Clinical Impact of ^{18}F-FDG PET in Thyroid Carcinoma Patients with Elevated Thyroglobulin Levels and Negative ^{131}I Scanning Results After Therapy

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^{18}F-FDG PET has been shown to effectively detect differentiated thyroid carcinoma (DTC) metastases with impaired iodine-trapping ability. This article evaluates the potential contribution of FDG PET in the follow-up of patients with differentiated thyroid carcinoma, elevated thyroglobulin (Tg) levels, and negative whole-body scan results obtained after high doses of ^{131}I. **Methods:** We prospectively assessed the ability of FDG to detect metastases in 37 DTC patients who had undergone total thyroidectomy and radioactive ablation and presented with persistent disease, as assessed from elevated Tg levels and negative results of whole-body scans performed after therapeutic doses of ^{131}I. Additional conventional imaging procedures were performed to detect residual disease, and the patients were divided into 2 groups: group 1, with positive conventional imaging findings (n = 10), and group 2, with negative conventional imaging findings (n = 27). **Results:** FDG PET showed positive findings in 28 patients and accurately localized tumor sites in 89% of them. In group 1, FDG PET confirmed 17 of 18 previously known tumor sites and detected 11 additional sites. In group 2, FDG PET findings were positive in 19 of 27 patients with no previously detected metastases. PET was effective for both low- and high-stage tumors. The FDG data led to a change in the clinical management of 29 of 37 patients with further surgical resection in 23 patients, 14 of whom achieved disease-free status, and external radiation therapy in 4 patients. **Conclusion:** FDG PET is able to detect metastases undetected by ^{131}I posttherapy whole-body scanning in patients with elevated Tg levels. It should be proposed as a first-line investigation in patients with persistent disease but negative findings on ^{131}I whole-body scans after treatment.

Key Words: FDG PET; differentiated thyroid carcinoma; ^{131}I posttherapy scan

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During the follow-up of patients with differentiated thyroid carcinoma (DTC) treated by total thyroidectomy and radioactive iodine (RAI) ablation therapy, an elevated serum thyroglobulin (Tg) concentration is a sensitive marker indicating persistent or recurrent disease (*1*). Elevated serum Tg concentration is usually associated with positive ^{131}I whole-body scan findings (*2*,*3*). However, some patients have true metastases that do not concentrate ^{131}I, even when it is given in therapeutic doses (*4*). Metastases unable to concentrate ^{131}I are often associated with aggressive clinical behavior (*5*,*6*) and must be thoroughly assessed. Morphologic imaging procedures, which include sonography, CT, MRI, or nuclear imaging procedures to detect and localize lesions, can be used to propose the most appropriate therapeutic options. The use of ^{18}F-FDG for PET has recently been established as an important new noniodine radionuclide imaging tool in clinical oncology (*7*). Several studies have shown that, in differentiated thyroid carcinoma, FDG PET can be used to detect recurrence or metastases with a high degree of sensitivity (80%–90%), which is especially valuable for those that do not take up RAI (*8*–*12*). The purpose of this study was to assess the clinical impact of FDG PET on the management of the few patients with differentiated thyroid carcinoma who had elevated Tg levels and negative ^{131}I whole-body scan results obtained after therapeutic doses of ^{131}I.

MATERIALS AND METHODS

Patients

Thirty-seven patients (19 men, 18 women; age range, 27–78 y; mean age, 50.2 y) with pathologically proven DTC, negative ^{131}I whole-body scan results after treatment, and elevated Tg levels were prospectively and consecutively submitted to FDG PET evaluation at our hospital. The initial treatment of the thyroid carcinomas, which consisted of total thyroidectomy followed by

^{131}I therapy (3.7 GBq) for the ablation of thyroid remnants, had been performed at various hospitals. Thirty of the 37 patients had undergone lymph-node dissection. During follow-up, the patients had received 1–6 therapeutic doses of ^{131}I to treat persistent or recurrent disease, with an average cumulative dose of 10.2 GBq ^{131}I and with a maximum cumulative dose of 22.2 GBq. Five patients had also required 3 successive cervical lymph node dissections and another 2 were submitted to external neck radiotherapy. The pathologic findings consisted of papillary thyroid carcinoma in 26 patients and follicular thyroid carcinoma in 11 patients, including 4 Hürthle-cell carcinomas. The clinical and pathologic staging was performed according to the American Joint Committee on Cancer and represents the highest stage reached during follow-up before FDG PET evaluation. The pathologic tumor stages were as follows: T1 in 2 patients, T2 in 5 patients, T3 in 12 patients, and T4 in 18 patients; the clinical stages were as follows: 15 stage I, 2 stage II, 16 stage III, and 4 stage IV patients (*13*). All patients gave written informed consent to participate in the study as required by the hospital's ethics committee and those with diabetes mellitus were not included.

^{131}I Whole-Body Scan After Therapy

Because of an increase in Tg levels during thyroid-stimulating hormone (TSH) suppression, a therapeutic dose of ^{131}I was given to each patient 4 wk after L-thyroxine withdrawal (it was the second dose for 1 patient, the third for 20, the fourth for 9, the fifth for 6, and the sixth for 1 patient). Consequently, whole-body scanning was performed 4–5 d after the therapeutic dose of 3.7 GBq ^{131}I, using a dual-head large-field gamma camera equipped with a high-energy collimator. Whole-body scan results were negative in all patients: no clear focus of abnormal iodine uptake was observed by visual inspection after checking for the absence of iodine contamination.

Tg and Antithyroglobulin Antibody Measurement

Blood samples for measuring serum Tg and anti-Tg antibody were taken during L-thyroxine withdrawal at the time of the whole-body scan and during suppression therapy. Using a commercial kit (BioRad Tg, Pasteur, France; and Dynotest antiTgn, Brahms, France) Tg and anti-Tg levels were determined by radioimmunoassay. Serum Tg levels were classified as abnormal if values >1 μg/L were found during TSH suppression or >10 μg/L were found during TSH stimulation. Tg antibody test results were negative in all patients.

Conventional Imaging

Additional conventional imaging (CI) procedures, including chest x-rays (all patients), neck sonography (all patients), thoracic CT ($n = 28$), MRI ($n = 6$), and bone scintigraphy ($n = 8$) performed after the negative whole-body scan results were obtained. To assess the role of FDG PET as an imaging strategy for patients with negative ^{131}I posttherapy scan results, the patients were divided in 2 groups: group 1, which consisted of 10 patients with positive CI results, and group 2, which consisted of 27 patients with negative CI findings.

FDG PET Imaging

All patients underwent FDG PET imaging during thyroxine therapy <3 mo after the negative posttherapy whole-body scan. The PET scan was performed 50–60 min after injection of 370 MBq FDG (after a fasting period of 12 h). PET data were obtained using an ECAT EXACT HR+ high-resolution whole-body scanner (Siemens-CTI, Knoxville, TN) with an axial field of view of 15.5 cm. All scanning was performed in 3-dimensional mode. The average axial resolution varied between 4.1-mm full width at half maximum in the center and 7.8 mm at 20 cm. Emission scanning was performed from the head to the femur for 7 min at each bed position. Images were reconstructed using filtered backprojection with a Hanning filter and a cutoff frequency of 0.4. No attenuation correction was applied and the total scanning time was approximately 1 h. Transaxial, sagittal, and coronal images were examined on a computer display monitor. Scans were interpreted independently by 2 experienced physicians blinded to the clinical situation and any disagreement was resolved by consensus. A visually abnormal focus of FDG uptake was defined as a focal uptake relatively higher than that of surrounding tissue with no similar activity seen in the contralateral side of the body. Lung metastases were arbitrarily classified as multiple if >4 sites were detected.

Statistical Analysis

Tumor detection rates were expressed as the percentage of patients with positive sites and compared using χ^2. The threshold of significance was set at 0.05.

RESULTS

FDG PET findings were positive in 28 of the 37 patients (76%) and CI findings were positive in 10 patients (27%), as summarized in Tables 1 and 2.

In the 10 patients in group 1 (Table 1), FDG confirmed 17 of 18 known tumor sites and detected an additional 11 sites. PET scanning detected cervical and mediastinal lymph nodes in 5 patients and distant metastases (lung and bone) in 5 patients. FDG imaging failed to detect a cervical lymph node metastasis in 1 patient. This was removed surgically and confirmed by histopathology. Figure 1 illustrates the case of patient 5, who was known to have lung metastases from Hürthle-cell carcinoma; FDG PET identified multiple lung metastases and an unknown mediastinal lymph node metastasis.

FDG results were positive in 19 of the 27 patients in group 2 and scanning identified 44 tumor sites (Table 2) affecting the following tissues: neck ($n = 14$ patients), mediastinum ($n = 2$), lung ($n = 3$), and bone ($n = 2$). FDG scanning results were negative in 8 patients. Figure 2 illustrates the case of patient 27, who had persistent papillary carcinoma disease despite total thyroidectomy, 2 therapeutic doses of ^{131}I, and 2 cervical lymph node dissections. FDG detected 2 cervical lymph node metastases, despite negative sonography findings, that were surgically removed and pathologically confirmed.

Overall, 9 cases of follicular carcinoma, including the 4 Hürthle-cell carcinomas, and 15 of 26 papillary carcinomas had positive PET findings. There was no statistical difference between the 2 groups with regard to FDG results ($P > 0.05$). For all types of cancer, the detection rate was significantly higher for stages III and IV (80%) than for stages I and II (47%) ($P < 0.05$). Malignancy was confirmed in 24 patients by biopsy (4 patients) or surgery (20 patients). In 2 patients, metastatic disease was assessed by repeated sonog-

TABLE 1
Patients with Positive CI Findings

Patient no.	Sex	Age (y)	H	PT	Stage	TCD (GBq)	TSH* on T_4	Tg† on T_4	TSH* off T_4	Tg† off T_4	CI findings (*n*)	FDG PET results (*n*)	Histo-pathology	FU TSH*	FU Tg†
1	F	70	P	T4	III	7.4	1.5	950	170	2,700	Lung on CT (+)	Lung (+)	Positive (B)	0.8	800 (Ext rad)
2	M	69	P	T4	III	7.4	2.1	1,820	110	5,100	Lung on CT (+)	Lung (+)	Positive (B)	0.24	2,200 (Ext rad)
3	M	60	FC	T4	III	7.4	0.64	12	81	48	Lung on CT (1)	Lung (2)	Positive (S)	0.11	<0.6
4	F	63	FC	T4	III	14.8	ND	21	>50	100	Doubtful on CT	Lung (+), CLN (2)	ND	0.6	50 (Ext rad)
5	F	64	HC	T4	III	3.7	0.01	869	141	6,000	Lung on CT (+)	Lung (+), MLN (1)	Positive (B)	<0.01	1,783
6	M	78	P	T4	III	7.4	0.11	29	>50	176	CLN on US, MRI (1)	CLN (3)	Positive (S)	ND	Deceased
7	M	65	HC	T3	IV	7.4	0.05	30	99	128	Bone on BS, MRI (1)	Bone (1)	Positive (S)	<0.05	0.5
8	F	45	P	T4	III	7.4	0.66	2.5	>50	15	CLN on US, CT (1)	CLN (1)	Positive (S)	0.02	<0.6
9	M	36	P	T2	I	11.1	0.2	2	>50	153	CLN on US (1)	Negative	Positive (S)	0.03	<0.3
10	M	38	P	T4	I	7.4	<0.1	5.2	>50	30	CLN on US, CT (1)	CLN (2)	Positive (S)	0.5	<0.3

*Data in mU/L.
†Data in μg/L.
H = histology of thyroid carcinoma; PT = primary tumor stage; TCD = total cumulative dose; T_4 = L-thyroxine; FU = follow-up; P = papillary carcinoma; + = multiple; B = biopsy; Ext rad = external radiation; FC = follicular carcinoma; S = surgery; ND = not done; CLN = cervical lymph node; HC = Hürthle-cell carcinoma; MLN = mediastinal lymph node; US = sonography; BS = bone scintigraphy.

raphy and CT or MRI. The PET findings led to a change in the management of 29 patients. Twenty-three patients underwent surgery for removal of a residual tumor, and the disease was pathologically confirmed in 20 of them. Fourteen of these patients achieved disease-free status with a mean follow-up interval of 6 mo (range, 3–24 mo). Four patients were treated with external radiotherapy because their lesions were not amenable to surgical excision. One patient with multiple mediastinal and lung metastases was placed on differentiation therapy in an attempt to stimulate ^{131}I uptake, and 1 patient declined further treatment. In 3 patients, in whom PET had identified high FDG uptake in cervical lymph nodes, pathology examinations revealed inflammatory disease.

Regardless of the imaging procedures used, the 8 negative and the 3 false-positive patients with persistent elevated Tg values continued to be carefully followed up until the end of the study, and, at the time of writing, remain without detectable metastases.

DISCUSSION

Our study of 37 DTC patients with elevated Tg levels shows that FDG PET has a high metastasis detection rate in cases undetected by ^{131}I posttherapy whole-body scanning. FDG findings were positive in 76% of patients and accurately localized the disease in 89% of them.

After the ablation of residual thyroid tissue, measurement of serum Tg levels and ^{131}I imaging usually provide sensitive tools for the early detection of recurrence. Unfortunately, a few patients with elevated Tg have tumors that do not take up ^{131}I even after administration of therapeutic doses, because of an impaired ability to trap iodine. FDG PET appears to offer an accurate functional method of detecting such tumors. This method has been shown to be highly sensitive in detecting thyroid carcinoma metastases, especially in the absence of ^{131}I uptake (*10–12*). However, most of the studies have involved patients with negative results obtained from scanning performed after diagnostic doses of ^{131}I (*9,10,12,14*). Alnafisi et al. (*15*) recently reported the effectiveness of FDG in 11 patients with persistent disease and negative ^{131}I whole-body scan results after therapy. However, their study was restricted to papillary thyroid carcinomas.

Our study shows that FDG is more effective than CI, with positive findings in 27 of 37 patients (70%) versus positive CI findings in 10 of 37 patients (27%) ($P < 0.001$). Morphologic imaging procedures are known to have low specificity—particularly in cases with postsurgical anatomic changes—and low sensitivity, because of their limited viewing field (*16*). In contrast, the PET scanner makes it possible to perform a whole-body examination with tomographic imaging, greater spatial resolution, and, therefore, high sensitivity. Furthermore, FDG PET is able to focus on a specific area of the body, thus facilitating radiologic interpretation.

Wang et al. (*12*) suggested that FDG uptake may correlate with the (tumor, node, and metastases [TNM]) stage of thyroid cancer. We found a significant correlation between FDG uptake and the stage of the thyroid cancer in both papillary carcinoma and follicular carcinoma. But, unlike Wang et al., we found that FDG was also effective in low-stage patients, because 5 of 6 of the patients with positive findings were confirmed to have stage-I cancer even after FDG. Only 1 patient seemed to have been un-

TABLE 2
Patients with Negative CI Findings

Patient no.	Sex	Age (y)	H	PT	Stage	TCD (GBq)	TSH* on T_4	Tg† on T_4	TSH* off T_4	Tg† off T_4	FDG PET results (*n*)	Histopathology	FU TSH*	FU Tg†
1	F	27	P	T3	I	7.4	0.5	7.9	50	80	CLN (1)	Positive (S)	<0.02	<0.6
2	M	47	P	T2	II	11.1	0.23	3.1	61	43	CLN (1)	Positive (S)	0.04	<0.3
3	F	27	P	T4	I	11.1	0.02	1.5	200	60	Negative	ND	1	6.5
4	M	48	P	T4	III	7.4	0.6	6.7	>50	285	CLN (1)	Positive (S)	<0.05	<0.6
5	F	36	P	T2	I	14.8	0.58	15	115	83	CLN (5)	Positive (S)	2	4.5
6	M	29	P	T3	II	7.4	0.29	10	285	69	Negative	ND	0.5	50
7	F	50	FC	T4	III	11.1	0.3	92	88	1,560	CLN (5), lung (+)	Positive (S)	0.05	<0.6
8	M	76	P	T4	IV	7.4	0.8	60	47	500	Lung (+)	Positive (B)	2.3	100 (Ext rad)
9	F	63	P	T4	III	7.4	0.08	25	102	80	CLN (2)	Positive (S)	<0.05	60
10	M	53	FC	T4	III	11.1	0.1	41	50	435	CLN (1)	Positive (S)	0.3	<0.3
11	M	39	P	T3	I	14.8	0.04	2.3	60	129	Negative	ND	ND	ND
12	F	37	P	T2	I	14.8	0.03	10	43	121	CLN (1)	Inflamed lymph nodes (S)	>50	60
13	F	62	P	T1	IV	22.2	0.05	43	61	415	Negative	ND	0.4	45
14	F	45	P	T4	III	7.4	0.06	2.8	48	30	CLN (3)	Inflamed lymph nodes (S)	<0.05	5
15	M	38	FC	T3	I	11.1	0.2	110	113	19,000	Bone (2)	Positive (S)	0.02	154
16	F	55	P	T3	III	11.1	0.07	55	110	178	CLN (2)	Inflamed lymph nodes (S)	<0.04	28
17	M	37	P	T3	I	11.1	0.43	15	44	93	Negative	ND	0.43	2
18	M	72	FC	T3	III	7.4	0.2	3	28	40	CLN (1), MLN (2)	Positive (S)	<0.05	<0.6
19	M	31	P	T3	I	14.8	0.4	1.5	176	37	Negative	ND	ND	ND
20	F	63	HC	T4	III	7.4	0.6	200	136	10,000	MLN (2)	Positive (S)	0.05	800
21	M	72	P	T3	IV	14.8	0.66	8	49	53	Bone (1)	Positive (S)	ND	Deceased
22	F	32	P	T3	I	7.4	0.01	1.5	60	113	CLN (2)	Positive (S)	<0.05	<0.6
23	F	78	HC	T4	III	7.4	0.13	2,800	78	22,100	Lung (+)	ND	0.10	2,000
24	M	40	FC	T4	I	7.4	0.01	30	196	800	Negative	ND	0.11	20
25	F	50	P	T2	II	11.1	0.5	39	144	105	CLN (1)	Positive (S)	<0.02	<0.6
26	F	35	P	T1	I	7.4	0.31	1.5	150	33	Negative	ND	0.2	2.5
27	M	28	P	T3	I	7.4	3.2	20	107	270	CLN (2)	Positive (S)	02	<0.6

*Data in mU/L.
†Data in μg/L.
H = histology of thyroid carcinoma; PT = primary tumor stage; TCD = total cumulative dose; T_4 = L-thyroxine; FU = follow-up; P = papillary carcinoma; CLN = cervical lymph node; S = surgery; ND = not done; FC = follicular carcinoma; + = multiple; B = biopsy; Ext rad = external radiation; MLN = mediastinal lymph node; HC = Hürthle-cell carcinoma.

derstaged, because FDG evaluation revealed bone metastases and this patient was consequently classified as having stage IV cancer. It is important to note that all our patients had elevated Tg levels.

PET scanning failed to detect any tumor tissue in 9 patients with persistent disease. This may have been attributable to a need to stimulate tumor foci by TSH or to some other methodologic problem. The possible effect of thyroxine on the accumulation of FDG in thyroid metastases has not yet been established, and all our PET scanning was performed while the patients were on thyroxine therapy. Although many authors have not observed any significant correlation between FDG uptake and thyroid hormone levels (*10*,*12*), others have reported a significant increase in

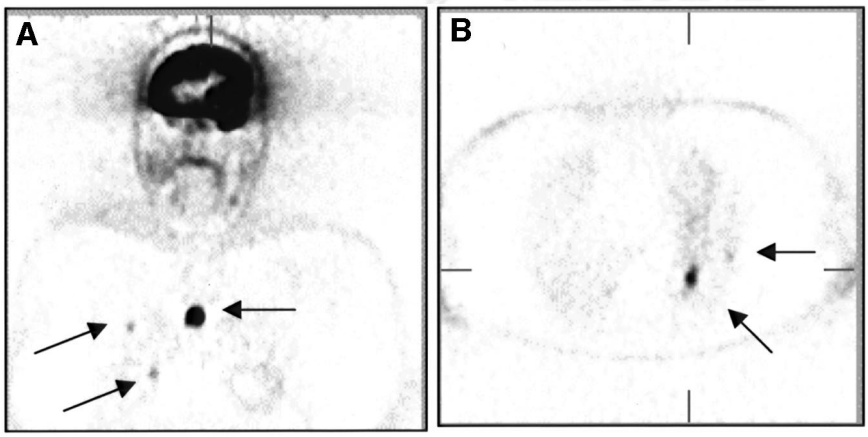

FIGURE 1. A 64-y-old woman with lung metastases from Hürthle-cell carcinoma. FDG PET confirmed lung metastases and revealed mediastinal lymph node metastasis. (A) Coronal slice shows both right lung and mediastinal lymph node metastases. (B) Axial slice confirms multiple left lung metastases (patient 5, group 1).

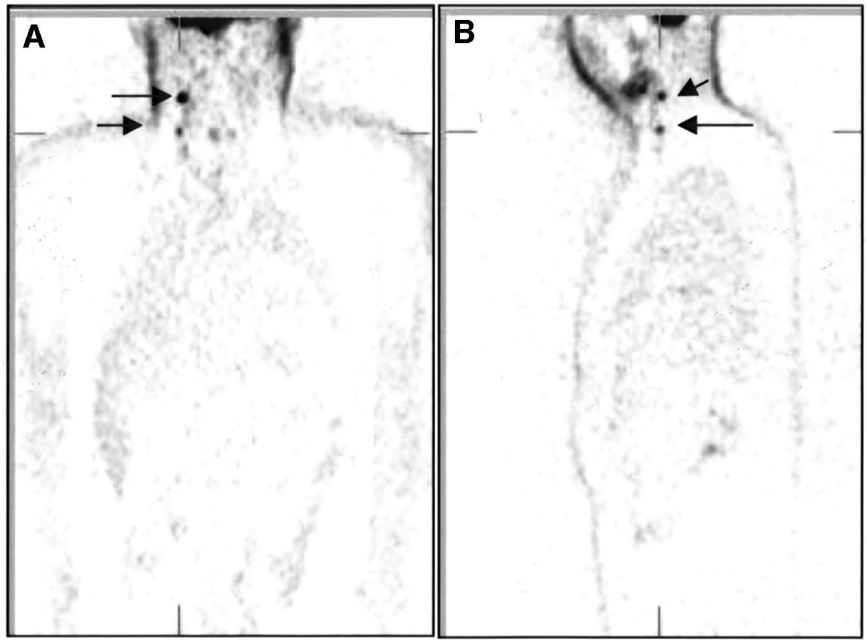

FIGURE 2. A 28-y-old man with papillary thyroid cancer who had previously required 2 cervical lymph node dissections. Neck sonography was negative, but FDG visualized on the coronal (A) and sagittal (B) slices 2 right cervical lymph nodes that were confirmed pathologically to be metastases (patient 27, group 2).

FDG uptake in response to TSH stimulation (*17,18*). Further studies using recombinant TSH may clarify the effect of TSH on FDG uptake without the disadvantage of L-thyroxine withdrawal.

Because the whole-body PET imaging in this study was performed without correction for tissue attenuation, deep tumors may have been missed because of their less obvious activity, with the possible consequence of a false-negative interpretation. However, in our group of patients we found that the only true-negative FDG result corresponded to a superficial cervical lymph node metastasis. Moreover, several clinical studies comparing images with and without attenuation correction showed no difference in tumor PET for lesion detection (*19,20*). In a series of 15 patients, Cutle (*21*) found no difference between corrected and uncorrected images with regard to the number and location of lesions found by experienced observers.

CONCLUSION

PET using FDG is of undeniable clinical value in patients with negative ^{131}I posttherapy whole-body scan results who are suspected of having a metastatic thyroid disease. It is able to detect significantly more tumor sites than can CI procedures. FDG may become a guide for additional imaging procedures, making it possible to detect Tg production sites accessible to surgery or external radiation therapy. We suggest that FDG PET be used as first-line investigation in patients with negative ^{131}I posttherapy scan results and elevated Tg levels.

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