^{124}I PET/CT to Predict the Outcome of Blind ^{131}I Treatment in Patients with Biochemical Recurrence of Differentiated Thyroid Cancer: Results of a Multicenter Diagnostic Cohort Study (THYROPET)

Jakob W. Kist[1], Bart de Keizer[2], Manfred van der Vlies[3], Adrienne H. Brouwers[4], Dyde A. Huysmans[5], Friso M. van der Zant[6], Rick Hermsen[7], Marcel P.M. Stokkel[1], Otto S. Hoekstra[8], and Wouter V. Vogel[1], for the THYROPET Study Group

[1]Department of Nuclear Medicine, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [2]Department of Nuclear Medicine, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Department of Diagnostics, Groene Hart Ziekenhuis, Gouda, The Netherlands; [4]Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [5]Department of Nuclear Medicine, Catharina Hospital Eindhoven, Eindhoven, The Netherlands; [6]Department of Nuclear Medicine, Medical Center Alkmaar, Alkmaar, The Netherlands; [7]Department of Nuclear Medicine, Radboudumc, Nijmegen, The Netherlands; and [8]Department of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, The Netherlands

Patients with suspected recurrence from differentiated thyroid carcinoma, based on an increased thyroglobulin (Tg) level and negative neck ultrasound (US), pose a clinical dilemma. Because standard imaging has a low yield identifying potential recurrence, blind ^{131}I treatment is often applied. However, a tumor-negative ^{131}I whole-body scintigraphy (WBS) prevails in 38%–50% of patients. We performed a prospective multicenter observational cohort study to test the hypothesis that ^{124}I PET/CT can identify the patients with a tumor-negative posttherapy ^{131}I WBS. **Methods:** Our study was designed to include 100 patients with detectable Tg and a negative neck US, who were planned for blind ^{131}I therapy. All patients underwent ^{124}I PET/CT after administration of recombinant human thyroid-stimulating hormone. Subsequently, after 4–6 wk of thyroid hormone withdrawal patients were treated with 5.5–7.4 GBq of ^{131}I, followed by WBS a week later. The primary endpoint was the number of ^{131}I therapies that could have been omitted using the predicted outcome of the ^{124}I PET/CT, operationalized as the concordance of tumor detection by ^{124}I PET/CT, using post-^{131}I therapy WBS as the reference test. The study would be terminated if 3 patients had a negative ^{124}I PET/CT and a positive posttherapy ^{131}I scan. **Results:** After inclusion of 17 patients, we terminated the study preliminarily because the stopping rule had been met. Median Tg level at ^{131}I therapy was 28 μg/L (interquartile range, 129). Eight posttherapy WBS were negative (47%), all of which were correctly predicted by negative ^{124}I PET/CT. Nine posttherapy WBS showed iodine-avid tumor, of which 4 also had positive ^{124}I PET/CT findings. Sensitivity, specificity, negative predictive value, and positive predictive value of ^{124}I PET/CT were 44% (confidence interval [CI], 14%–79%), 100% (CI, 63%–100%), 62% (CI, 32%–86%), and 100% (CI, 40%–100%), respectively. Implementation of ^{124}I PET in this setting would have led to 47% (8/17) less futile ^{131}I treatments, but 29% of patients (5/17) would have been denied potentially effective therapy. **Conclusion:** In patients with biochemical evidence of recurrent differentiated thyroid carcinoma and a tumor-negative neck US, the high false-negative rate of ^{124}I PET/CT after recombinant human thyroid-stimulating hormone ^{124}I PET/CT as implemented in this study precludes its use as a scouting procedure to prevent futile blind ^{131}I therapy.

Key Words: ^{124}I PET/CT; differentiated thyroid cancer; ^{131}I; radioactive iodine

J Nucl Med 2016; 57:701–707
DOI: 10.2967/jnumed.115.168138

Differentiated thyroid cancer (DTC) incidence is rising, and it is the most prevalent endocrine cancer. Although patients have an excellent 10-y survival rate of higher than 95% (*1,2*), up to 25% of patients will face recurrent locoregional disease or distant metastasis (*3*). Prognosis is less favorable when recurrences and metastases occur (*1*). When recurrence is suspected based on serum thyroglobulin (Tg) levels, without clinical evidence of locoregional metastasis, patients are treated empirically with high-dose ^{131}I (*4,5*). However, this blind therapy can be considered as futile in the 38%–50% of patients with a tumor-negative posttherapeutic whole-body scintigraphy (WBS) (*6–9*). On top of that, ^{131}I therapy induces substantial short- and long-term morbidity due to hormone withdrawal–associated hypothyroidism and early and late sialoadenitis in up to 30%, which can lead to xerostomia, dental cariës, and stomatitis (*10,11*). Moreover, societal costs are considerable because of productivity loss (*12,13*). Therefore, there is a need for a diagnostic modality to predict which patients are likely to benefit from high-dose ^{131}I therapy. The yield of low-dose ^{131}I and of ^{123}I WBS in this setting is low so that they are no longer recommended (*14–17*).

^{124}I PET/CT has been investigated in DTC patients for several years (*18–20*). Apart from the superior imaging characteristics of

Received Oct. 13, 2015; revision accepted Nov. 11, 2015.
For correspondence or reprints contact: Jakob W. Kist, Department of Nuclear Medicine, The Netherlands Cancer Institute, Plesmanlaan 121, 1066CX, Amsterdam, The Netherlands.
E-mail: j.kist@nki.nl
Published online Nov. 25, 2015.

PET (compared with SPECT), ^{124}I PET/CT offers lower radiation exposure for the patient in comparison to blind ^{131}I therapy, and it may be a tool for pretherapeutic dosimetry (*8,18,21*). Taken together, ^{124}I PET/CT potentially allows for accurate restaging of DTC, prediction of ^{131}I therapy outcome, and better selection of patients for ^{131}I treatment. However, prospective studies with clear eligibility criteria and standardized procedures, comparing ^{124}I PET/CT outcomes with posttherapy ^{131}I WBS in patients treated blind with ^{131}I, are lacking.

Iodine uptake in metastases can be stimulated exogenously, using recombinant human thyroid-stimulating hormone (rhTSH) (Thyrogen; Genzyme Corp.) or endogenously by thyroid hormone withdrawal (THW). Because the latter induces morbidity associated with severe hypothyroidism and may stimulate tumor growth, pretherapeutic scanning, aiming to predict uptake on ^{131}I WBS (and potential therapy efficacy), is preferably done after rhTSH stimulation. However, it is unclear whether and to which extent patient preparation with rhTSH rather than THW affects the diagnostic accuracy of ^{124}I PET/CT.

The clinical research question of this study was to determine whether futile ^{131}I treatment could be prevented by pretherapeutic imaging with ^{124}I PET/CT in patients with biochemical suspicion of recurrence without clinical evidence of locoregional metastases. Furthermore, we aimed to investigate the effect of the thyroid-stimulating hormone (TSH) method on diagnostic performance of ^{124}I PET/CT in this clinical setting.

MATERIALS AND METHODS

Study Design

The THYROPET study was designed as a prospective nationwide multicenter diagnostic cohort study (Clinicaltrials.gov identifier: NCT01641679) (*22*). The study was approved by the institutional review board of The Netherlands Cancer Institute and by the local institutional review boards of the 17 participating centers. This study was investigator-initiated and conducted in accordance with the principles of the Declaration of Helsinki and good clinical practice guidelines. All participants provided written informed consent.

Patients

Adult patients with biochemical suspicion of recurrence of previously treated DTC (serum Tg $>$ 2 ng/mL), without evidence of locoregional recurrence (negative ultrasound of the neck), who were planned for blind treatment with high-dose ^{131}I were eligible for inclusion (Table 1). Main exclusion criteria were recent ^{131}I therapy ($<$12 mo before inclusion) and any indication for another treatment modality (e.g., surgery).

Procedures

Pretherapeutic Phase. Patients received rhTSH (0.9 mg) intramuscularly on 2 consecutive days, 1 d after the second rhTSH administration; 74 MBq of ^{124}I were administered intravenously, followed by ^{124}I PET/CT 24 and 96 h later.

Therapeutic Phase. Patients were requested to keep a 1-wk low-iodine diet before ^{131}I therapy. When TSH was 25 mIU/L or more or after at least 4 wk of THW, patients were admitted for ^{131}I therapy (5.5 or 7.4 GBq). In centers in which local radiation safety regulations allowed such, patients underwent repeated ^{124}I PET/CT during ^{131}I treatment: a second dose of ^{124}I was intravenously injected directly after the administration of ^{131}I, and PET/CT was performed after 24 and 96 h. One week after ^{131}I, all patients underwent posttherapy WBS or SPECT/CT. In addition (data not presented here), all patients underwent ^{18}F-FDG PET/CT in the pretherapeutic phase and ^{18}F-FDG and ^{124}I PET/CT 6 mo after therapy (*22*).

Image Acquisition. PET/CT scanners of participating centers were calibrated for ^{124}I to ensure adequate image quality (*23*). All ^{124}I PET/CT scans were obtained according to the scan protocol associated to this study, which included an administered dose of 74 MBq and optimized settings for ^{124}I. Scan trajectories (PET and WBS) covered perineum-skull vertex, for a scan time of 30 min. A standard energy window was applied for all PET acquisitions. European Association of Nuclear Medicine Research Ltd. reconstruction parameters were used (*24*). If available, time-of-flight acquisition and reconstruction were performed. WBS was performed as planar scintigraphy, combined with SPECT/CT according to standard local procedures.

Image Interpretation. An expert panel of 3 independent experienced nuclear medicine physicians reviewed all PET/CT scans, blinded to the ^{131}I WBS results. The posttherapy ^{131}I WBS were assessed separately by 2 other experienced nuclear medicine physicians. All scans were scored as malignant, equivocal, or nonsuspicious. Any disagreement between reviewers was discussed to reach consensus. If a scan was scored as equivocal it was considered malignant in the analysis to obtain maximal sensitivity.

Quantitative analysis of ^{124}I PET/CT was performed using manually drawn volumes of interest, measuring the total activity (kBq) within the lesion, corrected with the calibration factor determined for that scanner at calibration (*23*).

TABLE 1
Inclusion and Exclusion Criteria of THYROPET Study

Inclusion criteria	Exclusion criteria
1. Patients with a history of DTC	1. Age $<$ 18 y
2. After complete thyroidectomy and ablation of functional remnants with ^{131}I	2. Pregnancy
3. Planned for blind treatment with high activity of ^{131}I based on biochemically suspected recurrence, defined as a Tg-level above 2.0 ng/mL	3. Incapacitated subjects
4. Ultrasonography of the neck performed $<$ 2 mo before inclusion	4. Contrast-enhanced CT performed $<$ 4 mo before inclusion
	5. ^{131}I therapy performed $<$ 12 mo before inclusion
	6. Indication for other therapy modality (i.e., surgery in case of a positive ultrasonography, radiotherapy, embolization, or chemotherapy)

Outcomes

The primary endpoint of this study was the accuracy of ^{124}I PET/CT to predict, at a patient level, the posttherapy ^{131}I WBS test result, as an operationalization of the impact of the implementation of ^{124}I PET/CT as a scouting procedure to set the indication for ^{131}I therapy. The secondary endpoint was a quantitative and visual comparison between ^{124}I PET/CT performed after rhTSH stimulation (rhTSH-^{124}I PET/CT) and after thyroid hormone withdrawal combined with low-iodine diet (THW-^{124}I PET/CT).

Statistical Methods

The study was designed to define the accuracy of ^{124}I PET/CT to predict the result of post-high-dose ^{131}I WBS. The power calculation was based on the (conservative) assumption of 40% futile blind ^{131}I treatments (*6,7*). With a sample size of 100 evaluable patients, a 2-sided 95.0% confidence interval (CI) for a single proportion using the Pearson–Clopper method for constructing the CI (exact binomial CI) would extend 10% from the observed proportion for an expected proportion of 40%.

Because wrongfully withholding potentially curative treatment for these patients is unacceptable, we decided to preleminary terminate the study if 3 patients had ^{124}I PET/CT scans that turned out false-negative (1-sided 95% CI upper limit, 12%). There was continuous monitoring of false-negative ^{124}I PET/CTs by the local study coordinators, followed by central adjudication by the central expert panel.

Patient demographic data, tumor characteristics, and data derived from the scans are described in frequency tables. Accuracy measures such as sensitivity, specificity, positive predictive value, and negative predictive value were calculated using the per-patient result of ^{124}I PET/CT and ^{131}I WBS as index and reference test, respectively.

RESULTS

The study was open for inclusion from December 2012 to May 2014. In May 2014, a third false-negative ^{124}I PET/CT (vs. ^{131}I WBS) was reported to the study coordinators, and when this finding was confirmed at central review, the study was preliminarily terminated according to the predetermined stopping rule. Because safety was not compromised, study procedures were completed in all 19 patients included until then. All patients underwent rhTSH-^{124}I PET/CT in the pretherapeutic phase, and 5 patients underwent additional THW-^{124}I PET/CT in the therapeutic phase.

Of these 19 patients, 2 were excluded from the ^{124}I PET/CT versus ^{131}I WBS comparison. One patient was excluded because other imaging, performed due to clinical signs and symptoms, had shown numerous distant metastases, among which were vertebral metastases threatening the spinal cord. In agreement with an escape rule in the protocol (i.e., allowing the attending physician to withdraw a subject from the study for urgent medical reasons), it was decided to refrain from ^{131}I therapy and to start immediate palliative radiotherapy on the spinal metastases. Another patient was excluded because the elevated Tg level at the time of inclusion was not reproduced at an additional assessment during the study before ^{131}I therapy.

The baseline characteristics of the 17 evaluable patients are listed in Table 2. Nine patients had previously received more than 1 ^{131}I treatment, with a mean interval between last ^{131}I treatment and inclusion of 5.6 y; the median serum Tg level at ^{131}I therapy was 28 μg/L (interquartile range, 129).

Patient-based analysis showed that 9 of 17 posttherapy ^{131}I scans were tumor-positive (53%; CI, 28%–77%). ^{124}I PET/CT scans showed uptake compatible with tumor activity in 4 of 17 scans (Table 3). In these 4 patients with a positive ^{124}I PET/CT finding, the posttherapy ^{131}I WBS was concordant (patients 2, 3, 7, and 16). In the 8 patients with negative posttherapy ^{131}I scans, ^{124}I PET/CT scans were also negative. However, of the 13 ^{124}I PET/CT scans with no pathologic uptake, 5 were false-negative (Figs. 1 and 2). One ^{124}I-positive lymph node was surgically removed before the ^{131}I therapy (i.e., protocol violation); this lesion was not included in the analysis (patient 14). At a patient level, the sensitivity, specificity, negative predictive value, and positive predictive value of ^{124}I PET/CT (vs. ^{131}I WBS) were 44% (CI, 14%–79%), 100% (CI, 63%–100%), 62% (CI, 32%–86%), and 100% (CI, 40%–100%), respectively (Table 4).

Lesion-based analysis showed that the posttherapy ^{131}I WBS revealed 14 lesions versus 8 on ^{124}I PET/CT (miliary lung metastases in patient 5 were counted as 1 lesion). The size of 3 of 7 lesions, false-negative at ^{124}I PET/CT, could not be determined because no anatomic substrate was seen on CT (patients 5, 9, and

TABLE 2
Baseline Characteristics of Subjects at Time of Inclusion (n = 17)

Characteristic	n or mean ± SD	% or range
Age at inclusion (y)	56 ± 16	23–80
Sex		
Male	9	53
Female	8	47
Histopathology		
Papillary thyroid carcinoma	10	59
Follicular thyroid carcinoma	3	18
Minimally invasive follicular thyroid carcinoma	1	6
Follicular variant of papillary thyroid carcinoma	2	12
Unknown*	1	6
Stage TNM		
T1–2N0M0	5	29
T1–2N1M0	4	24
T1–2N0M1	1	6
T3–4N0M0	4	24
T3–4N1M0	3	18
Time since primary tumor (mo)	88 ± 82	15–305
Time since last ^{131}I therapy (mo)	67 ± 72	15–304
Number of previous ^{131}I therapies		
1	8	47
2	4	24
3	3	18
4	2	12
Cumulative dose of ^{131}I before inclusion (GBq)	10 ± 7.2	1.9–29.6
Tg at time of therapy (μg/L)†	99 ± 151	2.1–531.3

*Patient was operated on abroad, histopathology primary tumor not known.

†After thyroid hormone withdrawal.

TABLE 3
Overview of Included Patients

Patient no.	Histology	TNM	Tg*	Pretherapy (after rhTSH), ^{124}I PET/CT, 24 h	Therapy phase (after THW)		Remarks and follow-up
					^{124}I PET/CT, 24 h	^{131}I WBS (+SPECT/CT)	
1	PTC	T2N1aM0	5	Negative	ND	N-S: thymus	Tg ⇑
2	PTC	T1aN0M1	32	Positive: C4	Positive: C4	Positive: C4	Quantitative analysis ^{124}I uptake (see text)
							Tg =
3	miFTC	T2N0M0	16	Positive: LN retrosternal	Positive: LN retrosternal	Positive: LN retrosternal	MRI, bone scan & target US liver/thoracic wall: negative
				Equivocal: liver/thoracic wall		Equivocal: liver/thoracic wall	Surgery: retrosternal LN resected: thymic remnant
							Tg ⇑
4	fvPTC	T2N1bM0	12	Negative	Negative	Negative	Tg decreased after surgery for ^{18}F-FDG avid LNM
5	PTC	T3N1bM0	184	Negative	ND	Disseminated lung metastasis	False-negative ^{124}I PET/CT
							Tg ⇓
6	miFTC	T3N0M0	27	Negative	ND	Negative	Tg ⇑
7	FTC	T3N0M0	148	Positive: LN aortopulmonary window	ND	Positive: LN aortopulmonary window	Tg ⇓
				Equivocal: nodule lung		Equivocal: nodule lung	
8	PTC	T2N0M0	13	Negative	ND	Negative	Tg ⇑
9	PTC	T3N0M0	38	Negative	Negative	Positive: nodule lung, no anatomic substrate on CT	False-negative ^{124}I PET/CT
						N-S: thymus	Tg ⇓
10	PTC	T2N0M0	2	Negative	ND	Negative	Tg =
11	PTC	T3N1bM0	3	Negative	Negative	Positive: 3 lung nodules; 7, 5 and 5 mm	False-negative ^{124}I PET/CT
							Tg ⇓
12	PTC	T1bN0M0	107	Negative	ND	Positive: LN neck level 6: 12 mm	False-negative ^{124}I PET/CT
						N-S: thymus	Surgery: node picking ^{131}I avid LN: metastasis
							Tg ⇑
13	PTC	T1bN1bM0	28	Negative	ND	Negative	Tg =
14	FTC	T1mN1bM0	127	Positive: LN supraclavicular†	ND	Positive: lung nodule, no anatomic substrate on CT	False-negative ^{124}I PET/CT
							Surgery: node picking supraclavicular: no metastasis‡
							Tg ⇓
15	NK	T1bN0M0	5	Negative	ND	Negative	Tg =
16	FTC	T4N1bM0	533	Positive: 2 LNs neck level 3	ND	Positive: 2 LNs neck level 3	Follow-up ^{124}I PET/CT scan: LNs not ^{124}I-avid anymore
							Tg ⇓, became undetectable
17	fvPTC	T3N0M0	400	Negative	ND	Negative	Tg ⇑

*Tg in μg/L at time of therapy (after THW).

†LN surgically removed before ^{131}I therapy, therefore not included in diagnostics accuracy calculations (i.e., protocol violation).

PTC = papillary thyroid cancer; ND = not done; N-S = not suspicious; Tg ⇑/⇓ = thyroglobulin level increased/decreased during follow-up; Tg= = thyroglobulin level remained stable during follow-up; miFTC = minimally invasive follicular thyroid cancer; LN = lymph node; US = neck ultrasound; LNM = lymph node metastases; fvPTC = follicular variant of papillary thyroid cancer; FTC = follicular thyroid cancer; NK = not known.

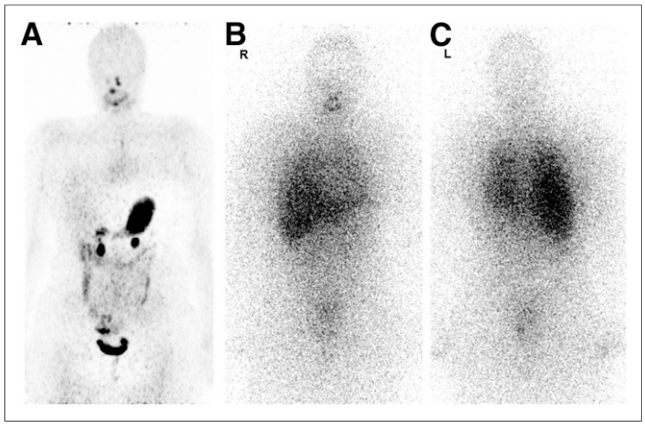

FIGURE 1. Patient 5 with negative ^{124}I PET/CT (A) with disseminated lung metastases on ^{131}I WBS (anterior [B] and posterior [C]).

16). The other false-negative lesions measured 5, 5, and 7 mm (all lung lesions, patient 11) and 12 mm in diameter (retroclavicular lymph node, patient 12).

The ^{124}I PET/CT scans after 24 and 96 h were on the patient level concordant in all but 2 patients (patients 3 and 14). In those patients, the lesions could not be depicted above the background noise after 96 h. No additional lesions were seen after 96 h.

Five patients underwent ^{124}I PET/CT after rhTSH stimulation as well as THW during ^{131}I therapy. No additional lesions were seen on THW-^{124}I PET/CT in comparison to the rhTSH-^{124}I PET/CT. Two of these patients (patients 2 and 3) showed pathologic ^{124}I uptake on either scan. Patient 2 showed enhanced uptake (residual disease) around an orthopedic cage placed in vertebra C4 after resection of a DTC metastasis (Fig. 3). At 24 h after ^{124}I administration, lesional tracer uptake was 13 kBq after rhTSH stimulation (0.02% of injected dose ^{124}I) versus 332 kBq after THW (0.56% of injected dose ^{124}I).

The positive lesion in patient 3 was located in the mediastinum and was thought to represent a lymph node metastasis (corresponding with a 3- to 4-mm node at CT). ^{18}F-FDG PET/CT had identified another suggestive mediastinal lymph node, negative on either iodine scan. At subsequent resection of this focus, the iodine-positive lesion was also removed. Histopathology revealed thymic tissue. ^{124}I uptake in this lesion was below 2 kBq, both after THW and after rhTSH, precluding reliable quantification.

DISCUSSION

Our results demonstrated that rhTSH-stimulated ^{124}I PET/CT as applied in this study was not suited to avoid futile blind ^{131}I therapy, because of its high false-negativity rate (38%; 5/13). If ^{124}I PET/CT results would have been used to guide therapy, potentially beneficial ^{131}I therapy would have been withheld in 5 of 17 (29%). To our knowledge, this is the first prospective study performing a head-to-head comparison of pretherapeutic ^{124}I PET/CT with posttherapy ^{131}I WBS in a well-defined cohort of patients planned for blind ^{131}I therapy. The high rate of futile therapies in our study, 47% (8/17), is consistent with published data, corroborating the need for better pretherapeutic diagnostic modalities (*6,7*).

Several publications described comparisons of ^{124}I PET/CT and ^{131}I WBS in thyroid cancer patients, but the results are inconsistent and difficult to compare with the results of the current study, because of variable clinical settings, study aims and inclusion criteria (*8,19,25–29*), methodologic design (*28,30*), different ^{131}I

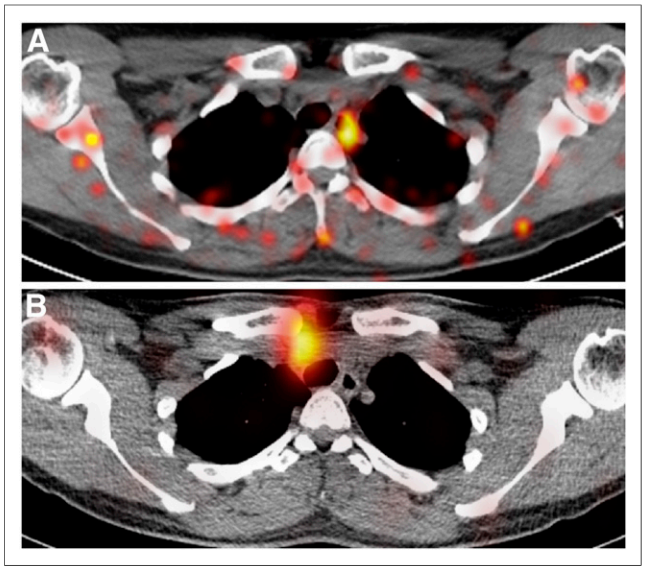

FIGURE 2. Patient 12 without pathologic uptake of ^{124}I on PET/CT, only physiologic uptake in esophagus (A) and a positive ^{131}I SPECT/CT finding, showing uptake in retroclavicular lymph node, which was confirmed as metastasis after surgical removal (B).

dosages (*8,29*), diagnostic ^{131}I WBS (*27,28*), and nonstandardized or variable patient preparation methods (*8,25,27,28,30*). Of these studies, the recent study by Khorjekar et al. is of interest because it specifically describes a cohort of 12 patients with suggestion of metastatic DTC, selected from different databases, in which a negative ^{124}I PET/CT finding was followed by a posttherapeutic ^{131}I WBS (*30*). In 10 patients, the ^{131}I WBS revealed pathologic uptake. Another study of interest reported that, similarly to patient 5 in our cohort (Fig. 1), ^{124}I PET can be false-negative in the case of disseminated lung metastases (*31*).

Biologic as well as technical issues may have caused ^{124}I PET/CT scans to be false-negative. First, the method of TSH stimulation by rhTSH, instead of by THW in combination with a low-iodine diet, might have compromised the sensitivity of ^{124}I PET/CT. This hypothesis seems to be supported by the observation in patient 2, in whom after THW and a low-iodine diet the ^{124}I uptake was 23 times higher than after rhTSH stimulation (Fig. 3). Quantification of ^{124}I might be affected by concurrent presence of ^{131}I. However, a recently published phantom study showed that ^{131}I did not affect the accuracy of ^{124}I quantification (*32*). One other study has reported that significantly more foci were detected on both ^{124}I PET and ^{131}I WBS after THW stimulation in comparison to rhTSH stimulation (*28*). However, in that study interpatient comparisons were used rather than the head-to-head comparison in our study.

TABLE 4
Patient-Based Analysis of Outcome of ^{124}I PET/CT and ^{131}I WBS

^{124}I PET/CT	^{131}I WBS, positive	^{131}I WBS, negative	Total
Positive	4	0	4
Negative	5	8	13
Total	9	8	17

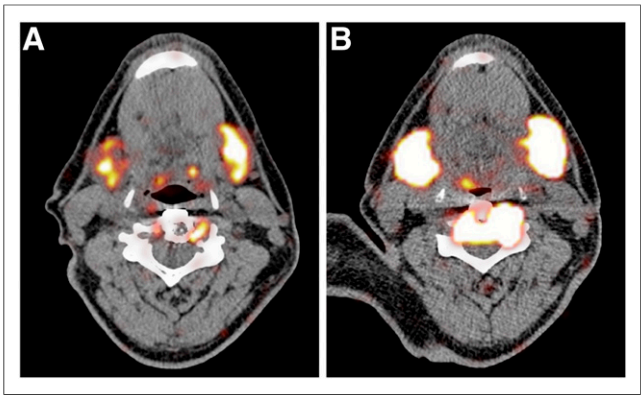

FIGURE 3. ^{124}I PET/CT of patient 2 with increased uptake of ^{124}I in metastatic lesion in C4 after THW (B) compared with rhTSH (A).

Only a few cases with intrapatient comparisons of imaging after both THW and rhTSH have been described in previous studies. Freudenberg et al. described 1 case in which both an adrenal and a lymph node metastasis were seen only on ^{124}I PET/CT after THW and not after rhTSH stimulation (*33*). Another study described 4 cases with 10 metastatic DTC lesions showing a 9%–62% higher iodine uptake after THW than rhTSH stimulation (*34*). Additionally, a dosimetric analysis of 3 patients with 22 metastatic lesions revealed an increased absorbed dose after THW in comparison to rhTSH in all but 2 lesions (*35*). Considering these results from previous studies and our findings, it might very well be that rhTSH patient preparation for ^{124}I PET/CT may lead to false-negative ^{124}I PET/CT scans; however, future studies with head-to-head comparisons are warranted to confirm this.

Second, we can only speculate whether the 74-MBq ^{124}I dosage in our study contributed to the observed false negativity. Even though this dosage is higher than in most published studies (23–64 MBq) (*25,27,30,31,36–38*), Ho et al. recently reported the use of 222 MBq of ^{124}I in patients with metastatic DTC refractory to radioiodine (*39*). Additionally, it is unclear whether improved PET scan technology (scanner design (*40*) or ^{124}I reconstruction protocols) will improve ^{124}I PET performance to a clinically relevant extent in this context. If in vitro data support the notion that detectability significantly improves by such innovations or higher ^{124}I dosages, the current study should be repeated.

In our opinion, a scouting procedure using ^{124}I PET/CT still remains the most rational strategy to reduce futile ^{131}I therapies, but optimization is clearly required.

CONCLUSION

In patients with biochemical recurrence of DTC and a negative ultrasound of the neck, ^{124}I PET/CT after rhTSH stimulation before blind ^{131}I therapy, as applied in this study, does correctly predict tumor-positive uptake on posttherapeutic ^{131}I WBS. Because of the high false-negative rate of ^{124}I PET/CT, ^{131}I should not be omitted based on a negative ^{124}I PET/CT.

DISCLOSURE

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. Research support was provided by the Dutch Cancer Society (NKI 2011-5024). BV Cyclotron VU (Amsterdam, the Netherlands) provided ^{124}I as an unrestricted study grant. No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

We acknowledge all the efforts of the participating centers. Furthermore, we thank the members of the independent review committee (Sakar Abdul-Fatah, Marnix Lam, and Pieter Raijmakers). The other members of the THYROPET Study group are John M.H. de Klerk, Meander Medical Center Amersfoort; Harm van Tinteren, Netherlands Cancer Institute; Jan Paul de Boer, Netherlands Cancer Institute; Hans Morreau, Leiden University Medical Center; Marc C. Huisman, VU University Medical Center; Eef G.W.M. Lentjes, University Medical Center Utrecht; Thera P. Links, University Medical Center Groningen; Jan W.A. Smit, Radboudumc; Jules Lavalaye, St. Antonius Hospital Nieuwegein; Piet L. de Jager, Isala Clinics; Corneline J. Hoekstra, Medical Center Jeroen Bosch; Martin Gotthardt, Radboudumc; Vanessa J.R. Schelfhout, Rijnstate Hospital; Wieger I. de Bruin, Medisch Spectrum Twente; Ferida Sivro, OLVG; Judit A. Adam, Amsterdam Medical Center; Ha T.T. Phan, Medical Center Leeuwarden; Gerrit W. Sloof, Groene Hart Hospital; and Nils R.L. Wagenaar, ZGT.

REFERENCES

1. Davies L, Welch HG. Current thyroid cancer trends in the United States. *JAMA Otolaryngol Head Neck Surg.* 2014;140:317–322.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin.* 2010;60:277–300.
3. Shaha AR. Recurrent differentiated thyroid cancer. *Endocr Pract.* 2012;18:600–603.
4. Links TP, Huysmans DAKCJM, Smit JWA, et al. Guideline "differentiated thyroid carcinoma," including diagnosis of thyroid nodules. *Ned Tijdschr Geneeskd.* 2007;151:1777–1782.
5. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2009;19:1167–1214.
6. Ma C, Xie J, Kuang A. Is empiric ^{131}I therapy justified for patients with positive thyroglobulin and negative ^{131}I whole-body scanning results? *J Nucl Med.* 2005;46:1164–1170.
7. van Tol KM, Jager PL, de Vries EGE, et al. Outcome in patients with differentiated thyroid cancer with negative diagnostic whole-body scanning and detectable stimulated thyroglobulin. *Eur J Endocrinol.* 2003;148:589–596.
8. Pettinato C, Spezi E, Nanni C, et al. Pretherapeutic dosimetry in patients affected by metastatic thyroid cancer using ^{124}I PET/CT sequential scans for ^{131}I treatment planning. *Clin Nucl Med.* 2014;39:e367–e374.
9. Smallridge RC, Diehl N, Bernet V. Practice trends in patients with persistent detectable thyroglobulin and negative diagnostic radioiodine whole body scans: a survey of American Thyroid Association Members. *Thyroid.* 2014;24:1501–1507.
10. Van Nostrand D. Sialoadenitis secondary to ^{131}I therapy for well-differentiated thyroid cancer. *Oral Dis.* 2011;17:154–161.
11. Fard-Esfahani A, Emami-Ardekani A, Fallahi B, et al. Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma. *Nucl Med Commun.* 2014;35:808–817.
12. Luster M, Felbinger R, Dietlein M, Reiners C. Thyroid hormone withdrawal in patients with differentiated thyroid carcinoma: a one hundred thirty-patient pilot survey on consequences of hypothyroidism and a pharmacoeconomic comparison to recombinant thyrotropin administration. *Thyroid.* 2005;15:1147–1155.
13. Dow KH, Ferrell BR, Anello C. Quality-of-life changes in patients with thyroid cancer after withdrawal of thyroid hormone therapy. *Thyroid.* 1997;7:613–619.
14. Pacini F, Agate L, Elisei R, et al. Outcome of differentiated thyroid cancer with detectable serum Tg and negative diagnostic ^{131}I whole body scan: comparison of patients treated with high ^{131}I activities versus untreated patients. *J Clin Endocrinol Metab.* 2001;86:4092–4097.

15. Cailleux AF, Baudin E, Travagli JP, Ricard M, Schlumberger M. Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid cancer? *J Clin Endocrinol Metab.* 2000;85:175–178.
16. Pacini F, Capezzone M, Elisei R, Ceccarelli C, Taddei D, Pinchera A. Diagnostic 131-iodine whole-body scan may be avoided in thyroid cancer patients who have undetectable stimulated serum Tg levels after initial treatment. *J Clin Endocrinol Metab.* 2002;87:1499–1501.
17. Pacini F, Molinaro E, Castagna MG, et al. Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. *J Clin Endocrinol Metab.* 2003;88:3668–3673.
18. Lubberink M, Abdul Fatah S, Brans B, Hoekstra OS, Teule GJJ. The role of ^{124}I-PET in diagnosis and treatment of thyroid carcinoma. *Q J Nucl Med Mol Imaging.* 2008;52:30–36.
19. Phan HTT, Jager PL, Paans AMJ, et al. The diagnostic value of ^{124}I-PET in patients with differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging.* 2008;35: 958–965.
20. Freudenberg LS, Jentzen W, Stahl A, Bockisch A, Rosenbaum-Krumme SJ. Clinical applications of ^{124}I-PET/CT in patients with differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging.* 2011;38(suppl 1):S48–S56.
21. Freudenberg LS, Jentzen W, Görges R, et al. ^{124}I-PET dosimetry in advanced differentiated thyroid cancer: therapeutic impact. *Nuklearmedizin.* 2007;46: 121–128.
22. Kist JW, de Keizer B, Stokkel MPM, Hoekstra OS, Vogel WV, THYROPET study group. Recurrent differentiated thyroid cancer: towards personalized treatment based on evaluation of tumor characteristics with PET (THYROPET Study): study protocol of a multicenter observational cohort study. *BMC Cancer.* 2014;14:405–413.
23. van der Vlies M, Kist J, Greuter H. Multi-center calibration of PET/CT scanners for iodine-124 [abstract]. *J Nucl Med.* 2013;54(suppl 2):373.
24. Boellaard R, O'Doherty MJ, Weber WA, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. *Eur J Nucl Med Mol Imaging.* 2010;37:181–200.
25. de Pont C, Halders S, Bucerius J, Mottaghy F, Brans B. ^{124}I PET/CT in the pretherapeutic staging of differentiated thyroid carcinoma: comparison with posttherapy ^{131}I SPECT/CT. *Eur J Nucl Med Mol Imaging.* 2013;40:693–700.
26. Freudenberg LS, Antoch G, Jentzen W, et al. Value of ^{124}I-PET/CT in staging of patients with differentiated thyroid cancer. *Eur Radiol.* 2004;14:2092–2098.
27. Van Nostrand D, Moreau S, Bandaru VV, et al. ^{124}I positron emission tomography versus ^{131}I planar imaging in the identification of residual thyroid tissue and/or metastasis in patients who have well-differentiated thyroid cancer. *Thyroid.* 2010;20:879–883.
28. Van Nostrand D, Khorjekar GR, O'Neil J, et al. Recombinant human thyroid-stimulating hormone versus thyroid hormone withdrawal in the identification of metastasis in differentiated thyroid cancer with ^{131}I planar whole-body imaging and ^{124}I PET. *J Nucl Med.* 2012;53:359–362.
29. Capoccetti F, Criscuoli B, Rossi G, Ferretti F, Manni C, Brianzoni E. The effectiveness of ^{124}I PET/CT in patients with differentiated thyroid cancer. *Q J Nucl Med Mol Imaging.* 2009;53:536–545.
30. Khorjekar GR, Van Nostrand D, Garcia C, et al. Do negative ^{124}I pretherapy positron emission tomography scans in patients with elevated serum thyroglobulin levels predict negative ^{131}I posttherapy scans? *Thyroid.* 2014;24:1394–1399.
31. Freudenberg LS, Jentzen W, Müller SP, Bockisch A. Disseminated iodine-avid lung metastases in differentiated thyroid cancer: a challenge to ^{124}I PET. *Eur J Nucl Med Mol Imaging.* 2008;35:502–508.
32. Braad PEN, Hansen SB, Høilund-Carlsen PF. Impact of high ^{131}I-activities on quantitative ^{124}I-PET. *Phys Med Biol.* 2015;60:5297–5312.
33. Freudenberg LS, Jentzen W, Petrich T, et al. Lesion dose in differentiated thyroid carcinoma metastases after rhTSH or thyroid hormone withdrawal: ^{124}I PET/CT dosimetric comparisons. *Eur J Nucl Med Mol Imaging.* 2010;37:2267–2276.
34. Pötzi C, Moameni A, Karanikas G, et al. Comparison of iodine uptake in tumour and nontumour tissue under thyroid hormone deprivation and with recombinant human thyrotropin in thyroid cancer patients. *Clin Endocrinol (Oxf).* 2006;65:519–523.
35. Plyku D, Hobbs R, Huang K, et al. ^{124}I-PET/CT based tumor dosimetry for ^{131}I therapy of metastatic differentiated thyroid cancer (DTC): a comparison of recombinant human thyroid-stimulating hormone vs thyroid hormone withdrawal patient preparation methods [abstract]. *J Nucl Med.* 2015;56(suppl 3):394.
36. Hartung-Knemeyer V, Nagarajah J, Jentzen W, et al. Pre-therapeutic blood dosimetry in patients with differentiated thyroid carcinoma using 124-iodine: predicted blood doses correlate with changes in blood cell counts after radioiodine therapy and depend on modes of TSH stimulation and number of preceding radioiodine therapies. *Ann Nucl Med.* 2012;26:723–729.
37. Freudenberg LS, Antoch G, Frilling A, et al. Combined metabolic and morphologic imaging in thyroid carcinoma patients with elevated serum thyroglobulin and negative cervical ultrasonography: role of ^{124}I-PET/CT and FDG-PET. *Eur J Nucl Med Mol Imaging.* 2008;35:950–957.
38. Nagarajah J, Jentzen W, Hartung V, et al. Diagnosis and dosimetry in differentiated thyroid carcinoma using ^{124}I PET: comparison of PET/MRI vs PET/CT of the neck. *Eur J Nucl Med Mol Imaging.* 2011;38:1862–1868.
39. Ho AL, Grewal RK, Leboeuf R, et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. *N Engl J Med.* 2013;368:623–632.
40. Nguyen NC, Vercher-Conejero JL, Sattar A, et al. Image quality and diagnostic performance of a digital PET prototype in patients with oncologic diseases: initial experience and comparison with analog PET. *J Nucl Med.* 2015;56:1378–1385.