Factors Associated with Positive F-18 Flurodeoxyglucose Positron Emission Tomography Before Thyroidectomy in Patients with Papillary Thyroid Carcinoma

Bum Soo Kim,¹ Seong-Jang Kim,^{1,2} In Joo Kim,^{1,2} Kyoungjune Pak,^{1,2} and Keunyoung Kim^{1,2}

Background: The role for pre-thyroidectomy (pre-Tx) imaging with F-18 flurodeoxyglucose (FDG) positron emission tomography (PET), FDG PET-computed tomography (CT), in differentiated thyroid cancer is controversial as is the significance of positive and negative FDG uptake in this setting. We reviewed the records of patients with papillary thyroid carcinoma (PTC) who had pre-Tx FDG PET-CT to determine whether FDG uptake was associated with features noted on pre-Tx ultrasonography (US) and parameters determined after post-Tx.

Methods: Patients were selected for a retrospective review of their records if they had a total Tx with central lymph node dissection for PTC and pre-Tx FDG PET-CT and US between 2006 and 2009. Sixty patients who met these criteria were studied. Patients who had a history of head and neck irradiation, surgery, or sclerotherapy with ethanol in the last 3 months were excluded. The clinicopathologic factors—age, sex, size, tumor-node-metastasis (TNM) staging, the presence of extrathyroidal extension, multifocality, cervical lymph node metastases (CLNM), Hashimoto thyroiditis, and US characteristics—were evaluated to determine whether they were associated with positive pre-Tx FDG uptake.

Results: Forty-three (71.6%) of patients in the study had positive FDG uptake. Larger tumors and the presence of CLNM were associated with a greater likelihood of positive FDG uptake. The sensitivity, specificity, positive predictive value, and negative predictive value for CLNM detection by FDG PET-CT showed low statistical values. When considering the excellence of US for evaluating a thyroid nodule size and the presence of CLNM, the clinical value of pre-Tx FDG PET-CT is comparatively limited.

Conclusion: Pre-Tx FDG PET is not recommended for routine use in patients with PTC.

Introduction

PAPILLARY THYROID CARCINOMA (PTC) is the most common type of thyroid malignancy. The overall 10-year survival rate for middle-aged adults with thyroid carcinomas is about 80%–95%. Although the prognosis of PTC is generally good, with high survival rate, up to 20% of patients with thyroid cancer develop locoregional recurrence (1). Therefore, the early detection of the recurrence or metastasis is essential for thyroid carcinoma.

Positron emission tomography (PET) with the glucose analogue F-18 fluorodeoxyglucose (FDG) is an important modality for evaluation of postoperative recurrence and metastasis. FDG PET-computed tomography (CT) is especially useful in detecting locoregional recurrence or metastasis with dedifferentiated recurrent thyroid carcinoma cells that lose their iodine-concentrating ability (2–5).

FDG uptake can be positive or negative prior to thyroidectomy (Tx) in patients with PTC. However, the factors influencing this have not been carefully studied. We postulated that additional research on the factors influencing FDG uptake in FDG PET-CT studies, as performed before Tx in patients with PTC, could provide useful clinical information. In the current study we compared clinical, pathological, and ultrasonography (US) features in patients with PTC who were FDG positive and FDG negative in group in FDG PET-CT studies performed before Tx.

Materials and Methods

Patients

This was a retrospective study of 60 patients with PTC who had F-18 FDG PET-CT and US prior to total Tx with central

¹Department of Nuclear Medicine and ²Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea.

lymph node (LN) dissection as their initial surgical treatment. Thyroid surgery was performed in the Department of Otorhinolaryngology Head and Neck Surgery of our institution from October 2006 to November 2009. Exclusion criteria were a history of head and neck irradiation, surgery, and sclerotherapy with ethanol in the 3 months prior to F-18 FDG PET/CT examination. Postoperative data on tumor characteristics included tumor size, extrathyroidal extension, number of neoplastic foci, and presence of Hashimoto thyroiditis, and regional cervical lymph node metastases (CLNM) was noted. tumor-node-metastasis (TNM) staging was determined according to the American Joint Committee on Cancer staging manual (6). This retrospective review protocol was approved by the Institutional Review Board at Pusan National University Hospital.

F-18 fluorodeoxyglucose PET-CT

All patients were examined on a dedicated PET/CT scanner (Gemini; Philips, Milpitas, CA), consisting of a dedicated germanium oxyorthosilicate full-ring PET scanner and a dual-slice helical CT scanner. Standard patient preparation included at least 8 hours of fasting and a serum glucose level of <120 mg/dL before F-18 FDG administration. F-18 FDG PET-CT imaging was performed 60 minutes after injection of F-18 FDG. At 60 minutes after administration of F-18 FDG, low-dose CT (30 mAs, 120 kV) covering the area from the base of the skull to the proximal thighs was performed for the purpose of attenuation correction and precise anatomical localization. Thereafter, the emission scan was conducted in the three-dimensional mode. Emission scan time per bed position was 3 minutes; nine bed positions were acquired. PET data were obtained using a high-resolution, whole-body scanner with an axial field of view of 18 cm. The average axial resolution varied between 4.2 mm full width at half maximum (FWHM) in the center and 5.6 mm at 10 cm. The average total PET/CT examination time was 30 minutes. After scatter and decay correction, PET data were reconstructed iteratively with attenuation correction and reoriented in axial, sagittal, and coronal slices. The row action maximum-likelihood algorithm was used for three-dimensional reconstruction.

Visual analysis of F-18 FDG PET-CT

FDG uptake in PTCs and CLNM were visually categorized as positive if there was a discernible FDG uptake compared with surrounding activity and negative if there was no discernible FDG uptake. The PET/CT images were independently reviewed by two experienced nuclear physicians and any disagreement was resolved by consensus.

Ultrasonography

Sonographic evaluation was performed by one radiologist using a US scanner (HDI 5000; Philips Medical Systems, Bothell, WA, and Vivid i; GE Healthcare, Milwaukee, WI) equipped with a 10–13 MHz linear probe. We determined whether the following US characteristics were present: (i) shape: as ovoid to round, irregular, or taller than wide; (ii) echogenicity: as isoechoic, hypoechoic, or markedly hypoechoic; (iii) tumor margin: as well-defined or ill-defined; (iv) calcification: as negative, microcalcification, or macro-

calcification; (v) vascularity: as negative, peripheral, or central; (vi) contact to the external thyroid capsule: as positive or negative; and (vii) location: right, left, or isthmus.

Statistical analysis

All continuous variables were expressed as mean $\pm$ standard deviation. Variables were dichotomized based on the ages <45 and $\geq$ 44, macrocarcinoma ($\geq$ 1 cm) or microcarcinoma (<1.0 cm), the presence or absence of extrathyroidal extension, the presence or absence of multifocality, the presence or absence of CLNM, and the presence or absence of Hashimoto thyroiditis. Univariate analysis (χ^2 tests or Fisher's exact tests) was used to determine the relationship between the factors described and FDG positivity. A binary logistic regression analysis was used for multivariate analysis of independent variables having a $p < 0.05$ in the univariate analysis. In addition, Pearson's correlation analysis was used to investigate the relationships between maximal standardized uptake value (SUV_{max}) and tumor size. The statistical analyses were performed using MedCalc[®] for windows version 8.1 and statistical significance was defined as $p < 0.05$.

Results

Figure 1 shows the distribution of SUV_{max} for the group of visually discernible FDG uptake in primary thyroid cancer patients. The mean SUV_{max} was 5.93 ± 5.65 (1.8–33.7). Figure 2 shows the relationship between SUV_{max} and tumor size in patients with PTC. There was a significant correlation between SUV_{max} and the tumor size ($p < 0.0001$).

The relationships between various clinicopathological factors and visually discernible FDG uptake are summarized in Table 1. The mean age of all patients was 50.2 ± 12.6 years (21–80 years). The mean size of all PTCs was 1.16 ± 0.79 cm (0.3–4.5 cm). Extrathyroidal extension was found in 35 of the patients (58.3%). PTC was multifocal in 16 (26.6%) patients. Thirty (50.0%) patients had CLNM. In 11 patients (18.3%) PTC was accompanied by Hashimoto thyroiditis as determined by histopathology. In the entire study there were 22 patients

FIG. 1. The maximal standardized uptake value (SUV_{max}) histogram for papillary thyroid carcinoma (PTC) patients who show visually discernible F-18 fluorodeoxyglucose (FDG) uptake.

FIG. 2. Correlation between tumor size and SUV_{max} from F-18 FDG positron emission tomography-computed tomography. SUV_{max} ($r=0.4760$, $p<0.0001$) showed statistically significant correlations with the size of PTC.

(36.6%) with stage I PTC, 1 (1.6%) with stage II PTC, 29 (48.3%) with stage III PTC, and 8 (13.3%) with stage IV PTC. Of the 60 patients, 43 (71.6%) had positive FDG uptake in their pre-Tx F-18 FDG PET-CT study and the remaining had negative FDG uptake in their pre-Tx F-18 FDG PET-CT study.

Table 2 shows the pre-Tx US findings. None of the US features that were assessed were significantly more frequent in patients with FDG uptake in their pre-Tx F-18 FDG PET-CT study than in those without FDG uptake in their comparable study.

Table 3 shows the results of univariate analyses of the various factors. The FDG positive and negative groups were similar in terms of age, gender, presence of extrathyroidal extension of their PTCs, and presence of Hashimoto thyroiditis. In contrast, there were marked differences in size of PTCs with positive FDG uptake compared with PTCs without positive FDG uptake. PTCs in patients with FDG positive uptake were 1.40 ± 0.81 cm, whereas those in the FDG negative group were 0.54 ± 0.17 cm ($p=0.0023$). Among the patients with microcarcinomas (<1 cm), the tumors of those with positive FDG uptake were 0.70 ± 0.19 cm; this was significantly greater in size than the mean value for the FDG negative group (0.54 ± 0.17 ; $p=0.0261$). FDG-positive patient group also had a higher frequency of CLNM ($p=0.0034$). Whereas 3 patients (17.6%) in FDG-negative group had CLNM, 27 patients (62.7%) in FDG-positive group had

CLNM. Also, there was a significant difference in the TNM staging of the groups with and without positive FDG uptake ($p=0.0340$). Whereas differences in tumor size and the presence of CLNM remained significant in the multivariate analysis (Table 4), this was not the case for differences in TNM staging. FDG-positive and FDG-negative patients were similar with regard to the frequency of extranodal metastases ($p=0.627$). In the patients with positive FDG uptake, there was no correlation between the percentage of involved LN and the SUV_{max} ($p=0.356$).

The sensitivity, specificity, positive predictive value, and negative predictive value of positive FDG uptake for prediction of CLNM were 10%, 90%, 50%, and 50%, respectively.

Discussion

Whether there is a role for FDG PET or FDG PET-CT before Tx in PTC is still controversial. Yun *et al.* showed that positive uptake of FDG in papillary thyroid microcarcinomas was correlated with extrathyroidal extension and CLNM (7). Choi *et al.* retrospectively reviewed false negative findings of FDG PET-CT when performed prior to Tx in patients with PTC (8). They found that negativity on initial FDG PET-CT scan correlated with the absence of perithyroidal and lymphovascular invasion. Jeong *et al.* argued that the glucose metabolism increases in proportion to the size of the primary thyroid cancer (9). Our results indicate that larger tumor size and the presence of CLNM are more likely to be associated with positive FDG uptake.

It seems unlikely that pre-Tx FDG studies are necessary, given their expense and radiation burden, in patients with PTC. Similar information can be obtained by US with several advantages. US can be easily performed, avoids radiation exposure, and provides accurate information on tumor size (10). In addition, according to Morita *et al.*, US images gave significantly better results than FDG PET-CT for detection of CLNM in the total neck compartment (11). Moreover, other than detecting cryptic extrathyroidal metastases, pre-operative FDG PET-CT does not provide any prognostic information that could not be obtained by histopathology of the Tx specimen.

Our study population included 29 patients (48.3%) with microcarcinomas. Of 29 patients, only 12 patients (41.3%) were positive on FDG uptake, but every patient with PTC

TABLE 1. PATIENT CHARACTERISTICS

Characteristics	FDG negative (n=17)	FDG positive (n=43)	Total (n=60)	p-Value
Age (years)	50.58 $\pm$ 10.95	50.04 $\pm$ 13.37	50.20 $\pm$ 12.64	0.8826
Sex (M/F)	1/16	4/39	5/55	1.0000
Size (cm)	0.54 $\pm$ 0.17	1.40 $\pm$ 0.81	1.16 $\pm$ 0.79	0.0001
Extrathyroidal extension (%)	7 (41.1)	28 (65.1)	35 (58.3)	0.1453
Multifocality (%)	4 (57.1)	12 (27.9)	16 (26.6)	1.0000
CLNM (%)	3 (17.6)	27 (62.7)	30 (50.0)	0.0034
Hashimoto thyroiditis (%)	1 (5.8)	10 (23.2)	11 (18.3)	0.1546
TNM staging (%)				0.0340
I	10 (58.8)	12 (27.9)	22 (36.6)	
II	0	1 (2.3)	1 (1.6)	
III	7 (41.2)	22 (51.1)	29 (48.3)	
IV	0	8 (18.6)	8 (13.3)	

FDG, F-18 flurodeoxyglucose; CLNM, cervical lymph node metastasis; TNM, tumor-node-metastasis.

TABLE 2. UNIVARIATE ANALYSIS OF ULTRASONOGRAPHIC FEATURES

Characteristics	FDG negative (n=17)	FDG positive (n=43)	Total (n=60)	p-Value
Shape (%)				0.297
Ovoid to round	4 (23.5)	16 (37.2)	20 (33.3)	
Irregular	7 (41.1)	16 (37.2)	23 (38.3)	
Taller than wide	6 (35.2)	11 (25.5)	17 (28.3)	
Echogenicity (%)				0.101
Isoechoic	0	10 (23.2)	10 (16.7)	
Hypoechoic	8 (47.0)	15 (34.8)	23 (38.3)	
Markedly hypoechoic	9 (52.9)	18 (41.8)	27 (45.0)	
Margin (%)				0.075
Well-defined	8 (47.0)	15 (34.8)	23 (38.3)	
Ill-defined	9 (52.9)	28 (65.1)	37 (61.7)	
Calcification (%)				0.279
Negative	9 (52.9)	28 (65.1)	37 (61.7)	
Microcalcification	2 (11.7)	6 (13.9)	8 (13.3)	
Macrocalcification	6 (35.2)	9 (20.9)	15 (25.0)	
Vascularity (%)				0.299
Negative	14 (82.3)	28 (65.1)	42 (70.0)	
Peripheral	0	4 (9.3)	4 (6.7)	
Central	3 (17.6)	11 (25.5)	14 (23.3)	
Contact (%)				0.208
Positive	7 (41.1)	10 (23.2)	17 (28.3)	
Negative	10 (58.8)	33 (76.7)	43 (71.7)	
Location (%)				0.822
Right	8 (47.0)	21 (48.8)	29 (48.3)	
Left	7 (41.1)	18 (41.8)	25 (41.7)	
Isthmus	2 (11.7)	4 (9.3)	6 (10.0)	

TABLE 3. UNIVARIATE ANALYSIS OF CLINICOPATHOLOGIC PROGNOSTIC FACTORS

Characteristics	Positive PET/CT, n (%)	p-Value
Age (years)		0.7426
<45	10/15 (66.6)	
≥45	33/45 (73.3)	
Sex		1.0000
Female	39/55 (70.9)	
Male	4/5 (80.0)	
Size (cm)		0.0023
<1 cm	12/29 (41.3)	
≥1 cm	31/31 (100.0)	
Extrathyroidal extension		0.1453
No	15/25 (60.0)	
Yes	28/35 (80.0)	
Multifocality		1.0000
No	31/44 (70.4)	
Yes	12/16 (75.0)	
Cervical lymph node metastasis		0.0034
No	16/30 (53.3)	
Yes	27/30 (90.0)	
Hashimoto thyroiditis		0.1546
No	33/49 (67.3)	
Yes	10/11 (90.9)	
TNM staging		0.0340
Stage I	12/22 (54.5)	
Stage II	1/1 (100.0)	
Stage III	22/29 (75.8)	
Stage IV	8/8 (100.0)	

PET, positron emission tomography; CT, computed tomography.

>1 cm was FDG positive. Such dependency of FDG uptake on tumor size seems to demonstrate partial volume effect (12–14). The partial volume effect on some of the small thyroid cancers might be the reason why the tumor size became one of the factors associated with positive FDG uptake. Therefore, the partial volume effect should not be overlooked when clinically interpreting glucose metabolism of microcarcinomas.

One of the major confusing issues regarding the clinical implication of FDG PET-CT for well-differentiated thyroid cancer is that FDG might pick up unsuspected distant metastases but this would be unlikely if preoperative evaluation indicated a low-grade tumor. However, the more advanced the tumor, the more likely distant metastases might be present but undetected. In thyroid cancer, FDG PET-CT avidity is well known to be a poor prognostic factor (15). Further, during follow-up in thyroid cancer patients after operation, radioiodine-negative/FDG-positive recurrence and metastasis are known to represent tumor dedifferentiation (16). This Flip-Flop phenomenon prohibits the routine clinical use of

TABLE 4. MULTIVARIATE LOGISTIC REGRESSION ANALYSIS OF F-18 FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY-COMPUTED TOMOGRAPHY POSITIVITY

Viable	SE	p-Value	OR	95% CI
Cervical LN metastasis	0.7794	0.0075	8.0347	1.7440–37.0157
Size	0.8111	0.0071	8.8768	1.8106–43.5199

SE, standard error; OR, odds ratio; CI, confidence interval; LN, lymph node.

preoperative FDG PET-CT in well-differentiated thyroid cancer patients.

Our study has several limitations. As the follow-up period was relatively short, we could not assess whether there was a relationship between FDG positivity and disease-free survival.

In summary, our results show that positive FDG uptake is predictive of the presence of CLNM and larger tumor size. In patients in whom a total Tx and LN dissection is planned, the information obtained by FDG PET seems to be limited though long-term follow-up of our patients may uncover prognostic information of potential importance. With the data available, we do not recommend routine pre-Tx FDG PET in patients whose preoperative diagnosis is PTC.

Acknowledgment

This study was supported by Biomedical Research Institute Grant (No. 2012-1), Pusan National University Hospital.

Disclosure Statement

The authors declare that no competing financial interests exist.

References

- Schlumberger MJ 1998 Papillary and follicular thyroid carcinoma. *N Engl J Med* **338**:297–306.
- Zuijdewijk MD, Vogel WV, Corstens FH, Oyen WJ 2008 Utility of fluorodeoxyglucose-PET in patients with differentiated thyroid carcinoma. *Nucl Med Commun* **29**:636–641.
- Razfar A, Branstetter BF 4th, Chistopoulos A, Lebeau SO, Hodak SP, Heron DE, Escott EJ, Ferris RL 2010 Clinical usefulness of positron emission tomography-computed tomography in recurrent thyroid carcinoma. *Arch Otolaryngol Head Neck Surg* **136**:120–125.
- Chung JK, So Y, Lee JS, Choi CW, Lim SM, Lee DS, Hong SW, Youn YK, Lee MC, Cho BY 1999 Value of FDG PET in papillary thyroid carcinoma with negative ¹³¹I whole-body scan. *J Nucl Med* **40**:993–994.
- Feine U, Lietzenmayer R, Hanke JP, Held J, Wöhrle H, Müller-Schauenburg W 1996 Fluorine-18-FDG and iodine-131-iodide uptake in thyroid cancer. *J Nucl Med* **37**:1468–1472.
- American Joint Committee on Cancer Staging 2002 Manual for Staging of Cancer, 6th ed. J.B. Lippincott, Philadelphia, PA.
- Yun M, Noh TW, Cho A, Choi YJ, Hong SW, Park CS, Lee JD, Kim CK 2010 Visually discernible [18F]fluorodeoxyglucose uptake in papillary thyroid microcarcinoma: a potential new risk factor. *J Clin Endocrinol Metab* **95**:3182–3188.
- Choi JW, Yoon YH, Yoon YH, Kim SM, Koo BS 2011 Characteristics of primary papillary thyroid carcinoma with false-negative findings on initial (18)F-FDG PET/CT. *Ann Surg Oncol* **18**:1306–1311.
- Jeong HS, Chung M, Baek CH, Ko YH, Choi JY, Son YI 2006 Can [18F]-fluorodeoxyglucose standardized uptake values of PET imaging predict pathologic extrathyroid invasion of thyroid papillary microcarcinomas? *Laryngoscope* **116**:2133–2137.
- Hoang JK, Lee WK, Lee M, Johnson D, Farrell S. 2007 US Features of thyroid malignancy: pearls and pitfalls. *Radiographics* **27**:847–860.
- Morita S, Mizoguchi K, Suzuki M, Iizuka K 2010 The accuracy of (18)F-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography, ultrasonography, and enhanced computed tomography alone in the preoperative diagnosis of cervical lymph node metastasis in patients with papillary thyroid carcinoma. *World J Surg* **34**:2564–2569.
- Srinivas SM, Dhurairaj T, Basu S, Bural G, Surti S, Alavi A 2009 A recovery coefficient method for partial volume correction of PET images. *Ann Nucl Med* **23**:341–348.
- Rousset OG, Ma Y, Evans AC 1998 Correction for partial volume effects in PET: principle and validation. *J Nucl Med* **39**:904–911.
- Kim SC, Machac J, Krynyckyi BR, Knesaurek K, Krellenstein D, Schultz B, Gribetz A, DePalo L, Teirstein A, Kim CK 2008 Fluoro-deoxy-glucose positron emission tomography for evaluation of indeterminate lung nodules: assigning a probability of malignancy may be preferable to binary readings. *Ann Nucl Med* **22**:165–170.
- Bogsrud TV, Hay ID, Karantanis D, Nathan MA, Mullan BP, Wiseman GA, Kasperbauer JL, Reading CC, Björö T, Lowe VJ 2011 Prognostic value of 18F-fluorodeoxyglucose-positron emission tomography in patients with differentiated thyroid carcinoma and circulating antithyroglobulin autoantibodies. *Nucl Med Commun* **32**:245–251.
- Khan N, Oriuchi N, Higuchi T, Zhang H, Endo K 2003 PET in the follow-up of differentiated thyroid cancer. *Br J Radiol* **76**:690–695.

Address correspondence to:
Seong-Jang Kim, M.D., Ph.D.
Department of Nuclear Medicine
Pusan National University Hospital
and Medical Research Institute
Pusan National University
Busan 602-739
Republic of Korea

E-mail: growthkim@daum.net;
growthkim@pusan.ac.kr