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# Relation Between F-18 FDG Uptake of PET/CT and *BRAFV*600E Mutation in Papillary Thyroid Cancer

*Seokho Yoon, MD, Young-Sil An, MD, PhD, Su Jin Lee, MD, PhD, Eu Young So, MD, PhD, Jang-Hee Kim, MD, PhD, Yoon-Sok Chung, MD, PhD, and Joon-Kee Yoon, MD, PhD*

**Abstract:** *BRAFV*600E mutation and F-18 fluorodeoxyglucose (FDG) uptake are potential prognostic factors of papillary thyroid cancer (PTC). This study was performed to investigate the relationship between the *BRAFV*600E mutation and F-18 FDG uptake in PTC.

We retrospectively included 169 PTC patients who underwent F-18 FDG positron emission tomography/computed tomography (PET/CT) before thyroidectomy from May 2009 to August 2012. Subjects were classified into overt PTC (>1 cm, n = 76) and papillary thyroid microcarcinoma (PTMC, n = 93) groups. Univariate and multivariate analyses were performed to assess the relationship between maximum standardized uptake value ($SUV_{max}$) of the primary tumors and clinicopathologic variables.

The *BRAFV*600E mutation was detected in 82.2% (139/169). In all subjects, the *BRAFV*600E mutation and tumor size were independently related to $SUV_{max}$ by multivariate analysis ($P = 0.048$ and $P < 0.001$, respectively). $SUV_{max}$ was significantly higher in tumors with the *BRAFV*600E mutation than in those with wild-type *BRAF* ($9.4 \pm 10.9$ vs $5.0 \pm 4.1$, $P < 0.001$). Similarly, in overt PTC group, the *BRAFV*600E mutation and tumor size were independently correlated with $SUV_{max}$ ($P = 0.032$ and $P = 0.001$, respectively). By contrast, in PTMC group, only tumor size was significantly associated with $SUV_{max}$ ($P = 0.010$).

The presence of the *BRAFV*600E mutation is independently associated with high F-18 FDG uptake on preoperative PET/CT in patients with overt PTC, but this relationship was not evident in PTMC. This study provides a better understanding of the relationship between F-18 FDG uptake and *BRAFV*600E mutation in patients with PTC.

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**Abbreviations**: FDG = fluorodeoxyglucose, HIF = hypoxia-inducible factor, MAPK/ERK = mitogen-activated protein kinase/extracellular signal-regulated kinase, PCR–RFLP = polymerase chain reaction–restriction fragment length polymorphism, PET/CT = positron emission tomography/computed tomography, PTC = papillary thyroid cancer, PTMC = papillary thyroid microcarcinoma, ROI = region of interest, SUVmax = maximum standardized uptake value.

## INTRODUCTION

Papillary thyroid cancer (PTC) is the most common histological type of thyroid cancer, accounting for more than 80% of all thyroid malignancies. By virtue of surgical removal of the tumor and radioiodine ablation therapy, well-differentiated PTC has a favorable prognosis, with an overall 5-year survival rate of 95% to 97%.[1,2] However, PTCs with aggressive behavior develop in some patients, often becoming the cause of mortality through tumor recurrence and refractoriness to radioiodine therapy.[3] For this reason, risk stratification and prognostic evaluation have been the focus of much effort by researchers.[4–6]

Positron emission tomography/computed tomography (PET/CT) with F-18 fluorodeoxyglucose (FDG) is a noninvasive diagnostic tool useful for the evaluation of a variety of malignant tumors.[7,8] F-18 FDG PET has been used to locate recurrent thyroid cancers, particularly in cases of elevated serum thyroglobulin concentrations and negative I-131 whole body scintigraphy, because the coincidence of losing radioiodine avidity and gaining the ability to concentrate glucose (the ''flip-flop'' phenomenon) is observed frequently in differentiated thyroid cancer patients.[9,10] In addition, F-18 FDG PET provides prognostic information. The size of the primary tumor, perithyroidal invasion, lymphovascular invasion, and cervical lymph node metastasis are associated with F-18 FDG uptake,[11–14] and larger tumor size is more likely to be associated with higher F-18 FDG uptake.[11]

*BRAF* mutations have been found in various cancers including melanoma, colon cancer, and thyroid cancer.[15,16] Among the *BRAF* mutations, the *BRAFV*600E mutation, a T1799A point mutation in the B-type Raf kinase gene, is the most common genetic alteration in PTC.[1] Similar to F-18 FDG uptake, the *BRAFV*600E mutation has received attention as a potential prognostic factor in PTC.[17–19]

In recent studies, the possible relationship between the *BRAFV*600E mutation and F-18 FDG uptake has been demonstrated. The *BRAFV*600E mutation was associated with increased GLUT-1 expression in both primary and metastatic PTCs.[10] *BRAF* was the most frequently mutated gene in F-18 FDG positive recurrent/metastatic thyroid cancers.[20] Despite these reports, the relationship between F-18 FDG uptake and the *BRAFV*600E mutation in PTC is still poorly recognized. Therefore, in the present study, we retrospectively evaluated the relationship between the *BRAFV*600E mutation and F-18 FDG uptake of the primary tumor on preoperative PET/CT by analyzing potential clinicopathologic factors affecting F-18 FDG uptake in patients with PTC. Our hypothesis was that

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From the Department of Nuclear Medicine and Molecular Imaging (SY, Y-SA, SJL, J-KY); Department of Surgery (EYS); Department of Pathology (J-HK); and Department of Endocrinology and Metabolism (Y-SC), Ajou University School of Medicine, Suwon, Republic of Korea.
Correspondence: Joon-Kee Yoon, Department of Nuclear Medicine and Molecular Imaging, Ajou University School of Medicine, 164, World Cup-ro, Yeongtong-gu, Suwon, Kyunggi-do 443-380, Republic of Korea (e-mail: jkyoon3@aumc.ac.kr).
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PTCs with *BRAFV*600E mutation show more increased F-18 FDG uptake than those with wild-type *BRAF*, and that even small-sized PTCs with the mutation are associated with higher F-18 FDG uptake.

## MATERIALS AND METHODS

### Patients

Study subjects were recruited through a medical record review from May 2009 to August 2012. During this period, a total of 177 consecutive patients underwent F-18 FDG PET/CT before total thyroidectomy. Of these patients, 1 patient with a final diagnosis of hyalinizing trabecular tumor and 7 patients with the interval from PET/CT to thyroidectomy longer than 7 months were excluded. Ultimately, 169 patients (male:female = 37:132) were included in this retrospective study. Most patients (n = 150) were referred for metastatic workup of thyroid cancers diagnosed by fine needle aspiration, ultrasonography, or CT. The rest of the cases (n = 19) were incidentalomas detected on PET/CT during the follow-up of other malignancies.

Information on the characteristics of the patients was collected retrospectively by medical record review. Tumor, Node, Metastasis (TNM) stage was determined using the 7th edition of the American Joint Committee on Cancer's Cancer Staging Manual. Tall cell and diffuse sclerosing variants were classified as aggressive histologic types.[21] A thyroglobulin concentration of 40 ng/mL was used as the cutoff value based on the normal range of a commercial radioimmunoassay kit (Radim, Milan, Italy). Patients were divided into 2 groups according to tumor size: overt PTC (>1 cm) and papillary thyroid microcarcinoma (≤1 cm, PTMC). Clinicopathologic factors affecting F-18 FDG uptake by primary tumors were analyzed with respect to age, sex, tumor size, histologic type, N-M stage, accompanying thyroid disorders affecting the ipsilateral thyroid and preoperative thyroglobulin concentration. Analysis was first performed in all patients with PTC, and then in those with overt PTC or PTMC.

All procedures were in accordance with the ethical standards of our institutional review board on human experimentation (Approval No. AJIRB-MED-MDB-12-316). The requirement to obtain informed consent from the patients was waived by our institutional review board.

### F-18 FDG PET/CT and Image Analysis

Patients were fasted for 6 hr before scanning. The blood glucose concentration was measured to ensure a level below 150 mg/dL. After an intravenous injection of 370 MBq of F-18 FDG, all patients were instructed to rest comfortably for 60 min. Emission PET data were acquired from the base of the skull to the upper thigh in 3-D mode using a Discovery ST scanner (GE Healthcare, Milwaukee, WI), and then they were reconstructed with noncontrast CT (tube rotation time 1 sec/revolution, 120 kV, 60 mA, 7.5 mm/rotation, acquisition time 60.9 sec, scan length 867 mm) by iterative reconstruction (ordered-subsets expectation maximization with 2 iterations and 30 subsets, field of view = 600 mm, slice thickness = 3.27 mm).

For the semi-quantitative analysis, polygonal regions of interest (ROIs) were first drawn on CT images and then copied to attenuation-corrected PET images using the Advantage Workstation (version 4.4, GE Healthcare). For tumors with a hypermetabolic lesion, ROIs were placed at every transaxial plane of CT images that contained the hypermetabolic lesion. Meanwhile, for those without visually discernible F-18 FDG uptake, ROIs were drawn to cover the whole tumor. In cases of multiple malignant nodules, an ROI was drawn on the largest 1. Maximum standardized uptake value ($SUV_{max}$) was calculated with the injected dose and patient's body weight.

### *BRAFV*600E Mutation Analysis

DNA was extracted from paraffin-embedded PTC tissue obtained during thyroidectomy. Tumor areas were transferred to an Eppendorf tube and digested with proteinase K (Promega, Madison, WI) at 56°C for 60 min. DNA was isolated using a protein precipitation solution (Qiagen, Hilden, Germany) and isopropanol. Polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) was performed using a forward (5′-ATAGGTGATTTTGGTCTAGCTCCGG-3′) and reverse primer (5′-GATTTTTGTGAATACTGGGAACT-3′). After amplification and purification, the PCR products were electrophoresed on a 3% TBE-Agarose SFR gel (Amresco, Solon, OH). The gels were photographed under UV trans-illumination using the Gel Doc XR+ System (Bio-Rad, Hercules, CA). One band of 189 base pair or 2 bands of 189/210 base pair was interpreted as the mutation, and 1 band of 210 base pair as the wild-type (Fig. 1). Results were reported within a few days of surgery.

### Statistical Analysis

All values are presented as the means ± SD. Student *t* test, the Mann–Whitney test, the Kruskal–Wallis test, or 1-way ANOVA was used for univariate analysis depending on the types of variables. Logistic regression analysis was used for multivariate analysis of factors associated with $SUV_{max}$. All statistical analyses were performed using a software (SPSS, version 22.0; SPSS, Inc., Chicago, IL). A $P$ value of $<0.05$ was considered statistically significant.

## RESULTS

### Patients' Characteristics

The *BRAFV*600E mutation was present in 82.2% of all patients (Table 1). The most common histologic variants were classical and follicular (164/169, 97.0%). The histopathologic examination of surgical specimens detected accompanying thyroid disorders which may increase F-18 FDG uptake in 84 patients (49.7%). All younger patients (≤45 years) had TNM stage I disease, whereas the most frequent stage in older

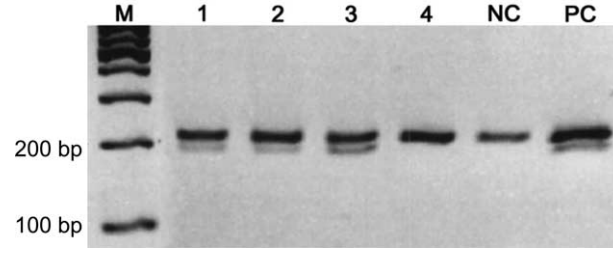


**FIGURE 1.** Polymerase chain reaction–restriction fragment length polymorphism to analyze the presence of *BRAFV*600E mutation in papillary thyroid cancer (PTC). Cases 1 to 3 show 2 bands of 189 and 210 base pair, indicating mutated *BRAF*. Case 4 with 1 band of 210 base pair is wild-type (M: marker [100–2000 base pair]; 1–4: DNA extracted from PTC; NC: negative control; PC: positive control).

**TABLE 1.** Clinicopathologic Characteristics of the Patients

| Variables | |
|---|---|
| Number of patients | 169 |
| Age, yr | 52 ± 12 (28–81) |
| Sex, M/F | 37/132 |
| *BRAFV*600E mutation, mutated/wild | 139/30 |
| Interval from PET/CT to thyroidectomy, d | 42 ± 40 (1–203) |
| Histologic variants, n | |
| Classical | 150 |
| Follicular | 14 |
| Tall cell | 2 |
| Oncocytic | 2 |
| Diffuse sclerosing | 1 |
| Accompanying thyroid disorders, n | |
| Nodular goiter | 51 |
| Thyroiditis | 22 |
| Adenomatous hyperplasia | 3 |
| Nodular goiter with thyroiditis | 7 |
| Adenomatous hyperplasia with thyroiditis | 1 |
| TNM stage, n | |
| Age < 45 yr | |
| I | 51 |
| Age ≥ 45 yr | |
| I | 25 |
| II | 1 |
| III | 64 |
| IVA | 25 |
| IVC | 3 |
| Tumor size, cm | 1.4 ± 1.2 (0.1–8.6) |
| Preoperative thyroglobulin, ng/mL | 87.9 ± 631.1 (0.1–7900.0)* |
| $SUV_{max}$, g/mL | 8.6 ± 10.2 (1.2–46.5) |

Data are presented as mean ± SD (range) or number of patients. PET/CT = positron emission tomography/computed tomography; $SUV_{max}$ = maximum standardized uptake value.
* n = 159.

patients (>45 years) was stage III. Average tumor size and $SUV_{max}$ were 1.4 cm and 8.6 g/mL, respectively. Preoperative thyroglobulin was measured in 159 patients and its mean value was 87.9 ng/mL.

## Relationships Between $SUV_{max}$ and Clinicopathologic Variables in All Patients With PTC

The results of univariate and multivariate analyses of clinicopathologic variables that potentially affect F-18 FDG uptake in the whole PTC population are shown in Table 2. The *BRAFV*600E mutation, tumor size, N stage, and preoperative thyroglobulin concentration were significantly associated with $SUV_{max}$. $SUV_{max}$ was significantly higher in the mutated group than in the wild-type group (9.4 ± 10.9 vs 5.0 ± 4.1, $P < 0.001$, Fig. 2). A pairwise comparison revealed that $SUV_{max}$ was significantly higher in patients with larger tumors (>2 cm, 20.5 ± 15.2, n = 32) than in those with smaller tumors (<1 cm, 4.5 ± 4.2, $P < 0.001$; 1–2 cm, 8.6 ± 7.9, $P < 0.001$). Greater extent of lymph node metastasis was also related to a higher $SUV_{max}$ ($P = 0.026$). Patients with increased preoperative thyroglobulin concentrations had higher $SUV_{max}$ values than those with normal thyroglobulin concentrations ($P < 0.001$). On the other hand, age, sex, histological variant, accompanying thyroid disorder, and M stage were not significantly associated with $SUV_{max}$.

A multivariate analysis with all variables included revealed that the *BRAFV*600E mutation ($P = 0.048$) and tumor size ($P < 0.001$) were independent variables affecting F-18 FDG uptake on preoperative PET/CT in patients with PTC.

## Relationships Between $SUV_{max}$ and Clinicopathologic Variables in Patients With Overt PTC

Similar to the whole PTC population, the *BRAFV*600E mutation was significantly associated with F-18 FDG uptake in overt PTC (Table 3). $SUV_{max}$ was significantly higher in the mutated group than in the wild-type group (15.0 ± 13.6 vs 6.8 ± 5.3, $P = 0.040$). There were also significant differences in $SUV_{max}$ depending on the tumor size ($P < 0.001$) and preoperative thyroglobulin concentration ($P = 0.039$) in this subpopulation. Age, sex, histological variant, accompanying thyroid disorder, N stage, and M stage were not associated with $SUV_{max}$.

Multivariate analysis revealed that the *BRAFV*600E mutation ($P = 0.032$) and tumor size ($P = 0.001$) were independent variables affecting F-18 FDG uptake on preoperative PET/CT in patients with overt PTC.

## Relationships Between $SUV_{max}$ and Clinicopathologic Variables in Patients With PTMC

To analyze the relationship between clinicopathologic variables and $SUV_{max}$ in PTMCs, we further categorized by tumor size: ≤0.5 and >0.5 cm. Unlike for the whole PTC and overt PTC populations, the *BRAFV*600E mutation was not significantly associated with $SUV_{max}$ (4.7 ± 4.5 for the mutated group and 3.7 ± 2.5 for the wild-type group, $P = 0.784$, Table 4). Only tumor size was significantly related to $SUV_{max}$, in both univariate ($P = 0.001$) and multivariate analyses ($P = 0.010$). $SUV_{max}$ was higher for PTMCs with a diameter of 5 to 10 mm than for those with a diameter of 0 to 5 mm (5.5 ± 4.7 vs 2.5 ± 1.2). The other variables, including N stage and preoperative thyroglobulin concentration, were not associated with $SUV_{max}$.

## DISCUSSION

This study was performed to investigate the relationship between the *BRAFV*600E mutation and F-18 FDG uptake on preoperative PET/CT in patients with PTC. The *BRAFV*600E mutation was independently related to $SUV_{max}$ in a multivariate analysis that included various clinicopathologic factors. In subgroup analyses, this relationship persisted in overt PTC, but not in PTMC. These results indicate that 2 potential prognostic factors, the *BRAFV*600E mutation and F-18 FDG uptake by the primary tumor, are closely related in patients with overt PTC.

Many studies have demonstrated that the *BRAFV*600E mutation is related to tumor aggressiveness and poor prognosis in PTC.[17–19] The *BRAFV*600E mutation was independently related to known prognostic factors such as extrathyroidal invasion, lymph node metastasis, advanced tumor stage

**TABLE 2.** Relationships Between Maximum Standardized Uptake Value and Clinicopathologic Variables in All Patients With Papillary Thyroid Carcinoma

| Variables | n | $SUV_{max}$ | Univariate *P* Value | Multivariate *P* Value |
|---|---|---|---|---|
| Age, yr | | | | |
| ≤45 | 51 | 9.3 ± 11.6 | 0.569 | 0.630 |
| >45 | 118 | 8.3 ± 9.6 | | |
| Sex | | | | |
| Male | 37 | 10.9 ± 13.0 | 0.211 | 0.568 |
| Female | 132 | 8.0 ± 9.2 | | |
| *BRAFV*600E mutation | | | | |
| Mutated | 139 | 9.4 ± 10.9 | <0.001 | 0.048 |
| Wild-type | 30 | 5.0 ± 4.1 | | |
| Histology | | | | |
| Nonaggressive | 166 | 8.4 ± 9.8 | 0.229 | 0.054 |
| Aggressive | 3 | 22.1 ± 22.0 | | |
| Accompanying thyroid disease | | | | |
| Present | 84 | 7.3 ± 9.0 | 0.085 | 0.282 |
| Absent | 85 | 10.0 ± 11.2 | | |
| Tumor size, cm | | | | |
| ≤1 | 93 | 4.5 ± 4.2 | <0.001 | <0.001 |
| 1–2 | 44 | 8.6 ± 7.9 | | |
| 2–4 | 29 | 20.3 ± 15.0 | | |
| >4 | 3 | 22.4 ± 20.9 | | |
| N stage | | | | |
| 0 | 82 | 6.5 ± 8.0 | 0.026 | 0.929 |
| 1a | 44 | 9.0 ± 9.1 | | |
| 1b | 43 | 12.3 ± 13.6 | | |
| M stage | | | | |
| 0 | 166 | 8.4 ± 9.9 | 0.120 | 0.200 |
| 1 | 3 | 20.7 ± 22.2 | | |
| Preoperative thyroglobulin, ng/mL | | | | |
| ≤40 | 130 | 7.2 ± 8.4 | <0.001 | 0.366 |
| >40 | 29 | 16.2 ± 14.8 | | |

$SUV_{max}$ = maximum standardized uptake value.

(III/IV), and aggressive subtypes. The presence of the *BRAFV*600E mutation was associated with the recurrence of PTC, even in a low-risk group.[17] In a retrospective multicenter study, *BRAFV*600E mutation-positive patients experienced more deaths per 1000 person-years than their wild-type counterparts (11.80 vs 2.25, hazards ratio = 3.53).[18]

Like the *BRAFV*600E mutation, F-18 FDG uptake is also accepted as a potential prognostic factor in thyroid cancer. F-18 FDG positivity, $SUV_{max}$ (>10 g/mL) and metabolic tumor volume (>125 mL) were significantly correlated with survival regardless of radioiodine avidity.[22] Survival of stage I–III patients with positive F-18 FDG uptake was as poor as that of stage IV thyroid cancer patients.[23]

Besides the role as a prognostic factor, there is a similarity between F-18 FDG uptake and the *BRAFV*600E mutation regarding the loss of radioiodine avidity. Similar to the ''flip-flop'' phenomenon of F-18 FDG uptake, in recurrent thyroid cancers, most (79%) of the I-131 negative group had the *BRAFV*600E mutation, while most (82%) of the I-131 positive group was wild-type.[24] Similarly, in patients with metastatic PTC, the I-131 negative group had a higher rate of *BRAFV*600E mutation (77%) than did the I-131 positive group (43%).[10] From the perspective of molecular changes, the *BRAFV*600E mutation in PTC is related to the silencing of thyroid iodide-metabolizing genes,[10,25] and also impairs the targeting of sodium/iodide symporter to the cell membrane.[19] Considering those previous reports, it is reasonable that in the present study the *BRAFV*600E mutation was associated with F-18 FDG uptake on preoperative PET/CT in PTC.

F-18 FDG uptake is based on enhanced aerobic glycolysis in cancer cells, known as Warburg effect.[26] There are some experimental evidence that *BRAF* mutation is involved in increased glycolysis in PTC. Mitochondrial localization of *BRAFV*600E led to the reduction of mitochondrial $O_2$ consumption and increased glucose uptake in PTC.[27] The expression of the M2 isoform of pyruvate kinase, which is the rate-limiting step of glycolysis, was also significantly higher in PTCs harboring *BRAFV*600E.[28,29] Meanwhile, GLUT1, GLUT3, and hexokinase II play an important role in the trapping of F-18 FDG by cancer cells.[30] At the transcriptional level, hypoxia-inducible factor (HIF)-1 exerts influence on glycolytic shift in cancer cells by targeting GLUT1, GLUT3, and hexokinase II.[31,32] Several studies demonstrated that GLUT1 expression and HIF-1α level were significantly higher in *BRAF*-mutated PTC compared with *BRAF*-wild type PTC.[10,25,33,34] HIF-1 can be upregulated via mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway to increase glycolysis.[35,36] This Ras-Raf-MEK–ERK pathway is aberrantly

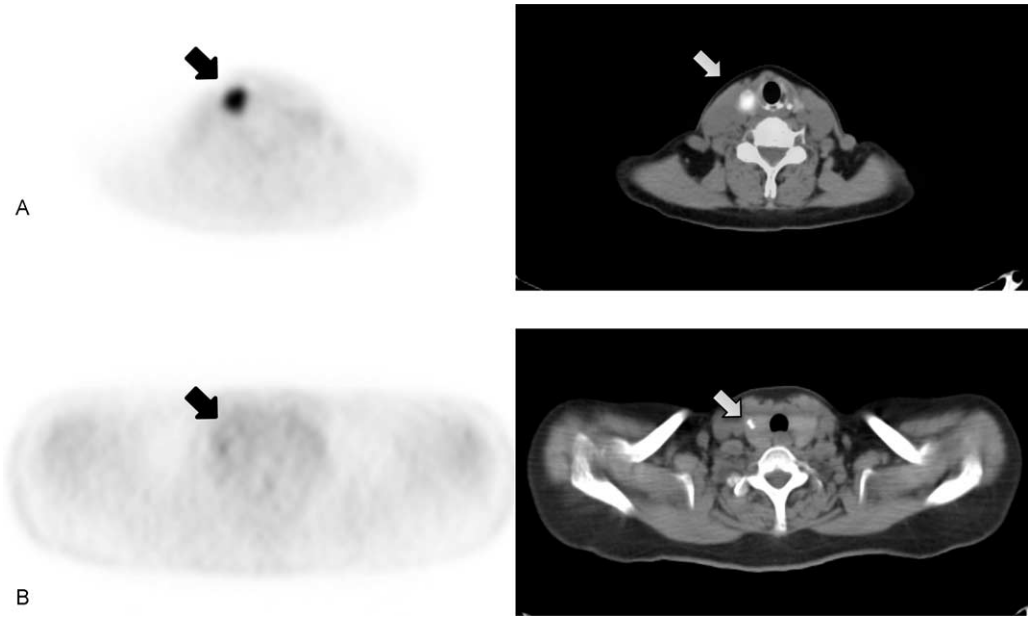


**FIGURE 2.** Representative cases for the relationship between *BRAFV*600E mutation and F-18 fluorodeoxyglucose uptake on positron emission tomography/computed tomography. (A) 68-year-old female, $SUV_{max} = 20.8$, *BRAF* (+), classical type, T3N1aM0, tumor size = 1.7 cm, thyroglobulin = 90.6 ng/mL, no associated thyroid disease. (B) 60-year-old female, $SUV_{max} = 2.2$, *BRAF* (−), classical type, T1bN1aM0, tumor size = 1.7 cm, thyroglobulin = 1.1 ng/mL, thyroiditis. Arrows: thyroid nodules. $SUV_{max}$ = maximum standardized uptake value.

**TABLE 3.** Relationships Between Maximum Standardized Uptake Value and Clinicopathologic Variables in Patients With Overt Papillary Thyroid Carcinoma

| Variables | n | $SUV_{max}$ | Univariate *P* Value | Multivariate *P* Value |
|---|---|---|---|---|
| Age, yr | | | | |
| ≤45 | 21 | 16.4 ± 14.7 | 0.387 | 0.724 |
| >45 | 55 | 12.5 ± 12.1 | | |
| Sex | | | | |
| Male | 18 | 17.2 ± 15.6 | 0.282 | 0.914 |
| Female | 58 | 12.5 ± 11.9 | | |
| *BRAFV*600E mutation | | | | |
| Mutated | 63 | 15.0 ± 13.6 | 0.040 | 0.032 |
| Wild-type | 13 | 6.8 ± 5.3 | | |
| Histology | | | | |
| Nonaggressive | 73 | 13.3 ± 12.5 | 0.542 | 0.148 |
| Aggressive | 3 | 22.1 ± 22.0 | | |
| Accompanying thyroid disease | | | | |
| Present | 33 | 11.5 ± 12.6 | 0.205 | 0.278 |
| Absent | 43 | 15.3 ± 13.0 | | |
| Tumor size, cm | | | | |
| 1–2 | 44 | 8.6 ± 7.9 | <0.001 | 0.001 |
| 2–4 | 29 | 20.3 ± 15.0 | | |
| >4 | 3 | 22.4 ± 20.9 | | |
| N stage | | | | |
| 0 | 24 | 11.7 ± 11.9 | 0.662 | 0.841 |
| 1a | 21 | 13.3 ± 11.1 | | |
| 1b | 31 | 15.3 ± 14.8 | | |
| M stage | | | | |
| 0 | 73 | 13.3 ± 12.5 | 0.491 | 0.822 |
| 1 | 3 | 20.7 ± 22.2 | | |
| Preoperative thyroglobulin, ng/mL | | | | |
| ≤40 | 49 | 11.5 ± 11.4 | 0.039 | 0.403 |
| >40 | 25 | 18.3 ± 15.0 | | |

$SUV_{max}$ = maximum standardized uptake value.

**TABLE 4.** Relationships Between Maximum Standardized Uptake Value and Clinicopathologic Variables in Patients With Papillary Thyroid Microcarcinoma

| Variables | n | $SUV_{max}$ | Univariate *P* Value | Multivariate *P* Value |
|---|---|---|---|---|
| Age, yr | | | | |
| ≤45 | 30 | 4.3 ± 4.3 | 0.740 | 0.980 |
| >45 | 63 | 4.6 ± 4.1 | | |
| Sex | | | | |
| Male | 19 | 4.9 ± 5.4 | 0.396 | 0.877 |
| Female | 74 | 4.5 ± 3.9 | | |
| *BRAFV*600E mutation | | | | |
| Mutated | 76 | 4.7 ± 4.5 | 0.784 | 0.568 |
| Wild-type | 17 | 3.7 ± 2.5 | | |
| Histology | | | | |
| Nonaggressive | 93 | 4.5 ± 4.2 | | |
| Aggressive | 0 | | | |
| Accompanying thyroid disease | | | | |
| Present | 51 | 4.5 ± 3.7 | 0.997 | 0.907 |
| Absent | 42 | 4.5 ± 4.8 | | |
| Tumor size, cm | | | | |
| ≤0.5 | 29 | 2.5 ± 1.2 | 0.001 | 0.010 |
| >0.5 | 64 | 5.5 ± 4.7 | | |
| N stage | | | | |
| 0 | 58 | 4.3 ± 4.2 | 0.198 | 0.680 |
| 1a | 23 | 5.1 ± 4.1 | | |
| 1b | 13 | 5.2 ± 5.1 | | |
| M stage | | 4.5 ± 4.2 | | |
| 0 | 93 | | | |
| 1 | 0 | | | |
| Preoperative thyroglobulin, ng/mL | | | | |
| ≤40 | 81 | 4.6 ± 4.3 | 0.682 | 0.935 |
| >40 | 4 | 5.1 ± 4.6 | | |

$SUV_{max}$ = maximum standardized uptake value.

activated by the mutation of *BRAF* gene[15,16] and has an important role in the tumorigenesis in PTC.[35] Therefore, the induction of MAPK pathway by *BRAF* mutation and the subsequent activation of HIF-1 resulting in increased glycolysis may explain the mechanism behind the association between F-18 FDG uptake and *BRAFV*600E mutation.

Clinicopathologic factors influencing F-18 FDG positivity of PTC on preoperative PET/CT have been previously evaluated by other researchers.[11] Univariate analysis revealed that size, cervical lymph node metastasis, and TNM stage were significantly correlated with F-18 FDG positivity. A multivariate analysis revealed that size and cervical lymph node metastasis were independent predictors of F-18 FDG positivity. Compared with this previous report, our study provided additional insight into the relationship between the*BRAFV*600E mutation and $SUV_{max}$ on PET/CT in PTC.

From a clinical perspective, PTMC is noteworthy in that most cases are detected incidentally, and aggressive behavior is not uncommon.[37] In the present study, an analysis with the PTMC subpopulation (93/169, 55%) showed that tumor size was significantly associated with $SUV_{max}$. This result was in accordance with a few previous reports.[13,38,39] Other than the size dependency of tumor metabolism itself, there is another contributing factor: the ''partial volume effect'' in PET/CT imaging. The partial volume effect leads to underestimation of the F-18 FDG uptake in small tumors,[40] and it may have influenced the significant positive correlation between $SUV_{max}$ and tumor size in the present study. Unfortunately, a commercial software for an automated partial volume correction in PET is not currently available.

In contrast to tumor size, the *BRAFV*600E mutation, in the present study, was not correlated with $SUV_{max}$ in PTMC. According to the literatures, there is a controversy over the clinical significance of the *BRAFV*600E mutation in PTMC. Lee et al[41] reported that the prevalence of *BRAFV*600E mutation was significantly higher in aggressive PTMC than in nonaggressive tumors. Virk et al[42] found that the *BRAFV*600E mutation occurred during an early stage of carcinogenesis and was associated with extrathyroidal invasion and lymph node metastasis. On the contrary, other researchers found that the *BRAFV*600E mutation was not associated with tumor recurrence in PTMC.[43,44] In a couple of studies with Korean population, which has a high prevalence of *BRAFV*600E mutation, no significant relationship was found between the *BRAFV*600E mutation and clinicopathologic factors.[45,46] Therefore, the role of the *BRAFV*600E mutation as a prognostic factor in PTMC is still uncertain, and our result in PTMC supports those negative results.

There were a few limitations in this work. We retrospectively analyzed PTC patients who had undergone preoperative F-18 FDG PET/CT and subsequent thyroidectomy. We set the maximum interval between PET/CT and surgery to 7 months.

Although PTCs are typically slow-growing, there can be a change in F-18 FDG uptake in some tumors. In addition, as we mentioned above, the partial volume effect may have influenced F-18 FDG uptake in PTMC. However, we were not able to perform partial volume correction, because the necessary in-house software has not been developed yet. Therefore, a further analysis implementing partial volume correction is required for the PTMC subpopulation to clarify the association between *BRAFV*600E mutation and F-18 FDG uptake in PTC.

In conclusion, 2 potential prognostic factors of PTC, the *BRAFV*600E mutation and F-18 FDG uptake, are closely related in overt PTC, but not in PTMC. The present study affords a better understanding of the relationship between the *BRAFV*600E mutation and F-18 FDG uptake in PTC. In addition, clinicians should notice that the clinical significance of F-18 FDG in PTC can be different between overt PTC and PTMC because of the technical limitation of PET/CT.

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