Incidental Diffuse Thyroid ^{18}F-FDG Uptake Related to Autoimmune Thyroiditis May Be a Favorable Prognostic Factor in Advanced Breast Cancer

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Patients with breast cancer have a relatively high prevalence of diffuse thyroid uptake of ^{18}F-FDG related to thyroid autoimmunity. It is postulated that the presence of thyroid autoimmunity has prognostic implications for breast cancer. The aim of this study was to evaluate the prognostic value of incidental diffuse thyroid uptake in breast cancer patients. **Methods:** This was a retrospective observational cohort study in a tertiary referral hospital. We evaluated a total of 564 patients who had undergone surgery for primary breast cancer between January 2006 and December 2009. Patients were divided into 2 groups according to their diffuse thyroid uptake. The main outcome measure was disease-free survival. **Results:** Of the 564 patients, 108 (19.1%) showed diffuse thyroid uptake. The median follow-up period was 36.0 mo (range, 1.0–77.0 mo). Both thyroperoxidase and thyroglobulin antibody titers were higher in patients with thyroid uptake than in those without ($P < 0.001$ for both). Of the 108 patients with thyroid uptake, 5 had a recurrence of breast cancer during the follow-up, whereas 85 without uptake had a recurrence (log-rank statics, 12.28; $P < 0.001$). The association between diffuse thyroid uptake and tumor recurrence was not significant in multivariate analysis of patients with early-stage breast cancer (hazard ratio, 0.26; 95% confidence interval, 0.06–1.10; $P = 0.067$). However, the association between diffuse thyroid uptake and breast cancer recurrence was statistically significant in multivariate analysis with adjustment for several prognostic variables (hazard ratio, 0.19; 95% confidence interval, 0.57–0.62; $P = 0.006$). **Conclusion:** Incidental diffuse thyroid uptake related to autoimmune thyroiditis was an independently favorable prognostic factor in advanced breast cancer. These findings support evidence that thyroid autoimmunity has a beneficial effect on the outcomes of breast cancer patients.

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Both breast cancer and thyroid disorders are commonly observed conditions in women all over the world. Many studies provide evidence for a relationship between breast cancer and thyroid disorders. Although the relationship between autoimmune thyroid disorders and breast cancer is not fully understood, some reports have shown that a high prevalence of autoimmune thyroid disorders was found in patients with breast cancer (*1–4*). These findings have led to investigations of the interaction between autoimmune thyroid disorders and breast cancer.

^{18}F-FDG PET CT is a useful imaging modality for detecting recurrences and for monitoring treatment outcome in various cancers, including breast cancer (*5*). In daily practice, incidental thyroid uptake of ^{18}F-FDG in PET/CT is often encountered (*6*). Patients with breast cancer have a relatively high prevalence of this condition (*7*), probably because they have a high prevalence of thyroid disorders (*8,9*). The incidental finding of diffusely increased uptake in the thyroid gland is primarily associated with chronic autoimmune thyroiditis, with or without the presence of hypothyroidism (*10,11*).

Interestingly, previous studies have demonstrated that the presence of autoimmune thyroid disorders is associated with a good prognosis in breast cancer patients (*8,12,13*). Thus, this study was conducted to determine whether incidental diffuse uptake of ^{18}F-FDG in the thyroid may have a good prognostic value in the outcomes of breast cancer patients.

MATERIALS AND METHODS

Patients

A total of 616 patients with both available PET/CT images and thyroid function test results were selected from patients who had undergone surgery for primary breast cancer at Pusan National

University Hospital between January 2006 and December 2009. Of these 616 patients, 52 were excluded because of the following reasons: coexisting papillary thyroid carcinoma ($n = 20$), focal thyroid uptake by benign thyroid nodules on PET/CT ($n = 17$), other concurrent malignancies ($n = 12$: cervical cancer, $n = 3$; lung cancer, $n = 2$; stomach cancer, $n = 2$; sigmoid colon cancer, $n = 2$; malignant lymphoma, $n = 1$; acute myeloid leukemia, $n = 1$; and gastrointestinal stromal tumor, $n = 1$), and death from other combined medical disorders ($n = 3$: hepatic failure, $n = 1$; liver cirrhosis, $n = 1$; and cardiovascular disorder, $n = 1$). Finally, a total of 564 were enrolled in this study. Patients were divided into 2 groups according to the absence or presence of incidental diffuse uptake of ^{18}F-FDG in the thyroid on PET/CT images.

Two surgeons performed all breast surgeries during the study period. Immunohistochemical analyses for the estrogen receptor (ER), progesterone receptor (PR), c-erb-B2 (protooncogene), and p53 were performed using specific monoclonal antibodies. Hormone therapy consisted of an ER antagonist or an aromatase inhibitor. Adjuvant radiotherapy, chemotherapy, and hormone therapy were used to treat patients according to the institution's protocol. Patients were also subdivided into 2 groups: those with early cancer and those with locally advanced (defined by the TNM classification as stages IIB, IIIA, and IIIB) and secondary cancer (*14*).

Patients diagnosed with breast cancer routinely underwent thyroid function tests (free T4 and thyroid stimulating hormone [TSH]) and thyroid autoantibody tests (thyroperoxidase or thyroglobulin antibodies) during the follow-up period after surgery. Serum thyroid autoantibody analyses were performed by radioimmunoassay with a commercial kit (Brahms, for both antithyroperoxidase and antithyroglobulin). The analytic sensitivities of the assays for antithyroperoxidase and antithyroglobulin antibodies were 5.5 and 5.5 IU/mL, respectively, and the intraassay coefficients of variation ranged from 2.9% to 4.5% and from 2.0% to 7.5%, respectively. The reference ranges for thyroperoxidase and thyroglobulin antibodies were less than 60 IU/mL each. If patients with breast cancer had an abnormal result in their thyroid function tests (TSH, either <0.3 or >5.0 mIU/L; or free T4, either <0.8 or >2.1 ng/dL) or PET/CT, they were routinely referred to the thyroid clinic and underwent thyroid ultrasonography or cytologic investigation. Thyroid ultrasonography was performed with a scanner (HDI 5000 [Philips] or Vivid *I* [GE Healthcare]) equipped with a 10- to 13-MHz linear probe. The ultrasonography examination was performed by 3 endocrinologists according to their schedule during the study period. The ultrasonography features of chronic (autoimmune) thyroiditis include fibrous, enlarged, and lobulated glands with ill-defined hypoechoic heterogeneous areas or micronodulation (*15*). Hypothyroidism (overt or subclinical) was defined as previous prescription of thyroid hormone or a TSH level of more than 5.0 mIU/L. Positivities for the 2 thyroid autoantibodies were defined as a thyroperoxidase antibody of at least 60 U/mL and a thyroglobulin antibody of at least 60 U/mL. Thyroid dysfunctions related to chronic autoimmune thyroiditis were defined as a positivity for either thyroperoxidase antibody or thyroglobulin antibody, cytologic confirmation of Hashimoto thyroiditis, or ultrasonography findings of chronic thyroiditis.

Physical examination was regularly performed on all patients during the follow-up period. The imaging studies for the detection of recurrence or metastasis of breast cancer were routinely performed in all patients every 6–12 mo after treatment. Mammography, ultrasonography of the breasts and abdomen, bone scanning, chest radiography or CT, and PET/CT were performed at the time of each imaging study for recurrence or metastasis of breast cancer. Recurrence was defined as the reappearance of disease after treatment and was confirmed by cytologic or histopathologic examination or by a suggestive lesion in imaging studies. The endpoint of the analysis was disease-free survival (DFS). DFS was defined as the length of time from the first operation until the event of recurrence or metastasis, or if no event occurred, until the last follow-up visit to our hospital. This study was approved by the Institutional Review Board of Pusan National University Hospital, and each patient gave informed consent to participate in the study.

^{18}F-FDG PET/CT Analysis

^{18}F-FDG PET/CT images were obtained with a dedicated PET/CT scanner (Gemini; Philips) consisting of a dedicated germanium oxyorthosilicate full-ring PET scanner and a dual-slice helical CT scanner. Standard patient preparation included at least 8 h of fasting and a serum glucose level of less than 120 mg/dL before ^{18}F-FDG administration. PET/CT was performed 60 min after injection of ^{18}F-FDG (mean dose ± SD, 383.7 ± 47.4 MBq; range, 314.5–488.4 MBq). After this administration of ^{18}F-FDG, low-dose CT (30 mAs, 120 kV) covering the area between the base of the skull and the proximal thighs was performed for the purpose of attenuation correction and precise anatomic localization. Thereafter, an emission scan was obtained in 3-dimensional mode. The emission scan time per bed position was 3 min, and 9 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 in full width at half maximum in the center and 5.6 mm at 10 cm. The average total PET/CT examination time was 30 min. 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 3-dimensional reconstruction.

^{18}F-FDG PET/CT images were reviewed by *2* experienced nuclear physicians on a workstation (Extended Brilliance Workstation; Philips) as maximum-intensity-projection coronal, sagittal, and axial images, both visually and quantitatively. Findings were recorded by consensus. A third reviewer was assigned to resolve differences in visual interpretation. The nuclear physicians were masked to all other clinical and imaging information. In ^{18}F-FDG PET/CT images, thyroid uptake was considered present when there was increased uptake in the thyroid gland above the physiologic background level (below or above the level of liver uptake). Diffuse thyroid uptake was defined as uniform distribution of the tracer above the background level throughout both lobes. To calculate maximal standardized uptake values (SUV_{max}), manually defined regions of interest were drawn over both lobes, with the higher of the 2 values used in the analyses.

Statistical Analysis

All statistical analyses were performed using SPSS (version 15.0; SPSS, Inc.). Continuous data are expressed as mean ± SD for normally distributed values and median and interquartile range for nonparametric values. The independent 2-sample *t* test was used to compare 2 independent groups. Categoric variables were compared using the χ^2 test. DFS was evaluated with the Kaplan–Meier method after surgery. Comparison of the overall DFS between the 2 groups was examined using the log-rank test in univariate analysis. Variables with a *P* value of less than 0.2 in univariate analysis were included in multivariate analysis. A Cox proportional hazards model and the forward stepwise method were used to analyze various prognostic factors for DFS in multivariate analysis. The relative importance of prognostic factors was presented

as hazard ratios (HRs) and 95% confidence intervals (95% CIs), which were calculated using binomial disturbance. A P value of less than 0.05 derived from the 2-tailed test was considered statistically significant.

RESULTS

Baseline Patient Characteristics

The mean age was 49.5 ± 10.5 y (range, 22–88 y). A unilateral tumor accounted for 97.2% of all breast malignancies (n = 548). Breast cancer patients were staged according to the TNM classification. There were 23 patients with stage 0 (4.1%), 186 with stage I (32.9%), 230 with stage II (40.8%), 106 with stage III (18.8%), and 19 with stage IV (3.4%). There were 368 patients with early cancer (65.1%) and 196 patients with locally advanced or secondary cancer (34.9%).

Of the 564 patients, 108 (19.1%) showed diffuse thyroid uptake on preoperative or postoperative PET/CT. Table 1 summarizes the baseline characteristics of patients with and without diffuse thyroid uptake on PET/CT images. There were no differences between the 2 groups in age, body mass index, tumor pathologic characteristics, tumor stage, and treatment modalities. However, patients with thyroid uptake did not have statistically lower frequencies of lymphovascular invasion than those without (25.9% vs. 38.2%, P = 0.053).

The serum free T4 levels did not significantly differ between the 2 groups (P = 0.234) (Table 2). Serum TSH levels were higher in patients with thyroid uptake than in those without (2.19 vs. 1.64 mIU/L; P = 0.001). Both thyroperoxidase and thyroglobulin antibody titers were higher in patients with thyroid uptake than in those without (50.4 vs. 17.4 U/mL, $P < 0.001$; and 66.1 vs. 19.0 U/mL, $P < 0.001$, respectively). Significantly higher prevalences of positivity for autoantibodies (thyroperoxidase and thyroglobulin antibodies) were found in patients with thyroid uptake than in those without (49.1% vs. 3.6%, $P < 0.001$; and 54.5% vs.

TABLE 1
Clinicopathologic Features According to Diffuse Thyroid Uptake

Variable	Total patients (n = 564)	Diffuse thyroid uptake		P
		Presence (n = 108)	Absence (n = 456)	
Age (y)	49.5 ± 10.5	48.4 ± 8.7	49.9 ± 10.9	0.120
BMI (kg/m^2)	23.2 ± 3.0	23.1 ± 2.7	23.2 ± 3.0	0.645
Nuclear grade				
1 and 2	325 (57.6)	61 (56.5)	264 (57.9)	0.795
3	229 (40.6)	45 (41.7)	184 (40.3)	
Unknown	10 (1.8)	2 (1.8)	8 (1.8)	
Lymphovascular invasion				
Presence	187 (33.2)	28 (25.9)	159 (38.2)	0.053
Unknown	21 (3.7)	2 (1.8)	19 (4.2)	
Necrosis				
Presence	212 (37.6)	38 (35.2)	174 (38.2)	0.504
Unknown	16 (2.8)	2 (1.8)	14 (3.1)	
ER				
Positivity	378 (67.0)	71 (65.7)	307 (67.3)	0.731
Unknown	1 (0.2)	0 (0)	1 (0.2)	
PR				
Positivity	351 (62.2)	65 (60.2)	286 (62.7)	0.606
Unknown	4 (0.7)	0 (0)	4 (0.9)	
C-erb-B2				
Positivity	146 (25.9)	29 (26.9)	117 (25.7)	0.808
Unknown	1 (0.2)	0 (0)	1 (0.2)	
p53				
Positivity	149 (26.4)	35 (32.4)	114 (25.0)	0.129
Unknown	4 (0.7)	0 (0)	4 (0.9)	
Stage				0.569
Early	368 (65.2)	73 (67.6)	295 (80.2)	
Locally advanced or secondary	196 (34.8)	35 (32.4)	161 (35.3)	
Operation method				0.201
BCS	378 (67.0)	78 (72.2)	300 (65.8)	
MRM	186 (33.0)	30 (27.8)	156 (34.2)	
Chemotherapy	525 (93.1)	104 (96.3)	421 (92.3)	0.144
Radiotherapy	301 (53.4)	55 (50.9)	246 (53.9)	0.571
Hormone therapy	366 (64.9)	68 (63.0)	298 (65.4)	0.640

Data are expressed as mean ± SD for continuous variables and frequency, with percentages in parentheses, for categoric variables.
BCS = breast conserving surgery; BMI = body mass index; MRM = modified radical mastectomy.

TABLE 2
Characteristics of Thyroid Function According to Diffuse Thyroid Uptake

Variable	Total patients (n = 564)	Diffuse thyroid uptake		P
		Presence (n = 108)	Absence (n = 456)	
Free T4 (ng/dL)	1.32 (1.17–1.52)	1.30 (1.14–1.55)	1.33 (1.17–1.51)	0.234
TSH (mIU/L)	1.70 (1.11–2.67)	2.19 (1.12–4.92)	1.64 (1.10–2.50)	0.001
Thyroperoxidase antibody (U/mL)	18.4 (12.9–25.7)	50.4 (17.4–1268.1)	17.4 (12.7–22.7)	<0.001
Thyroperoxidase antibody				
Positivity	69 (12.6)	53 (49.1)	16 (3.6)	<0.001
Unknown	16 (2.8)	0 (0)	16 (3.5)	
Thyroglobulin antibody (U/mL)	21.6 (14.8–36.9)	66.1 (25.5–135.9)	19.0 (14.3–27.7)	<0.001
Thyroglobulin antibody				
Positivity	86 (15.6)	58 (54.5)	28 (6.3)	<0.001
Unknown	14 (2.5)	1 (0.9)	13 (2.9)	
Hypothyroidism*	55 (9.6)	38 (35.2)	17 (3.7)	<0.001

*Defined as previous prescription of thyroid hormone or TSH level greater than 5.0 mIU/L.

Data are expressed as median, with interquartile range in parentheses, for continuous variables and frequency, with percentage in parentheses, for categoric variables.

T4 = thyroxine.

6.3%, $P < 0.001$, respectively). Overt or subclinical hypothyroidism was diagnosed in 38 patients with thyroid uptake and 17 patients without (35.2% vs. 3.7%, $P < 0.001$).

DFS for Breast Cancer

The median follow-up period was 36.0 mo (range, 1.0–77.0 mo). Of the 108 patients with thyroid uptake, 5 (4.6%) had a recurrence of breast cancer during the follow-up period, whereas 85 (18.6%) without thyroid uptake had a recurrence (log-rank statics, 12.28; $P < 0.001$) (Fig. 1). The DFS was evaluated according to the ER and PR status. In patients who were ER-positive (ER+), DFS was significantly longer in patients with thyroid uptake than in those without (log-rank statistics, 8.17; $P = 0.004$). In patients who were ER-negative (ER–), DFS was also significantly longer in patients with thyroid uptake than in those without (log-rank statistics, 5.92; $P = 0.015$). In patients who were PR-positive (PR+), DFS was significantly longer in patients with thyroid uptake than in those without (log-rank statistics, 9.67; $P = 0.002$). In patients who were PR-negative (PR–), DFS was significantly longer in patients with thyroid uptake than in those without (log-rank statistics, 4.76; $P = 0.029$).

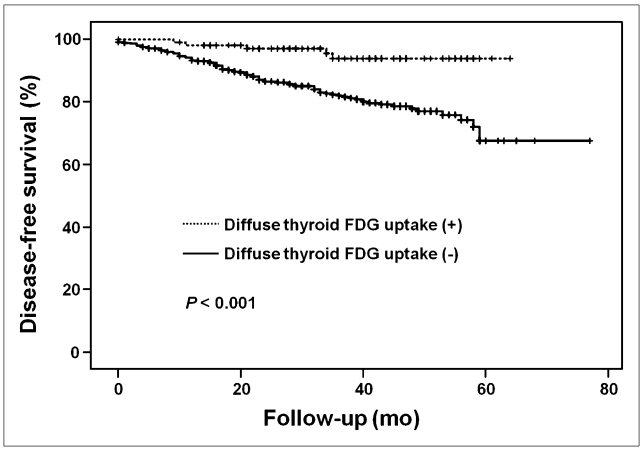

FIGURE 1. DFS of patients with breast cancer according to absence or presence of diffuse thyroid uptake. Survival rate was calculated using Kaplan–Meier method with log-rank test in patients with recurrences.

DFS was also evaluated in terms of tumor stage (early vs. locally advanced and secondary breast cancer). In patients with early-stage cancer, DFS was not significantly different between the 2 groups according to thyroid uptake (log-rank statistics, 3.69; $P = 0.055$) (Fig. 2A). However, in patients with locally advanced and secondary cancer, DFS was significantly longer in patients with thyroid uptake than in those without (log-rank statistics, 9.05; $P = 0.003$) (Fig. 2B).

The Cox proportional regression model was used to analyze the prognostic significance of several variables measured at baseline. In patients with early cancer, nuclear grade, lymphovascular invasion, necrosis, and hormonal receptor status were significantly associated with recurrence and persistent disease in univariate analysis ($P = 0.018$, $P < 0.001$, $P = 0.002$, and $P < 0.001$, respectively) (Table 3). Lymphovascular invasion (HR, 2.76; 95% CI, 1.36–5.62; $P = 0.005$) and hormonal receptor status (ER–/PR–: HR, 2.86; 95% CI, 1.22–6.70; $P = 0.016$) showed an independent association with recurrence and persistent disease in multivariate analysis. The association of diffuse thyroid ^{18}F-FDG uptake with tumor recurrence was not significant in multivariate analysis in patients with early cancer (presence of thyroid ^{18}F-FDG uptake: HR, 0.26; 95% CI, 0.06–1.10; $P = 0.067$) (Table 3). In patients with locally advanced and secondary cancer, vascular invasion, necrosis, hormonal receptor status, and diffuse thyroid uptake were significantly associated with tumor recurrence in univariate analysis ($P = 0.006$, $P = 0.020$, $P = 0.002$, $P = 0.023$, and $P = 0.003$, respectively) (Table 4). Lymphovascular

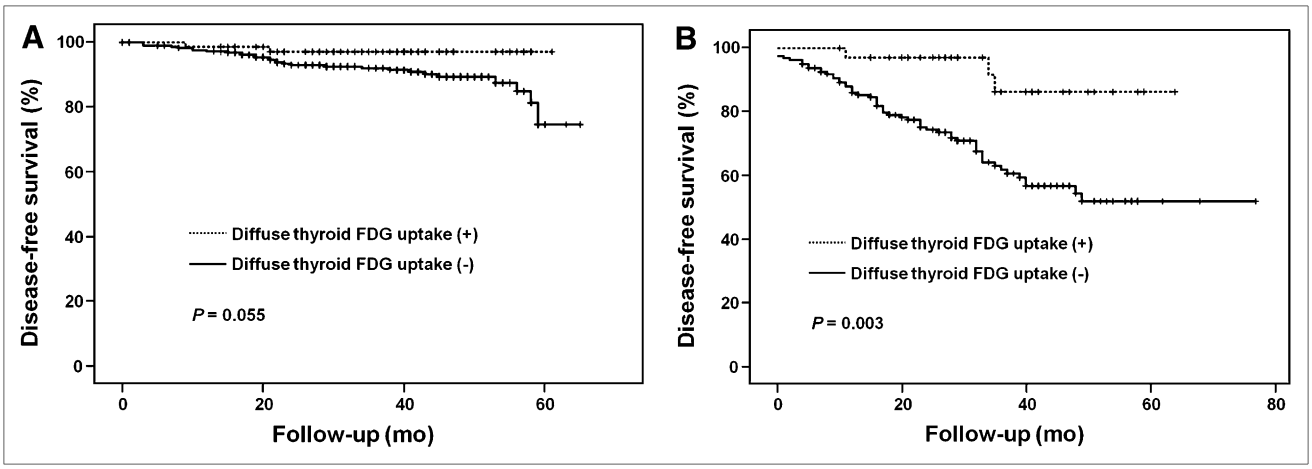

FIGURE 2. DFS of breast cancer patients with and without diffuse thyroid uptake according to tumor stage (early stage [A] and locally advanced and secondary cancer stage [B]).

invasion (HR, 1.87; 95% CI, 1.00–3.50; $P = 0.049$) and hormonal receptor status (ER–/PR–: HR, 2.68; 95% CI, 1.36–5.28; $P = 0.005$) showed an independent association with recurrence in multivariate analysis. In addition, the association between diffuse thyroid ^{18}F-FDG uptake and breast cancer recurrence was statistically significant in multivariate analysis after adjustment for several prognostic variables (presence of thyroid ^{18}F-FDG uptake: HR, 0.19; 95% CI, 0.57–0.62; $P = 0.006$) (Table 4).

Thyroid Abnormalities in Patients with Diffuse Thyroid ^{18}F-FDG Uptake

Diffuse thyroid uptake of ^{18}F-FDG was identified in both thyroid lobes in 99 (91.7%) of all patients with uptake, whereas it was observed in 1 thyroid lobe in 9 patients (8.3%). The median SUV_{max} of patients with diffuse thyroid uptake was 3.2 (range, 2.6–4.4). The SUV_{max} positively correlated with the presence of both thyroperoxidase and thyroglobulin antibodies ($r = 0.490$, $P < 0.001$; and $r = 0.250$, $P < 0.001$, respectively). Of the patients with diffuse thyroid uptake, 102 (94.4%) exhibited more than one of the thyroid abnormalities of chronic autoimmune thyroiditis based on tests performed after identification of thyroid uptake. There were 78 patients who were positive for thyroperoxidase or thyroglobulin antibodies. There were 28 patients who had cytologic findings of Hashimoto thyroiditis and 87 patients who had ultrasonography findings of Hashimoto thyroiditis.

DISCUSSION

This study found that incidental diffuse thyroid uptake of ^{18}F-FDG on PET/CT images preoperatively or postoperatively was independently associated with low tumor recurrence in patients with advanced breast cancer. Clinicians often encounter these incidental findings on PET/CT images during the follow-up in patients with breast cancer

TABLE 3
Univariate and Multivariate Analysis for Tumor Recurrence in Patients with Early-Stage Breast Cancer

Variable	Univariate analysis			Multivariate analysis		
	Log-rank statistics	df	*P*	HR	95% CI	*P*
Age, ≥50 y	0.75	1	0.386	–		–
BMI, ≥25 kg/m^2	0.21	1	0.651	–		–
Nuclear grade, 3	5.64	1	0.018	1.19	0.55–2.55	0.664
Lymphovascular invasion, presence	13.38	1	<0.001	2.76	1.36–5.62	0.005
Necrosis, presence	9.92	1	0.002	2.08	0.96–4.53	0.065
Hormonal receptor status	16.92	3	0.001			
ER+/PR+				1.00		
ER+/PR–				1.19	0.26–5.51	0.829
ER–/PR+				0.43	0.05–3.75	0.447
ER–/PR–				2.86	1.22–6.70	0.016
C-erb-B2, positivity	0.51	1	0.477	–		–
p53, positivity	1.68	1	0.195	1.37	0.62–3.01	0.434
Diffuse thyroid ^{18}F-FDG uptake, presence	3.69	1	0.055	0.26	0.06–1.10	0.067

BMI = body mass index.

TABLE 4
Univariate and Multivariate Analysis for Tumor Recurrence in Patients with Locally Advanced and Secondary Cancer Stage

Variable	Univariate analysis			Multivariate analysis		
	Log-rank statistics	df	*P*	HR	95% CI	*P*
Age, ≥50 y	1.67	1	0.197	1.61	0.91–2.85	0.104
BMI, ≥25 kg/m^2	2.71	1	0.099	0.54	0.28–1.04	0.066
Nuclear grade, 3	1.07	1	0.300	–		–
Lymphovascular invasion, presence	7.7	1	0.006	1.87	1.00–3.50	0.049
Necrosis, presence	5.4	1	0.020	0.97	0.51–1.85	0.932
Hormonal receptor status	9.51	3	0.023			
ER+/PR+				1.00		
ER+/PR–				1.78	0.70–4.52	0.223
ER–/PR+				2.56	0.75–8.79	0.132
ER–/PR–				2.68	1.36–5.28	0.005
C-erb-B2 positivity	0.94	1	0.333	–		–
p53 positivity	3.56	1	0.059	1.26	0.71–2.24	0.425
Diffuse thyroid uptake	9.05	1	0.003	0.19	0.57–0.62	0.006

BMI = body mass index.

(Fig. 3). Other causes of thyroid uptake, such as benign and malignant thyroid tumors, were excluded from the study, and diffuse thyroid uptake was related to chronic autoimmune thyroiditis with high prevalences of thyroid autoantibodies and thyroid dysfunction. To the best of our knowledge, there have been no other studies evaluating the prognostic value of incidental diffuse thyroid uptake of ^{18}F-FDG in patients with breast cancer. Our study results are consistent with those of previous studies that indicated that thyroid autoimmune changes have a good prognostic value in patients with breast cancer.

Various causes of diffuse thyroid uptake have been reported (*16*). Accumulation of ^{18}F-FDG in normal thyroid tissue is usually low to absent because free fatty acids are preferred substrates for the thyroid gland (*17*). Diffuse thyroid uptake is generally regarded as benign and results from inflammatory etiologies, such as thyroiditis (*18*). Fibroblast infiltration also leads to continuous uptake of ^{18}F-FDG after treatment in patients with chronic thyroiditis (*10*). Tateishi et al. (*7*) reported that diffuse thyroid uptake in patients with advanced breast cancer represents active inflammation caused by chronic thyroiditis. In our study, focal or diffuse thyroid uptake caused by benign or malignant thyroid tumors was excluded. In addition, 94.4% of the patients with diffuse thyroid uptake met the requirements for chronic autoimmune thyroiditis.

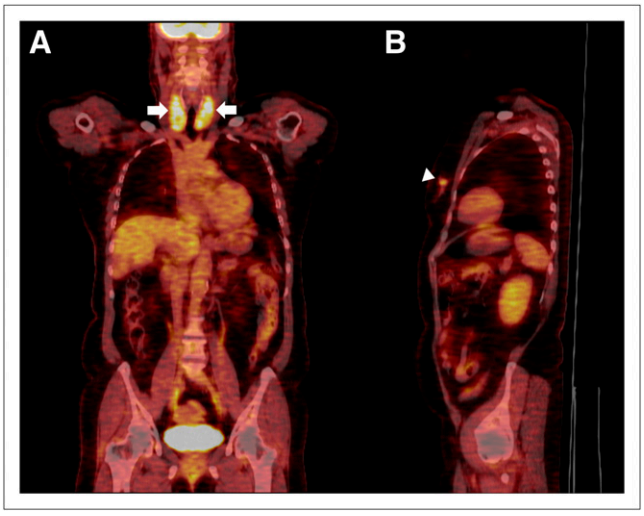

FIGURE 3. A 66-y-old woman with breast cancer. Preoperative ^{18}F-FDG PET/CT showed diffuse ^{18}F-FDG uptake in both thyroid lobes (arrows; SUV_{max}, 9.3) (A) and focal uptake in left breast mass (arrowhead; SUV_{max}, 3.9) (B).

Although diffuse thyroid uptake was associated with a beneficial effect on tumor recurrence in all patients, we stratified the patients according to tumor stage such as early and advanced stage, because the TNM classification represents important factors for prognosis in breast cancer. In locally advanced and secondary cancer, diffuse thyroid uptake was independently associated with tumor recurrence, whereas this association was lost in early breast cancer. ER and PR status are usually considered good predictors for prognosis in patients with breast cancer. Diffuse thyroid uptake was an independent prognostic factor after stratifying or adjusting for ER and PR status in this study. Diffuse thyroid uptake was not associated with ER and PR status in breast cancer. The results coincide with those of previous studies that reported no significant relationship of ER and PR status to the presence of serum thyroid antibodies (*1,15*).

Previous studies have shown that thyroid autoimmunity is associated with a significant improvement in the outcome of breast cancer patients (*8,14,15*), which is consistent with our results. An extensive retrospective study of 9,520 patients with breast cancer has suggested that the survival

rate is higher in breast cancer patients with autoimmune thyroid disorders than in those with healthy thyroid glands (*14*). It has been suggested that both thyroperoxidase antibody and thyroid volume are independently associated with prognosis in breast carcinoma (*8*). The concomitant status of ER and thyroid antibodies is an important factor for survival in highly aggressive breast cancer (*15*).

It has been hypothesized that thyroid antibodies exert an effect on the breast and the thyroid gland. Although thyroid autoantibodies, such as thyroperoxidase antibody, have been shown to be an important factor in antibody-dependent cell cytotoxicity in the thyroid (*19*), such evidence does not exist for the breast. The other possible beneficial effects may be ascribed to iodine on the basis of antioxidant mechanisms. IgG-mediated ^{125}I-uptake inhibition has been observed in patients with breast cancers, and the presence of ^{125}I uptake inhibition positively correlates with positivity for thyroperoxidase antibody in patients with breast cancer (*20*). A probable interconnection between the thyroid and breast is based on the ability of the thyroid and mammary glands to concentrate iodine through the membrane transport process (*1*). Breast cancer cells share some antigenic properties with thyroid tissue, such as sodium iodide symporter and peroxidase activity (*21*). However, because the presence of humoral or clinical evidence of thyroid autoimmunity is not associated with autoimmune morphologic changes in cancerous and peritumoral normal tissue, lymphocytic infiltration does not seem to play any role in tumorigenesis in patients with both breast cancer and thyroid autoimmunity (*22*).

Our results provide indirect evidence that other types of cancer also have significant associations between their prognosis and thyroid autoimmunity. The appearance of autoantibodies and clinical signs of autoimmunity are strongly associated with improved relapse-free and overall survival in patients with melanomas who are receiving interferon therapy (*23*). Our results support the result of a previous study by Kim et al. (*24*), which indicated that there is an association between the coexistence of chronic autoimmune thyroiditis and the good prognosis of differentiated thyroid cancer. However, the risk of papillary thyroid carcinoma is higher in patients with chronic autoimmune thyroiditis than in those without (*25*).

There were some different findings inconsistent with our results in regard to the relationship between thyroid autoimmunity and the good prognosis of breast cancer. The presence of autoimmune thyroid disease or thyroid autoantibodies (antithyroperoxidase or antithyroglobulin antibodies) does not influence relapse-free and overall survival in patients with breast cancer (*26*). The number of metastatic lymph nodes, vascular invasion, and tumor size significantly increase in breast cancer patients with thyroid disease (*27*). Kuijpen et al. (*28*) have reported that hypothyroidism is related to an increased risk of breast cancer, although the presence of thyroperoxidase antibody is not associated with the development of new breast carcinoma. However, primary hypothyroidism is associated with both a reduced risk of primary breast cancer and more indolent invasive disease (*9*). In our study, hypothyroidism was not associated with tumor recurrence in both early and advanced breast cancers.

The results of this study are subject to some limitations. First, thyroid ultrasonography was not performed to confirm chronic autoimmune thyroiditis for all patients without diffuse uptake of ^{18}F-FDG. Thus, we could not compare the prevalence of chronic autoimmune thyroiditis according to definite criteria between the 2 groups. We previously reported that diffuse thyroid uptake developed in breast cancer patients who showed no thyroid uptake before any treatments, including radiation (*29*). Thus, diffuse ^{18}F-FDG uptake may occur in reaction to the treatment of breast cancer or to a long-standing autoimmune disease. In our study, newly developed diffuse thyroid uptake had relatively less effect on prognosis because of a short duration of autoimmune disease. Second, diffuse thyroid uptake may not be a prognostic factor because this parameter is merely indicative of the presence of autoimmune thyroid disease. Despite these limitations, it is notable that incidental diffuse thyroid uptake on ^{18}F-FDG PET/CT scans is often encountered during the follow-up period after treatment of breast cancer.

CONCLUSION

The results of this study confirm the association between incidental diffuse thyroid uptake of ^{18}F-FDG related to autoimmune thyroiditis and a low tumor recurrence in advanced breast cancer. This incidental finding on PET/CT scans is often observed in clinical practice during the follow-up period in patients with breast cancer. Therefore, it is necessary to confirm whether this finding is related to autoimmune thyroiditis and whether it can be considered a prognostic factor in breast cancer. Because conflicting findings also exist, further study is needed to determine the molecular and immunologic mechanisms involved.

DISCLOSURE STATEMENT

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

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