Can increased tumoral vascularity on quantitative method be a predicting factor of lymph node metastasis in papillary thyroid microcarcinoma?

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Directed by Professor Jin Young Kwak

The Master's Thesis
submitted to the Department of Medicine
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree of Master of Medical Science

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June 2013

This certifies that the Master's Thesis of Hyun Joo Shin is approved.

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June 2013

ACKNOWLEDGEMENTS

I acknowledge my deep gratitude to Professor Jin Young Kwak, who is my thesis director, for supporting my efforts with total commitment and facilitating every step of the process. My appreciation for her guidance and encouragement is tremendous. I am also indebted to Professor Eun-Kyung Kim and Hang-Seok Chang, for their help for pertinent advice to assure the superior quality of this paper. Additionally, I thank Hee Jung Moon, Jung Hyun Yoon, Kyung Hwa Han for their advice.

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<ABSTRACT>

Can increased tumoral vascularity on quantitative method be a predicting factor of lymph node metastasis in papillary thyroid microcarcinoma?

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(Directed by Professor Jin Young Kwak)

Background: To evaluate the clinical implications of the vascular index (VI) as a predicting factor for central and lateral lymph node metastasis (LNM) in patients with papillary thyroid microcarcinoma (PTMC).

Methods: From January 2011 to October 2011, 588 patients (mean age, 45.2 years; 495 females, 93 males) who were diagnosed with PTMC were included. Clinicopathologic characteristics of patients and US features of the lesions including VI were evaluated retrospectively. The VI was measured using QLAB 7.0 quantification software using preoperative Doppler US images. Univariate and multivariate analysis were used to assess predictive factors of LNM.

Results: From 588 patients, 140 patients (23.8%) had central LNM and 26 patients (4.4%) had lateral LNM on pathologic results. Presence of lateral LNM [odd ratio (OR) 5.464; 95% confidence interval (CI) 2.189-13.642], bilaterality (OR 2.163; 95% CI 1.165-4.014) and increased tumor size (OR 1.151; 95% CI 1.036-1.279) were significant independent factors for predicting central LNM. Presence of central LNM (OR 5.577; 95% CI 2.215-14.043), upper third location of malignancy (OR 2.499; 95% CI 1.006-6.205), and tumor size (OR 1.336; 95% CI 1.031-1.731) were significant independent factors for predicting lateral LNM. However, the VI was not a significant predicting factor for both central and lateral LNM.

Conclusion: The VI of PTMC was not significantly associated with both central and lateral LNM. Central LNM was significantly associated with presence of lateral LNM, bilaterality, and increased tumor size. Lateral LNM was significantly associated with presence of central LNM, upper third location of PTMC and increased tumor size.

Key words : Thyroid, Ultrasound, Papillary thyroid microcarcinoma, Vascularity

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I. INTRODUCTION

Thyroid cancer is the most common endocrine malignancy. Among variety histologic types of thyroid cancer, papillary thyroid cancer (PTC) is the most common type of thyroid malignancy.[1] Increased use of high resolution US of thyroid glands can lead to small thyroid cancer. Although papillary thyroid microcarcinoma (PTMC) is usually indolent and good prognosis, an incidence of lymph node metastasis (LNM) is not negligiblerisk ranging from 3.1% to 28.9%.[2-5] Therefore, preoperative ultrasound (US) has been widely used for preoperative staging in patients with thyroid cancer to determine surgical extent.[6-8]

Tumor angiogenesis or neovascularization is a widely accepted factor of tumor growth and metastasis.[9-12] Several studies demonstrated that the degree of vascularity may be associated with metastasis and patients' survival.[13-16] To assess angiogenesis in tumors, microvessel density of tumors has been quantified using immunohistochemistry or microscopy, which was associated with the clinical outcome in patients with various tumors.[17-20] However, microvessel density cannot be gotten preoperatively in patients with cancer. Using color Doppler US, tumor vascularity can be calculated preoperatively.[15] Recent study demonstrated that higher blood supply which was represented as blood flow signal comparing with the surrounding thyroid tissue significantly was associated with regional lymph node metastasis of PTC.[21] However, degree of vasculaization in the study was very subjective. To overcome the limitation of US, we used a new quantitative US parameter, vascular index (VI), to measure tumoral vascularity more objectively.[22] VI was used to know the amount of color in regionof-interests (ROIs), by pixel counting technique using QLAB quantification software of Doppler US.[23-26] To our knowledge, there are no available studies evaluating the use of VI to assess LNM in PTMC. In this study, we investigated the clinical implications of vascular index (VI) of papillary thyroid microcarcinoma (PTMC) as a predicting factor for central and lateral lymph node metastasis (LNM) in patients with PTMC.

II. MATERIALS AND METHODS

The institutional review board of severance hospital approved of this retrospective obs ervational study and required neither patient approval nor informed consent for our review of patients' images and patients' medical records. However, written informed consent was obtai ned from all patients for US-FNA prior to each procedure as a daily practice.

1. Patients

From January 2011 to October 2011, a total of 1784 lesions underwent cervical US evaluation. Of those, 948 lesions were measured VI using QLAB 7.0 quantification software. Of 948 lesions, 70 lesions were excluded because they did not undergo surgery, 213 were excluded because they had PTC > 10mm and 77 were excluded because they did not have conventional PTC results on surgical pathology. Therefore, a total of 588 lesions of 588 patients were included in this study. The most aggressive lesion was selected as an index malignancy in 4 patients who had two lesions on FNA. In 588 patients, 93 patients (mean age, 44.9 years ± 11.1; range, 24-72 years) were men and 495 patients (mean age, 45.2 ± 11.1; range, 19-76 years for women) were women.

Not only the characteristics of thyroid cancer and also the presence of regional LNM divided as central and lateral LNM are assessed for preoperative US evaluation. Clinicopathologic characteristics of patients and US features of the lesions were evaluated, listed in *Table 1*.

Table 1. Characteristics of patients

Patients	Total (*n*=588)	Central LNM			Lateral LNM		
		Positive (*n*=140)	Negative (*n*=448)	*P* value	Positive (*n*=26)	Negative (*n*=562)	*P* value
Age (years, mean ± SD)	45.2 ±11.1	44.4 ±11	45.4 ±11.2	0.362	45.6 ± 9.4	45.2 ±11.2	0.837
Size (mm, mean ± SD)	6 ± 2.1	6.7 ± 1.9	5.8 ± 2.2	<0.001	7.7 ± 1.5	6 ± 2.1	<0.001
Gender				0.120			0.049
Male	93 (15.8%)	28 (20.0%)	65 (14.5%)		8 (30.8%)	85 (15.1%)	
Female	495 (84.2%)	112 (80.0%)	383 (85.5%)		18 (69.2%)	477 (84.9%)	
Location of the index malignancy				0.982			0.015
Upper third	134 (22.8%)	32 (22.9%)	102 (22.8%)		11 (42.3%)	123 (21.9%)	
Mid and lower third	454 (77.2%)	108 (77.1%)	346 (77.2%)		15 (57.7%)	439 (78.1%)	
Multifocal lesions							
Multifocal in affected lobe	81 (13.8%)	26 (4.4%)	55 (9.4%)	0.059	8 (1.4%)	73 (12.4%)	0.018
Multifocal in both lobes	64 (10.9%)	27 (4.6%)	37 (6.3%)	<0.001	8 (1.4%)	56 (9.5%)	0.004
Extrathyroidal extension of the index malignancy				0.017			0.011
Positive	243 (41.3%)	70 (50.0%)	173 (38.6%)		17 (65.4%)	226 (40.2%)	
Negative	345 (58.7%)	70 (50.0%)	275 (61.4%)		9 (34.6%)	336 (59.8%)	
Central LNM							<0.001
Positive	140 (23.8%)				18 (69.2%)	122 (21.7%)	
Negative	448 (76.2%)				8 (30.8%)	440 (78.3%)	
Lateral LNM				<0.001			
Positive	26 (4.4%)	18 (12.9%)	8 (1.8%)				
Negative	562 (95.6%)	122 (87.1%)	440 (98.2%)				

LNM lymph node metastasis, *SD* standard deviation

2. Preoperative TNM Classification Based on Preoperative US staging

Thyroid US was performed using a 5- to 12-MHz linear array transducer (iU22; Philips Medical Systems). US evaluation was performed by one of 12 board-certified radiologists who were aware of the patients' clinical records. To evaluate VI of the thyroid nodules, Doppler US images of thyroid nodule were obtained during the preoperative US evaluation. Findings on gray scale US were prospectively recorded in the radiological reports. Tumor location in the thyroid gland was assessed as upper and the remaining pole of thyroid gland. When there was more than one lesion in thyroid glands, multifocality was defined as multiple malignancies in one lobe, and bilaterality as multiple malignancies in both lobes, and sonographic features were evaluated about index malignancy.[27-31] If the malignant lesion showed > 25% of the perimeter of the tumor in contact with the thyroid capsule or if the echogenic capsule line in contact with the malignant lesion was lost, the lesion was classified as having extrathyroidal extension, T3.[7,32] For the evaluation of LNM, nodal groups were divided according to compartments rather than individual levels, such as central compartment and lateral compartments. On US examination, if the LN has diffuse or focal hyperechogenicity, cystic change, microcalcification, round shape, and chaotic or peripheral vascularity, it was classified as metastatic LN.[7,33]

For the assessment of US finding of index malignancy, tumor composition was divided as solid and mixed. The echogenicity of nodule was subgrouped as iso, hypo- and markedly hypoechogenicity compared to normal thyroid tissue. Margin was assessed as well defined or not well defined (microlobulated or irregular margin). Calcification was classified as present or absent. The shape of nodule was assessed whether they are parallel or nonparallel (greater in anteroposterior diameter than transverse diameter on scanned view). Sonographic grouping was divided as positive and negative.[31] Positive US finding were marked hypoechogenicity, microlobulated or irregular margin, microcalcifications, and nonparallel shape. Negative US finding was defined with no above positive features.

3. Tumor vascularity assessment

The vascularity of tumor was evaluated using QLAB 7.0 quantification software (Philips Medical Systems, Andover, MA). QLAB enabled color flow quantification using ROI for color loops.

It provided information about the vascularity and blood flow measured in a ROI, using a pixel counting technique. We used VI for tumor vascularity of thyroid cancer. VI represented amount of color detected in ROI, by describing the color percentage within the volume of interest. The equation used for achieving VI was as follow; VI of ROI = (number of color pixels)/(total pixels-background pixels).[22-26] The VI showed how many vessels can be detected within the tissue. If VI was measured as 46%, then it means 46% of the voxels in the volume are color. One radiologist who was known to the patient's final diagnosis reviewed US images using QLAB software and drawn ROIs along the tumor margin. Then the software calculated VI values of the ROI automatically, and represented VI graph as an absolute time to VI curve. Among these values, the peak VI value was obtained for the representative VI value of thyroid nodule (*Fig. 1*). Vascular index was obtained in two times with time interval of 6 months by the same radiologist with a blind-check of VI in the same patient.

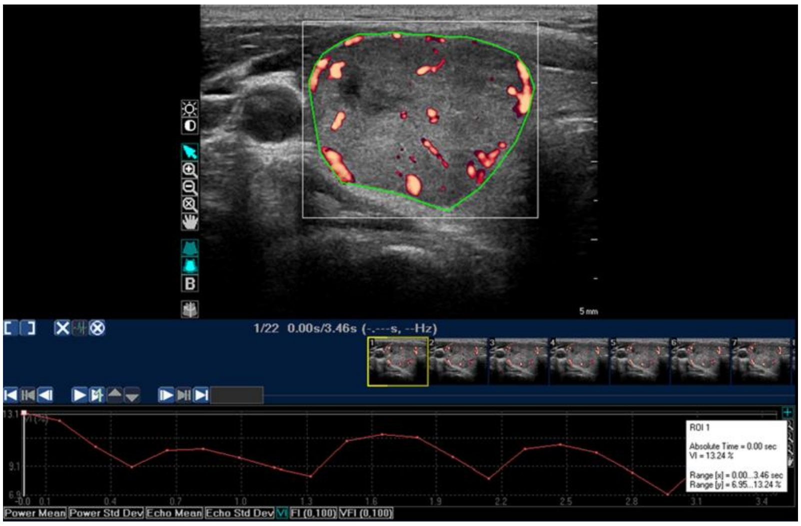

Fig. 1. Quantification of vascularity in a PTMC expressed as VI by Doppler US using QLAB software.

ROI was selected along the margin of the nodule. The software calculated VI values of the ROI automatically, and represented VI graph as an absolute time to VI curve. Among these values, the peak VI value (13.24 % in this nodule) was obtained for the representative VI value of a thyroid nodule.

4. Thyroid surgery

The extent of surgery is decided according to the guidelines of American Thyroid Association in our institution.[7,34] If the patients had multiple or bilateral lesions, large tumors (>4cm), extrathyroidal extension on surgery, a first-degree family history of thyroid carcinoma, and a history of head or neck radiation exposure, they underwent total thyroidectomy.[34] All patients underwent central compartment dissection, while ipsilateral central compartment dissection was done during hemithyroidectomy, and bilateral central compartment dissection during total or near-total thyroidectomy. Lateral compartment dissection was selectively performed in patients who were proven to have metastatic lateral LNs through preoperative US and fine needle aspiration biopsy.[7] If metastatic LNs were suspected on neck computed tomography or at the time of surgery, lateral neck node dissection was performed after frozen biopsy for that lesion showed metastatic result.

5. Histopathologic analysis

The histopathologic results were reviewed for the assessment of the largest size of tumor which was measured by the pathologist from surgical specimen, multifocality, bilaterality, presence of extrathyroidal extension, and N staging. The pathologic staging was performed according to the seventh edition of TNM classification by the AJCC.[35] Pathologic LNM were classified as N1a (level Ⅵ) and N1b (unilateral, bilateral, contralateral cervical or superior mediastinal nodes) separately.

6. Statistical analysis

Histopathologic results were final reference in this study. We used Chi-square test or Fisher's exact test for categorical variables and independent t-test for continuous variables to compare the clinicopathologic variables between with LNM and without LNM.

For VI, intraobserver variability was assessed using intraclass correlation coefficient (ICC) based on two-way random effects model. When the value of ICC is closer to 1, it means two values are more reliable. Mean values of VI were calculated and used for statistical analysis.

Univariate and multivariate logistic regression analysis was performed to identify clinicopathologic prognostic factors associated with central and lateral LNM, respectively. Multivariate logistic regression analysis was used to assess independent factors for central and lateral LN metastasis, respectively. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for all clinicopathologic and imaging factors after the adjustment of all factors.

Statistically significant result is assumed when *P* value is less than 0.05 in all cases. Analysis was performed using SAS software (version 9.1.3 ; SAS Institute, Cary, NC).

III. RESULTS

From 588 patients, surgical methods were total thyroidectomy in 246 (41.8%), near-total thyroidectomy in 58 (9.9%), and hemithyroidectomy in 284 (48.3%) patients. Ipsilateral central compartment dissection was done in 285 patients, bilateral central compartment dissection in 281 patients, and bilateral central compartment dissection with ipsilateral lateral compartment dissection in 22 patients. The mean tumor size of index malignancy was 6 ± 2.1 mm (range 1-10 mm). One hundred thirty four patients (22.8%, 134 of 588) had upper third location of index malignancy in thyroid gland, 243 patients (41.3%, 243 of 588) had extrathyroidal extension, 81 patients (13.8%, 81 of 588) had multifocal malignancies, and 64 patients (10.9%, 64 of 588) had bilateral malignancies. About LNM, 140 patients (23.8%, 140 of 588) had central LNM, and 26 patients (4.4%, 26 of 588) had lateral LNM on pathologic results.

For VI, ICC of two values was 0.97 (95% CI 0.965-0.974), which means reliable result based on two-way random effects model.

On univariate analysis, central LNM was significantly associated with larger tumor size, bilaterality, extrathyroidal extension, lateral LNM, and presence of calcifications on US. Lateral LNM was significantly associated with larger tumor size, male gender, upper third location of the index malignancy, multifocality, bilaterality, extrathyroidal extension, and central LNM. However, central and lateral LNM were not increased significantly as VI increased (*Tables 1, 2*).

On multivariate analysis, tumor size, bilaterality, and lateral LNM were statistically significant independent factors for predicting central LNM (*Table 3*). Presence of calcifications on US was not an independent predicting factor for central LNM (P = 0.074) when we regarded less than 0.05 of P value as significant. The most powerful predictive factor for central LNM was presence of lateral LNM (OR 5.464, 95% CI 2.189-13.642), in decreasing order was bilaterality (OR 2.163, 95% CI 1.165-4.014) and increased tumor size (OR 1.151, 95% CI 1.036-1.279). For lateral LNM, tumor size, upper third location of the index malignancy, and central LNM were independent predicting factors (*Table 4*). The most powerful predictive factor for lateral LNM was presence of central LNM (OR 5.577, 95% CI 2.215-14.043), in decreasing order were upper third location of index malignancy (OR 2.499, 95% CI 1.006-6.205), and tumor size (OR 1.336, 95% CI 1.031-1.731).The VI was not a significant predicting factor for both central and lateral LNM.

Table 2. Characteristics of US findings

US findings	**Total (*n*=588)**	**Central LNM**			**Lateral LNM**		
		Positive (*n*=140)	**Negative (*n*=448)**	***P* value**	**Positive (*n*=26)**	**Negative (*n*=562)**	***P* value**
Composition				0.929			0.622
Solid	562 (95.6%)	134 (95.7%)	428 (95.5%)		26 (100.0%)	536 (95.4%)	
Mixed	26 (4.4%)	6 (4.3%)	20 (4.5%)		0 (0.0%)	26 (4.6%)	
Echogenicity				0.962			0.286
Markedly hypoechogenicity	54 (9.2%)	13 (9.3%)	41 (9.2%)		4 (15.4%)	50 (8.9%)	
Iso- or hypoechogenicity	534 (90.8%)	127 (90.7%)	407 (90.8%)		22 (84.6%)	512 (91.1%)	
Margin				0.247			1.000
Not well defined margin	494 (84.0%)	122 (87.1%)	372 (83.0%)		22 (84.6%)	472 (84.0%)	
Well defined margin	94 (16.0%)	18 (12.9%)	76 (17.0%)		4 (15.4%)	90 (16.0%)	
Calcifications				0.010			0.139
Presence of calcifications	301 (51.2%)	85 (60.7%)	216 (48.2%)		17 (65.4%)	284 (50.5%)	
No calcification	287 (48.8%)	55 (39.3%)	232 (51.8%)		9 (34.6%)	278 (49.5%)	
Shape				0.775			0.949

Taller than wide	313 (53.2%)	76 (54.3%)	237 (52.9%)		14 (53.8%)	299 (53.2%)	
Wider than tall	275 (46.8%)	64 (45.7%)	211 (47.1%)		12 (46.2%)	263 (46.8%)	
Vascular index (mean ± SD)	21 ± 24.6	21.4 ± 25.6	20.9 ± 24.3	0.818	16.7 ± 21.4	21.2 ± 24.7	0.370

US ultrasound, *LNM* lymph node metastasis, *SD* standard deviation

Table3. Univariate and multivariate logistic regression for central lymph node metastasis

Independent variables	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Clinicopathologic characteristics				
Age (years)	0.992 (0.975-1.009)	0.361	0.986 (0.968-1.005)	0.140
Size (mm)	1.223 (1.115-1.341)	<0.001	1.151 (1.036-1.279)	0.009
Gender (male vs. female)	1.473 (0.902-2.406)	0.122	1.314 (0.767-2.250)	0.320
Location of the index malignancy (Upper third vs. mid and lower third)	1.005 (0.640-1.580)	0.982	0.823 (0.500-1.354)	0.443
Multifocal in affected lobe (positive vs. negative)	1.630 (0.978-2.716)	0.061	1.071 (0.597-1.921)	0.818
Multifocal in both lobes (positive vs. negative)	2.654 (1.550-4.545)	<0.001	2.163 (1.165-4.014)	0.014
Extrathyroidal extension of the index malignancy (positive vs. negative)	1.590 (1.085-2.329)	0.017	1.332 (0.861-2.062)	0.198
Lateral LNM (positive vs. negative)	8.115 (3.445-19.112)	<0.001	5.464 (2.189-13.642)	<0.001
US characteristics				
Composition (solid vs. mixed)	1.044	0.929	0.808	0.671

	(0.411-2.652)		(0.301-2.168)	
Echogenicity (Marked hypoechoic vs. hypo- or isoechogenicity)	1.016 (0.528-1.956)	0.962	0.743 (0.359-1.537)	0.422
Margin (ill-defined vs. well-defined)	1.385 (0.797-2.407)	0.249	1.571 (0.842-2.931)	0.156
Calcification (positive vs. negative)	1.660 (1.128-2.443)	0.010	1.463 (0.963-2.223)	0.074
Shape (taller than wide vs. wider than tall)	1.057 (0.722-1.547)	0.775	1.073 (0.702-1.642)	0.744
Mean Vascular index	1.001 (0.993-1.009)	0.814	1.003 (0.995-1.012)	0.421

US ultrasound, *OR* odds ratio, *95% CI* 95% confidence interval, *vs* versus

Table4. Univariate and multivariate logistic regression for lateral lymph node metastasis

Independent variables	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Clinicopathologic characteristics				
Age (years)	1.004 (0.969-1.040)	0.837	0.999 (0.960-1.040)	0.970
Size (mm)	1.491 (1.209-1.839)	<0.001	1.336 (1.031-1.731)	0.028
Gender (male vs. female)	2.494 (1.051-5.919)	0.038	1.874 (0.686-5.120)	0.221
Location of the index malignancy (Upper third vs. mid and lower third)	2.617 (1.172-5.844)	0.019	2.499 (1.006-6.205)	0.048
Multifocal in affected lobe (positive vs. negative)	2.977 (1.249-7.095)	0.014	1.980 (0.664-5.908)	0.221

Multifocal in both lobes (positive vs. negative)	4.016 (1.670-9.656)	0.002	1.550 (0.514-4.675)	0.436
Extrathyroidal extension of the index malignancy (positive vs. negative)	2.808 (1.230-6.410)	0.014	1.722 (0.661-4.482)	0.266
Central LNM (positive vs. negative)	8.115 (3.445-19.112)	<0.001	5.577 (2.215-14.043)	<0.001
US characteristics				
Composition (solid vs. mixed)	1.768 (0.297-infinity)	0.601	Infinity	NA
Echogenicity (Marked hypoechoic vs. hypo- or isoechogenicity)	1.862 (0.617-5.617)	0.270	1.530 (0.441-5.306)	0.502
Margin (ill-defined vs. well-defined)	1.049 (0.353-3.116)	0.932	0.816 (0.227-2.927)	0.755
Calcification (positive vs. negative)	1.849 (0.811-4.218)	0.144	1.212 (0.487-3.015)	0.679
Shape (taller than wide vs. wider than tall)	1.026 (0.466-2.258)	0.949	0.779 (0.309-1.959)	0.595
Mean Vascular index	0.991 (0.972-1.011)	0.374	0.990 (0.968-1.012)	0.360

US ultrasound, *OR* odds ratio, *95% CI* 95% confidence interval, *NA* nonapplicable, *vs* versus

IV. DISCUSSION

Tumors require blood supply for the progression of malignant tumors as well as the growth of the tumor. Many tumors had increased formation of irregular vessels or arteriovenous shunt. Furthermore, the degree of vascularity has been reported to may be associated with metastasis and patients' survival.[13-16] The quantification of microvessel density (MVD) of tumors has been widely used for assessing angiogenesis using specific markers for endothelial cells, such as vascular endothelial growth factor (VEGF), its receptor, KDR, or factor Ⅷ-related antigen, CD 31, and CD 34.[16,36] Several investigators also demonstrated that the association between MVD and the clinical outcome of patients with various solid tumors. VEGF was an important angiogenic factor in colon cancer, either primary or metastatic, and VEGF expression and vessel counts could predict the risk of metastasis from colon cancer.[19] In breast cancer, microvessel count in invasive breast cancer was significant correlation with metastasis.[37] Strong correlation was also seen in stomach cancer between vascularization of the cancer and overall survival and development of hematogeneous metastasis.[20,38]

With the technical development of Doppler US, power Doppler US can detect the smallest blood flow within tumors. In contrast to MVD, US has a greatest advantage of non-invasiveness. Therefore, Doppler US has been utilized in many previous studies to represent intratumor vascularization and it is demonstrated that the number and size of vessels visualized with Doppler US are significantly correlated with pathological parameters such as anti-factor Ⅷ antibody using immunochemical studies.[15] Also, increased tumor vascularity on Doppler US was significantly associated with locoregional metastasis of PTC.[21] VI is anew Doppler US parameter for evaluating tumoral vascularity and also for survival of cancer patients. For colon and stomach cancer, VI was statistically significantly correlated with MVD, and was a good preoperative indicator of recurrence and patient survival.[16,39]

The recurrence rate of PTC is increased twice in the patients with cervical LNM, and it is increased five-fold or greater particularly in the patients over 40 years of age.[40] And the extent of surgery is also influenced by the extent of LNM. Therefore, efforts to know and predict the lymph nodes involvement at preoperative evaluation become important in those reasons. In this study, we hypothesized that LNM will occur more frequently in the malignant thyroid nodule with increased intranodular vascularity than lower vascularity nodules, because tumor spread is possible by activated neoangiogenesis theoretically. We evaluated vascular index for the quantitative measurement of tumoral vascularity as a predicting factor affecting LNM in patients with PTMC.

Moreover, we assessed several clinicopathologic factors and US findings for predicting LNM, dividing central and lateral compartments, for the better assessment of LNM on preoperative US examination. Tumor size, bilaterality and lateral LNM were significant independent predictive factors for central LNM in this study. This result is comparable with other studies concerning about the predictive factors of central LNM in PTC.[41-43] The results can be explained by the rich network of lymphatic channels.[41,44] As the tumor increased in size and affect other lobe, the chance to involve lymphatic drainage and central lymph nodes are also increase. For lateral LNM, tumor size, upper third location of the index malignancy, and central LNM were independent factors for predicting metastasis in this study, which were similar to previous reports.[4,42] Nodal metastasis of PTC is spread to lateral compartment via ipsilateral, paratracheal, and pretracheal node because of the consistent lymphatic drainage pattern of thyroid gland.[42] This can explain why the most powerful independent predictive factor of lateral LNM was central LNM in our result. Previous reports explained that the lymphatic flow along the superior thyroid artery lead more frequent chance of spreading cancer cells to lateral lymph nodes when the tumor is located in upper third location of thyroid gland.[4,45] Moreover, tumor size was also an important risk factor for lateral LNM.[4,42]

Not many studies were reported about the relationship between central LNM and preoperative US findings, and there was a report concerning that the presence of calcifications was a significant association factors detected on US for central LNM in recent study.[41] In this study, presence of calcification of the cancer on US was significantly associated with central LNM on univariate analysis although it was not an independent factor of central LNM on multivariate analysis under the condition of less than 0.05 of *P* value as a significant. In lateral LNM, ill-defined margin, >25% contact with the adjacent capsule, and presence of calcification on US were significant independent predicting factors in patients with PTMC.[4,8,21,45] However, any US findings were not significant independent factors for predicting lateral LNM in patients with PTMC in this study. The different results may be explained by the interobserver variability of US for assessing thyroid nodule and the different confounding variables.[46]

Moreover, VI of PTMC was not significantly associated with both central and lateral LNM.

The differences between this study and other reports including other cancers such as stomach, colon, breast cancers can be as follows; most PTMC is latent and indolent course and VI in this study may has limitation to represent the whole vascularity of thyroid nodule because it shows maximum percentage of vascularity in one 2-dimensional image plane, not considering 3-dimensional volumetric information. The recent study which compared color Doppler results with histological vascularity in papillary thyroid cancers, found that color Doppler had a low sensitivity when differentiating benign and malignant thyroid nodules and that it detected intra-nodular microvessels only incompletely.[47] This was because papillary thyroid carcinomas have a very high percentage of microvessels, but the small vessels (<100 micrometers in diameter) are below the sensitivity of Doppler US. Further studies should be performed to validate this non-invasive imaging tool by directly comparing the histologically verified number of blood vessels with the VI.[47]

There were a few limitations in this study. First, the US evaluation of thyroid cancer and Doppler evaluation was done by one of 12 board-certified radiologists, and interobserver variability seems inevitable. Second, VI can have limitation to represent the whole vascularity of thyroid nodule because it shows maximum percentage of vascularity in one 2-dimensional image plane, not considering 3-dimensional volumetric information although we used the most representative2D images for this study. Third, in the aspect of measuring method, the noise of Doppler US and gain difference by US machines or examiners could affect the amount of color signals included in ROI. Prior report suggested that individual variation of tissue attenuation, patient's poor cooperation or movement, motions related with swallowing, breathing and pulsation of adjacent arterial structures, and over-pressing of thyroid tissue during the US examination can affect Doppler US results.[46] In this study, we tried to do our best to minimize the variation related to measurement of VI on US using the same machine and the same parameters. Also we excluded the images showing US noise. However, these technical issues might interrupt the precise evaluation of nodular vascularity. Forth, the patients who did not undergo lateral neck node dissection were considered as negative LNM group.This can lower the number of included patients of lateral LNM in our study. It is very likely that if lateral nodes were sampled more routinely, more metastatic sites would have been identified. Fifth, the number of patients with lateral LNM was so small which can lead to decreased power of the statistics.

V. CONCLUSION

In conclusion, VI of PTMC was not significantly associated with both central and lateral LNM. Central LNM was significantly associated with presence of lateral LNM, bilaterality, and increased tumor size. Lateral LNM was significantly associated with presence of central LNM, upper third location of PTMC and increased tumor size. Further studies are needed to define the association of tumor vascularity with LNM in patients with PTMC.

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ABSTRACT(IN KOREAN)

갑상선 유두암의 종양 내 혈류 증가가 림프절 전이를 시사하는 소견인가?

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목적: 갑상선 미세유두암 환자의 중심, 외측 림프절 전이를 예측하는 데에 있어서 종양의 vascular index (VI)가 갖는 임상적 의미를 평가하고자 한다.

대상 및 방법: 2011년 1월부터 2011년 10월까지 갑상선미세유두암으로 진단받은 588명 (평균 나이 : 45.2세, 여성 495명, 남성 93명)의 환자를 대상으로 하였다. 환자들의 임상적 정보와 병변의 병리적 특징 및 vascular index 를 포함한 병변의 초음파 소견을 후향적으로 분석하였다. 이 중 vascular index 는 수술 전 갑상선 초음파를 시행할 때 행한 도플러 초음파 영상에서 QLAB 7.0 quantification software 를 사용하여 측정하였다. 림프절 전이의 예측 인자를 평가하기 위하여 univariate, multivariate analysis 방법을 사용하였다.

결과: 총 588명의 환자 중, 병리 결과상 140명(23.8%)의 환자들이 중심 림프절 전이를 갖고 있었고, 26명 (4.4%)의 환자들이 외측 림프절 전이를 가지고 있었다. 중심 림프절 전이의 유의한 예측 인자는 외측 림프절 전이가 있을 때 [odd ratio (OR) 5.464; 95% confidence interval (CI) 2.189-13.642], 병변이 갑상선 내에서 양측성 일 때 (OR 2.163; 95% CI 1.165-4.014), 병변의 크기가 클 때 (OR 1.151; 95% CI 1.036-1.279) 순이었다. 외측 림프절 전이의 유의한 예측 인자는 중심 림프절 전이가 있을 때 (OR 5.577; 95% CI 2.215-14.043), 병변이 갑상선 내에서 위쪽 1/3에 위치하고 있을 때 (OR 2.499; 95% CI 1.006-6.205), 병변의 크기가 클 때 (OR 1.336; 95% CI 1.031-

1.731) 순이었다. 하지만, vascular index는 중심과 외측 림프절 전이의 예측에 있어서 유의한 예측 인자가 아니었다.

결론: 갑상선 미세유두암에서 vascular index는 중심, 외측 림프절 전이에 있어 유의한 예측인자가 아니었다. 중심 림프절 전이에 있어서는 외측 림프절 전이, 병변의 양측성 , 병변의 크기가 유의한 예측 인자였고, 외측 림프절 전이에 있어서는 중심 림프절 전이, 병변의 갑상선 내부 상위 1/3 위치, 병변의 크기가 유의한 예측 인자였다.

핵심되는 말 : 갑상선, 초음파, 갑상선 미세유두암, 혈류.