University of Groningen

18-Fluorodeoxyglucose Positron Emission Tomography in the Early Diagnostic Workup of Differentiated Thyroid Cancer Patients with a Negative Post-Therapeutic Iodine Scan and Detectable Thyroglobulin

van Dijk, Deborah; Plukker, John T. M.; Phan, Ha T. T.; Kobold, Anneke C. Muller; van der Horst-Schrivers, Anouk N. A.; Jansen, Liesbeth; Sluiter, Wim J.; Brouwers, Adrienne H.; Links, Thera P.

Published in:
Thyroid

DOI:
[10.1089/thy.2012.0498](https://doi.org/10.1089/thy.2012.0498)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2013

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

van Dijk, D., Plukker, J. T. M., Phan, H. T. T., Kobold, A. C. M., van der Horst-Schrivers, A. N. A., Jansen, L., Sluiter, W. J., Brouwers, A. H., & Links, T. P. (2013). 18-Fluorodeoxyglucose Positron Emission Tomography in the Early Diagnostic Workup of Differentiated Thyroid Cancer Patients with a Negative Post-Therapeutic Iodine Scan and Detectable Thyroglobulin. *Thyroid*, 23(8), 1003-1009.
<https://doi.org/10.1089/thy.2012.0498>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

18-Fluorodeoxyglucose Positron Emission Tomography in the Early Diagnostic Workup of Differentiated Thyroid Cancer Patients with a Negative Post-Therapeutic Iodine Scan and Detectable Thyroglobulin

Deborah van Dijk,¹⁻³ John T.M. Plukker,² Ha T.T. Phan,⁴ Anneke C. Muller Kobold,⁵
Anouk N.A. van der Horst-Schrivers,^{1,3} Liesbeth Jansen,² Wim J. Sluiter,^{1,3}
Adrienne H. Brouwers,⁶ and Thera P. Links^{1,3}

Background: Surgery and high-dose radioactive iodine (¹³¹I) treatment are the cornerstones in the treatment of differentiated thyroid cancer. Patients without ¹³¹I uptake on the post-therapeutic whole body scan (WBS), but with detectable thyroglobulin (Tg) during thyroxine withdrawal (Tg-off), are evaluated with an 18-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG-PET) for tumor localization within three months. The yield of ¹⁸F-FDG-PET imaging and clinical usefulness of a Tg-off cutoff value to predict a positive scan were assessed.

Methods: From 2002 to 2011, 52 patients with a negative WBS and concurrent detectable Tg-off were evaluated. Thirty-five PET scans were performed during initial treatment, 17 after recurrent disease. Thirty-two patients were on substitution therapy, 17 were evaluated with endogenous thyrotropin elevation, and 3 after recombinant human thyrotropin stimulation. To determine the Tg-off cutoff value, a receiver operating characteristic curve was used.

Results: Nine (17%) ¹⁸F-FDG-PET scans were true positive, 3 (6%) false positive, 36 (69%) true negative, and 4 (8%) false negative (sensitivity 69%, specificity 92%). In 13%, a true-positive scan resulted in a change in the clinical management. The area under the receiver operating characteristic curve is 0.82 [CI 0.64–0.99] ($p < 0.01$), and the Tg-off cutoff value is 38.00 ng/mL (sensitivity 67%, specificity 95%). Ninety percent of ¹⁸F-FDG-PET true-positive patients had a Tg-off >2.00 ng/mL.

Conclusions: An ¹⁸F-FDG-PET within three months after a negative WBS with detectable Tg-off showed additional tumor localization in 17% of the patients, leading to a change in clinical management in 13%. A clinically useful Tg-off cutoff value was not found, but 90% of positive ¹⁸F-FDG-PET scans occurred in patients with a Tg-off >2.00 ng/mL.

Introduction

DIFFERENTIATED THYROID CANCER (DTC) is a well-treatable malignant disease, with a high long-term survival rate of 80–95% (1). However, cancer-related death still occurs in up to 8% of patients (2,3). Several factors predict poor outcome in DTC patients, such as the presence of lymph nodes and distant metastases (3–6). Life expectancy is also significantly reduced in patients with persistent disease after recurrence (7). Early visualization of residual or recurrent tumor

tissue is important, since, consequently, additional curative (surgical) treatment can be initiated at an early stage.

Unfortunately, in some patients with detectable serum thyroglobulin (Tg) levels, the tumor cannot be localized by conventional imaging such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and/or radioactive iodine (¹³¹I) whole body scan (WBS). Loss of uptake on the ¹³¹I WBS could indicate a loss of the tumors' ability to take up iodine, while the possibility to produce Tg is still preserved, as seen in some dedifferentiated tumors. Also,

Departments of ¹Endocrinology, ²Surgical Oncology, ³Internal Medicine, ⁵Laboratory Medicine, and ⁶Nuclear Medicine and Molecular Imaging, Groningen University Medical Center, Groningen, The Netherlands.

⁴Department of Nuclear Medicine and Molecular Imaging, Leeuwarden Medical Center, Leeuwarden, The Netherlands.

functional imaging could suffer from limitations of spatial resolution. Lesions smaller than 1 cm are below detection limits and can be missed. Although routine anatomical imaging is much more sensitive with a possibility of detecting subcentimeter lesions, these modalities suffer from low specificity of interpretation based on lesion size criteria alone. Furthermore, the anatomical imaging may even be more hampered by the altered anatomical condition after surgery.

Dedicated functional imaging modalities, like ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET), using radioactively labeled glucose (8,9) can be useful in visualizing tumor presence at an early stage in this patient group. Many studies have been published regarding the role of the ^{18}F -FDG-PET in detecting residual or recurrent disease and in monitoring disease progression but mostly for tumor detection in WBS-negative, Tg-positive patients, with a reported sensitivity ranging from 57% to 100% and a specificity of 25–100% (9–14). These studies describe the role of the ^{18}F -FDG-PET in various time spans after the negative WBS; however, none of them focused on the early diagnostic value of ^{18}F -FDG-PET imaging.

To improve the therapeutic yield of early ^{18}F -FDG-PET imaging, patients could be selected based on their Tg level during thyroxine withdrawal (Tg-off) at the time of the post-therapeutic WBS. A correlation between the Tg level and a positive ^{18}F -FDG-PET scan has been described by several authors (15,16). A Tg cutoff value of 10 ng/mL as an optimum level for both sensitivity and specificity is described, however, regardless of stimulated or unstimulated Tg (17–19).

This study aimed to evaluate the additional value of the ^{18}F -FDG-PET in the early diagnostic workup of DTC patients with a negative post-therapeutic WBS and concurrent detectable Tg-off. The secondary aim was to investigate whether the Tg-off level during ^{131}I therapy can predict a positive ^{18}F -FDG-PET in the early diagnostic phase and, if so, to determine a Tg cutoff value.

Materials and Methods

Patients

Between June 2002 and January 2011, 217 patients with DTC underwent an early ^{18}F -FDG-PET scan at the University Medical Centre Groningen. We retrospectively selected 52 patients with a negative post-therapeutic WBS and either concurrent detectable Tg or Tg antibodies (TgAb) during thyroid hormone withdrawal and an ^{18}F -FDG-PET within three months. We included both stimulated (endogenous and recombinant human thyrotropin [rhTSH]) and unstimulated ^{18}F -FDG-PET scans. Patient characteristics are shown in Table 1 (20). Based on the retrospective design of the study, institutional review board approval was not required according to Dutch law.

Treatment protocol

All patients diagnosed with DTC were treated as described earlier and, since 2007, according to the Dutch guidelines (21–23). They underwent total thyroidectomy and lymph node dissection as indicated, followed by Tg-off measurement and high-dose (1850–5550 MBq) ^{131}I treatment (ablation therapy). Initial therapy (surgery and high-dose ^{131}I therapy) was completed if there was no evidence of disease; that is, the

TABLE 1. PATIENT CHARACTERISTICS AT DIAGNOSIS

Number	52
Male	16 (31%)
Female	36 (69%)
Age (mean $\pm$ SD)	44.6 $\pm$ 16.5
Histopathology	
Papillary, classical type	33 (63%)
Papillary, follicular variant	12 (23%)
Follicular	2 (4%)
Hürthle	4 (8%)
Papillary and follicular	1 (2%)
Staging ^a	
T1	6 (12%)
T2	16 (31%)
T3	11 (21%)
T4	19 (36%)
N0	19 (36%)
N1	31 (60%)
Nx	2 (4%)
M0	45 (86%)
M1	4 (8%)
Mx	3 (6%)

^aStaging followed TNM, 5th edition (20).

T, tumor; N, nodes; M, metastases; SD, standard deviation.

diagnostic WBS showed no uptake and Tg became undetectable (<1.00 ng/mL) 3–6 months after the last ^{131}I therapy. The patients then received regular follow-up with Tg-on measurement, clinical examination, and US of the neck. If additional ^{131}I treatment was necessary, a post-therapeutic WBS was performed after 7 (since July 2010) or 10 days (until July 2010). The patients with no uptake on the post-therapeutic WBS (after additional ^{131}I treatment), but with a detectable Tg, received anatomical imaging (US and/or MRI) to localize possible tumor deposits or to visualize a baseline situation according to our standard protocol. For patients in whom tumor localization could not be visualized or remained unclear, an ^{18}F -FDG-PET scan was performed (Fig. 1). Anatomical imaging was repeated two or three times per year during the first two years and once or twice per year thereafter. Depending on the outcomes of imaging and Tg slope, the frequency of cross-sectional imaging was tapered slowly.

Curation was defined as undetectable Tg-on (*i.e.*, Tg during substitution therapy) and no visible tumor either on diagnostic imaging or on physical examination for at least one year. Recurrence was defined as detectable Tg-on, visible tumor on either diagnostic imaging or physical examination, or histologically confirmed tumor after initial curation.

Persistent disease was defined as continuous microscopically (Tg, histopathological) or macroscopically (physical examination, imaging) detectable disease.

^{18}F -FDG-PET protocol

Of the 52 ^{18}F -FDG-PET scans, 35 were performed after initial treatment and 17 scans were performed after ^{131}I therapy for recurrent disease. Of the 35 patients with primary disease, 27 patients (77%) were on substitution therapy and 5 patients (14%) were imaged after thyroid hormone withdrawal while undergoing the ^{18}F -FDG-PET scan. The remaining three patients (9%) were rhTSH-stimulated. Of the 17 patients with a PET scan performed after treatment for

FIG. 1. A 75-year-old woman diagnosed with T3N1M0 papillary thyroid carcinoma. *Left:* A post-therapeutic ¹³¹I whole body scan shows physiological uptake in the nasal and oral pharynx, liver, and bowel; otherwise negative scan. *Right:* A ¹⁸F-FDG-PET scan 1 month later shows physiological uptake in the brain, heart, liver, and bladder and multiple suspicious lesions in the mediastinum; positive scan. Despite palliative radiotherapy, the patient developed progressive disease. ¹³¹I, radioactive iodine; ¹⁸F-FDG-PET, 18-fluorodeoxyglucose positron emission tomography.

recurrent disease, 12 patients (71%) underwent endogenous TSH stimulation and 5 patients (29%) were on substitution therapy (Fig. 2). All the patients were asked to fast with free water intake for 6 hours before injection of ¹⁸F-FDG. Blood glucose was measured at the beginning of the procedure. If the blood glucose level exceeded 180 mg/dL (10 mmol/L), the ¹⁸F-FDG-PET scan was canceled. Patients who were rhTSH-stimulated received an injection with 0.9 mg rhTSH 48 and 24 hours before the PET scan. Until 2007, ¹⁸F-FDG-PET scans were carried out 90 minutes after the intravenous administration of 5 MBq of ¹⁸F-FDG/kg body weight. From 2008, this

was done after 60 minutes. Most patients ($n=43$) were scanned on an Ecat Exact HR+PET camera (Siemens, Hoffman Estates, IL). Since November 2009, seven patients were scanned on a Biograph mCT (PET/64-slice CT) camera (Siemens). Before August 2004, two patients were scanned on an ECAT 951/31 PET camera (Siemens).

For this study, all scans were blindly re-evaluated after randomization by one of two experienced nuclear medicine physicians (A.H.B. and H.T.T.P.). In case of discrepancy between the original report and the re-evaluation, the scan was again blindly evaluated by the other nuclear medicine

FIG. 2. Proportion and outcome of ¹⁸F-FDG-PET scans after stimulation of endogenous TSH, with rhTSH, or on substitution therapy. TSH, thyrotropin; rhTSH, recombinant human TSH.

physician to reach agreement. In cases of remaining incongruity, A.H.B. re-evaluated the scans taking into consideration the clinical and imaging information that was available until the scan date, and a definitive decision was made.

Scoring of ^{18}F -FDG-PET

The ^{18}F -FDG-PET was considered true positive if lesions were histologically confirmed, or when conventional imaging (CT, MRI, US) showed an anatomical substrate, or if the subsequent ^{131}I WBS during follow-up showed corresponding uptake (12). When the ^{18}F -FDG-PET was positive, but other imaging modalities showed no tumor activity, and/or Tg-on remained undetectable and no histological confirmation was obtained for at least one year, it was considered false positive. It was considered true negative if conventional imaging showed no tumor localization and Tg-on remained undetectable for at least one year. If the ^{18}F -FDG-PET scan was negative, but other imaging modalities did show tumor activity and/or histological confirmation was obtained, it was considered false negative.

Laboratory methods

Routinely, the presence of Tg and TgAb was evaluated. During the inclusion of this study, from 2002 to 2011, different Tg and TgAb immunoassays were used in our hospital, as has been described previously (7). All assays were calibrated against the International Standard CRM-457.

Statistical methods

Data are expressed as mean $\pm$ standard deviation (SD) for values with normal distribution, and median with range for values with non-normal distribution. Differences in param-

eters were tested using the Mann-Whitney *U*-test. A receiver operating characteristic (ROC) curve was used to determine an optimal Tg cutoff point for a positive outcome of the ^{18}F -FDG-PET. Differences were accepted to be statistically significant at a two-sided $p < 0.05$. All statistical tests were carried out using PASW Statistics 18.

Results

Patients

Fifty-two patients were included. In 35 patients, ^{18}F -FDG-PET scans were performed after initial treatment and 17 scans were performed after ^{131}I therapy for recurrent disease. Of the 35 patients with primary disease, 27 patients (77%) were on substitution therapy and 5 patients (14%) underwent thyroid hormone withdrawal while undergoing the ^{18}F -FDG-PET scan. The remaining three patients (9%) were rhTSH-stimulated. Of the 17 patients with a PET scan performed after treatment for recurrent disease, 12 patients (71%) underwent endogenous stimulation and 5 patients (29%) were on substitution therapy (Fig. 2). The median TSH value of the 28 substituted patients was 0.036 mU/L (0.04–4.68), that of the 16 patients undergoing thyroid hormone withdrawal was 33.5 mU/L (4.10–240.00), and that of the 1 rhTSH-stimulated patient was 140.00 mU/L. In seven patients, TSH measurements were not available.

^{18}F -FDG-PET

Of the 52 ^{18}F -FDG-PET scans, 9 (17%) were true positive, 3 (6%) were false positive, 36 (69%) were true negative, and 4 (8%) were false negative, leading to a sensitivity of 69% and specificity of 94%, and a positive and negative predictive value of 75% and 90%, respectively (Figs. 2 and 3; Table 2).

FIG. 3. Flowchart clinical outcome ^{18}F -FDG-PET. *FNA was performed after positive MRI, US, or both and was negative in all cases. **US performed after false-positive MRI, all negative. ***In one patient, US was omitted because of logistical reasons. ****Histological confirmation of tumor was not obtained. CT, computed tomography; FNA, fine needle aspiration; LN, lymph node; MRI, magnetic resonance imaging; RTx, radiotherapy; US, ultrasound.

TABLE 2. PATIENT CHARACTERISTICS CLASSIFIED BY ¹⁸F-FDG-PET OUTCOME

	False negative		False positive		True positive		True negative	
	Init	Rec	Init	Rec	Init	Rec	Init	Rec
Number	3	1	3	0	4	5	25	11
Age at diagnosis (mean±SD)	52.33±21.55	53.00	27.33±8.51	—	58.00±13.19	57.00±11.66	43.33±17.56	38.36±11.26
Tg-off level (median±SD)	14.00±29.64	2.10	12.00±19.50	—	972.50±134.93	22.45±29.06	6.40±17.32	2.70±9.98
Papillary, classical type	1	1	1	—	3	5	16	6
Papillary, follicular variant	2	0	2	—	0	0	6	2
Follicular	0	0	0	—	1	0	0	1
Hürthle	0	0	0	—	0	0	3	1
Papillary and follicular	0	0	0	—	0	0	0	1
T1	0	0	0	—	1	0	1	4
T2	1	0	1	—	0	2	7	5
T3	0	1	1	—	0	1	7	1
T4	2	0	1	—	3	2	10	1
N0	1	0	2	—	0	2	8	6
N1	2	1	1	—	3	3	16	5
Nx	0	0	0	—	1	0	1	0
M0	3	1	3	—	1	5	21	11
M1	0	0	0	—	2	0	2	0
Mx	0	0	0	—	1	0	2	0

¹⁸F-FDG-PET, 18-fluorodeoxyglucose positron emission tomography; Init, patients after initial therapy; Rec, patients after recurrent disease; Tg-off, thyroglobulin during thyroxine withdrawal.

Of the nine patients with a true-positive scan, five underwent additional surgery and two patients received additional radiotherapy. Two patients were treated based on their symptoms in a palliative setting. One patient was known to have concurrent metastatic breast cancer; the other patient had an irresectable recurrence after 27 years, for which radiotherapy was already given eight months before the ¹⁸F-FDG-PET scan.

Two patients with a false-positive scan did not receive additional therapy because repeated US and MRI did not show any anatomical substrate that could be confirmed by fine needle aspiration. Both patients did not show recurrent disease during more than eight years of follow-up. One patient with a false-positive scan had a sternotomy with resection of retrosternal tissue based on abnormal uptake on the PET scan, but showed normal thymus and lymph nodes without malignancy on histological examination. None of the patients with a true-negative scan received additional treatment, and these patients have not been diagnosed with a recurrence after a median follow-up of 7.1 years (1.3–11.1).

Of the four patients with a false-negative scan, one underwent additional lymph node dissection and one had a metastasectomy (both with histological confirmation of cancer), whereas two did not undergo additional therapy because there was no metastasis growth as was shown by CT and chest radiography.

Contingent uptake

In eight patients, non-thyroid-cancer-related focal uptake was seen on the ¹⁸F-FDG-PET scan. In one patient, FDG-avid lesions were seen in the axilla. Subsequent CT and MRI showed normal lymph nodes. In another patient, a suspicious FDG-avid lesion was seen in the dorsal neck, but based on its extreme dorsal location, it was considered as non-thyroid cancer related. One scan showed suspicious focal uptake in the adrenal gland region, and on five other scans, focal bowel

uptake suggestive for intestinal polyps was seen. Because of the locations, possible metastases of thyroid cancer seemed unlikely and these incidental lesions were therefore considered negative for thyroid-related cancer. All these patients were monitored for more than five years and received additional imaging, which did not show malignant characteristics.

Tg levels

Five patients with positive TgAb were excluded from all calculations with Tg levels. Analyses were performed on the remaining 47 patients.

The median Tg-off value during ¹³¹I therapy was 8.40 ng/mL (0.18–1870.00), and the median TSH-off value during ¹³¹I therapy was 65.00 mU/L (14.00–224.00). The optimal Tg-off cutoff value to predict a positive scan was determined by an ROC curve analysis. The area under the ROC curve is 0.82 [CI 0.64–0.99], *p* < 0.01. The optimal cutoff value with a Tg-off of 38.00 ng/mL resulted in a sensitivity of 67% and a specificity of 95%. Ninety percent of patients with a positive ¹⁸F-FDG-PET have a Tg-off > 2.00 ng/mL. Ninety percent of patients with a negative ¹⁸F-FDG-PET have a Tg-off < 22.00 ng/mL (Fig. 4).

Discussion

This study evaluated the yield of ¹⁸F-FDG-PET imaging in the early follow-up of patients with a negative post-therapeutic WBS and detectable Tg-off. We have shown that ¹⁸F-FDG-PET imaging performed within three months was true positive in 17% (9 out of 52) of patients with a negative WBS with concurrent detectable Tg, leading to a change in clinical management in the majority (7 out of 9 patients). We did not find a clinically useful Tg cutoff point that could serve as a suitable predictor for a positive ¹⁸F-FDG-PET scan, but 90% of the patients with a positive ¹⁸F-FDG-PET scan have a Tg-off > 2.00 ng/mL. This underscores that in patients with a

FIG. 4. Tg-off values per patient during ^{131}I therapy. The dotted line represents a Tg level of 2.00 ng/mL. Black lines represent median Tg values of groups (5.95 and 44.00 ng/mL, respectively). Tg, thyroglobulin; Tg-off, Tg during thyroxine withdrawal.

Tg-off >2.00 ng/mL, ^{18}F -FDG-PET scanning could be a suitable diagnostic tool in the early workup.

Many studies have been published about the value of ^{18}F -FDG-PET scanning in WBS-negative, Tg-positive patients (8–10,13–16,18,24) with a wide time range between WBS and ^{18}F -FDG-PET scanning, varying from a few days before WBS, up until 23 years after. Some studies do not describe a time interval (8,9,15). Other studies also included WBS-positive and/or Tg-negative patients together with WBS-negative, Tg-positive patients without differentiating between stimulated or unstimulated Tg (8,18,24). To our knowledge, this is the first study with a strict selection of WBS-negative, Tg-positive patients and an early performed ^{18}F -FDG-PET scan.

In the current American Thyroid Association guidelines, the role of ^{18}F -FDG-PET scans in the early diagnostic follow-up is marginally described (25). This study supports arguments for the application of ^{18}F -FDG-PET imaging in a selected group of patients during the early workup after a negative ^{131}I WBS. However, further research with regard to costs and benefits of early ^{18}F -FDG-PET scanning for survival and early treatment of a small patient group is necessary.

Our results show a change of clinical management in seven out of nine patients with a Tg-off value >2.00 ng/mL. This Tg level is much lower than that of earlier studies, which suggest a cutoff value of 10.00 ng/mL (17–19). However, since different Tg assays were used over the years, this Tg cutoff value must be considered as an approximate value (26). If imaging remains negative but Tg remains detectable, the Tg slope or doubling time is important for monitoring disease (27). However, when Tg levels reflect active disease, adequate treatment should be initiated.

Some limitations are encountered in this study. Because of the retrospective design of this study, stimulated and unstimulated ^{18}F -FDG-PET scans were included. The role of stimulation (either endogenous or rhTSH) before the ^{18}F -FDG-PET is still unclear. Some studies show a higher uptake on the ^{18}F -FDG-PET scan in patients undergoing stimulation with endogenous TSH or after rhTSH stimulation (10,12,14,28), while others found opposite results (24,29). Remarkably, our data do not suggest a lower yield of unstimulated ^{18}F -FDG-PET scans; however, this may be due to

chance because of the limited number of patients in our subgroups. Moreover, availability and high costs play a role in the consideration and the desirability of using rhTSH stimulation. Over time, we used three different PET scanners. The vast majority of our patients ($n=45$) were scanned on a PET stand-alone camera. Eight patients were scanned on a PET/CT camera. Sensitivity and specificity seem to improve going from a PET to PET/CT camera, which is in line with previous studies (30,31). However, the size of this group is too small to draw definite conclusions.

Conclusions

Our study shows that ^{18}F -FDG-PET scanning in the early workup after a negative WBS with concurrent detectable Tg-off shows additional tumor localization in 17% (9 out of 52) of the patients and led to a change in clinical management in 7 of these 9 patients. Ninety percent of positive ^{18}F -FDG-PET scans occurred in patients with a Tg-off >2.00 ng/mL; however, a clinically useful Tg-off cutoff value could not be determined.

Author Disclosure Statement

No competing financial interests exist.

References

1. Mazzaferri EL, Kloos RT 2001 Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. *J Clin Endocrinol Metab* **86**:1447–1463.
2. Nixon IJ, Ganly I, Palmer FL, Whitcher MM, Patel SG, Tuttle RM, Shaha AR, Shah JP 2011 Disease-related death in patients who were considered free of macroscopic disease after initial treatment of well-differentiated thyroid carcinoma. *Thyroid* **21**:501–504.
3. Mazzaferri EL, Jhiang SM 1994 Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* **97**:418–428.
4. Podnos YD, Smith D, Wagman LD, Ellenhorn JD 2005 The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. *Am Surg* **71**: 731–734.
5. Schlumberger M, Challeton C, De Vathaire F, Travagli JP, Gardet P, Lumbroso JD, Francese C, Fontaine F, Ricard M, Parmentier C 1996 Radioactive iodine treatment and external radiotherapy for lung and bone metastases from thyroid carcinoma. *J Nucl Med* **37**:598–605.
6. Robbins RJ, Wan Q, Grewal RK, Reibke R, Gonen M, Strauss HW, Tuttle RM, Drucker W, Larson SM 2006 Real-time prognosis for metastatic thyroid carcinoma based on 2-[^{18}F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning. *J Clin Endocrinol Metab* **91**:498–505.
7. van Dijk D, Plukker JT, van der Horst-Schrivers AN, Jansen L, Brouwers AH, Muller-Kobold A, Sluiter WJ, Links TP 2011 The value of detectable thyroglobulin in patients with differentiated thyroid cancer after initial ^{131}I therapy. *Clin Endocrinol (Oxf)* **74**:104–110.
8. Zuidwijk MD, Vogel WV, Corstens FH, Oyen WJ 2008 Utility of fluorodeoxyglucose-PET in patients with differentiated thyroid carcinoma. *Nucl Med Commun* **29**:636–641.
9. Bertagna F, Bosio G, Biasiotto G, Rodella C, Puta E, Gabanelli S, Lucchini S, Merli G, Savelli G, Giubbini R, Rosenbaum J, Alavi A 2009 F-18 FDG-PET/CT evaluation of patients with differentiated thyroid cancer with negative

- I-131 total body scan and high thyroglobulin level. *Clin Nucl Med* **34**:756–761.
10. Vera P, Kuhn-Lansoy C, Edet-Sanson A, Hapdey S, Modzelewski R, Hitzel A, d'Anjou J, Basuyau JP 2010 Does recombinant human thyrotropin-stimulated positron emission tomography with [18F]fluoro-2-deoxy-D-glucose improve detection of recurrence of well-differentiated thyroid carcinoma in patients with low serum thyroglobulin? *Thyroid* **20**:15–23.
 11. Larson SM, Robbins R 2002 Positron emission tomography in thyroid cancer management. *Semin Roentgenol* **37**:169–174.
 12. van Tol KM, Jager PL, Piers DA, Pruim J, de Vries EG, Dullaart RP, Links TP 2002 Better yield of (18)fluorodeoxyglucose-positron emission tomography in patients with metastatic differentiated thyroid carcinoma during thyrotropin stimulation. *Thyroid* **12**:381–387.
 13. Wang W, Macapinlac H, Larson SM, Yeh SD, Akhurst T, Finn RD, Rosai J, Robbins RJ 1999 [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography localizes residual thyroid cancer in patients with negative diagnostic (131I) whole body scans and elevated serum thyroglobulin levels. *J Clin Endocrinol Metab* **84**:2291–2302.
 14. Leboulleux S, Schroeder PR, Busaidy NL, Auperin A, Corone C, Jacene HA, Ewertz ME, Bournaud C, Wahl RL, Sherman SI, Ladenson PW, Schlumberger M 2009 Assessment of the incremental value of recombinant thyrotropin stimulation before 2-[18F]-Fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography imaging to localize residual differentiated thyroid cancer. *J Clin Endocrinol Metab* **94**:1310–1316.
 15. Zoller M, Kohlfuerst S, Igerc I, Kresnik E, Gallowitsch HJ, Gomez I, Lind P 2007 Combined PET/CT in the follow-up of differentiated thyroid carcinoma: what is the impact of each modality? *Eur J Nucl Med Mol Imaging* **34**:487–495.
 16. Menzel C, Zaplatnikov K, Diehl M, Dobert N, Hamscho N, Grunwald F 2004 The influence of thyroglobulin on functional imaging in differentiated thyroid cancer. *Nucl Med Commun* **25**:239–243.
 17. Bertagna F, Biasiotto G, Orlando E, Bosio G, Giubbini R 2010 Role of (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in patients affected by differentiated thyroid carcinoma, high thyroglobulin level, and negative 131I scan: review of the literature. *Jpn J Radiol* **28**:629–636.
 18. Schluter B, Bohuslavizki KH, Beyer W, Plotkin M, Buchert R, Clausen M 2001 Impact of FDG PET on patients with differentiated thyroid cancer who present with elevated thyroglobulin and negative 131I scan. *J Nucl Med* **42**:71–76.
 19. Fletcher JW, Djulbegovic B, Soares HP, Siegel BA, Lowe VJ, Lyman GH, Coleman RE, Wahl R, Paschold JC, Avril N, Einhorn LH, Suh WW, Samson D, Delbeke D, Gorman M, Shields AF 2008 Recommendations on the use of 18F-FDG PET in oncology. *J Nucl Med* **49**:480–508.
 20. Sobin LH, Wittekind C (eds); International Union Against Cancer (UICC) 1997 TNM Classification of Malignant Tumors, 5th edition. John Wiley & Sons, Inc., New York.
 21. Links TP, Huysmans DA, Smit JW, de Heide LJ, Hamming JF, Kievit J, van Leeuwen M, van Pel R, de Klerk JM, van der Wel Y 2007 Guideline 'Differentiated thyroid carcinoma', including diagnosis of thyroid nodules. *Ned Tijdschr Geneesk* **151**:1777–1782.
 22. van Tol KM, Jager PL, de Vries EG, Piers DA, Boezen HM, Sluiter WJ, Dullaart RP, Links TP 2003 Outcome in patients with differentiated thyroid cancer with negative diagnostic whole-body scanning and detectable stimulated thyroglobulin. *Eur J Endocrinol* **148**:589–596.
 23. Working Group Thyroid Carcinoma 2007 Guideline 'Differentiated Thyroid Carcinoma', version 1.0. Available at <http://oncoline.nl/schildkliercarcinoom>. Accessed December 20, 2012.
 24. 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**:986–992.
 25. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM; American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer 2009 Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* **19**:1167–1214.
 26. Schlumberger M, Hitzel A, Toubert ME, Corone C, Troalen F, Schlageter MH, Claustrat F, Koscielny S, Taieb D, Toubreau M, Bonichon F, Borson-Chazot F, Leenhardt L, Schwartz C, Dejax C, Brenot-Rossi I, Torlonato M, Tenenbaum F, Bardet S, Bussiere F, Girard JJ, Morel O, Schneegans O, Schlienger JL, Prost A, So D, Archambeaud F, Ricard M, Benhamou E 2007 Comparison of seven serum thyroglobulin assays in the follow-up of papillary and follicular thyroid cancer patients. *J Clin Endocrinol Metab* **92**:2487–2495.
 27. Baudin E, Do Cao C, Cailleux AF, Leboulleux S, Travagli JP, Schlumberger M 2003 Positive predictive value of serum thyroglobulin levels, measured during the first year of follow-up after thyroid hormone withdrawal, in thyroid cancer patients. *J Clin Endocrinol Metab* **88**:1107–1111.
 28. Elisei R, Schlumberger M, Driedger A, Reiners C, Kloos RT, Sherman SI, Haugen B, Corone C, Molinaro E, Grasso L, Leboulleux S, Rachinsky I, Luster M, Lassmann M, Busaidy NL, Wahl RL, Pacini F, Cho SY, Magner J, Pinchera A, Ladenson PW 2009 Follow-up of low-risk differentiated thyroid cancer patients who underwent radioiodine ablation of postsurgical thyroid remnants after either recombinant human thyrotropin or thyroid hormone withdrawal. *J Clin Endocrinol Metab* **94**:4171–4179.
 29. Grunwald F, Menzel C, Bender H, Palmedo H, Willkomm P, Ruhlmann J, Franckson T, Biersack HJ 1997 Comparison of 18FDG-PET with 131iodine and 99mTc-sestamibi scintigraphy in differentiated thyroid cancer. *Thyroid* **7**:327–335.
 30. Nanni C, Rubello D, Fanti S, Farsad M, Ambrosini V, Rampin L, Banti E, Carpi A, Muzzio P, Franchi R 2006 Role of 18F-FDG-PET and PET/CT imaging in thyroid cancer. *Biomed Pharmacother* **60**:409–413.
 31. Palmedo H, Bucerius J, Joe A, Strunk H, Hortling N, Meyka S, Roedel R, Wolff M, Wardelmann E, Biersack HJ, Jaeger U 2006 Integrated PET/CT in differentiated thyroid cancer: diagnostic accuracy and impact on patient management. *J Nucl Med* **47**:616–624.

Address correspondence to:

Thera P. Links, PhD

Department of Endocrinology

University Medical Centre Groningen

P.O. Box 30.001

9700 RB Groningen

The Netherlands

E-mail: t.p.links@umcg.nl