Predicting Lymph Node Metastasis in Papillary Thyroid Carcinoma Patients by Vascular Index on Power Doppler US

Ji Hye Lee

Department of Medicine

The Graduate School, Yonsei University

Predicting Lymph Node Metastasis in Papillary Thyroid Carcinoma Patients by Vascular Index on Power Doppler US

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Ji Hye Lee

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연세대학교
YONSEI UNIVERSITY

This certifies that the Doctoral Dissertation
of Ji Hye Lee is approved.

Thesis Supervisor : Jin Young Kwak

Thesis Committee Member#1 : Eun Kyoung Kim

Thesis Committee Member#2 : Hyoung Ju Kwon

Thesis Committee Member#3 : Ji Hoon Kim

Thesis Committee Member#4 : Jandee Lee

The Graduate School
Yonsei University

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ABSTRACT

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Ji Hye Lee

Department of Medicine
The Graduate School, Yonsei University

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Background: Angiogenesis plays a crucial role in tumor growth and the metastatic spread of cancer. For patients with papillary thyroid carcinoma (PTC), lymph node metastasis (LNM) is associated with an increased recurrence rate. The purpose of this study was to investigate whether the vascular endothelial growth factor (VEGF), microvessel density (MVD), and vascular index (VI) can predict LNM in patients with PTC. **Methods:** From January 2011 to October 2011, 202 patients with PTCs underwent preoperative staging ultrasound (US) evaluation. To evaluate vascularity, we measured the VI, VEGF expression and MVD. **Results:** The VI was significantly correlated with MVD (P = 0.009). On multivariate analysis, young age showed a significant correlation with LNM (OR = 0.957, P = <0.001; OR = 0.955, P = <0.001; OR = 0.957, P = <0.001) and extrathyroidal extension had a marginal correlation with LNM (OR = 1.897, P = 0.058; OR = 2.155, P = 0.029; OR = 1.935, P = 0.053). However, the other clinicopathologic features, VEGF, MVD and VI failed to show any significant correlations with LNM. **Conclusions:** Although the VI showed significant

correlation with MVD, it was not significantly correlated to LNM.

Key words : papillary thyroid carcinoma, lymph node metastasis, vascular index, microvessel density, vascular endothelial growth factor

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I. INTRODUCTION

Tumor angiogenesis is necessary for tumor growth and the metastatic spread of cancer.[1,2] Vascular endothelial growth factor (VEGF) can induce endothelial cell growth and its increased expression is associated with poor prognosis, such as lymph node metastasis (LNM) and recurrence in several cancers.[3-5] For papillary thyroid carcinoma (PTC), LNM is associated with increased recurrence rates even after high dose iodine therapy.[6] To evaluate tumor vessels, microvessel density (MVD) has been measured and used as a predicting factor of the clinical outcomes of patients with cancer.[7,8] However, because its measurement demands biopsy specimens and is invasive, MVD may not be an ideal tool in a preoperative clinical setting.[9]

Color Doppler ultrasound (US) has been used to calculate tumor vascularity, which is associated with the prognosis of primary cutaneous melanomas.[10] Recently, the use of contrast-enhanced ultrasonography (CEUS) has been

investigated to detect microvessels and its results have been significantly correlated with MVD in patients with thyroid nodules.[11,12] Unfortunately, CEUS is slightly invasive in nature because the dye must be injected, thus, decreasing the merits of it being a noninvasive ultrasound technique. The vascular index (VI) is a quantitative US parameter which represents the amount of color in the region-of-interests (ROIs), and is calculated from the ratio of flow area within the ROIs.[13] It can be calculated and displayed as an absolute time to VI curve.

Regarding thyroid cancer, there have been few studies evaluating the correlation among VEGF, MVD and LNM.[14] However, the role of angiogenesis in LNM of PTC has not been fully explained, and to our knowledge, there has been no study elucidating the relationship among VEGF, MVD, and VI in thyroid cancer. In this study, we investigated the correlation between VEGF, MVD, and VI in PTC patients and whether VEGF, MVD, and VI can predict cervical LNMs in these patients.

II. MATERIALS AND METHODS

1. Patients

The institutional review board of Severance Hospital approved this study and required neither patient approval nor informed consent for our review of patients' images and records. However, written informed consent was obtained from all patients for US-guided fine-needle aspiration (FNA) prior to each

procedure as part of daily practice.

From January 2011 to October 2011, a total of 1784 lesions underwent preoperative staging US evaluation. Of those, 948 lesions had the VI measured with QLAB 7.0 quantification software. Of the 948 lesions, 70 lesions were excluded because they did not undergo surgery, 588 were excluded because they were microcarcinomas, 77 were excluded because they did not have conventional PTC results on surgical pathology, and 11 were excluded because cytologic slides were not available for additional immunohistochemistry. Finally, 202 conventional PTCs in 202 patients were included in this study. The mean age of the 202 patients included in this study was 43.4 ± 13.6 years (range, 19-76 years). The mean size of the nodules was 15.5 ± 5.3 mm (range, 11-45 mm).

2. Surgical procedures

The extent of the operation was decided according to the guidelines of the American Thyroid Association.[15] If the patients had large tumors (4cm), multiple or bilateral lesions, extrathyroidal extension, or if the patients had a first-degree family history of thyroid carcinoma or a history of head or neck radiation exposure, total thyroidectomy was performed.[16] All patients underwent central neck node dissection, while lateral neck node dissection was selectively performed in patients who were confirmed to have lateral neck node metastasis through preoperative US and fine-needle aspiration biopsies.[15] For cases in

which metastatic lymph nodes (LNs) were not suspected on preoperative US, but suspicious findings were found on neck computed tomography or at the operation field, frozen biopsies were done and lesions that had metastatic results then underwent lateral neck node dissection.

3. Preoperative US staging and Tumoral Vascularity Assessment

One of 12 board-certified radiologists (4 faculty and 8 fellows) with 1 to 15 years of experience in thyroid US performed preoperative staging neck US, using a 5- to 12-MHz linear array transducer (iU22; Philips Medical Systems, Andover, MA, USA). The radiologists were aware of each patient's clinical information.

During preoperative US imaging, Doppler US images of the thyroid tumor were captured, and the VIs of the tumors were evaluated using QLAB 7.0 quantification software (Philips Medical Systems, Andover, MA, USA). US images were taken with the same scanner settings and the same Doppler color maps for all cases. Quantification of the vascular color signals was automatically performed by drawing ROIs using color loops along the tumor margin with QLAB. Quantitative vascularity information and blood flow were measured with the pixel counting technique (Figure 1). The results were expressed as the VI of the ROI [(the number of color pixels)/(total pixels – background pixels)], and represented the amount of color in the ROI. Therefore,

the VI showed the ratio of the flow area to the total tumor area. QLAB calculated the VI and displayed data as an absolute time to VI curve. The peak VI was also obtained and used for quantitative analysis.[13] One board-certified radiologist who had performed the preoperative examination reviewed US images using QLAB and drew ROIs along the tumor margins. These margins were then matched with the tumor margins drawn on grayscale images.

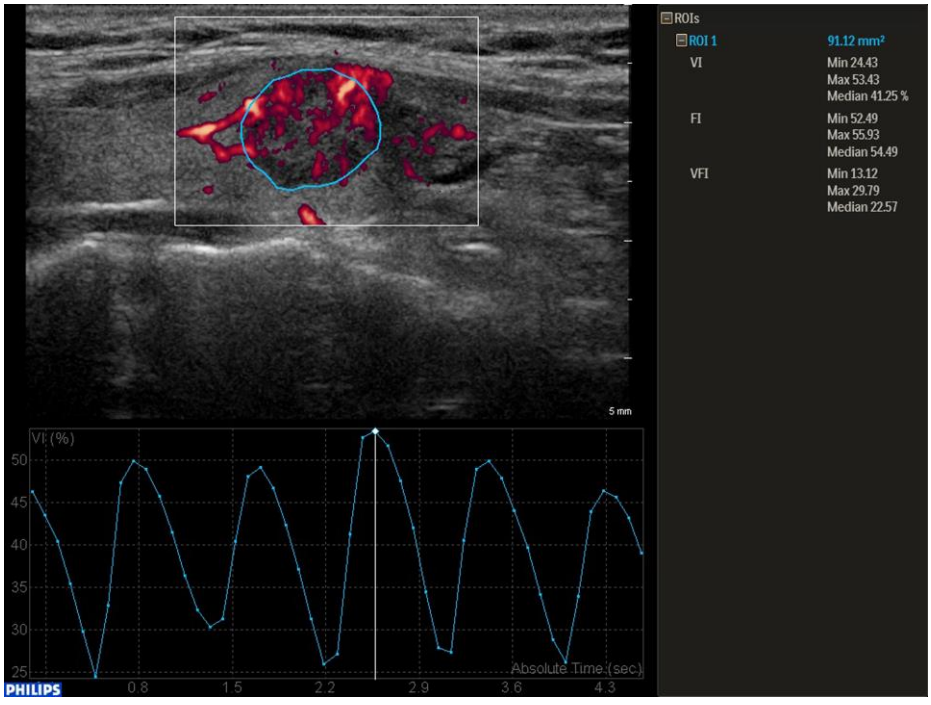

Figure 1. Quantification of tumor vascularity for the VI using power Doppler US with QLAB software. The ROI was draw along the margins of the nodule based on a gray-scale US image. The software calculated the VI values within the ROI automatically. The VI graph represents an absolute time to VI curve, and the peak VI value was obtained for the representative VI value.

4. Histopathologic Analysis

The histopathologic results were reviewed by pathologists to assess the size and number of tumors, extrathyroidal extension, and lymph node metastases from surgical specimens. Pathologic lymph node metastasis were classified as N1a (level Ⅵ) or N1b (unilateral, bilateral, contralateral cervical (level Ⅰ-Ⅴ) or superior mediastinal nodes (level Ⅶ), separately.

5. Immunohistochemistry

A core tissue (2mm in diameter) was obtained from individual paraffin blocks and placed in a new paraffin block using a trephine apparatus (Superbiochips Laboratories, Seoul, Korea). Additionally, five non-neoplastic thyroid parenchymal sections adjacent to the papillary carcinoma were also included in the tissue microarray blocks. Immunohistochemical staining was performed using the Bond-Max Autostainer (Leica Microsystems, Buffalo Grove, Illinois, USA). Using a microtome, the paraffin blocks were cut into 4-㎛-thick slices and immunostained with antibodies directed against VEGF and CD34 antigens. The primary antibodies used were monoclonal anti-VEGF (sc-7269) antibody (Santa Cruz Biotechnoloy, Santa Cruz, CA, USA; dilution 1:500) and anti-CD34 (0786) antibody (Immunotech, Brea, CA, USA; dilution 1:300). VEGF was expressed in cytoplasm. Immunostained slides of VEGF were scored using

the H-score method[17] which classifies the percentages of cells stained with intensities of 0, 1+, 2,+, and 3+ as follows: H-score = ∑ [intensity (0, 1, 2, 3) x extent of each staining intensity (%)]. The H-score ranged from 0 to 300. The definition of intensity was as follows: 0 for no detectable staining, 1+ for weak reactivity mainly detectable at high magnification (x 20–40 objective), and 2+ or 3+ for more intense (moderate or strong, respectively) reactivity easily detectable at low magnification (x 4 objective). CD34 expression was used to detect blood vessel density. The immunostained sections were scanned by light-microscopy at low magnification (x 4) and the areas of tissue with the greatest number of distinctly highlighted microvessels were selected. The microvessel density was determined by counting all immunostained vessels at x200.

6. Statistical analysis

Spearman correlation tests were used to determine the correlation between VI, VEGF, and CD34. We compared patients with LNM and without LNM according to categorical variables using the chi-square test or Fisher's exact test. The Kolmogorov-Smirnov test was performed to evaluate the normality of the variables. The Mann-Whitney *U* test was used to compare continuous variables between patients with LNM and without LNM because variables were not normally distributed. Statistical significance was assumed when the *P* value was less than 0.05. All reported *P* values are 2-sided. To evaluate independent

associations of LNM, multivariate logistic regression analysis was performed with adjustment for known clinicopathologic prognostic factors. Before performing multivariate logistic regression analysis, we examined multicolinearity using the variance inflation factor. Because the variance inflation factor of extent, intensity, and H-score of VEGF was larger than 10, we performed three separate multivariate logistic regression analyses. Odds ratios (ORs) with relative 95% confidence intervals (CIs) were also calculated to determine the relevance of all potential outcome predictors. Analysis was performed using SAS software (version 9.1.3; SAS Institute, Cary, NC, USA).

III. RESULTS

Table 1 summarizes comparisons of the two groups (patients with LNM and without LNM) for several factors. VEGF, MVD, and VI were not significantly different between PTC patients with LNM and without LNM. The frequency of LNM was significantly higher in younger patients with PTC. Other clinicopathologic features failed to show any significant association with LNM.

Table 1. Patient Characteristics

	Total (No. of patients=202)	Lymph node metastasis		*P* value
		Positive (No. of patients=113)	Negative (No. of patients=89)	
Age (year)	42 (33-52)	37 (29-49)	48 (40-53)	<0.001
Size (mm)	14 (12-18)	14 (12-19)	13 (12-16)	0.142
Sex				0.172
Female	159 (78.7 %)	85 (75.2%)	74 (83.2%)	
Male	43 (21.3%)	28 (24.8%)	15 (16.9%)	
Multifocality				0.500
No	130 (64.4%)	75 (66.4%)	55 (61.8%)	
Yes	72 (35.6%)	38 (33.6%)	34 (38.2%)	
Extrathyroidal extension				0.114
No	61 (30.2%)	29 (25.7%)	32 (36.0%)	
Yes	141 (69.8%)	84 (74.3%)	57 (64.0%)	
Vascular index	5.725 (2.19-13.31)	5.62 (1.61-12.15)	6.62 (2.78-13.87)	0.190
VEGF_extent	0 (0,5)	0 (0,5)	0 (0,3)	0.855
VEGF_intensity*				0.743
0	142 (70.3%)	80 (70.8%)	62 (69.7%)	
1	41 (20.3%)	22 (19.5%)	19 (21.4%)	
2	14 (6.9%)	7 (6.2%)	7 (7.9%)	
3	5 (2.5%)	4 (3.5%)	1 (1.1%)	
VEGF_H-score	0 (0,5)	0 (0,5)	0 (0,3)	0.915
CD34 (no/HPF, x200)	38 (28-48)	36 (28-47)	39 (29-48)	0.502

Data are expressed as median (interquartile range).

*Fisher's exact test

The VI was significantly correlated with MVD (Spearman's rho = 0.185, *P* = 0.009), but was not significantly correlated with the VEGF extent (Spearman's rho = -0.028, *P* = 0.696), VEGF intensity (Spearman's rho = -0.009, *P* = 0.895), and VEGF H-score (Spearman's rho = -0.024, *P* = 0.730).

On univariate analysis, young age showed a significant association with LNM (OR = 0.960, *P* = <0.001) (Table 2). On the other hand, LNM was not significantly associated with other patient characteristics. Multivariate analysis showed that young age was an independent predictor for LNM (OR = 0.957, *P* = <0.001; OR = 0.955, *P* = <0.001; OR = 0.957, *P* = <0.001), whereas extrathyroidal extension had a marginal correlation with LNM (OR = 1.897, *P* = 0.058; OR = 2.155, *P* = 0.029; OR = 1.935, *P* = 0.053) (Table 2). However, VEGF, MVD, and VI were not statistically significant predicting factors for LNM in PTC patients.

Table 2. Univariate and multivariate logistic regression for lymph node metastasis

	Univariate		Multivariate					
	Crude OR (95% CI)	***P* value**	**Adjusted OR* (95% CI)**	***P* value**	**Adjusted OR† (95% CI)**	***P* value**	**Adjusted OR‡ (95% CI)**	***P* value**
Age (year)	0.960 (0.939-0.981)	<0.001	0.957 (0.935-0.98)	<0.001	0.955 (0.932-0.978)	<0.001	0.957 (0.935-0.980)	<0.001
Size (mm)	1.057 (0.997-1.121)	0.062	1.046 (0.983-1.112)	0.158	1.040 (0.978-1.107)	0.212	1.045 (0.982-1.111)	0.167
Sex								
Female	Reference		Reference		Reference		Reference	
Male	1.625 (0.807-3.273)	0.174	1.743 (0.809-3.755)	0.156	1.756 (0.804-3.835)	0.158	1.733 (0.804-3.737)	0.161
Multifocality								
No	Reference		Reference		Reference		Reference	
Yes	0.820 (0.459-1.462)	0.501	0.913 (0.492-1.696)	0.774	0.948 (0.505-1.779)	0.868	0.911 (0.490-1.692)	0.768
Extrathyroidal extension								
No	Reference		Reference		Reference		Reference	
Yes	1.626 (0.888-2.977)	0.115	1.897 (0.979-3.676)	0.058	2.155 (1.081-4.294)	0.029	1.935 (0.992-3.772)	0.053
Vascular index	1.000 (0.982-1.018)	0.993	1.001 (0.982-1.021)	0.890	1.002 (0.983-1.021)	0.872	1.001 (0.982-1.021)	0.883

VEGF_extent	0.998 (0.988-1.008)	0.701	1.003 (0.991-1.016)	0.580				
VEGF_intensity								
0	Reference				Reference			
1	0.897 (0.447-1.803)	0.761			1.004 (0.462-2.184)	0.992		
2	0.775 (0.258-2.326)	0.649			1.231 (0.340-4.453)	0.751		
3	3.100 (0.338-28.435)	0.317			7.352 (0.624-86.681)	0.113		
VEGF_H-score	1.000 (0.995-1.004)	0.863					1.002 (0.996-1.007)	0.500
CD34 (no/HPF, x200)	0.995 (0.977-1.012)	0.552	0.989 (0.969-1.009)	0.272	0.991 (0.971-1.012)	0.406	0.989 (0.970-1.009)	0.274

CI = confidence interval, OR = odds ratio, VEGF = vascular endothelial growth factor.

*Multivariate analysis using VEGF_extent

†Multivariate analysis using VEGF_intensity

‡Multivariate analysis using VEGF_H-score

IV. DISCUSSION

PTC is known to have a good prognosis. However, the recurrence rate is not negligible ranging from 5-20% and most recurrences occur in the neck.[18,19] Also, LNM is a known risk factor associated with the increased recurrence rate of PTC.[20,21] Thus, preoperative factors capable of identifying increased risk of LNM can contribute to the recognition of high-risk tumors.

Angiogenesis plays a crucial role in the growth and metastasis of cancer.[1,22] And tumor vascularity is associated with metastasis and survival.[10,23] VEGF is a potent angiogenic factor which can stimulate endothelial cell proliferation and can promote tumor angiogenesis.[24] Increased expression of VEGF has also been correlated with poor clinical outcomes and increased metastases or recurrence rates in many human cancers such as esophageal cancer, colon cancer, gastric cancer, breast cancer, hepatocellular carcinoma, bladder cancer, and melanoma.[25-31] To assess tumor angiogenesis, MVD has been considered as an important reference that quantifies the amount of blood vessels.[23,32] It has been linked with clinical outcomes in various cancers such as gastric carcinoma, breast cancer, melanoma, cervical cancer, prostate cancer and colon cancer.[8,26,33-36] MVD has also been shown to be associated with the expression of VEGF.[37]

VEGF or MVD is widely used to assess angiogenesis, but their measurements demand invasive procedures and their values cannot be used preoperatively.[7-

[9,26,32] In comparison, Doppler US is non-invasive and can be utilized preoperatively.[10] Color Doppler is able to detect blood vessels of approximately 100 ㎛ or larger in diameter.[38] To date, several studies have evaluated whether tumor vascularity can effectively diagnose malignant thyroid nodules.[39-41] Still there is controversy on the potential benefits of vascularity assessment when differentiating benign and malignant thyroid tumors. Some of the studies reported a higher frequency of hypervascularity in malignant nodules than in benign nodules,[39,40] but, in a previous study performed in our institution, VI values were not found to be predictive of malignancy in thyroid nodules.[41] Therefore, we focused on the investigating predicting power of the VI for the outcomes of PTC patients in this study. The details of several studies which investigated differences in tumor vascularity between benign and malignant thyroid tumors are summarized in Table 3. [14, 39-49] In addition, a previous study investigated the differences in sonographic features of PTC between lymph node metastatic groups and nonmetastatic groups, and showed that the lymph node metastatic group had a higher degree of vascularization than the nonmetastatic group.[42] This study included only patients with PTC, as our study did, but, the vascularity of thyroid nodules was evaluated with color Doppler US, and vascularization distribution and vascularization degree were assessed by performers qualitatively. After the assessment, pulsed Doppler spectra were performed. In comparison, our study evaluated the vascularity of thyroid

nodules using power Doppler US, and calculated the VI quantitatively. To evaluate vascularity on Doppler US, we considered the VI, a new Doppler US parameter. The VI is a value calculated with QLAB quantification software and it represents the amount of color in ROIs.[40] The VI has been found to be significantly associated with MVD in stomach and colon cancer, and has proven its worth as a predicting factor for recurrence and patient survival.[50,51]

Table 3. Studies investigating tumor vascularity between benign and malignant thyroid nodules and between metastatic and non-metastatic groups in PTC

Reference	Publication year	Case number	Target	Method of evaluation	Result
Mary et al.[39]	2003	254	Benign vs Malignant thyroid nodule	Color Doppler US	Higher frequency of hypervascularity in malignant nodules than in benign nodules ($P < 0.001$)
Andrej et al.[40]	2007	86	Benign vs Malignant thyroid nodule	VI	Higher VI in malignant nodules than in benign nodules ($P < 0.001$)
Yoon et al.[41]	2015	1309	Benign vs Malignant thyroid nodule	VI	VI values were not predictive of malignancy in thyroid nodules ($P = 0.516$)
Zhan et al.[42]	2012	155	LNM in PTC	Color Doppler US	Higher vascularization degree in the LN metastatic group than in the non-metastatic group ($P = 0.032$)
Stabenow et al.[43]	2005	30	LNM in PTC	MVD	Higher MVD among LN metastatic tumors in the classic and the tall cell variants of PTC ($P = 0.02$)
Bunone et al.[44]	1999	33	LNM in malignant thyroid tumors	VEGF, VEGF-C	Higher VEGF-C mRNA levels in the LN metastatic group than in the non-metastatic group
Klein et al.[45]	2001	19	Metastatic disease in PTC	VEGF	Higher VEGF immunostaining score in the metastatic group than in the non-metastatic group ($P = 0.001$)
Tanaka et al.[46]	2002	41	LNM in PTC	VEGF-A, VEGF-B, VEGF-C, and VEGF-D	Higher expression of the VEGF-C mRNA in the LN metastatic group than in the non-metastatic group ($P = 0.013$)
Hung et al.[47]	2003	15	LNM in PTC	VEGF-C	No significant difference in VEGF-C expression between the LN metastatic group and non-metastatic group

Yasuoka et al.[48]	2005	49	LNM in PTC	VEGF-D	Higher VEGF-D messenger RNA transcript levels (P = 0.027) and VEGF-D immunoreactivity (P = 0.019) in the LN metastatic group than in the non-metastatic group
Siironen et al.[49]	2006	106	LNM in PTC	VEGF-C	Higher VEGF-C expression in the older LN metastatic group than in the younger LN metastatic group (P = 0.001)
Lee et al.[14]	2012	72	LNM in PTC	VEGF-A, VEGF-C, and MVD	Higher expression of VEGF-C (P = 0.002) in the LN metastatic group than in the non-metastatic group

US = ultrasound, VI= vascular index, PTC = papillary thyroid carcinoma, LN = lymph node, LNM = lymph node metastasis, MVD = microvessel density, and VEGF = vascular endothelial growth factor.

In the few studies done on the relationship among LNM in patients with PTC, MVD and VEGF, the association between VEGF or MVD with LNM of PTC still remains controversial.[14,43-49] The details of previous studies investigating tumor vascularity between metastatic and nonmetastatic groups in PTC are summarized in Table 3. In this study, the VI was not associated with LNM although the VI was correlated with MVD. MVD and VEGF were not associated with LNM either. When we first designed this study, we expected that higher values of VEGF, VI or MVD would be significantly correlated with LNM, but our results showed that there were no significant correlations. This may be because increased angiogenesis is not the only prerequisite for tumor spread and progression in PTC. PTC can metastasize via the blood vessels or the lymphatic vasculature, and not only angiogenesis but also lymphangiogenensis can play a role in the dissemination of PTC. Recent studies have shown that increased lymphatic vessel density is associated with the aggressive behavior of malignant thyroid nodules.[14,48] We did not assess lymphatic vasculature in this study, but further studies evaluating tumor lymphatic vascularity will be meaningful in understanding the pathology of tumor spread in PTC.

There were a few limitations in this study. First, when assessing the VI, the whole vascularity of the thyroid nodule could not be represented, because the VI was defined by the percentage of the vascular color signal in a 2D image

plane. To overcome this weakness, we chose images that best represented the vascularity of the nodule. Second, we did not classify subtypes of VEGF such as VEGF-C or VEGF-D which may be crucial for LNM.[46,48,49] Some reports have shown correlations between LNM and VEGF-C expression[44,46] and increased levels of VEGF-D have also been reported to be correlated with LNM.[48] Third, we did not evaluate micrometastatic LNs and patients with micrometastatic LNs could have been misclassified as the non-metastatic group. Fourth, all patients underwent central compartment dissection, whereas lateral compartment dissection was selectively performed in patients who were proven to have lateral neck node metastasis through preoperative US and fine-needle aspiration biopsies. Therefore, not all patients underwent lateral neck node dissection, and lateral neck node metastases might have been missed. Fifth, each preoperative staging US evaluation and Doppler study were done by only one radiologist in our clinical setting, and we used the images retrospectively. Therefore, we were unable to evaluate interobserver variability. Sixth, this study was retrospectively designed and selection bias might exist.

V. CONCLUSION

In conclusion, although the VI of PTC was significantly correlated with MVD, there was no significant association between VI and LNM and there were no significant associations among VEGF, MVD and LNM. LNM was significantly

associated with young age and had marginal correlation with extrathyroidal extension. Further studies are needed to elucidate the association between vascularity and LNM in patients with PTC.

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ABSTRACT(IN KOREAN)

파워도플러 초음파의 혈관 지수와 미세혈관 밀도 그리고 혈관내피성장인자를 이용하여 유두갑상샘암종 환자에서의 림프절 전이의 예측에 대한 유용성

<지도교수 곽 진 영>

연세대학교 대학원 의학과

이 지 혜

목적 : 유두갑상샘암 환자에서 도플러 초음파 검사 상의 혈관 지수와 혈관내피성장인자, 미세혈관밀도간의 연관성을 밝혀 비침습적인 혈관 지수로도 림프절전이를 예측하는데 도움을 받을 수 있는 지 알아보고자 한다. 대상 및 방법 : 2011년 1월부터 2011 10월까지 병기결정 초음파를 시행하였고 수술을 통해 유두암으로 진단된 202개의 결절이 대상이 되었다. 혈관 분포 상태 (Vascularity)를 평가하기 위하여 도플러 초음파 (Doppler US) 상에서 종양의 혈관지표 (Vascular index, VI)가 측정되었으며, 병리학적 검토를 통해 혈관내피성장인자 (Vascular endothelial growth factor, VEGF) 와 CD4 항원에 대한 항체를 이용하여 면역염색검사를 시행하여 VEGF의 발현 정도와 미세혈관밀도 (Microvessel density, MVD)에 대해 평가하였다. 결과 : VI와 MVD간에는 통계학적으로 유의미한 연관성이 있는 것으로 나타

났다 (P=0.009). 다변량 분석을 통하여 환자의 나이가 어릴수록 림프절 전이가 증가하는 것으로 나타났으며, (OR = 0.957, P = <0.001; OR = 0.955, P = <0.001; OR = 0.957, P = <0.001), 결절의 과갑상선 신장 (extrathyroidal extension) 이 림프절 전이와 약간의 연관성이 있는 것으로 나타났으나 (OR = 1.897, P = 0.058; OR = 2.155, P = 0.029; OR = 1.935, P = 0.053), VEGF, MVD와 VI는 유두갑상샘암 환자에서의 림프절 전이와 유의미한 연관성을 보이지 못하였다. 결론 : VI는 유두갑상샘암 환자에서의 림프절 전이와는 연관성을 보이지 못하였으나, MVD와는 유의미한 연관성이 있는 것으로 나타났으므로, 혈관 분포 상태를 평가하는 데에 있어 침습적인 방법인 MVD를 대체할 가능성을 제시하였다.

핵심되는 말 : 갑상선 결절, 초음파, 도플러 초음파, 혈관 지수, 미세혈관 밀도, 혈관내피성장인자