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Original Article

Prognostic Impact of Ultrasonography Features and ^{18}F-Fluorodeoxyglucose Uptake in Patients With Papillary Thyroid Microcarcinoma

Ji Won Seo[1] · Sang Hyun Hwang[2] · Arthur Cho[2] · Hye Sun Lee[3] · Eun-Kyung Kim[1] · Hee Jung Moon[1]
Jung Hyun Yoon[1] · Jin Young Kwak[1]

[1]Department of Radiology, Research Institute of Radiological Science, [2]Division of Nuclear Medicine, Department of Radiology, [3]Department of Research Affairs, Biostatistics Collaboration Unit, Yonsei University College of Medicine, Seoul, Korea

Objectives. To evaluate the prognostic impact of ultrasonography (US) features and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake in patients with papillary thyroid microcarcinoma (PTMC).

Methods. This study included 74 patients with a single PTMC diagnosed pathologically. Patients underwent total thyroidectomy, or near-total thyroidectomy and staging thyroid US and positron emission tomography (PET) were performed prior to surgery. US features of thyroid nodules were reviewed retrospectively and the maximum standard uptake value (SUV) of nodules was semiquantitatively analyzed on ^{18}F-FDG PET/computed tomography (CT). Patients were followed-up for recurrence, which was defined as PTC on cytology results, elevated serum thyroglobulin (Tg) or anti-Tg antibody levels, or uptake on whole-body scintigraphy. We used univariate and multivariate analyses to evaluate whether poor prognostic outcomes were associated with US features or SUV values derived from PET/CT of nodules. In addition, subjects were divided into 2 groups for subgroup analyses: one with nodules equal to or larger than 5 mm and one with nodules smaller than 5 mm.

Results. Among the 74 patients, there was no recurrence. Thus we evaluated the correlation between SUV value and US features with poor prognostic factors of PTMC which included extrathyroid extension, central and lateral lymph node (LN) metastasis. However no clinicopathologic factors were associated with extrathyroid extension, central LN metastasis, or lateral LN metastasis.

Conclusion. In patients with PTMC, US features and SUV values on FDG-PET were not related to extrathyroid extension or LN metastasis. However, future studies with a larger sample size and longer follow-up should be performed to verify the results of this study.

Keywords. *Thyroid; Papillary Thyroid Microcarcinoma; Ultrasonography; Positron Emission Tomography*

INTRODUCTION

The incidence of thyroid cancer is increasing rapidly worldwide [1]. Papillary thyroid cancer (PTC) is the most common cancer of the thyroid and accounts for 87.3% of all thyroid cancers [2]. Papillary thyroid microcarcinoma (PTMC) is defined as a PTC measuring less than 1 cm in greatest dimension according to the World Health Organization classification system for thyroid tumors [3]. The incidence and prevalence of PTMC has increased due to improvements in the sensitivity of diagnostic techniques for thyroid cancer and increasing use of imaging modalities for screening, such as high-resolution thyroid ultrasonography (US) and fine-needle aspiration (FNA), which have enabled the detection of subclinical thyroid disease [4].

PTMC has been reported to follow an indolent course and show favorable prognosis [5]. However, a few studies have dem-

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• Corresponding author: **Jin Young Kwak**
Department of Radiology, Research Institute of Radiological Science, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-7400, Fax: +82-2-393-3035
E-mail: docjin@yuhs.ac

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onstrated that extrathyroid invasion, lymph node (LN) metastasis, and distant metastasis occur in a significant number of patients with PTMC [6,7]. Additionally, the mortality, LN recurrence, and distant recurrence rates of patients with PTMC are 1%, 5%, and 2.5%, respectively [8-10]. The range of treatment options for PTMC varies from close observation to total thyroidectomy with or without cervical LN dissection and postoperative radioactive iodine (RAI) ablation [11]. Prediction of the aggressiveness and poor prognostic potential of PTMC at the time of diagnosis would allow clinicians to make appropriate decisions about treatment on an individual patient basis.

Positron emission tomography (PET) is increasingly being accepted as a useful imaging modality for evaluation of distant metastasis associated with thyroid cancer at the time of diagnosis as well as post-operative recurrence [12]. In addition, PET/computed tomography (CT) is not just used for detection of primary tumor or recurred lesion, but also fluorodeoxyglucose (FDG) uptake on PET/CT is used as a predictor of aggressive behavior and a poor prognosis in many other malignancies [13]. Likewise, FDG uptake of PTMC could be used to predict poor prognosis potential in advance and it would be much PET is useful for planning proper treatment for each patient. It could be worthy to discover whether there is LN metastasis or distant metastasis before the patient undergoes surgery. In addition, the patient might benefit to discover other primary malignancies. It was recently reported that discernible FDG uptake by PTMC on PET is associated with significant extrathyroid invasion and central LN metastasis, which are predictors of poor prognosis, therefore FDG uptake on PTMC may be a risk factor for poor prognosis [14]. A recent study revealed that patients with PTC presenting with US features of a benign nodule appeared to have a better prognosis than patients with PTC showing typical US features of malignancy, although this tendency was not evident in the patients with PTMC [15]. To our knowledge, no prior study has evaluated the association between US features and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake on PET-CT and poor prognosis in PTMC. Therefore, we evaluated whether US features and/or ^{18}F-FDG uptake were associated with poor prognostic factors in patients with PTMC.

MATERIALS AND METHODS

Study population

This retrospective study was approved by the institutional review board and required neither patient approval nor informed consent for review of patients' images and medical records. From March 2008 to September 2008, 455 consecutive patients underwent total thyroidectomy, or near-total thyroidectomy due to thyroid cancer. Among them, 141 patients were confirmed to have PTMC, of which 48 patients had multifocal thyroid cancers. The FDG uptake of multiple PTMC could be uneven and it could disturb exact evaluation of relationship of FDG uptake and poor prognosis thus patients with multifocal cancers were excluded. Eighty-seven (16 men and 71 women; mean age, 48 years; range, 24 to 72 years) of 93 patients underwent both US and FDG-PET for the purpose of staging the cancer. FDG-PET was performed according to patient preference. Thirteen patients who showed diffuse FDG uptake in the thyroid on PET/CT due to underlying thyroiditis were excluded. A total of 74 patients (16 men and 58 women; mean age, 48 years; range, 24 to 72 years) were finally included in this study. The mean tumor size was 5.7±2.0 mm (range, 2 to 10 mm).

Preoperative staging US

Preoperative staging US was performed with a 7- to 15-MHz linear array transducer (HDI 3000 or 5000, Philips Medical Systems, Bothell, WA, USA), 8- to 15-MHz linear array transducer (Acuson Sequoia, Siemens Medical Solutions, Mountain View, CA, USA), or 5- to 12-MHz linear array transducer (iU22, Philips Medical Systems) for evaluation of the entire thyroid gland and bilateral central and lateral cervical LN-bearing areas. Compound imaging was performed in all cases using HDI 5000 or iU22 machines. Real-time staging US was performed by one of 4 radiologists specializing in thyroid imaging who were aware of the patients' clinical information. The scanning protocol in all cases included both transverse and longitudinal real-time imaging of thyroid nodules with the use of a picture archiving and communications system to retrospectively review all patient data.

A radiologist (JYK) retrospectively reviewed all US images, including internal components, echogenicity, margin, calcifications, and shape, based on our previous report [16]. Internal component was defined as either solid, mixed, or cyst. A mixed component meant the mass had both solid and cystic components, and US images for masses with mixed components were evaluated based on the internal solid component. Echogenicity was classified as hyperechoic, isoechoic, hypoechoic, or markedly hypoechoic. When the echogenicity of a nodule was similar to that of the thyroid parenchyma, we classified it as isoechoic. Hypoechoic was defined as decreased echogenicity compared to thyroid parenchyma, but increased echogenicity compared to the surrounding strap muscle. Marked hypoechogenicity was defined as decreased echogenicity compared to the surrounding strap muscle. Margins were described as well circumscribed, microlobulated, or irregular. A microlobulated margin was defined as the presence of many small lobules on the surface of a nodule. Calcifications were classified as microcalcifications, macrocalcifications, or none. Hypoechoic foci 1 mm or less in diameter or tiny, punctuated hyperechoic foci, either with or without acoustic shadows, were classified as microcalcifications. Hyperechoic foci larger than 1 mm were considered macrocalcifications. Shape was categorized as taller than wide or wider than tall. A taller-than-wide shape was defined as being greater in its anteroposterior dimension than transverse dimension. Malignant US features were defined as marked hypoechogenicity (lower echogenicity than the

surrounding strap muscle), microlobulated or irregular margins, microcalcifications, and being more tall than wide (greater anteroposterior dimension than transverse dimension) [17,18]. US results were classified into one of two groups: "suspicious malignancy" or "probably benign." If one of the above findings was present on US, the final US assessment was defined as "suspicious malignancy."

A LN was considered pathologic if it exhibited at least one of the following: focal or diffuse hyperechogenicity, internal calcifications, cystic change, or a round shape [19-22].

^{18}F-FDG PET/CT imaging

Scanning was initiated 60 minutes after intravenous administration of ^{18}F-FDG. Images from the neck to the proximal thighs were obtained by either a GE PET scanner (DSTe, GE Healthcare, Milwaukee, WI, USA) with a spatial resolution of 5 mm in the center of field of view, or a Philips PET system (Allegro, Philips Medical Systems) with a spatial resolution of 5.3 mm in the center of field of view. With the GE Advance scanner, approximately 370 MBq of FDG was injected, and PET was performed at 5 minutes per bed position in 2-dimensional mode. The Allegro scanner acquired data in 3-dimensional mode after administration of 5.18 MBq/kg of FDG. Emission images were acquired for 3 minutes per bed position, and transmission scans from low dose CT were used for attenuation correction. Images were then reconstructed using the low-action maximal-likelihood algorithm [23].

^{18}F-FDG PET/CT images were analyzed by one of two experienced nuclear medicine physicians (AC and SHH). At the time of image review, both physicians were aware of the cytologic and US results in all patients who underwent FDG-PET for the purpose of staging of thyroid cancer. Special attention was paid to FDG uptake in thyroid cancer seen on US. Regions of interests were drawn to quantify ^{18}F-FDG uptake by thyroid lesions, and the maximum standard uptake value (SUV) was semiquantitatively analyzed according to the following equation: SUV= A/(ID/BW), where A is the decay-corrected activity in tissue (MBq/mL), ID is the injected dose of ^{18}F-FDG (MBq), and BW is the patient's body weight (g).

Surgery and histopathologic analysis

In our institution, total thyroidectomy, or near-total thyroidectomy was done. If extrathyroid extension (ETE) or LN metastasis was suspected, total thyroidectomy or near-total thyroidectomy was performed even though the size of tumor was less than 1 cm. Central LN dissection is routinely performed in all patients with PTMCs and lateral compartment dissection is selectively performed in patients with LN metastasis diagnosed based on prior US-FNA [24,25]. In cases of suspicious LNs during surgery, LN sampling is performed and frozen sections are made. It was done when lateral LN metastasis was suspicious on preoperative US but the result of FNA did not come out concordantly. If LN metastasis is present, the surgeon routinely dissects the lateral compartment. In our 74 patients, lateral compartment dissection included levels 2, 3, 4, and anterior 5. Unilateral modified neck dissection was performed in two patients and LN sampling was performed in 2 patients. Using pathology reports, tumor size, underlying lymphocytic thyroiditis, ETE, and central and lateral compartment LN metastasis were evaluated.

Postoperative management and follow-up

All patients underwent thyroid-stimulating hormone-suppressive therapy with levothyroxine after surgery. RAI ablation was usually performed for remnant ablation, and then 131 I whole-body scintigraphy (WBS) was performed in patients with ETE or LN metastasis at diagnosis. In this study, RAI ablation (1,110 MBq) was performed in 36 of 74 patients with total thyroidectomy. Postthyroidectomy thyroglobulin (Tg) concentrations were measured 3 months after thyroid surgery. Patients were followed up every 6 months in the first 3 years after surgery and every 12 months thereafter. Routine follow-up evaluation consisted of clinical examination every 6 months and measurement of serum thyroid-stimulating hormone, free thyroxine, Tg and anti-Tg antibody levels, chest X-ray, and neck US examination every 12 months. WBS, chest computed tomography, or fluorodeoxyglucose PET with computed tomography was performed only in selective cases (e.g., detectable serum Tg or persistent anti-Tg antibody without recurrence on US or WBS). WBS was performed after withdrawal of levothyroxine for 2 or 3 weeks.

Recurrence was defined as PTC on cytology results, elevated serum Tg or anti-Tg antibody levels, or uptake on WBS. US-FNA was usually performed for a suspected recurrent mass on US. Cytopathologic results were obtained by US-FNA and surgical excision. Patients with lesions diagnosed as benign by cytology underwent annual US follow-up. Patients with undetectable serum Tg or anti-Tg antibody levels, no evidence of regional recurrence on neck US or benign cytology results, and no regional or distant metastasis on WBS were considered disease-free. To evaluate patient survival and recurrence, data for the included patients were obtained from Severance Hospital and the National Cancer Center Registry.

Statistical analyses

Continuous data are presented as means±standard deviations with minimum and maximum values, and categorical data are presented as numbers with percentages. Categorical comparisons were compared with the chi-square test or Fisher exact test. Independent two-sample *t*-tests were performed to compare continuous variables. Multivariate logistic regression analyses were performed to assess independent associations of ETE and LN metastasis with all clinicopathologic factors with adjustment for all factors. Analysis of the associations between lateral LN metastasis and suspicious US features was performed via exact logistic regression because there was no lateral LN metas-

tasis in the absence of suspicious US features. Each analysis was repeated after dividing subjects into 2 groups: a group with nodules equal to or larger than 5 mm in size and a group with nodules smaller than 5 mm. Mann-Whitney *U*-test was performed for analysis between the subgroups since the variables did not show normal distribution. Results are presented as odds ratio with 95% confidence intervals and *P*-values. A *P*-value <0.05 was considered significant. Statistical analyses were performed using SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Of 74 patients, there was no recurrence. Table 1 shows the demographics of the included patients. The mean age of patients was 47.8±11.1 years (range, 24 to 72 years). Fifty-eight patients (78.4%) were female, and 16 (21.6%) were male patients. Mean size of the primary tumor was 5.7±2.0 mm (range, 2 to 10 mm). At the time of diagnosis, 62 patients (83.8%) were classified as having suspicious US features. PTMC of the other 12 patients presented benign features, which include hypoechogenicity, nonmicrolobulate margin, wider-than-taller shape, and absence of microcalcification. However most of them underwent fine needle aspiration biopsy in other clinic and were already informed of their cancer. Thirty-six (48.7%) patients had ETE and 21 patients (28.4%) had central LN metastasis. Two patients (2.7%) had lateral LN metastasis and central LN metastasis as well. In addition all patients were found to have classical papillary carcinoma. After total or near-total thyroidectomy, 36 patients (48.6%) underwent RAI. The mean SUV value of PTMC on PET was 2.6±1.8 (range, 0.8 to 10.6). The mean follow-up interval was 59.5±13.2 months (range, 13 to 74.2 months).

Because no patients with PTMC had recurrence during the follow-up period, we evaluated the association of US features and SUV values from PET-CT of the primary cancer with poor prognostic outcomes. Analysis of patient demographics and clinical characteristics revealed that patients with a PTMC larger than or equal to 5 mm had a significant tendency to have RAI ablation after surgery and a higher SUV value on PET. Other characteristics were not significantly different between the 2 groups (Table 1). Size of the thyroid nodule was significantly associated with ETE (Table 1). This finding was not significant in the subgroup of nodules equal to or larger than 5 mm (Table 2).

On multivariate analysis, the size of the thyroid nodule was an independent predictor of ETE. However, size was not significantly associated with ETE in patients with PTMC equal to or larger than 5 mm in size (Table 2). Only the size of tumor was independent factor of central LN metastasis in subgroup of equal to or larger than 5 mm in size. Other than that, central LN metastasis did not show an association with any clinicopathologic factor. Younger patients with PTMC equal to or larger than 5 mm in size were significantly more likely to have ETE, although this was not evident when all patients were analyzed (Table 2). Other clinicopathologic factors, including US grouping and SUV on PET, were not associated with ETE (Table 2), central LN metastasis (Table 3), or lateral LN metastasis (Table 4).

DISCUSSION

In this study, no patient was diagnosed with recurrent thyroid cancer over a mean follow-up interval of 59.5 months, therefore we were not able to analyze the relationship between recurrence and clinical and imaging factors. Known PTMC factors associated with poor prognosis include tumor size, ETE, and LN metastasis [8]. Most patients with PTMC show an indolent

Table 1. Patient demographics and clinical characteristics for the thyroid nodules

Variable	Total (n=74)	Size of the thyroid nodule (mm)		*P*-value*
		<5 (n=21)	≥5 (n=53)	
Age (yr)	47.8±11.1 (24–72)	49.5±11.1 (29–72)	47.1 ±11.1 (24–68)	0.395
Sex				0.361
Male	16 (21.6)	6 (28.6)	10 (18.9)	
Female	58 (78.4)	15 (71.4)	43 (81.1)	
Primary tumor size (mm)	5.7±2.0 (2–10)	3.2±0.8 (2–4)	6.7±1.4 (5–10)	<0.001
Extrathyroid extension	36 (48.7)	7 (33.3)	29 (54.7)	0.097
Nodal involvement				
Central compartment	21 (28.4)	6 (28.6)	15 (28.3)	0.982
Lateral compartment	2 (2.7)	1 (4.8)	1 (1.9)	0.492
RAI ablation	36 (48.6)	6 (28.6)	30 (56.6)	0.040
Suspicious US features	62 (83.8)	19 (90.5)	43 (81.1)	0.326
SUV value on PET	2.6±1.8 (0.8–10.6)	1.7±0.5 (0.8–2.6)	3±2 (1–10.6)	0.002

Values are presented as mean±standard deviation (range) or number (%).
RAI, radioactive iodine; US, ultrasonography; SUV, standard uptake value; PET, positron emission tomography; PTMC, papillary thyroid microcarcinoma.
**P*-value is calculated for the group with PTMCs smaller than 5 mm versus the group with PTMCs equal to or larger than 5 mm.

Table 2. Analysis of associations of extrathyroid extension and clinicopathologic findings in patients with papillary thyroid microcarcinomas

Variable	Extrathyroid extension (+)			Extrathyroid extension (–)			*P*-value*	*P*-value†	Univariate analysis		Multivariate analysis	
	Size of the thyroid nodule (mm)			Size of the thyroid nodule (mm)								
	Total	<5	≥5	Total	<5	≥5			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
No. of patients (n=74)	36	7	29	38	14	24						
Age (yr)	45.5 (27–68)	50.1 (37–60)	44.3 (27–68)	49.9 (24–72)	49.2 (29–72)	50.4 (24–67)	>0.999	0.023	0.963 (0.922–1.005)	0.085	0.964 (0.919–1.010)	0.126
Sex												
Male	7 (19.4)	2 (28.6)	5 (17.2)	9 (23.7)	4 (28.6)	5 (20.8)	>0.999	0.742	1.286 (0.422–3.916)	0.658	1.385 (0.404–4.754)	0.605
Female	29 (80.6)	5 (71.4)	24 (82.8)	29 (76.3)	10 (71.4)	19 (79.2)			Reference		Reference	
Size (mm)	6.4 (3–10)	3.9 (3–4)	7 (5–10)	5.1 (2–9)	2.9 (2–4)	6.3 (5–9)	0.01	0.064	1.437 (1.103–1.872)	0.007	1.426 (1.063–1.912)	0.018
Lymph node metastasis	11 (30.6)	1 (14.3)	10 (34.5)	10 (26.3)	5 (35.7)	5 (20.8)	0.603	0.277	1.232 (0.448–3.389)	0.686	1.117 (0.366–3.404)	0.846
Suspicious US features	29 (80.6)	6 (85.7)	23 (79.3)	33 (86.8)	13 (92.9)	20 (83.3)	0.686	0.711	0.628 (0.180–2.194)	0.466	0.858 (0.208–3.535)	0.832
SUV value on PET	2.9 (1.1–10.6)	1.7 (1.1–2.3)	3.2 (1.1–10.6)	2.4 (0.8–8.6)	1.8 (0.8–2.6)	2.8 (1–8.6)	0.255	0.687	1.172 (0.887–1.548)	0.264	1.003 (0.725–1.387)	0.986

Values are presented as mean (range) or number (%).
OR, odds ratio; CI, Confidence interval; US, ultrasonography; SUV, standard uptake value; PET, positron emission tomography; NA, not available.
*Size of the thyroid nodule<5 mm. †Size of the thyroid nodule≥5 mm.

Table 3. Analysis of associations of central LNM and clinicopathologic findings of patients with papillary thyroid microcarcinomas

Variable	Central LNM (+)			Central LNM (–)			*P*-value*	*P*-value†	Univariate analysis		Multivariate analysis	
	Size of the thyroid nodule (mm)			Size of the thyroid nodule (mm)								
	Total	<5	≥5	Total	<5	≥5			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
No. of patients (n=74)	21	6	15	53	15	38						
Age (yr)	49.2 (29–72)	50.7 (29–72)	48.6 (32–68)	47.2 (24–67)	49.1 (31–64)	46.5 (24–64)	0.97	0.601	1.017 (0.971–1.065)	0.486	1.020 (0.970–1.073)	0.435
Sex												
Male	5 (21.7)	2 (33.3)	3 (20.0)	11 (17.2)	4 (26.7)	7 (18.4)	0.85	0.896	0.838 (0.251–2.793)	0.774	1.862 (0.249–2.992)	0.816
Female	18 (78.3)	4 (66.7)	12 (80.0)	53 (82.8)	11 (73.3)	31 (81.6)			Reference		Reference	
Size (mm)	6.1 (2–9)	3.2 (2–4)	7.3 (6–9)	5.5 (2–10)	3.3 (2–4)	6.4 (5–10)	0.91	0.023	1.155 (0.888–1.503)	0.283	1.169 (0.866–1.579)	0.308
Lymph node metastasis	13 (56.5)	1 (16.7)	10 (66.7)	29 (45.3)	6 (40.0)	19 (50.0)	0.443	0.277	1.232 (0.448–3.389)	0.686	1.157 (0.384–3.487)	0.795
Suspicious US features	20 (87.0)	6 (100)	12 (80)	53 (82.8)	13 (86.7)	31 (81.6)	0.533	0.896	1.227 (0.298–5.062)	0.777	1.179 (0.257–5.419)	0.832
SUV value on PET	2.7 (0.8–7.4)	1.9 (0.8–2.6)	3 (1.7–7.4)	2.6 (1.0–0.6)	1.7 (1.1–2.5)	3 (1–10.6)	0.97	0.447	1.037 (0.787–1.366)	0.799	0.973 (0.698–1.357)	0.871

Values are presented as mean (range) or number (%).
OR, odds ratio; CI, Confidence interval; US, ultrasonography; SUV, standard uptake value; PET, positron emission tomography; NA, not available.
*Size of the thyroid nodule<5 mm. †Size of the thyroid nodule≥5 mm.

Table 4. Analysis of associations of lateral LNM and clinicopathologic findings of patients with papillary thyroid microcarcinomas

Variable	Lateral LNM(+)			Lateral LNM(-)			*P*-value*	*P*-value†	Univariate analysis		Multivariate analysis	
	Size of the thyroid nodule (mm)			Size of the thyroid nodule (mm)								
	Total	<5	≥5	Total	<5	≥5			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
No. of patients (n=74)	2	1	1	72	20	52						
Age (yr)	62.5 (53–72)	72 (72–72)	53 (53–53)	47.4 (24–68)	48.4 (29–64)	47 (24–68)	0.095	0.642	1194 (0.970–1.469)	0.095	1.411 (0.796–2.500)	0.239
Sex												
Male	1 (50.0)	0 (0)	1 (100)	15 (20.8)	6 (30.0)	9 (17.3)	0.85	0.038	0.263 (0.016–4.457)	0.366	0.155 (0.002–6.434)	0.292
Female	1 (50.0)	1 (100)	0 (50.0)	57 (79.2)	14 (70.0)	43 (82.7)			Reference		Reference	
Size (mm)	5 (2–8)	2 (2–2)	8 (8–8)	5.7 (2–10)	3.3 (2–4)	6.7 (5–10)	0.19	0.415	0.827 (0.398–1.719)	0.611	1.250 (0.377–4.151)	0.715
Lymph node metastasis	1 (50.0)	1 (100)	1 (100)	35 (48.6)	7 (35.0)	28 (53.9)	0.799	0.363	1.057 (0.064–17.560)	0.961	9.498 (0.079–999.999)	0.361
Suspicious US features	2 (100)	1 (100)	1 (100)	60 (83.3)	18 (90.0)	42 (80.8)	0.952	0.63	0.468 (0.035–999.999)	>0.999	0.286 (0.007–999.999)	>0.999
SUV value on PET	2.3 (2.2–2.4)	2.2 (2.2–2.2)	2.4 (2.4–2.4)	2.6 (0.8–0.6)	1.7 (0.8–2.6)	3 (1–10.6)	0.667	0.151	0.867 (0.300–2.508)	0.792	0.585 (0.113–3.036)	0.524

Values are presented as mean (range) or number (%).
OR, odds ratio; CI, Confidence interval; US, ultrasonography; SUV, standard uptake value; PET, positron emission tomography; NA, not available.
*Size of the thyroid nodule<5 mm. †Size of the thyroid nodule≥5 mm.

course and favorable prognosis, while some patients present with an aggressive biological course with lymphatic metastasis or distant metastasis [4,26]. Therefore, it is important to determine the factors that affect the prognosis of PTMC.

Imaging biomarkers such as ^{18}F-FDG uptake on PET or suspicious US features have been suggested to be useful indicators of poor prognosis in patients with PTMC [14,15]. Patients with PTMC with visually discernible FDG uptake had a significantly higher prevalence of ETE and central LN metastasis than those with lower FDG uptake [14]. An ill-defined tumor edge on US could be a predictor of aggressive behavior in that these tumors demonstrated more lateral LN metastasis [27,28].

Therefore, we analyzed the relationships between prognostic factors, such as ETE and LN metastases, and SUV values on PET and suspicious US features. In this study, 42 patients (48.3%) had ETE and 23 patients (26.4%) were pathologically confirmed to have LN metastases. Only 2 patients had both central and lateral LN metastases. The size of the PTMC at diagnosis showed a significant association with ETE, which is one of the prognostic factors indicating aggressive tumor behavior. This tendency was more apparent in the subgroup of patients with a PTMC larger than or equal to 5 mm in maximum dimension. Younger patients also presented with ETE more frequently than older patients.

Several studies have been performed to identify the relationship between PTMC size and biological behavior. A previous study showed that patients with PTMC larger than or equal to 8 mm had a more aggressive clinical course, defined as the presence of neck LN involvement and distant metastasis [4]. Similarly, it was proposed to subdivide PTMCs according to their sizes into 'minute' PTMCs (<5 mm) and tiny PTMCs (5–10 mm in maximum diameter) [29]. This was based on evidence that tiny PTMCs presented with more LN metastasis and locoregional recurrence than minute PTMCs [26,29]. Our findings are consistent with these previous reports in that PTMC size was significantly associated with ETE, which is one of the prognostic factors for PTMC. Specifically, the association between tumor size and ETE was more noticeable in patients with a PTMC less than 5 mm in maximum diameter.

However, neither FDG uptake nor aggressive US feature of PTMC was associated with poor prognostic factors of PTMC. Our study showed discrepancy with previous study, which reported that discernible FDG uptake could be prognostic factor of PTMC [14]. This could result from partial volume effect, which implies that SUV may be measured falsely lower if the lesion is smaller than 3 cm. This may decrease the correlation of SUV with poor prognostic factor of PTMC. Additionally, they evaluated visual discernibility of PTMC, which might rack objectivity and bias may interfere if they were provided information that the patient was diagnosed thyroid cancer.

This study had some limitations. First, it was a retrospective study and included a total of 74 patients, which is a relatively

small sample size. Additionally, only 2 patients had lateral LN metastasis which reduced the impact of statistics. Second, we did not perform a long-term survival study. The mean follow-up interval was 59.5 months. There is the possibility that a longer follow-up would have resulted in discovery of recurrent tumors. Third, only 1 radiologist reviewed the US features of thyroid nodules, which may have resulted in a less objective interpretation than one based on inter-observer agreement [30].

In conclusion, US features and SUV values on FDG-PET were not related to ETE or LN metastasis in patients with PTMC. However, future studies with larger sample sizes and a longer follow-up duration are required to verify our findings.

CONFLICT OF INTEREST

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

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All patients in this study have been reported in a previously published article (Yun M, Noh TW, Cho A, Choi YJ, Hong SW, Park CS, et al. Visually discernible [18F]fluorodeoxyglucose uptake in papillary thyroid microcarcinoma: a potential new risk factor. J Clin Endocrinol Metab. 2010 Jul;95(7):3182-8.) which evaluated the value of ^{18}F-FDG uptake in PTMC as a potential risk factor for preoperative risk stratification. The study focused on the value of ^{18}F-FDG uptake in PTMC as a potential risk factor for preoperative risk stratification without analyzing US feature of PTMCs by comparison with histopathologically-proven extrathyroidal extension and central LN metastasis. Our study differs from the prior report in that the association of poor prognostic factors with PTMC was evaluated after adjusting for both US features and ^{18}F-FDG uptake on PET-CT and including follow-up data of a mean interval of 59.5 months.

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