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Better Yield of ^{18}F Fluorodeoxyglucose-Positron Emission Tomography in Patients with Metastatic Differentiated Thyroid Carcinoma during Thyrotropin Stimulation

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To determine whether ^{18}F fluorodeoxyglucose-positron emission tomography (FDG-PET) for the detection of recurrences or metastases of differentiated thyroid carcinoma should be performed during thyrotropin (TSH) suppression or TSH stimulation, eight patients were studied sequentially. After the second FDG-PET scan, a therapeutic ^{131}I dose was administered with posttherapy scans obtained 10 days later. Both FDG-PET scans were compared with each other and with the ^{131}I posttherapy whole body scans by two independent observers. Findings were verified using other imaging modalities or biopsies. Median TSH was 0.04 mU/L during TSH suppression and 64 mU/L during TSH stimulation. The FDG-PET scans during TSH suppression showed abnormalities in four patients and the FDG-PET scan during TSH stimulation in five patients. One patient was only positive during TSH stimulation. In two other patients the FDG-PET scan during TSH stimulation clearly identified more lesions, and in all positive patients lesion contrast was better during TSH stimulation. In two patients FDG-PET findings during TSH stimulation led to a change in clinical management. Thus, the performance of FDG-PET during TSH stimulation was either superior or equal to FDG-PET during TSH suppression, but never inferior. To detect metastatic or recurrent differentiated thyroid carcinoma FDG-PET should be performed during hypothyroidism, leading to TSH stimulation.

Introduction

IMAGING OF GLUCOSE METABOLISM using ^{18}F fluorodeoxyglucose-positron emission tomography (FDG-PET) is a promising method for the detection of many types of tumors because of their high glycolytic demand. In 1987 Joensuu and Ahonen (1) first showed imaging of metastases in three patients with advanced differentiated thyroid cancer with FDG-PET. Since then several reports were published about the relevance of FDG-PET scanning in patients with differentiated thyroid carcinoma (2–17). In differentiated thyroid cancer the uptake of FDG seems to be associated with poor differentiation and low iodine uptake on diagnostic ^{131}I scanning (3,18). Although the clinical significance of this phenomenon has not been fully defined, in clinical practice FDG-PET scanning is now the method of choice for the detection of ^{131}I -negative metastases of differentiated thyroid carcinoma (19–21).

For FDG-PET scanning, the withdrawal of thyroid hormones is suggested not to be necessary. This in contrast to radioiodine scanning, because for this, thyroid hormone withdrawal is essential. However, only a few reports have

mentioned the possible influence of the serum thyrotropin (TSH) level on FDG uptake in thyroid carcinoma tissue and in these studies conflicting results concerning this influence are found (3,7,12,13). A potential drawback of these studies is that FDG-PET findings were compared between groups of patients with low TSH and elevated TSH but, patients were not compared intraindividually.

Therefore, we performed a prospective study in patients with suspected recurrent or metastatic differentiated thyroid cancer to study the effect of serum TSH on FDG-PET uptake patterns. These patients were studied sequentially under TSH suppression and TSH stimulation through thyroid hormone withdrawal. In addition, FDG-PET findings were compared with posttherapy ^{131}I whole-body scans obtained after subsequent treatment with high-dose ^{131}I during TSH stimulation.

Patients and Methods

Patients

Between November 1997 and April 2000, patients with differentiated thyroid carcinoma suspected of having recurrent

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or metastatic disease and scheduled for another treatment with 5.6 GBq of ¹³¹I were asked to participate in the study. The study was approved by the local medical ethics committee and all patients provided informed consent. Eight patients (6 male, 2 female; mean age, 48 years range, 26–27 years) underwent whole-body FDG-PET examinations both during TSH suppression and during TSH stimulation (Table 1). All patients had undergone total thyroidectomy and radioiodine ablation and used triiodothyronine or thyroxine to induce TSH suppression. The patients were suspected of having recurrent or metastatic disease because of elevated thyroglobulin (Tg) levels during TSH suppression or during a previous period of hypothyroidism or because of the presence of serum Tg-antibodies. For this reason the patients were scheduled for another treatment with 5.6 GBq of ¹³¹I. The first FDG-PET scan was performed several weeks prior to the ¹³¹I treatment, during TSH suppression, before stopping the thyroid hormone suppression therapy. The second FDG-PET scan was performed 35 days (median, range 21–49 days) after the first FDG-PET scan, after stopping the thyroid hormone suppression therapy leading to sufficient TSH stimulation. Treatment with 5.6 GBq of ¹³¹I followed 4 to 7 days after the second FDG-PET scan. A posttherapy ¹³¹I whole-body scan was performed 10 days later.

Laboratory measurements

Blood samples for measuring serum Tg and TSH were taken before performing both FDG-PET scans. Serum TSH was measured by a commercial available fluoroimmuno-metric assay (AutoDELFIA hTSH Ultra, Perkin Elmer, Turku, Finland) with a normal range of 0.4–7.2 mU/l. Serum Tg was measured by a commercial available radioimmunoassay (Cis Bio International, Gif-sur-Yvette, France) with a lower detection limit of 1.5 ng/mL. The presence of Tg antibodies was evaluated by recovery of standard Tg to the patient serum sample.

FDG-PET scanning and interpretation

FDG-PET was performed with an ECAT HR+ camera (Siemens/CTI, Knoxville, TN). Patients fasted overnight before the investigation. Ninety minutes after intravenous in-

jection of 370 MBq of FDG, a whole-body image was acquired from top of the skull to the knees. Images were reconstructed using iterative methods without attenuation correction. PET images were read from computer monitors. We compared the results of both whole-body FDG-PET. FDG-PET images were originally interpreted by an experienced nuclear physician. The first and second FDG-PET scan of an individual patient were simultaneously reanalyzed later by another nuclear medicine physician, blinded for the previous reading, blinded for all other imaging results and blinded for TSH values. When the original reading and the second reading were discordant, a consensus was reached. Suspicion of malignancy in a lesion was based on a qualitative assessment of the high lesion contrast with background. Normal patterns, such as (e.g., laryngeal) muscle uptake patterns were recognized. The FDG-PET scans were scored negative (–) if no abnormal lesions were seen and the scans were scored positive (+) if there were lesions seen suspicious for malignancy. Both FDG-PET scans were compared. A scan was scored ++, if lesions were better visualized and a scan was scored +++, if there were more lesions found compared to the other scan. Because of the small size of several lesions in some patients, we choose not to perform calculation of tumor/background ratios.

Posttherapy ¹³¹I whole-body scans were performed using a two-headed gamma camera (Multispect 2, Siemens) with a high-energy collimator acquired 10 days after treatment with 5.6 GBq of ¹³¹I. Posttherapy ¹³¹I whole-body scans were read from monitors or hard copies. ¹³¹I images were separately interpreted by two independent nuclear medicine physicians and later compared with the FDG-PET images.

Additional radiologic imaging, including computed tomography (CT) scan, magnetic resonance imaging (MRI), x-ray-imaging or ultrasonography, was performed in order to verify the suspicious lesions. In case of palpable cervical lymph nodes a fine-needle biopsy was performed.

Results

The first FDG-PET whole-body scan was performed under TSH suppression with a median TSH of 0.04 mU/L (range, 0.01–2.4 mU/L) and a median serum Tg of 1.6 ng/mL (range, <1.5–90 ng/mL) (Table 1). The second FDG-PET scan

TABLE 1. PATIENT CHARACTERISTICS

Patient number	Gender	Age	Histology	TNM	TSH suppression		TSH stimulation	
					TSH (mU/L)	Tg (ng/mL)	TSH (mU/L)	Tg (ng/mL)
1	F	28	PTC	T4 N1 M1	0.017	<1.5 ^a	132	<1.5 ^a
2	M	60	PTC	T4 N1 M0	0.342	<1.5	16.7	31.7
3	M	60	PTC	T4 N1 M0	0.032	9.0	160	NA
4	M	32	PTC	T2 N0 M0	0.054	<1.5	52	15
5	M	52	PTC	T2 N0 M0	0.267	2.6	22.9	615
6	F	77	FTC	T2 N0 M0	2.4	10.1	26.5	29.6
7	M	43	FTC	T3 N0 M0	0.01	<1.5	76	21
8	M	26	PTC	T2 N1 M0	0.019	1.6	83	7

^aTg not measurable because of Tg-antibodies.
PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; NA, not available; TSH, thyrotropin; Tg, thyroglobulin; M, male; F, female.

TABLE 2. RESULTS OF BOTH FDG-PET SCANNING, POSTTHERAPY ¹³¹I WBS, AND ADDITIONAL IMAGING OR BIOPSIES

Patient	FDG-PET under TSH stimulation	Score	FDG-PET under TSH stimulation	Score	Posttherapy ¹³¹ I WBS	Additional radiologic or biopsy findings
1	Negative	–	Right lung	+	Left cervical lesion	CT lungs and cervical MRI: solitary small lung metastasis in the right lung and pathological cervical lymph nodes at the left side Biopsy right cervical lesion: positive PTC
2	Right cervical lesion	+	Right cervical lesion, mediastinal lesion, both lungs	+++	Right cervical lesion	
3	Both lungs, liver, left femur	+	Both lungs, liver, left femur	+++	Mediastinal lesion	CT lungs and abdomen: metastases of both lungs and liver, MRI femur: bone metastasis
4	Left cervical lesion	+	Left cervical lesion	++	Left cervical lesion	—
5	Right cervical lesion	+	Right cervical lesion	++	Negative	Biopsy right cervical lesion: positive for PTC
6	Negative	–	Negative	–	Vague thoracic lesion	X-ray, MRI abdomen and bone scintigraphy: negative
7	Negative	–	Negative	–	Uncertain abdominal lesion	Abdominal ultrasound and CT: negative
8	Negative	–	Negative	–	Negative	Biopsy right cervical lesion: negative

WBS, whole body scan; PTC, papillary thyroid carcinoma; FDG-PET, ¹⁸fluorodeoxyglucose-positron emission tomography; TSH, thyrotropin; CT, computed tomography; MRI, magnetic resonance imaging.

was performed during TSH stimulation with a median TSH level of 64 mU/L (range, 17–160 mU/L) and a median serum Tg of 25.3 ng/mL (range, <1.5–615 ng/mL) (Wilcoxon-rank test, $p < 0.05$). One patient (patient 1) showed an unmeasurable Tg both during TSH suppression and stimulation because of Tg-antibodies.

In FDG-PET image interpretation there was concordance by the two reviewers with regards to the presence of lesions, the number of lesions and lesion contrast in 6 of 8 patients. In the remaining patients both reviewers and one to two other nuclear medicine physicians together reached a consensus. These two cases involved (1) differentiation between low-intensity uptake lesions and background activity by nonspecific muscle uptake concluded to be normal for both scans, and (2) doubt about a low-intensity lesion only faintly visible on the second FDG-PET scan, concluded to be normal. In the ^{131}I studies there was complete agreement in 7 of 8 patients. In the remaining patient both readers agreed on the presence of abnormal uptake, but there was discussion whether one or two ^{131}I accumulations were present in the neck, finally concluded to be one.

The results of both FDG-PET scans and posttherapy ^{131}I whole-body scans in all patients are summarized in Table 2. The most striking difference between both FDG-PET scans was observed in patient 1. This patient presented at diagnosis with a papillary carcinoma with extrathyroidal growth and metastatic cervical lymph node metastases. Pulmonary metastases were seen on the posttherapy whole-body scan after ablation with 5.6 GBq of ^{131}I , but not on a x-ray of the chest. The patient was scheduled for another treatment with 5.6 GBq of ^{131}I 3 months later and for FDG-PET scans according to the protocol. In this patient the FDG-PET scan under TSH suppression showed no uptake, but the FDG-PET scan during TSH stimulation, causing hypothyroidism, showed uptake in the right lung (Fig. 1). Posttherapy ^{131}I whole-body scan after the second treatment with 5.6 GBq of ^{131}I showed only uptake in the left cervical lymph nodes. Additional radiologic imaging confirmed the presence of a pulmonary metastasis in the right lung as seen on the FDG-PET scan under TSH stimulation and multiple cervical lymph nodes on the left side as was seen on the posttherapy ^{131}I whole-body scan. Thus, the patient was considered to have FDG-negative cervical lymph node metastases and a ^{131}I -negative pulmonary metastasis. For this reason further treatment with ^{131}I was stopped and the patient was scheduled for an additional cervical lymph node dissection. Such a different uptake pattern of FDG and ^{131}I within 1 patient has also been described by others (3,10,20).

Four patients (patients 2, 3, 4, and 5) showed uptake patterns suspicious for recurrent or metastatic differentiated thyroid carcinoma at both FDG-PET scans. In all four patients the lesions during hypothyroidism clearly showed increased lesion-to-background contrast and in two patients the FDG-PET scan during hypothyroidism showed more lesions. Additional imaging and biopsies confirmed the presence of recurrent or metastatic differentiated thyroid carcinoma in these four patients. In patient 2 additional metastatic lesions were seen on the TSH-stimulated FDG-PET scan in the mediastinal lymph nodes and both lungs, which were not visualized both on the posttherapy ^{131}I scan and the FDG-PET scan during TSH suppression. For this reason, the intended cervical lymph node dissection was not performed.

A

B

FIG. 1. **A:** Equivalent coronal ^{18}F fluorodeoxyglucose-positron emission tomography (FDG-PET) slices during thyrotropin (TSH) suppression (EU) and TSH stimulation (HYPO) in a 28-year old female (patient 1) with a metastatic papillary thyroid carcinoma. Only during hypothyroidism a significant pulmonary lesion is visualized (arrow). In the right panel the thymus is seen (T). **B:** The posttherapy ^{131}I whole-body scan (^{131}I -WBS) only shows uptake in the left cervical region, which is suspicious for cervical lymph node metastases.

In patient 3 widespread metastatic disease was found, but even more metastatic lesions, especially in both lungs, were seen under TSH stimulation (Fig. 2).

In three patients (patients 6, 7, and 8) both FDG-PET scans were scored negative, despite detectable Tg levels during hypothyroidism. Also, the posttherapy ^{131}I whole-body scans and additional radiologic imaging showed no lesions suspicious for differentiated thyroid carcinoma.

Thus, after careful visual examination by two independent nuclear physicians, in three of eight patients, more lesions were found on the FDG-PET scan during TSH stimulation

FIG. 2. Widespread metastatic papillary thyroid carcinoma in a 60-year-old male (patient 3). **A:** Compared to the ^{18}F -fluorodeoxyglucose-positron emission tomography (FDG-PET) scan during thyrotropin (TSH) suppression (EU), the FDG-PET scan during TSH stimulation (HYPO) is showing many more lesions in both lungs. Other metastatic lesions are also better visualized during TSH stimulation. I denotes the injection site in the right panel. **B:** On the posttherapy ^{131}I whole-body scan (^{131}I -WBS), only uptake in the mediastinal area is seen.

compared to the FDG-PET scan during TSH suppression. In two of these three patients (patients 1 and 2) the results of the FDG-PET scan during TSH stimulation changed clinical management, since there was more widespread disseminated disease than was suspected on the basis of the FDG-PET scan during TSH suppression.

Discussion

Our study clearly shows that FDG-PET scanning for the detection of recurrent or metastatic differentiated thyroid carcinoma under TSH stimulation results in the detection of more lesions. This was seen in three of eight patients, leading to a change in clinical management in two patients. In

two other patients, lesion-contrast was improved. The FDG-PET under TSH suppression was never superior to the FDG-PET scan under TSH stimulation.

The better yield of FDG-PET in these patients could be expected because it was already recognized in cultured rat thyroid cells that glucose uptake is stimulated by TSH by increasing the number of glucose carriers in the thyroid plasma membrane (22,23). Thus, higher accumulation of FDG in thyroid cancer cells could be expected in case of an elevated serum TSH level. This was first observed *in vivo* by Sisson et al. (24) in 1993, who described the detection of a pulmonary metastasis in a patient with differentiated thyroid cancer. The pulmonary metastasis was readily seen during hypothyroidism, but uptake appeared less with suppressed TSH.

In contrast to this observation and the data from cultured thyroid rat cells, suggesting higher glucose uptake under TSH stimulation, several clinical studies do not support this finding. This is because of fact that in these studies no sequential FDG-PET scans were performed in the same patients. Only in the study of Feine et al. (3), who studied 41 patients with differentiated thyroid cancer during follow-up, 4 patients were mentioned with sequential FDG-PET scans with low and high TSH levels and they did not exhibit different uptake patterns. No significant difference in metastatic uptake in the other patients with or without thyroid hormone replacement therapy was found.

Another explanation for the discrepancy between the observation of Sisson et al. (24) and other studies is that the conclusions about the effect of TSH on the results of the FDG-PET scans, were based on statistical analysis between groups with low and high TSH lacking extreme variations in TSH levels. Grunwald et al. (7) observed no significant influence of $\text{TSH} < 0.4 \text{ mU/L}$ versus $\text{TSH} > 0.4 \text{ mU/L}$ on the sensitivity of FDG-PET in 47 patients with differentiated thyroid cancer. Wang et al. (13) performed FDG-PET in 37 patients with differentiated thyroid cancer and negative diagnostic radioiodine imaging. No difference in scan outcome was found, when patients with TSH levels greater than 5.0 mU/L were compared to the patients with TSH levels less than 5.0 mU/L . In a large multicenter study in Germany, in 222 patients with differentiated thyroid cancer, who were evaluated by FDG-PET, sensitivity was 91% if FDG-PET was performed under thyroid hormone therapy ($\text{TSH} < 5.0 \text{ mU/L}$), compared to a sensitivity of only 67% in the presence of high TSH levels ($\text{TSH} > 5.0 \text{ mU/L}$) (12). Also in this study, scan outcome was compared groupwise and not intraindividually. However, TSH levels above 0.4 mU/L or even 5.0 mU/L are only slightly elevated and not equivalent to the range of stimulated TSH as in our study levels (TSH levels 0.04 vs. 64 mU/L).

Recently, another prospective study of 10 patients with differentiated thyroid carcinoma with sequential FDG-PET scans was published by Moog et al. (25). Ten elderly patients with known metastatic disease were studied both under TSH suppression and TSH stimulation. In 3 of 10 patients TSH stimulation resulted either in detection of new lesions or classification of the FDG uptake pattern as suspicious for malignancy. These results are in full agreement with our results. Additionally, in this study the tumor-to-background ratio was calculated in 17 lesions showing significant increased FDG uptake of 63.1% during TSH stimulation. They also

found a mean decreased counting rate of the background of 21.6% during TSH stimulation because of the overall decreased metabolic activity.

In an invited commentary by Grunwald and Biersack (19) in the same journal, it was suggested that the time elapsed between both FDG-PET scans could have altered the results by progression of disease over time. However, mean time between both FDG-PET scans in our study was even shorter, namely 35 days, compared to Moog et al. (25). Because differentiated thyroid carcinomas usually progress slowly and even the more aggressive tumors show a relatively good prognosis, it is unlikely that the time elapsed between both FDG-PET scans is responsible for the differences in uptake pattern between both scans. A crossover study, as was suggested by Grunwald and Biersack (19), could also introduce bias because the period of hypothyroidism leading to TSH stimulation, could stimulate tumor growth, and thus, could alter the results of the FDG-PET scans.

Our study, although in a small number of patients, is the second prospective study with sequential FDG-PET scans in the same patients with differentiated thyroid carcinoma. It is remarkable that both sequential studies reach the same conclusion, suggesting that studies based on group comparison are less reliable. It should be noted that compared to the study of Moog et al. (25), our patients differed in two ways. Moog et al. (25) studied elderly patients and patients with known metastatic disease. We studied younger patients, who were only suspected of having recurrent or metastatic differentiated thyroid cancer due to, sometimes only slightly, elevated serum Tg levels during hypothyroidism. If we had analyzed our patients only with FDG-PET during TSH suppression and radioiodine we had missed additional clinical relevant lesions in 2 of 8 patients. Thus, the optimal condition for performing FDG-PET scanning in patients with differentiated thyroid cancer is under TSH-stimulation, although larger studies are needed to confirm these results. However, the recommendation to perform FDG-PET scanning after stopping thyroid hormone therapy, leading to TSH stimulation, has clinical implications for these patients. A new challenge is to study the difference in FDG-PET scan outcome under TSH suppression and after administration of recombinant TSH, leading to TSH stimulation.

Conclusion

Our study shows that hypothyroidism enhances FDG uptake and results in the detection of more lesions suspicious for malignancy in patients with differentiated thyroid carcinoma. For some patients this could alter clinical management of their disease. Therefore, we recommend that clinicians perform a FDG-PET scan, if indicated, during hypothyroidism.

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