were compared using Fisher's exact test. An unpaired *t* test or the Mann-Whitney U test was used (as appropriate) to compare SDs, LDs, and L/S ratios between benign and metastatic LNs among US indeterminate LNs. The incidences of laterality and index tumor size between the two groups were compared with Fisher's exact test and the Mann-Whitney U test, respectively. Cohen's unweighted kappa (κ) coefficients were calculated to evaluate interobserver agreements for US classification of LNs. A κ coefficient of 0.00–0.20 indicated slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.00 almost perfect agreement (18).

RESULTS

Baseline Characteristics of Thyroid Nodules and LNs

The histology of the primary tumor comprised PTC in 339 LNs, anaplastic carcinoma in 3 LNs, medullary thyroid carcinoma in 4 LNs, minimally invasive follicular thyroid carcinoma in 1 LN, and poorly differentiated carcinoma in 1 LN. The mean largest diameter of the index tumors was 11.8 mm (range 2.0–52.0 mm). The mean SD and LD of the LNs were 6.0 mm (range, 2.2–29.1 mm), and 10.3 mm (range, 3.2–49.7 mm), respectively. The demographic data based on each diagnostic criterion for all LN final diagnoses are provided in Table 1.

Malignancy Risk according to US Classification

US imaging-based LN diagnoses were probably benign in 20.7% (72 of 348) cases, indeterminate in 23.6% (82 of 348), and suspicious in 55.7% (194 of 348). The final diagnosis was confirmed as benign in 51.1% (178 of 348), and as metastatic in 48.9% (170 of 348) of the LNs by FNA (*n* = 292), CNB (*n* = 40), or both FNA and CNB (*n* = 16). The malignancy risk of US indeterminate LNs {19.5% (95%

confidence interval [CI]: 10.9%, 28.1%}) was significantly higher than that of the US probably benign LNs (2.8% [95% CI: 0%, 6.6%]) ($p = 0.002$), and lower than that of the US suspicious LNs (78.4% [95% CI: 72.6%, 84.1%]) ($p < 0.001$) (Table 2).

US Characteristics of Indeterminate LNs

Comparison of SD, LD, and L/S Ratios between Benign and Metastatic LNs

Median SDs, LDs, and L/S ratios for all ($n = 82$), central ($n = 10$), and lateral ($n = 72$) compartments are provided in Table 3. No statistically significant differences between benign and metastatic LNs were found in SD or LD ($p = 0.619$ and $p = 0.590$; respectively) (Figs. 1, 2). The malignancy risk varied from 11.5% to 33.3%, with no tendency towards increased malignancy with increasing SD: 31.3% (2 mm \leq size < 3 mm [5 of 16]), 11.5% (3 mm \leq size < 4 mm [3

of 26]), 15.8% (4 mm \leq size < 5 mm [3 of 19]), 20.0% (5 mm \leq size < 6 mm [3 of 15]), and 33.3% (\geq 6 mm [2 of 6]). The malignancy risk varied from 8.3% to 25.0%, with no tendency towards increased malignancy with increasing LD: 25.0% (2 mm \leq size < 4 mm [1 of 4]), 16.7% (4 mm \leq size < 6 mm [3 of 18]), 23.1% (6 mm \leq size < 8 mm [6 of 26]), 22.7% (8 mm \leq size < 10 mm [5 of 22]), and 8.3% (\geq 10 mm [1 of 12]). In addition, the L/S ratio did not significantly differ between benign and metastatic LNs ($p = 0.652$) (Figs. 1, 2).

Comparison of Laterality and Index Tumor Size between Benign and Metastatic LNs

We found no significant difference in laterality between benign (ipsilaterality: 83.3% [55 of 66]), and metastatic LNs (82.4% [13 of 16]) ($p = 1.000$). Furthermore, index tumor size did not significantly differ between benign (median, 6.9 mm [interquartile range, 5.1–9.7 mm]) and metastatic LNs (median, 10.2 mm [interquartile range, 6.7–15.1 mm]) ($p = 0.068$).

Interobserver Agreement for US Classification of LNs

Cohen’s unweighted κ coefficient for US classification of LNs was 0.812 (95% CI: 0.757–0.866), indicating almost perfect agreement.

Table 2. Malignancy Risks according to US Classification

US Classification	Total	Benign	Malignancy	Malignancy Risk (%)*
US suspicious	194	42	152	78.4 (72.6–84.1)
US indeterminate	82	66	16	19.5 (10.9–28.1)
US probably benign	72	70	2	2.8 (0–6.6)

*Data in parentheses are 95% confidence intervals. US = ultrasonographic

Table 3. Comparison of US Findings between Benign and Metastatic LNs in US Indeterminate LNs

US Findings	Benign LNs (n = 66)	Metastatic LNs (n = 16)	P
All (n = 82)			
SD (mm)	3.9 (3.1–4.8)	3.8 (2.8–5.3)	0.619
LD (mm)	7.3 (5.9–9.2)	7.3 (6.0–8.7)	0.590
L/S ratio	1.9 (1.5–2.2)	1.9 (1.6–2.1)	0.652
Central (n = 10)			
SD (mm)	4.0 (3.0–4.3)	4.5 (NA)	0.087
LD (mm)	6.7 (4.1–6.9)	8.0 (NA)	0.087
L/S ratio	1.5 (1.3–1.9)	1.6 (NA)	0.820
Lateral (n = 72)			
SD (mm)	3.9 (3.1–5.0)	3.0 (2.7–5.2)	0.221
LD (mm)	7.6 (6.0–9.5)	7.1 (5.7–8.5)	0.269
L/S ratio	2.0 (1.7–2.2)	1.9 (1.7–2.3)	0.821
Ipsilaterality (%)*	83.3 (55 of 66)	82.4 (13 of 16)	1.000
Index tumor size (mm)	6.9 (5.1–9.7)	10.2 (6.7–15.1)	0.068

Unless otherwise indicated, data are reported as medians (interquartile range). *Data in parentheses are raw data. LD = long diameter, L/S = long-to-short diameter, NA = not available, SD = short diameter

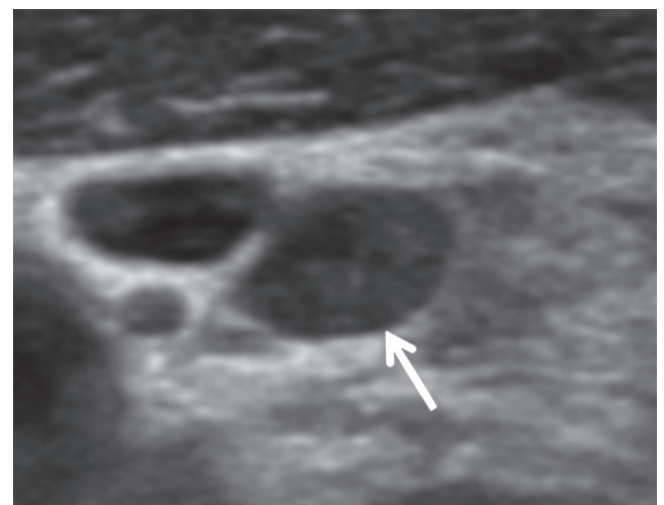


Fig. 1. Representative case of ultrasonographic indeterminate lymph node with final diagnosis of metastasis in 55-year-old woman with papillary thyroid carcinoma. Grayscale ultrasonographic image shows relatively round lymph node (short diameter: 3.6 mm; long diameter: 4.8 mm; L/S ratio: 1.3) (arrow) with no definite echogenic hilum or suspicious feature at left neck level IV. L/S = long-to-short diameter

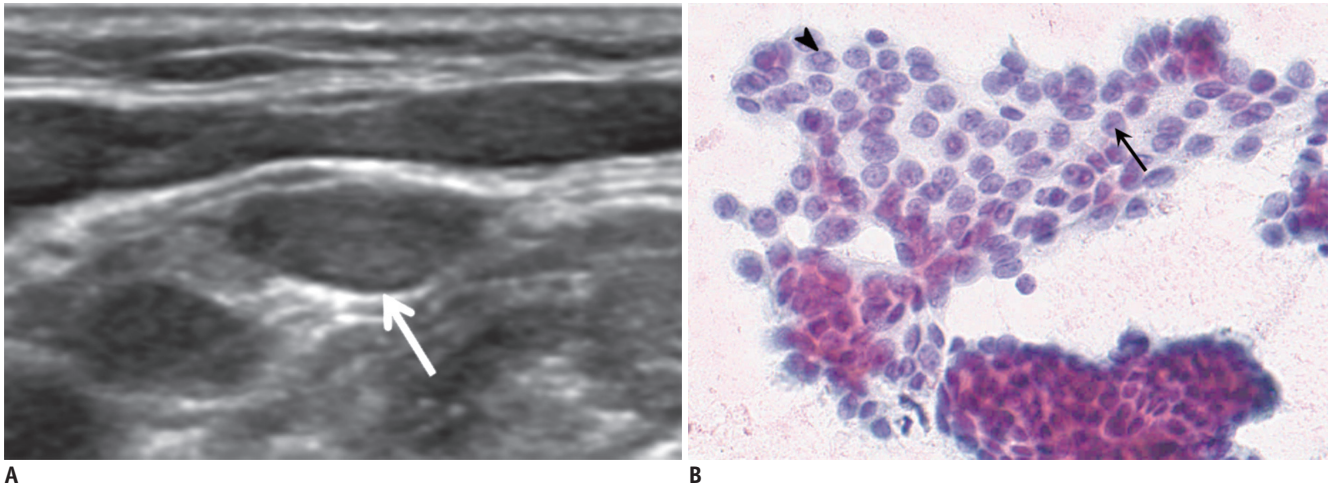


Fig. 2. Representative case of ultrasonographic indeterminate lymph node with final diagnosis of metastasis in 48-year-old woman with papillary thyroid carcinoma.
A. Grayscale ultrasonographic image demonstrates ovoid lymph node (short diameter, 4.1 mm; long diameter, 9.1 mm; L/S ratio, 2.2) (arrow) with no definite echogenic hilum or suspicious feature at left neck level IV. **B.** Fine-needle aspiration specimen shows characteristic nuclear cytology of papillary thyroid carcinoma including ground glass chromatin, intranuclear cytoplasmic inclusions (arrowhead), and nuclear grooves (arrow) (hematoxylin-eosin staining, magnification, x 100).

DISCUSSION

Although the term “indeterminate LNs” has been recently used in guidelines published by the European Thyroid Association and Korean Society of Thyroid Radiology (14, 15), this is the first study to perform in-depth analysis focusing on US indeterminate LNs based on trichotomous categorization in thyroid cancer patients, unlike many studies and guidelines based on dichotomous categorization (6-12, 19, 20). The results of this study support trichotomous categorization by demonstrating that US indeterminate LNs that did not fall under a probably benign or suspicious category were not infrequent and that their malignancy risk was different from those of US probably benign LNs and suspicious LNs. In fact, some studies have already suggested that the absence of fatty hilum and a round shape are related to intermediate malignancy rates (8, 14, 21). However, none of the studies analyzed those US features separately from the traditional suspicious US features. Furthermore, unlike many previous studies based on level-by-level correlation including both microscopic as well as macroscopic metastatic LNs, we performed a node-by-node correlation by FNA or CNB, and thus, most of the metastatic LNs included in this study were clinically apparent LNs (cN1) with a macroscopic tumor detected by US.

Regarding size criteria, Leboulleux et al. (21) suggested an LD of 10 mm and an SD of 5 mm for suspicious LNs in

dichotomous categorization, regardless of the presence of other coexisting suspicious US features. Similarly, the European Thyroid Association specified cutoff values for SD in the definition of indeterminate LNs (8 mm in level II, and 5 mm in levels III and IV) (14). However, our study showed that the SD and LD of metastatic LNs in US indeterminate LNs were not significantly different from that of benign LNs in US indeterminate LNs. In other words, the incidence of metastatic LNs with large SDs and LDs having indeterminate US appearance without any other suspicious US feature was low. For this reason, we speculated that metastatic LNs would eventually accompany suspicious features when they become sizable, even if they initially manifested as US indeterminate LNs.

Traditionally, the L/S ratio has been used as an imaging parameter to reflect the LN shape in cervical lymphadenopathy. An L/S ratio of 1.5–2.0, regardless of the presence of suspicious findings, had previously been used as the cutoff value for discriminating benign LNs from malignant LNs in various types of cervical lymphadenopathy, including thyroid cancer (6-9, 22-24). However, in our study, the L/S ratio of metastatic LNs in US indeterminate LNs was not significantly different from that of benign LNs in US indeterminate LNs. Our result implies that although round shape may be an imaging feature found in suspicious LNs along with other US features predictive of malignancy, round shape alone may not be useful in discriminating benign LNs and metastatic LNs among US indeterminate LNs.

It may be questionable why the metastatic foci in the US indeterminate LNs did not show any specific suspicious features, including hyperechogenicity, cystic change, or calcification. We speculate as follows. First, we might have overlooked suspicious US features. In reality, determining the echogenicity of LNs in comparison with the strap muscles may be confusing in some cases, partly due to artifactual inhomogeneous echogenicity of the strap muscles. Second, we might have missed micrometastatic foci of the LNs. Third, some US indeterminate LNs with metastatic foci might have a conventional US architecture similar to normal LNs.

In terms of clinical implications, the findings that US indeterminate LNs are frequently encountered in our clinical practice and that they have an intermediate malignancy risk between US probably benign and suspicious LNs, suggest that a distinct management strategy may be required to triage US indeterminate LNs during preoperative LN evaluation in thyroid cancer patients. The lack of discriminative power of size criteria and L/S ratio suggests that FNA should still be considered a confirmative diagnostic test. However, the clinical decision as to whether to perform FNA for US indeterminate LNs must be based on surgical strategy (curative vs. palliative) given their relatively lower malignancy risk compared to US suspicious LNs. In addition, other factors such as the aggressiveness of primary tumors and LN size, which potentially represent a clinically important tumor burden, should also be considered. Specifically, US indeterminate LNs may be assumed to be benign LNs, and FNA may be deferred in cases with a conservative policy. However, FNA may be actively performed to reduce the chance of repetitive surgery in patients with a high risk for LN metastasis, if the SD of US indeterminate LNs exceeds 3–5 mm (which is the size cutoff for US suspicious LNs according to the guideline of the Korean Society of Thyroid Radiology).

Our study had various limitations. First, owing to the retrospective nature of this study, there was inevitable selection bias in the LNs available for evaluation. US scanning was performed by different operators using various US machines, and thus our results might have been confounded by operator dependence. Second, the sample size was not large enough, particularly for central LNs compared to lateral LNs. The discrepancy in the sample size was due to the practice in our hospital in which prophylactic central compartment neck dissection is performed as part of lobectomy or total thyroidectomy

in most cases. A further multicenter prospective study based on a larger sample size is warranted to strengthen the statistical power of the findings of this study. Third, malignancy risks could have been overestimated for US probably benign and indeterminate LNs because not all US probably benign and indeterminate LNs underwent FNA in this study. Fourth, given that we performed node-by-node correlation by FNA or CNB (not level-by-level correlation by operative findings), it is likely that most microscopic metastatic tumors less than 2 mm in size would have been missed. However, we believe that our study is more clinically relevant because we focused on preoperatively identified macroscopic metastatic LNs, with nodal prognostic significance.

In conclusion, in thyroid cancer patients, US indeterminate LNs were not infrequently encountered, and the malignancy risk of US indeterminate LNs was intermediate between US probably benign and suspicious LNs. Given the lack of discriminative power of size criteria and L/S ratio for differentiating benign LNs and metastatic LNs, clinical factors (such as surgical strategy and tumor aggressiveness) in addition to the intermediate malignancy risk and the node size should be taken into account for proper triage of US indeterminate LNs.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

ORCID iDs

Ji-hoon Kim

<https://orcid.org/0000-0002-6349-6950>

Roh-Eul Yoo

<https://orcid.org/0000-0002-5625-5921>

Jeong Mo Bae

<https://orcid.org/0000-0003-0462-3072>

Inpyeong Hwang

<https://orcid.org/0000-0002-1291-8973>

Koung Mi Kang

<https://orcid.org/0000-0001-9643-2008>

Tae Jin Yun

<https://orcid.org/0000-0001-8441-4574>

Seung Hong Choi

<https://orcid.org/0000-0002-0412-2270>

Chul-Ho Sohn

<https://orcid.org/0000-0003-0039-5746>

Jung Hyo Rhim

<https://orcid.org/0000-0001-5822-9770>

Sun-Won Park

<https://orcid.org/0000-0002-5063-2685>

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