CLINICAL STUDY

Postablation ^{131}I scintigraphy with neck and thorax SPECT–CT and stimulated serum thyroglobulin level predict the outcome of patients with differentiated thyroid cancer

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Abstract

Objective: Neck and thorax single photon emission computed tomography with computed tomography (SPECT–CT) improves the reliability of postablation ^{131}I whole-body scan (WBS) for differentiated thyroid cancer (DTC). The aim of this study was to assess the prognostic value for persistent or recurrent disease of postablation ^{131}I scintigraphy combining WBS and neck and thorax SPECT–CT with that of the previously known predictive factors.

Methods: This is a single referral center prospective study with a median follow-up of 29 months. Postablation ^{131}I WBS and neck and thorax SPECT–CT were performed in 170 consecutive patients treated between 2006 and 2008. Stimulated serum thyroglobulin (Tg) and anti-thyroglobulin antibodies (TgAb) levels were measured. The impact on disease-free survival of age; gender; postablation ^{131}I scintigraphy; stimulated serum Tg level; T, N, and M status; and macroscopic lymph node involvement was assessed by univariate and multivariate analyses.

Results: Persistent or recurrent disease was observed in 32 (19%) patients. In the whole group of patients, only positive WBS with SPECT–CT was related to an increased risk of persistent or recurrent disease (hazards ratio (HR)=65.21, 95% confidence interval (CI)=26.03–163.39, $P<0.0001$). In patients without TgAb ($n=146$), both positive WBS with SPECT–CT (HR=18.86, 95% CI=5.02–70.85, $P<0.0001$) and serum Tg level ≥ 58 ng/ml (HR=4.42, 95% CI=1.18–16.53, $P=0.0271$) were associated with an increased risk.

Conclusion: In patients with DTC, the cross analysis of postablation ^{131}I scintigraphy with neck and thorax SPECT–CT and stimulated serum Tg level enables early assessment of the risk of persistent or recurrent disease.

European Journal of Endocrinology 164 961–969

Introduction

Persistent or recurrent disease in lymph nodes or in the thyroid bed occurs in ~5–25% of patients with differentiated thyroid cancer (DTC) depending on the selection of patient, and distant metastases are observed in about 5% of cases. In clinical practice, there is a need for early identification of patients with residual disease and those at a risk of developing such recurrences. At present, the risk assessment is based on the AJCC/UICC pTNM classification (1), initially developed to predict risk for death. A three-level stratification for the assessment of risk for recurrence was also recently proposed by the American Thyroid Association (ATA) considering other variables such as histological subtype, results of postablation ^{131}I scintigraphy, or possibly thyroglobulin (Tg) level (2).

Recently, we and others have shown that routine neck and thorax single photon emission computed tomography with computed tomography (SPECT–CT) greatly improves the interpretation of postablation ^{131}I whole-body scan (WBS) owing to the direct correlation between functional and anatomical imaging (3, 4). In accordance with previous studies (5–7), we also reported, though on a limited number of patients, that persistent/recurrent disease was associated with high, stimulated serum Tg level at ablation (> 30 ng/ml) and with initial macroscopic lymph node involvement (3).

The aim of this study was to assess the prognostic value for persistent or recurrent disease of postablation ^{131}I scintigraphy combining WBS and neck and thorax SPECT–CT with that of previously known clinical, biological, and pathological predictive factors.

Materials and methods

Patients

The study group included 170 consecutive patients with DTC who underwent radioiodine ablation from January 2006 to December 2008 (Table 1). Of these, 55 patients, treated in 2006, were part of a previous report (3). 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 4–58) weeks after surgery, either after withdrawal of thyroid hormone treatment or after two injections of recombinant TSH (rhTSH) (Thyrogen, Genzyme Corp., Cambridge, MA, USA). Serum TSH, Tg, and anti-thyroglobulin antibodies (TgAb) were measured immediately before administration of radioiodine.

Postablation ^{131}I scintigraphy was performed using a double-head gamma camera equipped with 1.5875 cm (5/8 in) NaI crystals and a multidetector (two rows) spiral CT (Symbia T2, Siemens Medical Solutions, Malvern, PA, USA) as described previously (3). Each patient had a postablation ^{131}I scan combining WBS

and SPECT–CT acquisitions of the neck and thorax. Of the total patients, four patients also had SPECT–CT on the abdomen and pelvis due to dubious foci on WBS. Postablation ^{131}I scan was performed 5 ($n=151$), 4 ($n=7$), or 2 ($n=12$) days after treatment. It was interpreted by two experienced nuclear medicine physicians (N A, S B) and a head and neck surgeon (J P R) for the first previously reported 55 patients and by at least one nuclear medicine physician (N A or/and S B) for the remaining 115 patients. The final conclusion was based on the analysis of SPECT–CT for neck and thorax. Other than neck and thorax, the conclusion was based on WBS except when SPECT–CT was available. Each focus of ^{131}I uptake was scored negative (benign), positive (malignant), or indeterminate according to the definitions reported by Aide *et al.* (3). At patient level, postablation ^{131}I scan was scored negative (benign) when all foci were negative, positive (malignant) when at least one focus was positive, or indeterminate when at least one focus was considered indeterminate without any positive foci.

Tg and TgAb evaluation

Serum Tg and TgAb measurements were simultaneously performed. From January 2006 to May 2008, serum Tg was measured using the immunometric assay

Table 1 Patient characteristics.

Characteristics	All patients ($n=170$)	Persistent or recurrent disease ($n=32$)	Disease free ($n=138$)	P value
Gender				0.0809
Women	123 (72%)	19 (59%)	104 (75%)	
Male:female ratio	0.38	0.68	0.33	
Age at diagnosis (years)	48 (9–87)	49 (9–86)	48 (11–87)	0.5945
Neck dissection				0.0036
No dissection	71 (42%)	8 (25%)	63 (46%)	
Central compartment only	52 (30%)	9 (28%)	43 (31%)	
Lateral compartment only	3 (2%)	1 (3%)	2 (1%)	
Central and lateral compartments	41 (24%)	11 (35%)	30 (22%)	
Adenectomy	3 (2%)	3 (9%)	0 (0%)	
TNM classification (2002)				
T status				
T1	86 (51%)	9 (28%)	77 (56%)	<0.0001
T2	46 (27%)	8 (25%)	38 (27%)	
T3	36 (21%)	13 (41%)	23 (17%)	
T4	2 (1%)	2 (6%)	0 (0%)	
N status				
N0	42 (25%)	1 (3%)	41 (30%)	<0.0001
N1 (total)	56 (33%)	23 (72%)	33 (24%)	
N1a	25 (4 macro ^a)	8 (2 macro)	17 (2 macro)	
N1b	31 (29 macro)	15 (15 macro)	16 (14 macro)	
Nx	72 (42%)	8 (25%)	64 (46%)	
M status				
M0	157 (92%)	19 (59%)	138 (100%)	<0.0001
M1 ^b	13 (8%)	13 (41%)	0 (0%)	
Histology				0.3610
Papillary thyroid cancer	151 (89%)	27 (84%)	124 (90%)	
Follicular thyroid cancer	19 (11%)	5 (16%)	14 (10%)	

^aMacro for macroscopic lymph node involvement according to Bardet *et al.* (7).

^bMetastases discovered before thyroid surgery in three patients and on postablation scintigraphy in ten patients.

Tg-Kryptor (Brahms, Hennigsdorf, Germany) with a lower detection limit of 0.2 ng/ml and a functional sensitivity of 0.8 ng/ml. For comparison with CRM-457-calibrated assays, the values should be multiplied by 1.92 according to the manufacturer's recommendation. During the same period, serum TgAb was measured using Immulite TgAb (Diagnostic Product Corporation, Los Angeles, CA, USA). From June 2008 to August 2010, serum Tg was measured using Roche Cobas 6000 Tg (Roche Diagnostics) with a lower detection limit of 0.1 ng/ml and a functional sensitivity of 1.0 ng/ml and serum TgAb using Roche Cobas 6000 anti-Tg assay.

Management after initial treatment and clinical outcome assessment

As described previously (3), patients with a negative postablation ^{131}I scan were observed at 3 months on L-Thyroxine (LT_4) treatment for serum TSH, Tg, and TgAb determinations. When Tg level was <1 ng/ml in the absence of TgAb, disease status was assessed at 9 months by serum rhTSH-stimulated Tg determination and neck ultrasound (US). Diagnostic scintigraphy after 185 MBq of ^{131}I was performed in 16 patients, nine of them with high TgAb level. When evaluation at 9 months was normal (i.e. stimulated Tg level ≤ 1 ng/ml and negative US), patients were followed up on an annual basis on LT_4 treatment. Otherwise, imaging modalities such as CT of the neck and thorax or FDG-PET were performed. In patients with positive or indeterminate postablation ^{131}I scintigraphy and/or with Tg level >1 ng/ml on LT_4 at 3 months, complementary imaging modalities such as neck US or magnetic resonance imaging (MRI), CT of the neck and thorax, or FDG-PET were performed.

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

Patient characteristics were compared using Fisher's exact test or the Kruskal-Wallis test as appropriate. Time to persistent or recurrent disease was calculated from the day of postablation ^{131}I scintigraphy to the date of diagnosis of persistent or recurrent disease, or August 1st 2010, whichever came first. Date of diagnosis was either date of biopsy or surgery, or that of positive imaging modalities, or that of postablation ^{131}I scintigraphy when persistent tumor was shown only on scintigraphy. In this latter case, time to persistent disease was arbitrarily defined as 1 month. The Kaplan-Meier method was used to estimate the

probability of survival. The following variables were analyzed: age at diagnosis (<45 vs ≥ 45 years); gender; postablation ^{131}I WBS with SPECT-CT (negative or indeterminate versus positive); serum Tg level at ablation (<58 vs ≥ 58 ng/ml) in patients with or without TgAb; T3 or T4 vs T1 or T2), N (N1a or N1b vs N0 or Nx), and M status according to the 2002 TNM classification; and macroscopic lymph node involvement (N1 macroscopic versus N1 microscopic or N0 or Nx) as described previously (7). The 58 ng/ml cutoff for serum Tg level was obtained by multiplying the previously reported threshold of 30 ng/ml (3, 5) by 1.92 as described earlier for comparison with CRM-457-calibrated assays. The estimates in each group were compared using the log-rank test (univariate analysis). An analysis of prognostic factors was performed using the multivariate Cox regression model with a stepwise selection. Statistical significance was defined as $P < 0.05$. All tests were two sided. SAS 9.2 statistical software (SAS Institute, Cary, NC, USA) was used to analyze the data.

Results

Patient characteristics

Table 1 reports the clinical and pathological features of the 170 patients using the pTNM classification.

Radioiodine treatment was given after withdrawal of thyroid hormone treatment ($n=133$) or after rhTSH ($n=37$) with a mean activity of 3752 MBq (range 925–4810). All TSH values at time of radioiodine administration were above 30 mU/l. Overall, the median follow-up was 29 months (range 8–54).

Of the 170 patients, 32 (19%) showed persistent or recurrent disease up to 44 months after postablation ^{131}I scintigraphy (Tables 1 and 2). All but one had radioiodine ablation after withdrawal of thyroid hormones. Eighteen patients had persistent or recurrent disease in the neck only, eight patients showed distant metastases (lung and/or bone) only, and six patients exhibited both neck tumor and distant metastases. At the time of last visit, 21 (66%) of these patients were considered disease free.

Postablation scintigraphy

Postablation scintigraphy in the 32 patients with persistent or recurrent disease was considered positive in 25 (78%) and negative in the remaining seven patients (22%). It was negative or indeterminate in all 138 (100%) patients who remained disease free. As a result, sensitivity and specificity for postablation scintigraphy were estimated at 78 (95% confidence interval (CI): 60–91%) and 100% respectively.

SPECT-CT clearly demonstrated isolated, lymph node involvement in 12 patients (patients 3, 6, 9, 11–14, 16,

Table 2 Patients with persistent or recurrent disease.

Initial presentation				Radioiodine ablation			Persistent or recurrent disease			Status on 1st August 2010		
Sex	Age (years)	Histology	TNM	Dissection modalities	Tg off T ₄ (ng/ml)/ TgAb ^{a,b}	WBS and SPECT/CT results at patient level		Time to ¹³¹ I scintiscan (months)	Abnormal imaging modalities ^{d,e}	Site/treatment	Second recurrence site/treatment	Active disease (AD)/disease free (DF)
						N/P ^c	Uptake site					
1	F	73	PTC	C & L Bil	161/N	N		5	CT ^d , PET	Tracheal invasion/ external irradiation		AD (trachea)
2	M	79	PTC	L ipsi	361/N	N		16	US, CT ^d , PET	L neck/surgery		AD – dead
3	F	42	PTC	C Bil	1187/N	P	L LN	2	US, CT ^e , PET	Lung/therapeutic trial		DF
4	F	69	PTC	C ipsi	39/N	N		44	PET	C neck/surgery	C neck/surgery	DF
5	F	18	PTC	C & L Bil	135/N	N		4	US	L neck/surgery		DF
6	M	69	PTC	Adenectomy	117/P	P	L LN	7	US, CT ^d	L neck/IG surgery		DF
7	F	10	PTC	C & L Bil	59/N	P	RLN; lung	1	CT ^d , MRI	RLN/surgery		AD (lung)
8	F	82	FTC	No dissection	728/N	P	Lung	5	CT ^e	Lung/ ¹³¹ I (3.4 GBq)		AD (lung)
9	F	73	PTC	C & L Bil	10/N	P	C LN	44		Lung/ ¹³¹ I (12.1 GBq)	L neck, lung/ ¹³¹ I (4.1 GBq)	AD (LN, lung)
10	M	33	PTC	Adenectomy	1298/N	P	C & L LN; lung	5	US, CT ^e	C & L neck/IG surgery		AD (LN, lung)
11	F	61	PTC	C & L Bil	0.1/P	P	L LN	1		Lung/ ¹³¹ I (12.1 GBq)		DF
12	M	27	PTC	Adenectomy	86/N	P	C & L LN	3	US, CT ^d	L neck/ ¹³¹ I (4 GBq)	C neck/surgery	DF
13	F	14	PTC	C Bil, L ipsi	104/N	P	C LN	16		C & L neck/IG surgery		DF
14	M	77	PTC	No dissection	129/N	P	C & L LN	5		C neck/IG surgery		DF
15	F	52	FTC	No dissection	6/N	P	Lung	1		C & L neck/surgery		DF
16	F	52	PTC	C & L Bil	15/P	P	L LN	8		Lung/ ¹³¹ I (7.9 GBq)	Lung/ ¹³¹ I (8 GBq)	DF
17	F	68	PTC	C ipsi	4082/N	N		5	US, CT ^d , PET	L neck/surgery, ¹³¹ I (12 GBq)		DF
18	F	27	PTC	C Bil	31/P	P	C & L LN	4	US	C & L neck/IG surgery		DF
19	M	31	PTC	C & L Bil	221/N	P	C & L LN; lung	4		C & L neck/IG surgery		DF
20	M	49	PTC	C Bil	12/N	P	C & L LN	4	US	C & L neck/IG surgery		DF
21	F	43	PTC	No dissection	96/N	N		11	US	C & L neck/surgery		DF
22	M	61	PTC	C Bil	15/N	P	Bone	1	MRI, PET	Bone/ ¹³¹ I (4.1 GBq)		DF
23	M	61	FTC ^h	No dissection	27888/N	P	Thyroid bed; bone	2		Bone, thyroid bed/external irradiation, surgery, ¹³¹ I, therapeutic trial		AD (bone, thyroid bed)
24	M	24	PTC	C Bil	133/N	P	L LN	6		L neck/IG surgery		DF
25	F	53	FTC ^h	No dissection	61018/N	P	Lung; bone	1	MRI, PET	Bone, lung/surgery, external irradiation, ¹³¹ I (12 GBq)	Bone/surgery	AD (bone)
26	F	40	PTC	C ipsi	4/N	P	Lung	1		Lung/ ¹³¹ I (8.3 GBq)		DF
27	F	32	PTC	C & L Bil	46/N	P	Lung	1		Lung/ ¹³¹ I (8 GBq)		DF

Table 2 Continued

Initial presentation				Radioiodine ablation			Persistent or recurrent disease			Status on 1st August 2010
Sex	Age (years)	Histology	TNM	Dissection modalities	Tg off T ₄ (ng/ml)/TgAb ^{a,b}	WBS and SPECT/CT results at patient level	Time to ¹³¹ I scintiscan (months)	Abnormal imaging modalities ^{d,e}	Second recurrence site/treatment	Active disease (AD)/disease free (DF)
						N/P ^c	Uptake site			
28 F	36	PTC	T2NXM1	No dissection	33/N	P	Bone			DF
29 M	86	PTC	T1N1bM0 ^f	C ipsi	604/N	P	L LN	US, PET		AD (LN)
30 M	60	PTC	T1N1bM0 ^f	C & L ipsi	60/N	N		US		DF – dead
31 M	9	PTC	T3N1bM1 ⁱ	C & L Bil	758/N	P	C LN; lung	US, CT ^d	C neck/IG surgery	AD (lung)
32 F	69	FTC	T2NXM1 ^g	No dissection	2887/N	P	Lung	CT ^e , PET	Lung/ ¹³¹ I (1.9 GBq)	AD (lung)
									Lung/ ¹³¹ I (16.6 GBq)	

C, central compartment; L, lateral compartment; Bil, bilateral; ipsi, ipsilateral; LN, lymph node; RLN, Retropharyngeal LN; IG surgery, ¹³¹I guided surgery.^aN, no TgAb; P, presence of TgAb.^bAll patients underwent withdrawal of thyroid hormones except patient 21 (rhTSH).^cN, negative; P, positive.^dIntegrated CT of hybrid equipment plus diagnostic CT.^eIntegrated CT of hybrid equipment only.^fMacroscopic lymph node involvement.^gMetastases discovered before thyroid surgery.^hPoorly differentiated.

18, 20, 24, and 29), all with papillary thyroid cancer (PTC). Of the 12 patients, eight underwent surgery (patients 3, 6, 12–14, 18, 20, and 24) including radioiodine-guided dissection for seven patients, and all were disease free at last visit; and the remaining four (patients 9, 11, 16, and 29) were treated by radioiodine of who two developed second recurrence in lungs. At last follow-up, two of these four patients were disease free.

SPECT-CT also showed neck lymph node involvement associated with lung metastases in four patients (patients 7, 10, 19, and 31). Patient 19 with central and lateral nodal persistent disease and lung foci, without nodules on integrated CT, was disease free after both surgery and a 5.9 GBq cumulative activity of radioiodine.

WBS with SPECT-CT depicted iodine-avid distant metastases in nine patients: lung metastases in five patients (patients 8, 15, 26, 27, and 32), bone metastases in two patients (patients 22 and 28), both lung and bone metastases in one patient (patient 25), and bone metastases with neck residual disease in one patient (patient 23).

Of these 25 positive results, postablation scintigraphy detected previously unknown distant metastases in ten patients (patients 7, 8, 10, 15, 19, 22, 26–28, and 31). For seven of them, conventional imaging remained negative. In patients 22 and 28, WBS and SPECT-CT revealed bone uptake without lesions on integrated CT. Bone scan, MRI, and PET were also negative. Complete remission, i.e. disappearance of bone uptake and undetectable stimulated Tg level, was obtained after one or three radioiodine treatments. Similarly, four patients (patients 15, 19, 26, and 27) with lung uptake and normal integrated CT were cured after two radioiodine treatments.

Among the seven patients with a negative postablation scintigraphy, one (patient 1) had persistent tracheal invasion, one (patient 2) showed lung metastases and neck nodal disease, and five (patients 4, 5, 17, 21, and 30) exhibited neck nodal disease only. In all these iodine non-avid patients, persistent/recurrent disease was demonstrated by US and/or FDG-PET. In three patients, residual tumor was also suspected on the integrated CT of hybrid equipment. All seven patients but one had stimulated Tg level above 58 ng/ml. Patient 4 with Tg level at 39 ng/ml showed the latest nodal recurrence at 44 months.

Stimulated serum Tg

Serum TgAb was present in 24 (14%) patients. In the whole group of patients ($n = 170$), stimulated serum Tg at ablation was higher in patients with persistent or recurrent disease (median: 110 ng/ml, range 0.1–61018) than in patients in complete remission (2 ng/ml, 0.1–94; $P < 0.0001$). Similar results were observed in patients without serum TgAb ($n = 146$), i.e. 131 ng/ml (4–61018, $n = 28$) vs 2 ng/ml (0.1–94,

Figure 1 Receiver operating characteristic (ROC) curves for stimulated serum Tg in patients with or without TgAb. The optimal 58 ng/ml cutoff level is indicated (arrow).

$n = 118$) respectively ($P < 0.0001$). A receiver operating characteristics (ROC) study confirmed that the optimal cutoff for stimulated serum Tg to predict persistent or recurrent disease was 58 ng/ml (Fig. 1). In the whole group of patients, the sensitivity and specificity for that cutoff were 66 (95% CI: 58–73%) and 98% (95% CI: 94–99%) respectively. The figures in patients without serum TgAb were 71 (95% CI: 63–79%) and 98% (95% CI: 95–100%).

In the whole group of patients, three with stimulated serum Tg ≥ 58 ng/ml did not develop persistent or recurrent disease as defined in this study. Of the three patients, one had large pretracheal thyroid remnants well demonstrated on postablation scintigraphy and on US. The rhTSH-stimulated Tg at 9 months was undetectable, with negative 185 MBq ^{131}I scintigraphy and neck US. The remaining two patients received a second radioiodine treatment 8 and 12 months later respectively. Serum Tg levels after hormone withdrawal was 52 and 14 ng/ml with still a negative post-therapeutic scintigraphy. Neck US, thoracic CT scan, bone scan, and PET were also negative in both the patients.

Conversely, 11 patients (patients 4, 9, 11, 15, 16, 18, 20, 22, 26, 27, and 28) with stimulated serum Tg < 58 ng/ml, of whom three had serum TgAb, showed persistent/recurrent disease. All but one had a positive postablation scintigraphy consistent with persistent disease in the neck ($n = 5$) or with distant metastases ($n = 5$). The remaining one patient (patient 4 already described) presented a late nodal recurrence. Complete remission was obtained after radioiodine treatment and/or surgery in all but one patient.

The data also show that, in patients without persistent or recurrent disease, stimulated serum Tg was higher after withdrawal of thyroid hormones

(3 ng/ml, 0.1–86, $n = 102$) than after rhTSH (0.6 ng/ml, 0.1–94, $n = 36$; $P = 0.004$).

Prognostic analysis

In the whole group of patients ($n = 170$), six variables were significantly associated with disease-free survival by univariate analysis: T, N, and M status according to the 2002 TNM classification, macroscopic lymph node involvement, serum Tg level at ablation and WBS with SPECT-CT ($P < 0.0001$ for each variable; Fig. 2). Gender and age at diagnosis were not significantly associated with disease-free survival ($P = 0.0564$ and $P = 0.7618$ respectively). All these variables were then included in a multivariate Cox regression model except age. Only positive WBS with SPECT-CT (HR = 65.21, 95% CI = 26.03–163.39, $P < 0.0001$) was associated with an increased risk of persistent or recurrent disease (Table 3).

When only patients without serum TgAb ($n = 146$) were considered, both positive WBS with SPECT-CT (HR = 18.86, 95% CI = 5.02–70.85, $P < 0.0001$) and

Figure 2 Disease-free survival in the whole group of patients ($n = 170$), according to risk category: gender; age; T, N, and M status according to the 2002 pTNM classification; macroscopic lymph node involvement; WBS with SPECT-CT; and stimulated serum Tg.

Table 3 Multivariate prognostic analysis: initial and final models.

	Patients at risk	Initial model			Final model		
		Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Gender				0.5105			
Women	123	1.0					
Male	47	0.741	0.303–1.810				
Age at diagnosis				0.1697			
<45 years	70	1.0					
≥45 years	100	1.774	0.783–4.022				
WBS with SPECT-CT				<0.0001			<0.0001
Negative or indeterminate	145	1.0			1.0		
Positive	25	22.050	6.437–75.535		65.213	26.028–163.392	
Macroscopic lymph node involvement				0.5351			
Negative or microscopic	137	1.0					
Macroscopic	33	0.719	0.254–2.037				
TNM classification (2002)							
T status				0.4960			
T1 or T2	132	1.0					
T3 or T4	38	0.749	0.325–1.723				
N status				0.0198			
N0 or Nx	114	1.0					
N1	56	4.761	1.282–17.685				
M status				0.1675			
M0	157	1.0					
M1	13	1.971	0.752–5.169				
Stimulated serum Tg				0.0820			
<58 ng/ml	146	1.0					
≥58 ng/ml	24	2.748	0.880–8.583				

95% CI, confidence interval.

serum Tg level at ablation ≥ 58 ng/ml (HR=4.42, 95% CI=1.18–16.53, $P=0.0271$) were related to an increased risk by multivariate analysis. The corresponding 24-month disease-free survival was 100% in patients with negative or indeterminate postablation scintigraphy and Tg level < 58 ng/ml, 25% (95% CI, 4–56%) in patients with negative or indeterminate scintigraphy and Tg level ≥ 58 ng/ml, 14% (95% CI, 1–46%) in patients with positive scintigraphy and Tg level < 58 ng/ml, and 7% (95% CI, 1–27%) in positive scintigraphy and Tg level ≥ 58 ng/ml (Fig. 3; $P<0.0001$).

Discussion

Planar ^{131}I scintigraphy is known to be associated with a substantial number of equivocal results, or even false positives (8). In recent years, it has been shown that the analysis of SPECT-CT images helps to precisely localize focal iodine uptake and to characterize it as either normal or abnormal. In postablation setting, neck and thorax SPECT-CT improves the N staging of patients with DTC (4, 9). SPECT-CT data may also reduce the need for additional cross-sectional imaging in 20% of patients and alter the ATA risk of recurrence classification in 6% of patients (10). In a primary report, we demonstrated that a positive postablation SPECT-CT

predicted treatment failure at 2 years better than a positive WBS (3). Because of a limited number of patients and lack of statistical power, the prognostic value of postablation scintigraphy with SPECT-CT could not be assessed in that study in comparison with that of known prognostic factors. In this study, including 170 consecutive and unselected patients with a median follow-up of 29 months, postablation scintigraphy was shown to be the sole independent prognostic variable for disease-free survival. Combining WBS and SPECT-CT enabled to identify previously unknown distant metastases in ten patients. Interestingly, conventional imaging, including integrated CT, remained negative in seven patients, stimulated serum Tg level was below 58 ng/ml in five patients, and six patients with lung or bone uptake were considered disease free after one to three radioiodine treatments. This strongly suggests that most of these patients presented with distant micrometastases and emphasizes both the diagnostic and the therapeutic role of radioiodine ablation in such patients. SPECT-CT also clearly showed isolated, persistent lymph node disease in 12 patients and allowed an experienced surgeon to plan reoperation with confidence, i.e. radioguided surgery a few days after a second therapeutic activity of radioiodine as previously reported (11). Complete remission could be safely achieved in all operated patients providing better results than those recently reported (12). Half of the

Figure 3 Disease-free survival in patients without serum TgAb ($n=146$). Blue curve shows patients with negative or indeterminate postablation scintigraphy and stimulated serum Tg level <58 ng/ml ($n=117$), the red curve patients with negative or indeterminate scintigraphy and Tg level ≥ 58 ng/ml ($n=8$), the green curve patients with positive scintigraphy and Tg level ≥ 58 ng/ml ($n=14$), and the black curve patients with positive scintigraphy and Tg level <58 ng/ml ($n=7$).

patients treated by radioiodine only also achieved complete remission, suggesting that this treatment can also be effective in that setting, at least in small-volume tumors as recently published (13). Although highly sensitive, post-ablative scintigraphy was negative in $\sim 20\%$ of patients who had persistent/recurrent disease. In most of these patients, however, high stimulated Tg levels led to other imaging modalities, i.e. neck US, thorax CT scan, and FDG-PET, which detected iodine non-avid persistent disease. In one patient (patient 4), who showed the latest recurrence, stimulated Tg level below 58 ng/ml was most likely related to a small tumor burden that progressively increased until detectable. As previously reported (3, 4), the main advantage of SPECT-CT is to accurately localize iodine foci and clearly characterize them as normal or abnormal. This allows nuclear medicine physicians to interpret scintigraphy with confidence and with an improved specificity.

High stimulated serum Tg level at ablation (≥ 58 ng/ml) was also shown as an independent prognostic factor for disease-free survival in the subgroup of patients where its measurement is known to be entirely reliable, i.e. in patients with no TgAb (14). This subgroup of patients represented 86% of the whole cohort, the proportion of TgAb being consistent with that of the earlier reports (15, 16). Few studies have focused on the prognostic value of stimulated Tg at ablation (5, 6, 16). In a retrospective study of 212 patients with no TgAb and a 5-year follow-up, Toubeau *et al.* (5) showed that a serum Tg level >30 ng/ml and the presence of node invasion were predictive of disease progression. In another retrospective study of patients treated between 1986 and 2000, Heemstra *et al.* (16) reported that a similar stimulated serum Tg level cutoff at 27.5 ng/ml was found as an independent prognostic

factor for disease-free survival with a sensitivity of 84% and a specificity of 89%. In the study by Kim *et al.* (6) 35 of the 268 patients (13%) showed recurrence during a mean 5-year follow-up. Of the 35 patients, 23 (66%) had stimulated serum Tg level >29 ng/ml. In a preliminary attempt to determine which group of patients might particularly benefit from SPECT-CT, we also found that a 30 ng/ml threshold might be appropriate (3). Therefore, in this study, we conducted the statistical analysis using this cutoff which actually corresponded to 58 ng/ml after multiplication by the 1.92 CRM-457-calibration factor. ROC analyses *a posteriori* validated this cutoff as the optimal one in our cohort, providing the best sensitivity and specificity. Is this cutoff as appropriate in patients treated after hormone withdrawal as in patients treated after rhTSH? This issue cannot be resolved in this study because of a limited number of patients treated by rhTSH and the occurrence of only one event in such patients. However, the observation in patients who remained disease free that stimulated serum Tg was significantly higher after hormone withdrawal than after rhTSH, suggests that the Tg cutoff might be not equivalent in each group.

At ablation, stimulated serum Tg level is likely to be correlated with the volume of normal thyroid remnants, and if present, with the burden of the residual tumor. As discussed earlier, stimulated Tg 'false negatives' were mostly observed in patients with micrometastases evidenced by postablation scintigraphy only and were successfully treated by radioiodine. Although not found in the present cohort, poorly differentiated histological subtypes might also be associated with false negatives, not only for Tg but also for postablation scintigraphy. Conversely, stimulated Tg 'false positives' can be related to large thyroid remnants as we observed in one patient. Finally, two other Tg false positives would not have been observed if patients with isolated detectable Tg level were also considered as having persistent or recurrent disease. This suggests that the definition of persistent/recurrent disease, which can vary from one study to another, may also be critical for data analysis.

Recent reports suggest that, both in low-risk (17) and in intermediate/high-risk subjects (18), the risk stratification can be refined by ongoing assessment within the first 2 years. Our data demonstrate that an accurate risk assessment can be achieved very early, at ablation, using postablation scintigraphy with SPECT-CT and stimulated Tg level. Each of these tools enables to identify patients at high or low risk of residual or recurrent tumor with good sensitivity and specificity. The cross analysis of both variables further improves the categorization of patients. Those combining negative postablation scintigraphy and low stimulated serum Tg level clearly show a very limited risk of persistent/recurrent disease. On the contrary, owing to an excellent specificity, positive postablation scintigraphy is related to a high risk of residual tumor, whatever serum Tg level and TgAb status. Finally, when

postablation scintigraphy is negative, the simultaneous finding of a high stimulated serum Tg level enables to target patients with ~30% risk of presenting persistent/recurrent disease.

Conclusion

These data provide evidence for a new risk stratification system dedicated to persistent/recurrent disease. This system would be based on the analysis of ¹³¹I postablation scintigraphy combining WBS and neck-thorax SPECT-CT and of stimulated Tg level. These imaging modalities and biological assays, now available in routine practice, would optimize the management of most patients with DTC.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

We thank Helen Lapasset for assistance in reviewing the manuscript.

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Received 1 April 2011

Accepted 4 April 2011