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Validation of CT-Based Risk Stratification System for Lymph Node Metastasis in Patients With Thyroid Cancer

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Objective: To evaluate the computed tomography (CT) features for diagnosing metastatic cervical lymph nodes (LNs) in patients with differentiated thyroid cancer (DTC) and validate the CT-based risk stratification system suggested by the Korean Thyroid Imaging Reporting and Data System (K-TIRADS) guidelines.

Materials and Methods: A total of 463 LNs from 399 patients with DTC who underwent preoperative CT staging and ultrasound-guided fine-needle aspiration were included. The following CT features for each LN were evaluated: absence of hilum, cystic changes, calcification, strong enhancement, and heterogeneous enhancement. Multivariable logistic regression analysis was performed to identify independent CT features associated with metastatic LNs, and their diagnostic performances were evaluated. LNs were classified into probably benign, indeterminate, and suspicious categories according to the K-TIRADS and the modified LN classification proposed in our study. The diagnostic performance of both classification systems was compared using the exact McNemar and Kosinski tests.

Results: The absence of hilum (odds ratio [OR], 4.859; 95% confidence interval [CI], 1.593–14.823; $P = 0.005$), strong enhancement (OR, 28.755; 95% CI, 12.719–65.007; $P < 0.001$), and cystic changes (OR, 46.157; 95% CI, 5.07–420.234; $P = 0.001$) were independently associated with metastatic LNs. All LNs showing calcification were diagnosed as metastases. Heterogeneous enhancement did not show a significant independent association with metastatic LNs. Strong enhancement, calcification, and cystic changes showed moderate to high specificity (70.1%–100%) and positive predictive value (PPV) (91.8%–100%). The absence of the hilum showed high sensitivity (97.8%) but low specificity (34.0%). The modified LN classification, which excluded heterogeneous enhancement from the K-TIRADS, demonstrated higher specificity (70.1% vs. 62.9%, $P = 0.016$) and PPV (92.5% vs. 90.9%, $P = 0.011$) than the K-TIRADS.

Conclusion: Excluding heterogeneous enhancement as a suspicious feature resulted in a higher specificity and PPV for diagnosing metastatic LNs than the K-TIRADS. Our research results may provide a basis for revising the LN classification in future guidelines.

Keywords: Thyroid; Thyroid cancer; Lymph node; Computed tomography; Metastasis

INTRODUCTION

Differentiated thyroid cancer (DTC) is the most common type of thyroid cancer, accounting for more than 95% of all cases, with an increasing incidence rate [1,2]. Although DTC has an excellent prognosis, cervical lymph node (LN) metastasis is present in 20%–50% of patients at the time of diagnosis and may present even when the primary tumor

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is small [3-5]. LN metastasis is associated with poor overall survival outcomes and increased risk of recurrence [6,7]. Currently, most recurrent diseases following initial curative therapy for DTC are recognized as persistent diseases due to incomplete preoperative staging and subsequent incomplete surgery [8-10]. The role of therapeutic compartmental LN dissection is well accepted for clinically evident nodal disease. However, wider neck dissection confers increased morbidity, including hypoparathyroidism and temporary or permanent nerve paralysis [11-13]. Considering these findings, an accurate preoperative assessment of LN metastases using imaging is warranted.

Current guidelines recommend ultrasonography (US) for preoperative imaging evaluation of LN metastasis in thyroid cancer [13,14]. However, US is an operator-dependent technique, and its ability to visualize the mediastinal, infraclavicular, retropharyngeal, and parapharyngeal areas is limited [13,15]. In addition, acoustic shadowing from normal anatomical structures may interfere with the sonographic view. Considering these constraints, contrast-enhanced computed tomography (CT) offers several advantages over US [16-18]. CT can be considered a relatively objective imaging modality that provides unlimited coverage of the neck. Moreover, it can provide detailed anatomical information regarding nodal locations and their relationships with the anatomical landmarks for surgery [18,19].

Several recent articles have evaluated the performance of CT in diagnosing cervical LN metastasis in patients with thyroid cancer in routine clinical practice, including the added diagnostic value of CT imaging as an adjunct to US in the detection of LN metastasis from thyroid cancer [18,20-22]. The Korean Thyroid Imaging Reporting and Data System (K-TIRADS), proposed by the Korean Society of Thyroid Radiology, suggests suspicious features for diagnosing metastatic LNs on CT, and provides a CT-based risk stratification system for LNs according to their malignancy risk [23]. However, few studies have investigated the appropriateness of each suspicious CT feature suggestive of a metastatic LN [24]. Thus, in this study, we aimed to evaluate CT features for diagnosing metastatic LNs in patients with DTC and validate the CT-based risk stratification system suggested by the K-TIRADS guidelines.

MATERIALS AND METHODS

This retrospective study was approved by Asan Medical Center review board, which waived the requirement for informed consent (IRB No.2021-1300, date of approval: August 25, 2021). Methods and data reporting were performed in accordance with the Standards for Reporting of Diagnostic Accuracy Studies guidelines [25].

Patient Selection

This study enrolled consecutive patients with DTC who underwent US-guided fine needle aspiration (FNA) of the LNs at Asan Medical Center between January 2014 and December 2018. Patients were included if they 1) were diagnosed with DTC, 2) underwent CT for preoperative staging, and 3) underwent FNA of the LNs for preoperative evaluation. Patients were excluded if they 1) did not undergo preoperative CT with an appropriate protocol, 2) underwent FNA of the LNs for persistent or recurrent disease after surgery for thyroid cancer, or 3) did not undergo subsequent surgical resection or follow-up imaging for at least one year. Finally, 463 LNs from 399 patients were included (Fig. 1).

CT Protocol

Imaging was performed using a 128-channel CT scanner (Somatom Definition Flash, Siemens). CT scanning began at the aorticopulmonary window and continued toward the skull base. For the arterial phase scan, a 25 s scan delay was left after injecting 75 mL of iodinated contrast agent at a rate of 3.5 mL/s, followed by 50 mL of normal saline at the same rate. Delayed scanning was performed 70 s after the contrast injection. Arterial phase (at 25 s delay) images were acquired in the dual-energy mode. The scanning parameters were as follows: 80/140 kVp tube voltage for

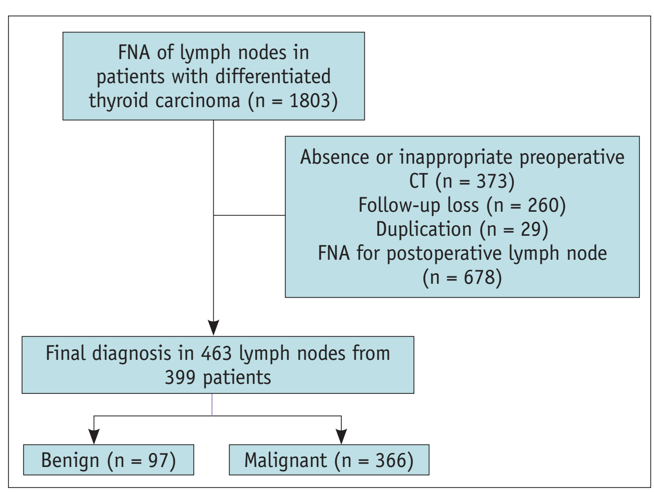

Fig. 1. Flow chart of the study population. FNA = fine needle aspiration, CT = computed tomography

the arterial phase and 120 kVp for the delayed phase; 200 effective mA; 22-cm display field of view (FOV); 50-cm large-body scan FOV; 32 x 0.6 mm detector collimation; 0.5 s gantry rotation time; pitch of 1.0; 0.75-mm-thick sections; 0.7 mm section increments; 256 x 256 matrix; and 2-mm axial/coronal/sagittal reconstructed slice thickness with soft-tissue algorithm reconstruction. Real-time automatic tube current modulation software (CARE Dose4D; Siemens) was used to regulate the tube current according to the patient's anatomical structure. Virtual non-contrast images from dual-energy images were generated using the post-processing software Syngo.via (Siemens Healthineers), and mixed images comprising 60% of the 140 kVp and 40% of the 80-kVp scans were uploaded to the Picture Archiving and Communication System (PACS). The median time interval between US-FNA and CT examinations was 8 days (interquartile range, 0–26 days) and that between CT examinations and surgery was 15 days (interquartile range, 7–22 days).

Imaging Analysis

CT images were matched with US images on a node-by-node basis to identify the LNs depicted on US. An LN confirmed by US-guided FNA was chosen and labeled on CT images by matching the images and reports of CT, US, and the final pathological examination. This matching was performed by a radiologist with eight years of experience in head and neck imaging using the hospital's picture archiving and communication system.

All CT images were independently analyzed by two neuroradiologists with 8 and 1 years of experience in head and neck imaging who were unaware of the patients' cytopathology results. Consensus results were obtained by resolving any discrepancies in the individual interpretations. Before the evaluations, the two neuroradiologists completed a training session using CT images from ten patients to help them achieve a standardized interpretation of the imaging findings.

The following CT features of the LNs were evaluated: presence or absence of a hilar structure, cystic changes, calcification, strong cortical enhancement (focal or diffuse) greater than that of adjacent muscles, and heterogeneous enhancement (Figs. 2–5) [23]. Strong cortical enhancement and heterogeneous enhancement were determined based on images obtained during the arterial phase. The cystic changes of LNs were evaluated on images obtained at both arterial and delayed phases: LNs showing a persistent low "water" attenuation (below 25 Hounsfield units) on both images.

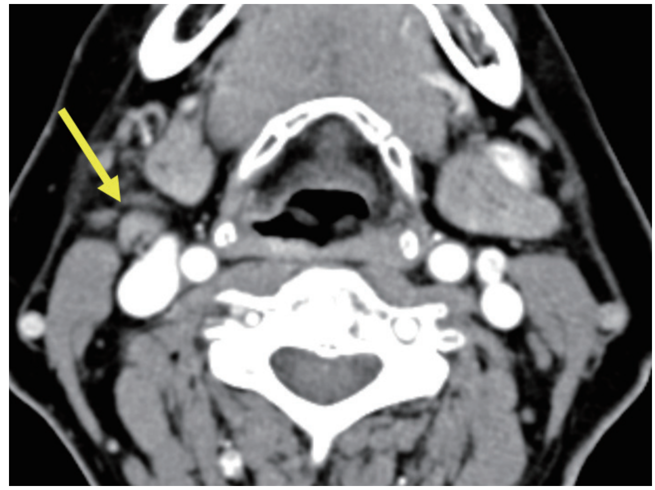

Fig. 2. Axial computed tomography scan shows a lymph node with preserved hilar fat and hilar vessels but no internal cystic changes, heterogeneous enhancement, calcification, or strong enhancement (arrow). This lymph node would be classified into a probably benign category according to K-TIRADS. K-TIRADS = Korean Thyroid Imaging Reporting and Data System

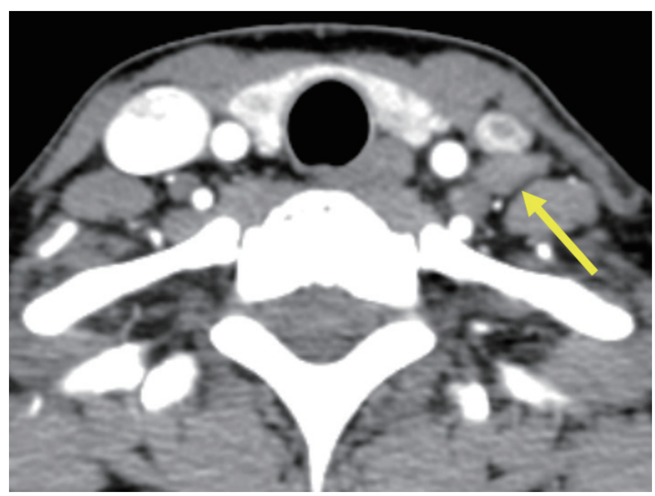

Fig. 3. Axial computed tomography scan shows a lymph node without a hilar structure, internal cystic changes, heterogeneous enhancement, calcification, or strong enhancement (arrow). This lymph node would be classified into an indeterminate category according to K-TIRADS. K-TIRADS = Korean Thyroid Imaging Reporting and Data System

Virtual pre-contrast enhancement images were used to evaluate the presence of calcification within the LNs. The LN size was determined according to the maximal short-axis diameter.

The evaluated CT features were used to classify the LNs into three categories according to the K-TIRADS: probably benign, indeterminate, and suspicious [23]. LNs were interpreted as suspicious if one of the following features was present on CT scan: cystic changes, calcification, strong enhancement, or heterogeneous enhancement. Probably benign LNs were defined as LNs that did not have the features of suspicious LNs and showed CT features of typical benign LNs, including hilar fat or hilar vessel enhancement. Indeterminate LNs were defined as those without imaging features of suspicious or benign LNs.

US-guided FNA

All US examinations and US-guided FNAs were performed by radiologists under the supervision of staff radiologists with > 14 years of clinical experience in evaluating thyroid US images. US-guided FNA of indeterminate or suspicious LNs was performed according to the K-TIRADS [23] when it affected the surgical extent of thyroid cancer, regardless of their size. Sonographically benign LNs were examined at the clinician's request. When multiple suspicious LNs were present in one compartment, an easily accessible LN was selected for FNA.

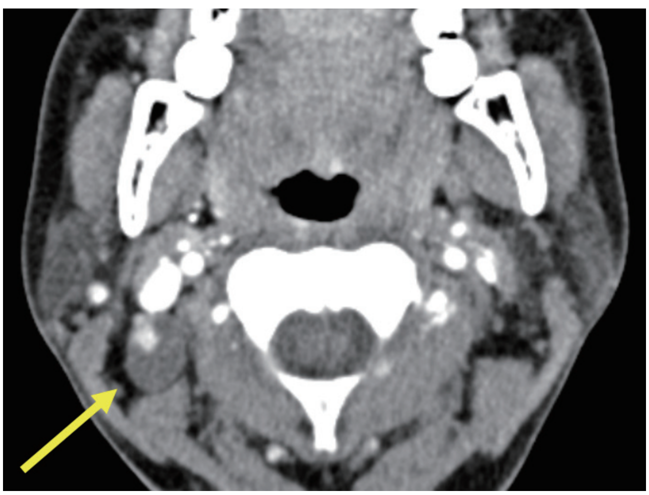

Fig. 4. Axial computed tomography scan shows a lymph node with cystic change with an eccentric strong enhancing solid portion that gives the lymph node a heterogeneous enhancement pattern (arrow). No normal hilar structure can be seen. This lymph node would be classified into a suspicious category according to K-TIRADS. K-TIRADS = Korean Thyroid Imaging Reporting and Data System.

Reference Standard

LNs were diagnosed as metastatic if they showed malignant cytology and/or elevated washout thyroglobulin (Tg; > 8.3 ng/mL) on FNA [26]. In cases of increased washout Tg levels with benign or insufficient cytological results, the diagnosis of metastasis was confirmed by repeat biopsy or surgical resection. In cases of benign or indeterminate FNA cytology with normal washout Tg, LNs were finally diagnosed as benign if at least one of the following criteria was satisfied: 1) confirmed as benign on surgical resection, 2) benign cytology on subsequent repeat FNA or core-needle biopsy, and 3) decreased size on follow-up imaging after more than one year.

Statistical Analysis

For comparisons of clinicoradiological features between metastatic and benign LNs, independent *t* tests were used for continuous variables, and chi-square or Fisher's exact tests were used for categorical variables. Multivariable logistic regression analysis with a forward selection method was performed to determine independent CT features associated with metastatic LNs among those that were statistically significant in the univariable analysis ($P < 0.2$). A Chi-square test was performed to determine whether there was an association between suspicious CT features. The diagnostic performance of the CT features for metastatic LNs was evaluated in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and

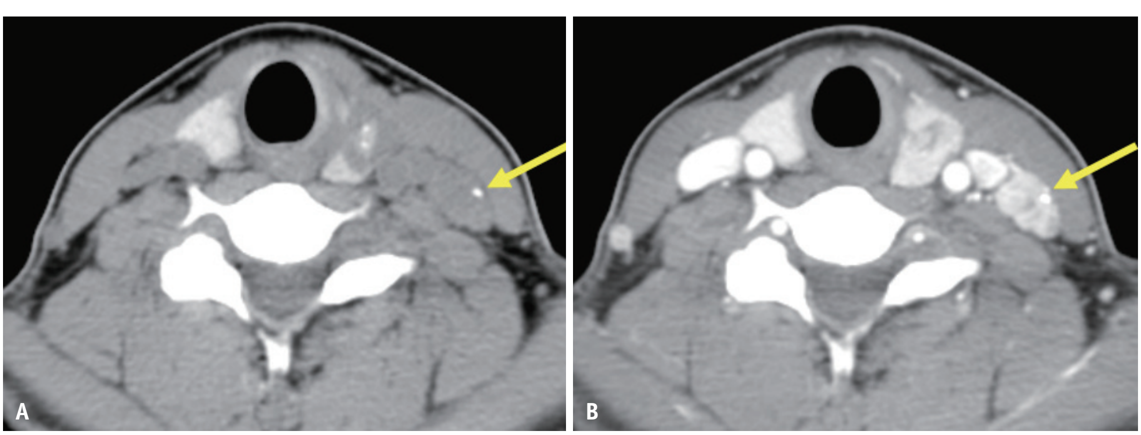

Fig. 5. In axial precontrast computed tomography scan **(A)**, the lymph node contains discrete calcification (arrow), and in the post-contrast enhancement image **(B)**, the lymph node shows strong and heterogeneous enhancement without hilar structure (arrow).

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diagnostic accuracy.

CT features were used to classify LNs according to the K-TIRADS, and malignancy rates were calculated for three categories: probably benign, indeterminate, and suspicious [23]. The LNs were also classified according to the modified LN classification system proposed in this study, and the malignancy rate was calculated for each category.

To compare the diagnostic performance of the K-TIRADS and modified LN classification, LNs were dichotomized into two groups: suspicious (test positivity) and indeterminate or benign (test negativity). The sensitivity, specificity, and accuracy were compared using McNemar's exact test. The PPV and NPV were compared using the weighted generalized score test statistical approach developed by Kosinski [27]. Additionally, the diagnostic performance of biopsy-indicated LNs was compared between the K-TIRADS and modified LN classification by applying the size criteria suggested by the K-TIRADS.

All statistical analyses were performed using SAS version 9.4 (SAS Institute). All tests were two-sided, and a *P*-value < 0.05 was considered statistically significant.

RESULTS

Study Population

The patient demographics and CT features of the LNs are summarized in Table 1. In total, 463 LNs from 399 patients were included in this study, of which 97 (21%) were benign and 366 (79%) were metastatic. The pathological diagnosis of the primary tumor was conventional papillary thyroid cancer (PTC) (82.5% [329/399]), tall cell variant PTC (9% [36/399]), follicular variant PTC (3.3% [13/399]), columnar cell variant PTC (1.5% [6/399]), clear cell variant PTC (1.5% [6/399]), diffuse sclerosing variant PTC (1% [4/399]), solid variant PTC (0.8% [3/399]), Warthin like variant PTC (0.3% [1/399]), and follicular thyroid carcinoma (0.3% [1/399]). The mean largest diameter of the primary tumor was 1.8 cm (range 0.3–6.6 cm). Metastatic LNs were associated with male sex (35.2% vs. 22.7%, *P* = 0.019) and a larger primary tumor size (1.86 ± 1.10 cm vs. 1.58 ± 1.05 cm, *P* = 0.024) compared with benign LNs. The nodal stations of malignant LNs were not significantly different from those of benign LNs (*P* = 0.089). The short diameters of metastatic LNs were significantly larger (0.59 ± 0.32 cm vs. 0.42 ± 0.14 cm, *P* < 0.001) than those of benign LNs, whereas the long diameters showed no significant difference between the two groups (1.17 ± 0.56 cm vs. 1.14 ± 0.53 cm, *P* = 0.593).

Table 1. Summary of demographic and CT features of the lymph nodes

Characteristic	Benign (n = 97)	Metastatic (n = 366)	*P*
Sex			0.019
Male	22 (22.7)	129 (35.2)	
Female	75 (77.3)	237 (64.8)	
Age, yr	48.08 ± 12.95	47.6 ± 13.55	0.751
Mean size of primary tumor, cm	1.58 ± 1.05	1.86 ± 1.10	0.024
Location			0.089
Level 2	10 (10.3)	39 (10.7)	
Level 3	23 (23.7)	130 (35.5)	
Level 4	54 (55.7)	176 (48.1)	
Level 5	10 (10.3)	21 (5.7)	
Short diameter, cm	0.42 ± 0.14	0.59 ± 0.32	< 0.001
Long diameter, cm	1.14 ± 0.53	1.17 ± 0.56	0.593

Values are presented as mean ± standard deviation or n (%).
CT = computed tomography

Table 2. Malignancy rates and univariable and multivariable logistic regression analysis of the association between CT features and metastatic lymph node

CT features	Benign	Metastatic	Malignancy risk (%)	Univariable analysis		Multivariable analysis	
				OR (95% CI)	*P*	OR (95% CI)	*P*
Absence of hilum	64 (66)	358 (97.8)	84.8	23.074 (10.194–52.228)	< 0.001	4.859 (1.593–14.823)	0.005
Strong enhancement	29 (29.9)	338 (92.3)	92.0	28.305 (15.833–50.603)	< 0.001	28.755 (12.719–65.007)	< 0.001
Heterogeneous enhancement	25 (25.8)	281 (76.8)	91.8	9.521 (5.685–15.945)	< 0.001	1.586 (0.771–3.263)	0.210
Cystic change	1 (1)	90 (24.6)	98.9	31.767 (4.367–231.086)	< 0.001	46.157 (5.07–420.234)	0.001
Calcification	0 (0)	21 (5.7)	100	454205970.3 (0–NA)	0.998	5.466×10^7 (0–NA)	0.998
Short diameter, cm	0.42 ± 0.14	0.59 ± 0.32	NA	35.564 (8.44–149.862)	< 0.001	6.666 (0.923–48.113)	0.060

Values are presented as mean ± standard deviation or n (%) unless otherwise indicated.
CT = computed tomography, OR = odds ratio, CI = confidence interval, NA = not available

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Korean Journal of Radiology KJR

Association between CT Features and Metastatic LNs from Thyroid Cancer

Table 2 shows the malignancy risk for each CT feature and the results of univariable and multivariable logistic regression analyses to determine the independent CT features for diagnosing metastatic LNs. The CT features of the absence of a hilum, strong enhancement, heterogeneous enhancement, cystic changes, and calcification showed a high malignancy risk of 84.8%–100%. According to the univariable logistic regression analysis, the absence of a hilum (odds ratio [OR], 23.074; 95% confidence interval [CI], 10.194–52.228; P < 0.001), strong enhancement (OR, 28.305; 95% CI, 15.833–50.603; P < 0.001), heterogeneous enhancement (OR, 9.521; 95% CI, 5.685–15.945; P < 0.001), cystic changes (OR, 31.767; 95% CI, 4.367–231.086; P < 0.001), and maximal short diameter (OR, 35.564; 95% CI, 8.44–149.862; P < 0.001) were associated with metastatic LNs. As all 21 LNs that showed calcification were diagnosed as metastases, the value of calcification could not be interpreted in the univariable and multivariable logistic regression analyses. In the multivariable analysis, the absence of a hilum (OR, 4.859; 95% CI, 1.593–14.823; P = 0.005), strong enhancement (OR, 28.755; 95% CI, 12.719–65.007; P < 0.001), and cystic changes (OR, 46.157; 95% CI, 5.07–420.234; P = 0.001) were independently associated with metastatic LNs. However, heterogeneous enhancement was not independently associated with metastatic LNs in the multivariable analysis (OR, 1.586; 95% CI, 0.771–3.263; P = 0.21).

When investigating the relationship between the CT features, heterogeneous enhancement was significantly associated with both strong enhancement and cystic changes (P < 0.001 and P < 0.001, respectively). However, no statistically significant association was found between strong enhancement and cystic changes (P = 0.666). Only 10 (3.3%) LNs showed heterogeneous enhancement without any other suspicious features, and among these 10 LNs, 3 (30%) were diagnosed with metastases, demonstrating a malignancy risk of 30%. The diagnostic performance of each suspicious feature, without other suspicious features, is presented in Supplementary Table 1.

Diagnostic Performance of CT Features

The diagnostic performance measures of the CT features of the LNs for determining metastasis are summarized in Table 3. The absence of a hilum showed the highest sensitivity (97.8%) for diagnosing metastatic LN but the lowest specificity (34.0%). LNs with cystic changes and calcification showed very high specificities of 99.0% and 100%, respectively; however, the sensitivities were low at 24.9% and 5.7%, respectively. LNs with strong enhancement showed high sensitivity (92.4%), moderate specificity (70.1%), and the highest diagnostic accuracy (87.7%). Heterogeneous enhancement showed moderate sensitivity (76.8%) and specificity (74.2%).

LN Classification According to K-TIRADS Guidelines and Modified LN Classification

The overall malignancy risks in the probably benign, indeterminate, and suspicious categories were 6.7%, 13.2%, and 90.9%, respectively (Table 4). Based on the results of our study, we defined suspicious features as cystic changes, calcification, and strong enhancement, excluding heterogeneous enhancement. Although the absence of a hilum was an independent CT feature associated with metastatic LN and showed the highest sensitivity of 97.8%, it was limited by a low specificity of 34%, indicating that it is appropriate to include it as a feature of the indeterminate category.

According to the modified LN classification proposed in this study, the overall malignancy risks of LNs in the probably benign, indeterminate, and suspicious categories were 6.5%, 17.0%, and 92.5%, respectively (Table 4). Compared to the K-TIRADS, the malignancy risks for indeterminate and suspicious LNs were higher in the modified LN classification (indeterminate: 13.2% vs. 17.0% and suspicious: 90.9% vs.

Table 3. Diagnostic performance of CT features in the diagnosis of metastatic lymph node

CT features	Sensitivity	Specificity	PPV	NPV	Accuracy
Absence of hilum	97.8 (358/366)	34.0 (33/97)	84.8 (358/422)	80.5 (33/41)	84.5 (391/463)
Strong enhancement	92.4 (338/366)	70.1 (68/97)	92.1 (338/367)	70.8 (68/96)	87.7 (406/463)
Heterogeneous enhancement	76.8 (281/366)	74.2 (72/97)	91.8 (281/306)	45.9 (72/157)	76.2 (353/463)
Cystic change	24.9 (91/366)	99.0 (96/97)	98.9 (91/92)	25.9 (96/371)	40.4 (187/463)
Calcification	5.7 (21/366)	100 (97/97)	100 (21/21)	22.0 (97/442)	25.5 (118/463)

Data are % with the raw numbers in parentheses.
CT = computed tomography, PPV = positive predictive value, NPV = negative predictive value

Table 4. Malignancy rates of lymph nodes classified according to the K-TIRADS and modified guidelines

	K-TIRADS	Modified LN classification
Probably benign	6.7 (2/30)	6.5 (2/31)
Indeterminate	13.2 (5/38)	17.0 (8/47)
Suspicious	90.9 (359/395)	92.5 (356/385)

Data are % with the raw numbers in parentheses.
K-TIRADS = Korean Thyroid Imaging Reporting and Data System, LN = lymph node

Table 5. Comparison of diagnostic performance using suspicious features categorized by K-TIRADS and modified LN classification for detecting metastatic lymph node

	K-TIRADS	Modified LN classification	*P*
TP*	359	356	
TN*	61	68	
FP*	36	29	
FN*	7	10	
Sensitivity, %	98.1 (96.7–99.5)	97.3 (95.6–98.9)	0.250
Specificity, %	62.9 (53.3–72.5)	70.1 (61.0–79.2)	0.016
PPV, %	90.9 (88.1–93.7)	92.5 (89.8–95.1)	0.011
NPV, %	89.7 (82.5–96.9)	87.2 (79.8–94.6)	0.239
Accuracy, %	90.7 (88.1–93.4)	91.6 (89.1–94.1)	0.344

Data in parentheses are 95% confidence intervals.
*Data are number of lymph nodes.
K-TIRADS = Korean Thyroid Imaging Reporting and Data System, LN = lymph node, TP = true positive, TN = true negative, FP= false positive, FN = false negative, PPV = positive predictive value, NPV = negative predictive value

92.5%), whereas the malignancy rate of probably benign LNs was lower (6.7% vs. 6.5%).

Diagnostic Performance of K-TIRADS Guidelines and Modified LN Classification

Table 5 compares the diagnostic performances of the K-TIRADS and modified LN classifications for the diagnosis of metastatic LNs when the suspicious category was defined as a positive test result. By excluding heterogeneous enhancement as a suspicious feature, 10 LNs categorized as suspicious on the K-TIRADS were reclassified into indeterminate or benign categories. Of these 10 LNs, 7 were finally diagnosed as benign and 3 were confirmed to be metastatic. Consequently, the modified LN classification resulted in a decrease of seven false-positive cases and an increase of three false-negative cases. Both the K-TIRADS and modified LN classifications showed high sensitivity rates of 98.1% and 97.3%, respectively, for diagnosing metastatic LN, without any statistically significant difference (P = 0.250). The modified LN classification demonstrated higher specificity and PPV than K-TIRADS, with values of 70.1% vs. 62.9% (P = 0.016) and 92.5% vs. 90.9% (P = 0.011), respectively. There was no statistically significant difference in the accuracy.

When comparing the diagnostic performance based on biopsy size cutoff for the suspicious LN (≥ 3 mm) and indeterminate LN (≥ 5 mm), the modified LN classification showed a significantly higher PPV compared to K-TIRADS (88.3% vs. 89.4%, P = 0.034) (Supplementary Table 2). However, there were no significant differences in the sensitivity, specificity, NPV, or accuracy between the two classification systems. When using a biopsy cutoff of ≥ 5 mm for the suspicious LN and indeterminate LN, both classifications showed perfect agreement without differences.

DISCUSSION

Our study demonstrated that the absence of a hilum, strong enhancement, calcification, and cystic changes on CT were independently associated with metastatic LN in patients with DTC. In detecting LN metastasis, strong enhancement, cystic changes, and calcification showed moderate to high specificity (70.1%–100%) with variable sensitivity (5.7%–97.8%). The absence of a hilum showed the highest sensitivity (97.8%) but was limited by low specificity (34.0%). Therefore, it is appropriate to include it as a feature of the indeterminate category. We proposed a modified LN classification that excludes heterogeneous enhancement from the four features in the suspicious category of K-TIRADS. Excluding heterogeneous enhancement as a suspicious feature resulted in higher specificity and PPV for diagnosing metastatic LNs compared to that of K-TIRADS.

US is the primary imaging modality for evaluating metastatic LNs in patients with thyroid cancer; however, there has been an increasing number of studies on the diagnostic performance of CT in the assessment of LN metastasis [28]. Several studies have reported that the addition of CT to US improves the detection of LN metastases in both the central and lateral neck compartments [17,18,21-23,29], and two meta-analyses on the diagnostic performance of CT have been published [22,28]. However, the criteria for defining metastatic LNs vary across studies. The K-TIRADS recommends contrast-enhanced CT as a complementary imaging modality in the preoperative assessment of the extent of primary tumors

Korean Journal of Radiology
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and nodal metastases in patients with thyroid cancer, and suggests four suspicious features for diagnosing metastatic LN: cystic changes, calcification, strong enhancement, and heterogeneous enhancement. However, to date, no studies have validated these criteria for diagnosing metastatic LNs using CT. Therefore, we performed multivariable logistic regression analysis to determine the independent CT features suggestive of metastatic LNs among those presented in the K-TIRADS and commonly mentioned in previous studies, including cystic changes, calcification, strong enhancement, heterogeneous enhancement, absence of a hilum, and size of LNs.

According to the multivariable logistic regression analysis, heterogeneous enhancement and maximal short diameter were not independent features for diagnosing metastatic LN. Analysis of the relationship between heterogeneous enhancement and other suspicious features revealed an association between heterogeneous enhancement and cystic changes or strong enhancement. Only a small percentage of LNs (3.3%, 10/306) showed heterogeneous enhancement alone without any other suspicious features, and the malignancy rate in these cases was low (30%). This association indicated that heterogeneous enhancement was not an independent feature suggestive of metastasis.

Furthermore, we analyzed the diagnostic performance of each CT feature. The imaging features for diagnosing metastatic LN should ideally have high specificity and PPV to reduce false positives. Suspicious features of strong enhancement, cystic changes, and calcification showed moderate-to-high specificity (70.1%–100%) and PPV (91.8%–100%). In particular, calcification showed 100% specificity and PPV although its prevalence was low (4.5%). The absence of a hilum had high sensitivity (97.8%) but low specificity (34.0%), making it reasonable to classify it as an indeterminate feature for predicting metastatic LN. Wu et al. [24] analyzed CT parameters for the preoperative evaluation of cervical LN metastasis from papillary thyroid carcinoma and reported similar results in that calcification and cystic or necrotic degeneration showed 100% specificity and PPV for diagnosing metastatic LN. In their study, obvious enhancement showed a degree of specificity similar to that in our study (69.8% vs. 70.1%, respectively) but a lower PPV (64.2% vs. 92.1%, respectively).

In this study, we proposed a modified LN classification system that excluded heterogeneous enhancement as a suspicious feature for diagnosing metastatic LNs because it was not found to be an independent factor in our analysis. This modified classification defines suspicious LNs as those exhibiting cystic changes, calcification, or strong enhancement. The modified LN classification demonstrated a greater divergence in malignancy risk among each group and exhibited improved specificity and PPV for diagnosing metastatic LNs compared to the K-TIRADS. By excluding heterogeneous enhancement as a suspicious feature, it would have been possible to avoid unnecessary biopsies of the seven LNs, which accounted for 1.51% of the 463 LNs assessed. In addition, modification of the LN classification simplifies the risk stratification system and has the potential to reduce inter-observer variability. However, it is important to note that three more false-negatives were identified, representing 0.65% of the total LNs. It is crucial to acknowledge the potential consequences of missed metastases, as they can significantly affect surgical planning and patient prognosis. Therefore, a comprehensive evaluation of the risks and benefits of this classification is essential.

Our study has several limitations. First, it was subject to inevitable selection bias because of the retrospective nature of the study; all patients were recruited from a single tertiary referral center and had LNs that were selected for US-guided biopsy. Second, the high prevalence of metastatic LNs in the study population may have led to an overestimation of the malignancy risk for each CT feature. Third, different CT protocols for patients with thyroid cancer may yield different results. Finally, inter-observer variability may have occurred when interpreting the CT features of the LNs. Thus, prospective multicenter studies are required to validate the generalizability of our findings.

In conclusion, our study demonstrated that heterogeneous enhancement is not an independent feature of metastatic LNs. Excluding heterogeneous enhancement as a suspicious feature resulted in higher specificity and PPV for diagnosing metastatic LNs than the K-TIRADS. Our research results may provide a basis for revising the LN classification in future guidelines.

Supplement

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Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Jeong Hyun Lee, the section editor, and Jung Hwan Baek, the editor board member of the *Korean Journal of Radiology*, were not involved in the editorial evaluation or decision to publish this article. All authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Sae Rom Chung. Data curation: Sae Rom Chung, Yun Hwa Roh. Formal analysis: Sae Rom Chung. Investigation: Sae Rom Chung, Yun Hwa Roh, Jung Hwan Baek. Methodology: Sae Rom Chung, Tae Yong Kim, Tae-Yon Sung, Dong Eun Song. Project administration: Sae Rom Chung. Supervision: Sae Rom Chung. Validation: Sae Rom Chung, Yun Hwa Roh. Visualization: Yun Hwa Roh. Writing—original draft: Yun Hwa Roh. Writing—review & editing: Sae Rom Chung, Young Jun Choi, Jeong Hyun Lee.

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