Clinical Relevance of Single-Photon Emission Computed Tomography/Computed Tomography of the Neck and Thorax in Postablation ^{131}I Scintigraphy for Thyroid Cancer

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Context: In patients with differentiated thyroid carcinoma, postablation ^{131}I scintigraphy aims to detect residual neck disease and distant metastases, usually found in lungs and bones. New hybrid single-photon emission computed tomography/computed tomography (SPECT-CT) cameras that permit functional and anatomical image fusion may improve its clinical relevance.

Objective: Our objective was to test the added value of neck and thorax SPECT-spiral CT to whole-body scan (WBS) in postablation ^{131}I scintigraphy.

Design and Setting: This was a single-referral-center prospective study with a median follow-up of 21 months.

Patients and Methods: Postablation ^{131}I WBS and neck and thorax SPECT-CT were performed in 55 consecutive patients treated in 2006. WBS and SPECT-CT data were blindly reviewed, scored negative (benign), positive (malignant), or indeterminate and were correlated to the patient outcome.

Results: At patient level, WBS and SPECT-CT were negative in 67 and 78% of patients, positive in 4 and 15%, and indeterminate in 29 and 7%, respectively. Overall, nine patients (16%) presented treatment failure (persistent or recurrent disease) 1–16 months after radioiodine ablation. In the 16 patients with indeterminate WBS, negative SPECT-CT ruled out suspicion of disease in nine of nine patients, and positive SPECT-CT confirmed malignant lesions in four of five patients. Positive SPECT-CT predicted treatment failure better than positive WBS (McNemar's test, $P = 0.03$).

Conclusions: This study demonstrates the complementary role of neck and thorax SPECT-CT to WBS in postablation ^{131}I scintigraphy. Because SPECT-CT allows one to confirm or to rule out residual disease in most cases where WBS remains indeterminate, we recommend its use when available. **(*J Clin Endocrinol Metab* 94: 2075–2084, 2009)**

The initial treatment of patients with differentiated thyroid cancer (DTC) is based on a combination of surgery followed by administration of high-activity ^{131}I, at least in high-risk patients (1, 2). The goal of radioiodine ablation is to destroy postsurgical normal thyroid remnants and loco-regional residual disease (mainly lymph node involvement) or distant metastases (mainly lung and bone lesions). Total body scintigraphy is performed several days after treatment, taking advantage of high radioiodine activity that makes this scintigraphy very sensitive. Radioiodine scintigraphy usually includes planar images of whole body scan (WBS) associated with static acquisitions centered at least on neck and mediastinum (3). The interpretation of planar images

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Abbreviations: CI, Confidence interval; DTC, differentiated thyroid cancer; HU, Hounsfield units; rhTSH, recombinant human TSH; Tg, thyroglobulin; TgAb, anti-Tg antibodies; US, ultrasound; WBS, whole body scan.

may be difficult, even in the hands of experienced nuclear medicine physicians, due to the lack of anatomical landmarks. It may thus be difficult to differentiate between uptake in normal thyroid remnants and lymph node metastases, or between uptake in lung and rib lesions. New hybrid single-photon emission computed tomography/computed tomography (SPECT-CT) equipments combine a γ-camera for tomographic images and a CT scan and permit direct correlation between functional and anatomical imaging. SPECT-CT availability offers the opportunity of improving the relevance of postablation ^{131}I scintigraphy by its capacity to detect small volumes of iodine-avid tissue and localize them with great accuracy (4).

We conducted a prospective study to assess the diagnostic value of neck and thorax SPECT-CT compared with that of WBS in patients with DTC who had radioiodine ablation and were followed up in a single referral institution.

TABLE 1. Patient characteristics

	n
Patients at risk	55
Gender	
Female	39 (71%)
Male	16 (29%)
Age at diagnosis, yr (range)	49 (10–82)
Neck dissection	
No dissection	16 (29%)
Central compartment only	15 (27%)
Ipsilateral	2
Contralateral	5
Bilateral	8
Lateral compartment only	2 (4%)
Ipsilateral	1
Bilateral	1
Central and lateral compartments	19 (35%)
Both lateral compartments	14
Ipsilateral compartments	5
Adenectomy	3 (5%)
TNM classification[a]	
Tumor	
T1	26 (47%)
T2	16 (29%)
T3	12 (22%)
T4	1 (2%)
Nodes	
N1	24[b] (44%)
N1a	11
N1b	13
N0	15 (27%)
Nx	16 (29%)
Metastases	
M0	52 (95%)
M1[c]	3 (5%)
Histology	
Papillary	51 (93%)
Follicular	4 (7%)

[a] 2002 Tumor Node Metastasis (TNM) classification (6).

[b] Including 14 cases with macroscopic lymph-node involvement (MLNI) according to Bardet *et al.* (15). There were 2 MLNI among the 11 N1a cases and 12 among the 13 N1b cases.

[c] Iodine avid lung metastases diagnosed on postablation scintigraphy.

Patients and Methods

Patients

From January to December 2006, 55 consecutive patients with DTC referred for postsurgical radioiodine ablation underwent a postablation ^{131}I scan combining WBS and SPECT-CT acquisitions of neck and thorax (Table 1). Diagnosis of DTC was based on the written pathological report.

Radioiodine ablation and postablation ^{131}I scintigraphy

Radioiodine ablation treatment was given at a median interval of 10 (range, 4–39) weeks after surgery, either after withdrawal of thyroid hormone treatment or after recombinant human TSH (rhTSH) (Thyrogen; Genzyme Corp., Cambridge, MA). Serum TSH, thyroglobulin (Tg), and anti-Tg antibodies (TgAb) were measured immediately before administration of radioiodine.

Postablation^{131}I scintigraphy was performed 5 d after treatment, using a double-head γ-camera equipped with 1.5875-cm (5/8-in) NaI crystals and a multidetector (2 rows) spiral CT (Symbia T2; Siemens Medical Solutions, Malvern, PA). WBS planar images were first acquired at a scanning speed of 8 cm/min after which SPECT-CT was performed. The SPECT volume session included the neck and thorax with an axial field of view of 53.3 $\times$ 38.7 cm. For SPECT acquisition of tomographic images, a 128 $\times$ 128 matrix was used, and 64 30-sec projections were acquired over 360 degrees. SPECT data were reconstructed using a three-dimensional iterative algorithm (ordered-subsets expectation maximization with four iterations and eight subsets). Images were smoothed with a three-dimensional spatial Gaussian filter. Immediately after SPECT acquisition, a CT topogram was acquired followed by a spiral CT acquisition performed on a volume session similar to that of SPECT acquisition. CT acquisition parameters were as follows: tube current, 60 mA; collimation, 2 $\times$ 2.5 mm; pitch, 2. For CT data reconstruction, a 3-mm slice thickness with 2-mm slice increment and a B70 kernel filter were used. No contrast medium was injected during the procedure.

WBS and SPECT-CT data were analyzed on an e-soft workstation, providing transaxial, sagittal, and coronal slices of SPECT, CT, and fused SPECT-CT data. CT scan data were displayed at the neck [level, 50 Hounsfield units (HU); width, 250 HU], at the mediastinum (40 and 250 HU), or at the lung window settings (level, −600 HU; width, 1200 HU). This routine interpretation served as the basis for clinical management of patients.

Management after initial treatment

Patients for whom postablation ^{131}I scintigraphy was considered normal were seen at 3 months on L-T_4 treatment, for serum TSH, Tg, and TgAb determinations. When Tg level was less than 1 ng/ml in the absence of TgAb at 3 months, disease status was always assessed at 9 months by physical examination, serum rhTSH-stimulated Tg determination (except in one patient for whom thyroid hormone withdrawal was used), and neck ultrasound (US). Diagnostic scintigraphy after 185 MBq ^{131}I was performed in five patients, three of them with high TgAb levels. When evaluation at 9 months was normal (*i.e.* stimulated Tg level $\leq$1 ng/ml and negative US), patients were followed up on an annual basis, with neck US and TSH, Tg, and TgAb assays on L-T_4 treatment. Otherwise, imaging modalities such as CT of the neck and thorax or [^{18}F]fluorodeoxyglucose positron emission tomography were performed.

In patients for whom postablation ^{131}I scintigraphy was considered abnormal and/or Tg level greater than 1 ng/ml on L-T_4 at 3 months, complementary imaging modalities such as neck US or magnetic resonance imaging, CT of the neck and thorax or [^{18}F]fluorodeoxyglucose positron emission tomography were performed.

Tg and TgAb evaluation

Serum Tg measurements were performed in duplicate and results reported as the average of duplicate values, using the immunometric assay Tg-Kryptor (BRAHMS). The functional sensitivity of the assay was 0.2 ng/ml. Serum TgAb were measured simultaneously using Immulite TgAb (Diagnostic Products Corp., Los Angeles, CA).

Clinical outcome assessment

Treatment failure (*i.e.* persistent or recurrent disease) was defined as evidence of tumor in the thyroid bed, lymph-node metastases, or distant metastases after completion of initial treatment (surgery and radioiodine ablation). Confirmation was obtained either by histology or by complementary imaging modalities and follow-up. Otherwise, patients were considered disease free.

Data analysis

For each patient, WBS and SPECT-CT data were blindly analyzed by two experienced nuclear medicine physicians (N.A. and S.B.) and a specialized head and neck surgeon (J.P.R.) during three review sessions. For each imaging modality, the observers were asked to list all foci of ^{131}I uptake in the neck (either in median or lateral areas), in the mediastinum, or elsewhere in the thorax. Each focus was scored negative (benign), positive (malignant), or indeterminate on each imaging modality. The interpretation of WBS was based on the assumed location of ^{131}I foci, whereas that of SPECT-CT was based both on the accurate location of foci and on the presence of structural abnormalities on related CT. In the neck, WBS was considered as follows: 1, negative when there were median/paramedian foci deemed to correspond to thyroid or thyroglossal duct remnants; 2, positive when there was a lateral focus supposed to be lymph-node involvement; or 3, indeterminate when there was a paramedian or low median focus compatible either with thyroid remnant or lateral or central lymph-node involvement. SPECT-CT was considered as follows: 1, negative when median/paramedian foci were localized either in the lower thyroid bed (usually posterolaterally to the trachea), in the upper thyroid bed, or in thyroglossal duct remnants; 2, positive when a focus was localized in front of a round lesion congruent with a lymph node; or 3, indeterminate when a focus was localized at another place than typical thyroid remnants and/or with a doubt on a matching structural abnormality. In the thorax, WBS was considered as follows: 1, negative when no focus was visible; 2, positive when diffuse or focal lung uptake was obvious; or 3, indeterminate in other cases. SPECT-CT was considered as follows: 1, negative when no focus was visible or when a focus could be ascribed on related CT to esophageal or skin contamination or to thyroid remnants; 2, positive when diffuse lung uptake was visible or when a focus could be ascribed on related CT to a structural abnormality in the mediastinum, lung, or bone; or 3, indeterminate in other cases. The agreement obtained by consensus (at least two observers) was used in data analysis. At patient level, one imaging modality (*i.e.* WBS or SPECT-CT) was considered negative when all foci were negative, positive when at least one focus was positive, and indeterminate when at least one focus was considered indeterminate without any positive foci.

Agreement between WBS and SPECT-CT was measured at patient level using κ-statistics. A treatment failure was considered in the present analysis if it occurred within 24 months after radioiodine ablation. The proportions of patients with positive imaging on WBS and SPECT-CT and who experienced treatment failure were compared using the McNemar's test. Time to treatment failure was calculated from the day of postablation ^{131}I scintigraphy to the date of treatment failure or September 1, 2008, whichever came first. The cumulative probability of treatment failure was calculated as 1 minus the probability of survival without treatment failure. The Kaplan-Meier method was used to estimate the probability of survival. Ninety-five percent confidence intervals (95% CI) for cumulative probability estimates were calculated by the Rothman and Boice method (5). All tests were two-sided. SAS statistical software was used to analyze the data.

Results

Patient characteristics

Table 1 reports the clinical and pathological features of the 55 patients using the tumor node metastasis classification (6). Radioiodine treatment was given after withdrawal of thyroid hormone treatment (n = 50) with a TSH level of 65 μU/ml (range, 29–75) or after rhTSH (n = 5). Fifty-four adult patients had a median activity of 3848 MBq (range, 2960–4010) and a 10-yr-old child, with a body weight of 30 kg, received 1106 MBq. Overall, the median follow-up was 21 months (range, 9–29).

Of the 55 patients, nine (16%) showed persistent or recurrent disease 1–16 months after postablation ^{131}I scintigraphy (Table 2). One patient had residual disease in the tracheal wall, one patient showed persistent lung metastases only, four patients had nodal recurrence in the neck, and three patients had both cervical nodal recurrence and lung metastases. All nine patients but one had macroscopic lymph-node involvement at initial surgery, and all had Tg level of at least 30 ng/ml at the time of ablation. The other 46 patients remained disease free (Table 3). Of these, only six patients had macroscopic lymph-node involvement at initial surgery, and none had Tg level of 30 ng/ml or higher at ablation.

Relationship between WBS and SPECT-CT data and clinical outcome

Figure 1 reports WBS and SPECT-CT data at patient level according to clinical outcome. WBS was negative in 37 patients (67%), positive in two patients (4%), and indeterminate in 16 (29%). With SPECT-CT, the number of indeterminate examinations decreased dramatically (n = 4, 7%), whereas the number of negative (n = 43, 78%) and positive (n = 8, 15%) examinations increased. A low value of κ (0.31; 95% CI, 0.11–0.51) indicates disagreement between WBS and SPECT-CT results.

Table 2 shows the characteristics of the nine patients who presented persistent or recurrent disease. Among the three patients with no abnormal ^{131}I uptake (patients 1–3), the integrated CT of SPECT-CT enabled us to suspect a lung metastasis in patient 2 and tracheal wall invasion in patient 3 at the time of ablation. In the four patients with indeterminate WBS and positive SPECT-CT (patients 4–7), the latter permitted us to clearly localize paramedian or lower median neck foci in lateral or central compartments in front of nodal involvement. This was later confirmed by probe-guided surgery after a second therapeutic ^{131}I activity. In the two patients with positive WBS and SPECT-CT at the patient level, SPECT-CT was also able to show that a paramedian neck focus was an unusual retropharyngeal adenopathy in patient 8 (Fig. 2) and to demonstrate an additional endotracheal lesion in patient 9 (7).

Table 3 reports data in the 46 patients who remained disease free. WBS and SPECT-CT were both negative in 31 patients (patients 1–31). One patient had no visible thyroid remnant, although no excess iodine was shown. Thirty patients had one to four neck foci considered as normal thyroid remnants either in the thyroid bed or in the thyroglossal duct. Although 27 patients had rhTSH-stimulated Tg levels less than 1 ng/ml at 9 months with negative neck US, four showed stimulated Tg levels above

TABLE 2. Patients with persistent or recurrent disease

	Initial presentation				Radioiodine ablation			Persistent or recurrent disease				Status at September 1, 2008	
Patient	Sex	Age (yr)	Histology/ TNM	Dissection modalities[a]	Tg off T_4 (ng/ml)/ TgAb[b]	WBS results: site/ interpretation[c] and conclusion at patient level	SPECT-CT results: site/ interpretation[c] and conclusion at patient level	Tg on T_4 (ng/ml) at 3 months/TgAb[b]	Time since ^{131}I Scintiscan (months)	Imaging modalities	Site/treatment	Tg (ng/ml)/TgAb[a]	Active disease (AD)/disease free (DF)
1	F	18	PTC/T2N1bM0[d]	C and L Bilateral	70/N	Median neck focus/N	Thyroid bed/N	7/N	4	Neck US	Lateral neck LNR[e]/Surgery	<0.2 on T4/N	DF
						Conclusion: N	Conclusion: N						
2	M	79	PTC/T3N1bM0[d]	L Ipsilateral	188/N	Median and right paramedian neck foci/N	Thyroid bed/N	49/N	16	Neck US	Subclavicular LNR[e]/Surgery	24 on T4 /N	AD (Lung)
						Conclusion: N	Conclusion: N			Lung CT[f] PET	Lung[e]/Therapeutic trial		
3	F	73	PTC/T4aN1bM0[d]	C and L Bilateral	84/N	Median neck focus/N	Thyroid bed/N	10/N	5	Neck CT[f] PET	Tracheal invasion[e]/External irradiation	4 on T4 /N	AD (Tracheal invasion)
						Conclusion: N	Conclusion: N						
4	M	27	PTC/T1N1bM0[d]	Adenectomy	45/N	Left/right paramedian neck foci/N	Thyroid bed/N	4/N	3	Neck CT[g] Neck US	LNR in central and right lateral neck/^{131}I guided surgery	0.4 on T4/N	DF
						Low median neck focus/I	Low median neck focus/I						
						Upper right paramedian neck foci/I	2 right foci related to 10 and 25 mm LN/P						
						Conclusion: I	Conclusion: P						
5	M	69	PTC/T1N1aM0[d]	Adenectomy	60/P	Median neck focus/N	Thyroid bed/N	1/P	7	Neck US Neck CT[f]	LNR in left lateral neck/ ^{131}I guided surgery	<0.2 on T4/N	DF
						Left paramedian neck foci/I	3 left foci related to 12 to 17 mm LN/P						
						Right paramedian neck focus/I	Thyroid bed/N						
						Conclusion: I	Conclusion: P						
6	F	42	PTC/T2N1aM0[d]	C Bilateral	618/N	Right paramedian neck/N	Focus related to a 30 mm cervical LN/P	ND	2	Neck US Neck CT[g] PET	LNR in left subclavicular area/^{131}I guided surgery	<0.2 after rhTSH/N	DF
						Left paramedian neck/N	Focus related to a 20 mm subclavicular LN/P						
						2 right paramedian neck foci/I	Thyroid bed/N						
						Conclusion: I	Conclusion: P						
7	M	33	PTC/T3N1bM1[d]	Adenectomy	676/N	Right paramedian neck/N	Low right focus related to a 20 mm central LN/P	68/N	5	Neck US	LNR in central and lateral (right and left) compartments/^{131}I guided surgery	48 off T4/N	AD (central neck, lung)
						Left paramedian neck/N	Thyroid bed/N			Lung/^{131}I			
						Bilateral paramedian/ lateral neck foci/I	Foci related to 10 to 20 mm bilateral LN/P			Neck and lung CT[g]			
						Lung/I	Lung/P						
						Conclusion: I	Conclusion: P						

(*continued*)

TABLE 2. Continued

	Initial presentation				Radioiodine ablation			Persistent or recurrent disease				Status at September 1, 2008	
Patient	Sex	Age (yr)	Histology/TNM	Dissection modalities[a]	Tg off T_4 (ng/ml)/TgAb[b]	WBS results: site/interpretation[c] and conclusion at patient level	SPECT-CT results: site/interpretation[c] and conclusion at patient level	Tg on T_4 (ng/ml) at 3 months/TgAb[b]	Time since ^{131}I Scintiscan (months)	Imaging modalities	Site/treatment	Tg (ng/ml)/TgAb[a]	Active disease (AD)/disease free (DF)
8	F	10	PTC/T1N1bM1[d]	C and L Bilateral	30/N	Median neck focus/N	Thyroid bed/N	ND	1	Neck and lung CT[f]	Retropharyngeal LNR/Surgery	<0.2 on T4/P	AD (Lung)
						Left paramedian neck focus/I	Focus related to a 15 mm retropharyngeal LN/P			Neck MRI			
						Lung/P	Lung/P				Lung/^{131}I		
						Conclusion: P	Conclusion: P						
9	F	82	FTC/T3NXM1	No dissection	379/N	Median neck/N	Median thyroid bed/N	36/N	5	CT[g]	Lung/^{131}I	18 on T4/N	AD (Lung)
						Lung/P	Lung/P						
						Conclusion: P	Discovery of an endotracheal focus/M (endoscopy[h])						
							Conclusion: P						

F, Female; M, male.

[a] C, Central compartment; L, lateral compartment.

[b] N, No TgAb; P, presence of TgAb.

[c] Considered as a negative lesion (N), a positive lesion (P), or an indeterminate lesion (I).

[d] With macroscopic lymph-node involvement.

[e] Lesions with no ^{131}I uptake.

[f] Integrated CT of hybrid equipment plus diagnostic CT.

[g] Integrated CT of hybrid equipment only.

[h] Clinical case already reported in Ref. 7.

TABLE 3. Patients without persistent or recurrent disease

Patient	Sex	Age (yr)	Histology/TNM	Tg off T_4 (ng/ml)/TgAb[a]	WBS results[b]	SPECT-CT results[b]	Tg on T_4 (ng/ml)/TgAb[c] at 3 months	rhTSH Tg (ng/ml)/TgAb[c] at 9 months	Negative imaging modalities[d]	Follow-up (months)	Tg on T4 (ng/ml)/TgAb[c] at last visit
Negative WBS and negative SPECT-CT (n = 31)											
1–31	25 F/6 M	48 (17–76)	30 PTC/1 FTC	≤1 (n = 16) /P (n = 4)	No visible neck focus in one patient	No visible neck focus in one patient	<0.2 (n = 20)/P (n = 1)	<1 (n = 27)/P (n = 3)	US (n = 27)	24	<1/N
			T1N0M0 (n = 3) T1N1aM0 (n = 3) T1N1bM0 (n = 3[c]) T1NXM0 (n = 8)	1 < Tg ≤ 10 (n = 12) 10 < Tg ≤ 20 (n = 3)	68 foci in the median or paramedian neck in 30 patients	68 foci of thyroid remnants in 30 patients	0.2 < Tg ≤ 1 (n = 6)/ P (n = 1) ND (n = 1)		^{131}I Sc (n = 3)	(19–29)	
			T2N0M0(n = 5) T2NXM0 (n = 5)		60 foci considered in the thyroid bed	45 remnants in the lower thyroid bed					
			T3N0M0 (n = 2) T3N1aM0 (n = 2)		8 foci considered as thyroglossal duct remnants	9 remnants in the upper thyroid bed	0.5/N	1.1/N	US	29	<0.2/N
						14 thyroglossal duct remnants	<0.2/N	2/N	US	21	<0.2/N
							<0.2/N	4.1/N	US, CT	21	<0.2/N
							3/N	12/N	US, CT, PET	29	1.5/N
Negative WBS and indeterminate SPECT-CT (n = 2)											
32	F	22	PTC/T1N1aM0	4.9/N	Median and paramedian neck foci	Lower paramedian neck focus with doubt on a 10-mm mass/LNI?	<0.2/N	<1/N	US	23	<0.2/N
33	M	54	PTC/T3N0M0	4.2/N	One median and two paramedian neck foci	Lower paramedian neck focus with doubt on a 3-mm mass/LNI?	<0.2/N	<1/N	US	25	<0.2/N
Negative WBS and Positive SPECT-CT (n = 1)											
34	F	73	PTC/T4N1bM0[c]	5.3/N	Two median and one paramedian neck foci	Lower median neck focus related to an 8-mm lymph-node/CNI? Dubious focus in the retrosternal area/NI?	<0.2/N	2/N	US	25	0.9/N

(continued)

TABLE 3. Continued

Patient	Sex	Age (yr)	Histology/TNM	Tg off T_4 (ng/ml)/TgAb[a]	WBS results[b]	SPECT-CT results[b]	Tg on T_4 (ng/ml)/TgAb[c] at 3 months	rhTSH Tg (ng/ml)/TgAb[c] at 9 months	Negative imaging modalities[d]	Follow-up (months)	Tg on T4 (ng/ml)/TgAb[c] at last visit
Indeterminate WBS and negative SPECT-CT (n = 9)											
35	M	43	PTC/T1N1bM0	1/N	Shoulder/bone metastasis?	Skin contamination	ND	1.6/N	US	27	0.2/N
36	M	45	PTC/T3N1aM0	5.7/N	Lower median neck focus/CNI?	Remnants in the lower thyroid bed	<0.2/N	0.3[e]/N	US, ^{131}I Sc	25	<0.2/N
37	M	47	PTC/T3N1bM0[c]	4.1/N	Upper paramedian neck focus/LNI?	Remnants in the upper thyroid bed	<0.2/N	0.5/N	US	24	<0.2/N
38	F	70	PTC/T1N0M0	1.1/N	Lower median neck focus/CNI?	Remnants in the lower thyroid bed	<0.2/N	<1/N	US	24	<0.2/N
39	F	37	FTC/T1N0M0	3.3/N	Upper paramedian neck focus/LNI?	Remnants in the upper thyroid bed	<0.2/N	<1/N	US	24	<0.2/N
40	F	28	PTC/T1NXM0	0.2/P	Lower mediastinum focus/NI?	Esophageal contamination	<0.2/P	<0.2/P	US, ^{131}I Sc	21	<0.2/P
41	M	29	PTC/T2N0M0	1.3/N	Upper mediastinum focus/NI?	Remnants in the lower thyroid bed	<0.2/N	<1/N	US	23	<1/N
42	F	25	PTC/T2N0M0	1.6/N	Lower median neck focus/CNI?	Remnants in the lower thyroid bed	<0.2/N	<1/N	US	25	<0.2/N
43	M	64	PTC/T2NXM0	3.1/N	Upper paramedian neck focus/LNI?	Remnants in the upper thyroid bed	0.3/N	<1/N	US	14	<1/N
Indeterminate WBS and indeterminate SPECT-CT (n = 2)											
44	M	61	FTC/T1N1aM0	2/N	Upper paramedian neck focus/LNI?	Lateral neck focus without matching structural abnormality/LNI?	<0.2/N	<1/N	US	23	<1/N
45	F	42	PTC/T2N1aM0	0.2/N	Lower paramedian neck focus/CNI?	Lower neck focus without matching structural abnormality/CNI?	<0.2/N	<0.2/N	US	22	<0.2/N
Indeterminate WBS and positive SPECT-CT (n = 1)											
46	F	61	PTC/T3N1bM0[c]	0.2/P	Upper paramedian neck focus/LNI?	Upper neck focus related to an 8-mm spinal lymph-node/LNI?	<0.2/P	<0.2/P	US, CT, PET	18	<0.2/P

F, Female; M, male.

[a] N, No TgAb; P, presence of TgAb.

[b] CNI, Central node involvement; NI, node involvement; LNI, lateral node involvement.

[c] With macroscopic lymph-node involvement.

[d] CT, Diagnostic CT of the neck and thorax; ^{131}I Sc, diagnostic scintigraphy after 185 MBq ^{131}I; PET, FDG-PET; US, neck US.

[e] Obtained after L-T_4 treatment withdrawal.

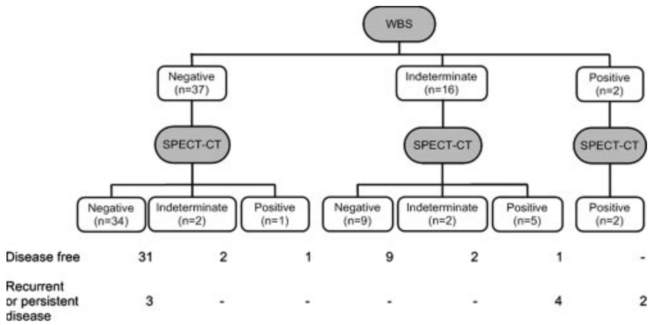

FIG. 1. Postablation ^{131}I WBS and SPECT-CT results according to clinical outcome.

this limit. Complementary imaging modalities remained negative in these patients, however.

In two patients (32 and 33), WBS was negative and SPECT-CT was indeterminate with a doubt about nodal involvement in the lateral compartment. In another patient (34), SPECT-CT was scored positive; in this case, the rhTSH-stimulated Tg level was 2 ng/ml at 9 months, and Tg level was 0.9 ng/ml on suppressive L-T_4 treatment at 25 months.

Nine patients had indeterminate WBS and negative SPECT-CT (patients 35–43). On WBS, the dubious foci were localized in the lower neck area with suspicion of central node involvement (n = 3), in the paramedian neck area with suspicion of lateral node involvement (n = 3), in the upper (Fig. 3) or lower mediastinum with suspicion of mediastinal node involvement (n = 2), or on shoulder with suspicion of bone metastasis (n = 1). On SPECT-CT, these doubtful foci were related to thyroid remnants (n = 6), to skin contamination (n = 2), and to esophageal contamination (n = 1).

In two patients (44 and 45), WBS and SPECT-CT remained indeterminate. Finally, patient 46 showed indeterminate WBS and positive SPECT-CT with suspicion of ipsilateral spinal nodal involvement.

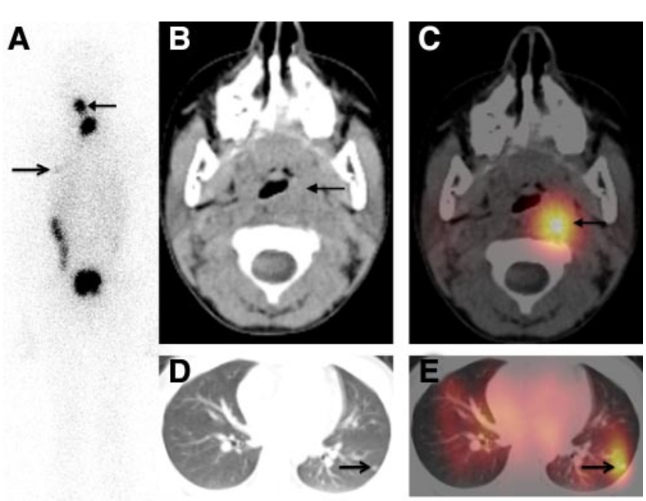

FIG. 2. Postablation ^{131}I WBS and SPECT-CT in patient 8 described in Table 2. A left paramedian neck focus scored as indeterminate on the posterior view of planar WBS (A) was ascribed to retropharyngeal lymph-node involvement and scored positive on SPECT-CT (B and C; CT and fused SPECT-CT transaxial slices). Also, a left thoracic focus of moderate intensity on WBS was clearly confirmed positive on SPECT-CT in front of a 5-mm lung nodule (D and E).

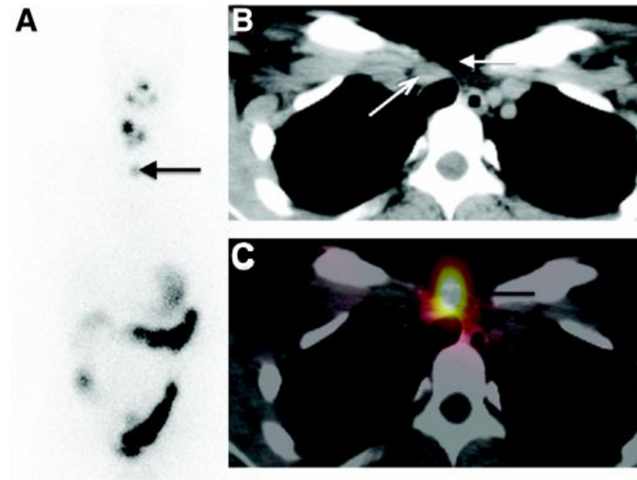

FIG. 3. Postablation ^{131}I WBS and SPECT-CT in patient 41 described in Table 3. A, Intense focus of iodine uptake localized in the mediastinum and scored as indeterminate on the anterior view of planar WBS. SPECT-CT enabled identification of this focus as normal thyroid remnant located at the cervicomediastinal junction, in front of the brachiocephalic vein (B and C, CT and fused SPECT-CT transaxial slices). This patient remained disease free after a follow-up of 23 months.

Prognostic analysis

The estimated 24-month cumulative probability of treatment failure associated with negative or indeterminate WBS was 13% (95% CI, 7–26%). The two patients with positive WBS experienced treatment failure 1 and 5 months after radioiodine ablation (patients 8 and 9, Table 2). The estimated 24-month cumulative probability of treatment failure associated with negative or indeterminate SPECT-CT was 7% (95% CI, 2–19%; 47 patients), and that associated with positive SPECT-CT was 75% (95% CI, 44–96%; eight patients). The comparison of WBS and SPECT-CT favored the latter (McNemar's test for paired data, $P = 0.03$).

Discussion

In the last few years, several clinical cases (7–10) and original studies (11, 12) dealing with SPECT-CT in patients with DTC have been reported. In a retrospective study, Tharp *et al.* (11) showed that SPECT-CT had an incremental diagnostic value over planar imaging for 41 of 71 patients (58%). The imaging modalities and the study population were heterogeneous, however, including three groups of patients referred either for a scintigraphy performed after 185 MBq ^{131}I (n = 17) or postsurgical radioiodine ablation (n = 28) or radioiodine treatment of known or suspected metastases (n = 26). In addition, there was a lack of follow-up in up to 20% of patients. Ruf *et al.* (12) studied 25 patients after radioiodine ablation, all with inconclusive findings on WBS, and showed that, compared with SPECT images alone, SPECT-CT improved the anatomic localization for 44% of suspected lesions and could influence therapeutic management in 25% of patients. More recently, similar results were reported in 23 patients using the same integrated SPECT-CT camera (Millennium VG Hawkeye; GE Medical System) after a therapeutic activity of ^{131}I (13). In the present study, we prospectively assessed both diagnostic and prognostic value of routine neck and thorax SPECT-CT in a series of consecutive and unselected patients referred for radioiodine ablation, using an integrated spiral CT scan allowing a 3-mm slice thickness and an acquisition time of less than 1 min.

The present data show that SPECT-CT focused on neck and thorax enables more accurate diagnosis than WBS. Actually, SPECT-CT reduces the number of indeterminate examinations (from 29% with WBS to 7% with SPECT-CT), therefore increasing both the proportion of positive exams (from 4 to 15%) and that of negative exams (from 67 to 78%). On the one hand, SPECT-CT is able to rule out the suspicion of disease suggested by WBS. In some patients, suspicion of central or lateral node involvement on WBS, and even of mediastinal involvement, was finally related to thyroid remnants on SPECT-CT. Similarly, suspicion of mediastinal or bone involvement on WBS in two patients was easily ascribed to esophageal or skin contamination. On the other hand, SPECT-CT can reliably confirm residual disease in patients with doubtful foci on WBS. This was observed in four patients with central and/or lateral node involvement, one of whom also showed lung metastases. Regarding neck node involvement, the additional value of SPECT-CT is to demonstrate that dubious foci on WBS correspond to nodular masses (even of small size, 5–10 mm) outside the thyroid bed that can be localized accurately in central or lateral compartments. The number of indeterminate results in planar imaging might have been reduced if static images had been also available. The acquisition of such spot images is time consuming (10–15 min per view), however, and although they can help to roughly localize radioiodine foci, they do not allow direct correlation with anatomic imaging. Very recently, Schmidt *et al.* (14) showed findings comparable to ours using similar SPECT-spiral CT cameras, although equipped with thinner crystals, theoretically less adapted to high-energy emitters. Compared with planar imaging including WBS and spot images on the neck, SPECT-CT was able to alter N staging in 20 of 57 patients (35%) by upstaging ($n = 8$) or downstaging ($n = 12$) their disease. Although not illustrated in the present study, another advantage of SPECT-CT is to differentiate, in a single exam, lung from rib metastasis for patients with chest radioiodine uptake and to better characterize bone lesions, with or without soft tissues involvement, especially in the pelvis.

Persistent or recurrent disease was observed in 16% of patients during a follow-up of almost 2 yr, that is, in a period of time where most recurrences appear (15). No patients were lost to follow-up. All were monitored in a single, specialized center using the follow-up procedures of international guidelines, including the rhTSH stimulation test at 9 months, combined with neck US (1, 2, 16). Malignant residual or recurrent disease was always found in the neck (mainly lymph node involvement) or in the thorax (lung metastases) and was proven by surgery or adequate imaging. Data demonstrate that SPECT-CT predicted treatment failure better than WBS. As expected (17), three of nine patients (33%) with recurrent disease showed no iodine uptake and account for false-negative SPECT-CT exams. Nevertheless, in two of these patients, the integrated spiral CT was able to detect iodine nonavid metastasis early, at the time of ablation, before complementary imaging such as diagnostic CT and PET. Two false positives (4%) were also observed. Although controversial, the potential effects of radioiodine ablation on microscopic disease might be an explanation for these false positives (18, 19). Another reason might be that DTC biomarkers, including ultrasound and Tg level determination, are not always sensitive enough to detect minimal residual disease. In accordance with previous studies (15, 20), data also show that the presence of macroscopic lymph node involvement at diagnosis and of a Tg level above 30 ng/ml at the time of radioiodine ablation appear to be associated with treatment failure. A larger series and longer follow-up are needed, however, to confirm clearly which subgroups of patients might particularly benefit from SPECT-CT at ablation.

The combination of both WBS and SPECT-CT of the neck and thorax is feasible in routine practice. Overall, the acquisition takes less than 1 h. With the new-generation hybrid equipment, SPECT acquisition lasts approximately 25 min, whereas that of CT lasts less than 1 min. Using a scanning speed of 8 cm/min, as generally recommended (3), WBS also lasts 20–25 min. WBS remains mandatory to detect distant metastases outside the chest (mainly bone lesions). Another SPECT-CT acquisition may be required in a few cases to analyze doubtful foci outside the neck and thorax better. The radiation dose to the patient from low-dose CT scan is very limited, approximately 2–4 mSv (21). By comparison, assuming 0 or 0.5% thyroid uptake after total thyroidectomy, the effective dose is estimated to be 240-1700 mSv after administration of 3700 MBq ^{131}I, according to ICRP 53 (22).

From an economical point of view, a SPECT-CT camera costs between 0.7–1 million euros (compared with 0.3–0.5 million euros for a double-head camera without integrated CT); the exam duration is moderately increased when it combines WBS plus SPECT-CT (about 1 h) compared with WBS plus static images (about 45 min). Reimbursement procedures vary from one country to another; in France, the Health Insurance refunds approximately 312 euros for WBS plus SPECT-CT *vs.* 270 euros for WBS plus static images. The reimbursement corresponding to SPECT-CT acquisition is identical to that of SPECT alone because CT acquisition as a nondiagnostic CT is not considered. Although cost-effectiveness assessment was not the goal of the study, it is clear that SPECT-CT allows us to confirm or to rule out residual disease in most cases where WBS remains indeterminate and precludes performing confirmatory imaging modalities in these patients.

One remaining issue is the lowest activity of ^{131}I that could be detected by SPECT-CT and, subsequently, the possible clinical relevance of SPECT-CT after low diagnostic activities (from 37–370 MBq), either for treatment planning or during follow-up in patients with elevated serum Tg. Radioiodine uptake was not estimated in the present study. Further work is clearly needed in that domain. Compared with planar scintigraphy, SPECT-CT technology allows performing optimized dosimetry studies by providing three-dimensional assessment, proper attenuation correction of the image data, and CT assessment of target volumes (21). From a clinical point of view, multicentric prospective studies are also necessary to ascertain the impact of diagnostic SPECT-CT after low diagnostic activities. Dosimetry and clinical studies can also be achieved with ^{124}I PET/CT, another promising functional imaging tool. It was recently shown that similar findings could be observed on ^{124}I PET scan and on postablation ^{131}I WBS in a limited series of patients with advanced DTC (23). As in our study using hybrid SPECT-CT equipments, Freudenberg *et al.* (24) also showed that the sensitivity of ^{124}I PET was superior with PET/CT cameras than with PET alone.

In conclusion, this study demonstrates the complementary role of neck and thorax SPECT-CT to WBS in the posttherapeutic scintigraphy performed after radioiodine ablation. Because SPECT-CT allows confirming or ruling out residual disease in most cases where WBS remains indeterminate, we recommend its use when available.

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