REVIEW

Endocrine-Related Cancer (2011) **18** R29–R40

Persistent disease and recurrence in differentiated thyroid cancer patients with undetectable postoperative stimulated thyroglobulin level

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Abstract

^{131}I is given in differentiated thyroid cancer (DTC) without taking into account thyroglobulin (Tg) levels at the time of ablation, whereas 6–18 months later it is a major criterion for cure. This single-center retrospective study assessed the frequency and risk factors for persistent disease on postablation whole body scan (WBS) and postoperative neck ultrasonography (n-US) and for recurrent disease during the subsequent follow-up, in patients with DTC and undetectable TSH-stimulated Tg level (TSH–Tg) in the absence of Tg antibodies (TgAb) at the time of ablation. Among 1031 patients ablated, 242 (23%) consecutive patients were included. Persistent disease occurred in eight cases (3%) (seven abnormal WBS and one abnormal n-US), all with initial neck lymph node metastases (N1). N1 was a major risk factor for persistent disease. Among 203 patients with normal WBS and a follow-up over 6 months, TSH–Tg 6–18 months after ablation was undetectable in the absence of TgAb in 173 patients, undetectable with TgAb in 1 patient and equal to 1.2 ng/ml in 1 patient. n-US was normal in 152 patients and falsely positive in 3 patients. After a mean follow-up of 4 years, recurrence occurred in two cases (1%), both with aggressive histological variants. The only risk factor for recurrence was an aggressive histological variant ($P=0.03$). In conclusion, undetectable postoperative TSH–Tg in the absence of TgAb at the time of ablation is frequent. In these patients, repeating TSH–Tg 6–18 months after ablation is not useful. ^{131}I ablation could be avoided in the absence of N1 and aggressive histological variant.

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Introduction

According to the recent ATA recommendations, radioactive iodine (^{131}I) administration after total thyroidectomy for differentiated thyroid cancer (DTC) is indicated in patients with moderate to high risk of recurrence, based on age, tumor size, lymph node status, extrathyroidal extension, and histological type of the thyroid tumor (Cooper *et al*. 2009). However, TSH-stimulated serum thyroglobulin (Tg) level at the time of ablation was not taken into account for this indication, although in patients with a normal postablation whole body scan (WBS), assessment of cure at 6–18 months after ablation is based on an undetectable TSH-stimulated serum Tg level in the absence of circulating Tg antibody (TgAb) together with a normal neck ultrasonography (US; Frasoldati *et al*. 1999, Pacini *et al*. 2003, Torlontano *et al*. 2006). The negative predictive value of an undetectable stimulated Tg level at 6–18 months after ablation is very high, reaching 97% or even more (Cailleux *et al*. 2000, Mazzaferri & Kloos 2002, Pacini *et al*. 2002, Torlontano *et al*. 2004, Toubeau *et al*. 2004), and in these patients, persistent disease was mostly related to

1351–0088/11/018–R29
DOI: 10.1677/ERC-10-0292
Online version via http://www.endocrinology-journals.org

the presence of small lymph node metastases on n-US (Bachelot *et al*. 2002).

At the time of ablation, detectable postoperative TSH-stimulated Tg (TSH–Tg) level may be related to the presence of persistent disease or normal thyroid remnant (Grunwald *et al*. 1996, Ronga *et al*. 1999, Oyen *et al*. 2000, Toubeau *et al*. 2004), but it is undetectable in 30–57% of patients after total thyroidectomy (Rosario *et al*. 2011, Tala Jury *et al*. 2010, Vaisman *et al*. 2010).

The aims of this single-center retrospective study in consecutive patients with undetectable serum Tg level at the time of ablation were first, to assess the frequency and risk factors for abnormal postablation WBS and postoperative n-US, and second, to assess the frequency and risk factors for recurrence in patients with both undetectable serum Tg level and normal postablation WBS at the time of ablation.

Patients and methods

Patients

Approval from our institutional review board was obtained for the study. Files of consecutive patients treated with ^{131}I between March 2001 and December 2008 were reviewed. Inclusion criteria were i) patients with DTC; ii) confirmed pathological diagnosis of malignancy by our pathologist (A A G); iii) first ^{131}I treatment given after total thyroidectomy with or without neck lymph node dissection; iv) undetectable serum-stimulated Tg level (Tg <1 ng/ml) with a recovery test above 80% or in the absence of TgAb (<2.2 UI/ml) on the day when ^{131}I was given in case of ablation performed after thyroid hormone withdrawal (THW) (with a serum TSH level above 30 mUI/l) or 3 days after the second rhTSH administration in case of rhTSH-mediated radioactive ablation; and v) the absence of known local disease or distant metastasis.

Records of 1031 consecutive DTC patients were reviewed. Stimulated serum Tg level was unknown in 6 patients, above 1 ng/ml in 707 patients, <1 ng/ml in 318 patients, among whom 243 had a recovery test above 80% or no detectable TgAb. In one of these 243 patients, TSH level was equal to 7 mUI/l despite THW. Overall, 242 patients (24%) met the inclusion criteria and formed the basis of this report (Fig. 1).

Radioiodine (^{131}I) ablation

Patients were treated after THW (202 cases) or rhTSH (40 cases) with 30, 50, or 100 mCi ^{131}I (Fig. 1). A WBS was performed 3–5 days after ^{131}I administration using

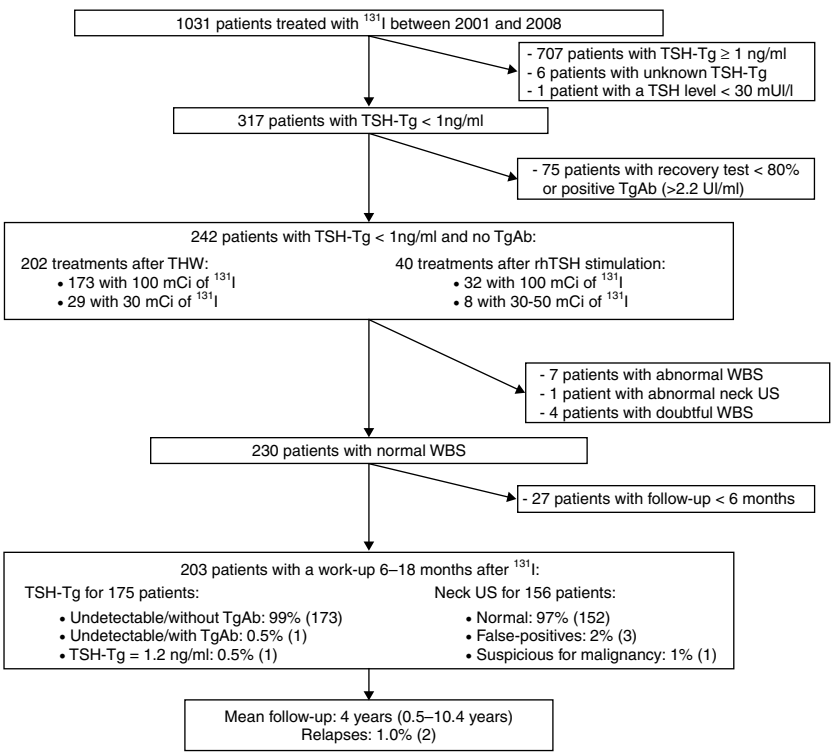

Figure 1 Initial patients' selection; occurrence of persistent disease and recurrence during subsequent follow-up. TSH–Tg, TSH-stimulated thyroglobulin level; TgAb, thyroglobulin antibody; US, ultrasonography; WBS, whole body scan.

a dual-head gamma camera equipped with high-energy collimators and thick crystals. In case of persistent disease diagnosed by foci of ^{131}I uptake outside the thyroid bed, specific therapeutic procedures were undertaken.

All WBS were reviewed by a board certified nuclear medicine physician (S L). WBS was classified as i) normal, ii) abnormal in case of iodine uptake outside the thyroid bed, or iii) suspicious in case of neck iodine uptake consistent with either a normal thyroid remnant or a lymph node or in case of uptake outside the thyroid bed consistent with an underlying disease. Discrepancies with the routine WBS report were resolved by consensus reviewing with a second board certified nuclear medicine physician (M S). For the analysis of risk factors for abnormal WBS, the final consensus reading was used.

Tg level measurements

From 2001 until 2005, serum Tg was measured using an IRMA (SELco Tg, Medipan Diagnostica, Selchow, Germany). The analytical sensitivity was 0.3 ng/ml and Tg level was considered as not accurately measured when the routine recovery test (performed in all serum samples) was $<80\%$. From 2006 to 2008, Tg was measured using a chemiluminescent immunoenzymatic 'sandwich' assay (Access Tg, automated on UniCel DxI 800 instruments, Beckman Coulter, Villepinte, France) with an analytical sensitivity of 0.1 ng/ml. The Tg level was considered as not accurately measured in the presence of TgAb at the Access Thyroglobulin Antibody II assay (Beckman Coulter).

Neck ultrasonography

US was performed on the day of ^{131}I administration and also 6–18 months after ^{131}I ablation with a high-resolution ultrasound system (Aplio ultrasound machine; Toshiba Medical, Puteaux, France) equipped with a high-energy 14 MHz linear probe (LZT; Toshiba), allowing to work in fundamental B-mode (lateral resolution: 0.17 mm; axial resolution: 0.11 mm) and in power Doppler mode (rate of 12 frames/s, limit detection of 5 cm/s with a pulse repetition frequency of 17 KHz). US examination included the thyroid bed and both central and lateral neck compartments. Suspicion of malignant lymph node was based on the following criteria: hyperechoic punctuations, cystic appearance, hypervascularization, round shape node without hyperechoic hilum, and a short axis >7 mm (Leboulleux *et al*. 2007). n-US was considered abnormal when lymph node metastasis was confirmed with a fine needle aspiration biopsy (FNAB) for cytology and Tg measurement in the aspirate fluid. n-US was considered falsely positive in case of suspicious findings with no evidence of malignancy in FNAB and/or when subsequent n-US was normal. In the other cases, n-US was considered as suspicious for malignancy.

Follow-up of patients with normal postablation ^{131}I WBS and normal postoperative n-US

In patients without detectable ^{131}I uptake outside the thyroid bed on the postablation WBS, levothyroxine (L-T_4) treatment was initiated with the aim of decreasing TSH to low levels (<0.5 mUI/l) without inducing clinical thyrotoxicosis. Six to eighteen months later, TSH-stimulated serum Tg was measured and n-US was performed. Patients with undetectable TSH–Tg (<1 ng/ml) and normal n-US were subsequently followed up at yearly intervals with clinical examination and serum Tg measurement on L-T_4 treatment at a replacement dose (serum TSH level between 0.5 and 1 mUI/l). In patients with detectable Tg under L-T_4 treatment and/or detectable stimulated Tg, and/or abnormal clinical examination, and/or abnormal n-US during the subsequent follow-up, morphological evaluations, including chest computed tomography and fluorodesoxyglucose positron emission tomography, were performed. When a recurrence was documented, specific treatments were given.

Statistical analysis

Quantitative data were expressed in mean and S.D. and qualitative data were expressed in percentage. Risk factors for abnormal posttherapeutic WBS or n-US or for persistent disease were analyzed by univariate and multivariate logistic regression and included the following characteristics: sex, age (≤ 45 vs >45 years), tumor size (≤ 20 mm, 20–40 mm, and >40 mm), bilaterality of the tumor, extension beyond the thyroid capsule, neck dissection at initial surgery, aggressive histological variant, and presence of metastatic lymph node (N1 versus N0–N*x*).

Variables associated with an abnormal WBS or persistent disease with a *P* value lower than 0.10 in the univariate analysis were included in the multivariate regression analysis. All reported *P* values are two sided and the significance level is 0.05. Analyses were performed using SAS statistical software (SAS Institute, Inc., Cary, NC, USA).

Results

Patients

Clinical characteristics and initial treatment

The clinical characteristics of the 242 patients are reported in Table 1. The cancer was papillary in 86% of cases, follicular in 13%, and distinct foci of papillary and follicular were present in 2% of the cases. Aggressive subtypes of DTC were found in 6% of the cases. Initial treatment consisted of total thyroidectomy in all cases and neck lymph node dissection in 80% of the patients. Initial surgery was performed in our center in 141 (58%) cases and in other centers in 101 (42%) cases. Mean size of the primary thyroid tumor was 20.5 mm (range 3–80, median 17 mm). pTNM and staging according to the 2010 pTNM scoring system are detailed in Table 1 (AJCC 2010). Among patients with lymph node metastases, the mean number of lymph node metastases was 4.4 (range 1–23) and the mean number of lymph node metastases with extracapsular extension was 0.5 (range 0–13). Median interval of time between surgery and ^{131}I ablation was 64 days (range 18–1653 days).

Table 1 Characteristics of patients

	***n*=242 patients**
Sex	
M/F	54 (22%)/188 (78%)
Mean age (range)	47±14 (14; 81)
Papillary thyroid cancer	207 (85.5%)
Follicular thyroid cancer	31 (12.8%)
Papillary and follicular thyroid cancer	4 (1.7%)
Variant of thyroid cancer	
Tall cell	5 (2.1%)
Oncocytic	3 (1.2%)
Diffuse sclerosing	3 (1.2%)
Poorly differentiated	4 (1.7%)
Stage	
I	138 (57.0%)
II	22 (9.1%)
III	79 (32.6%)
IV	3 (1.2%)
Classification	
pT1N0/pT1N1/pT1Nx	34/53/26
pT2N0/pT2N1/pT2Nx	22/13/13
pT3N0/pT3N1/pT3Nx	30/37/10
pT4N0/pT4N1/pT4Nx	0/4/0
Bilateral tumor	69 (28.5%)
Multifocal tumor	117 (48.3%)
Tumor size	
≤20 mm	156 (64.5%)
20–40 mm	67 (27.7%)
>40 mm	17 (7.0%)
Unknown	2 (0.8%)
CND	
None	49 (20.2%)
Central only	25 (10.3%)
Central+ipsilateral	127 (52.6%)
Central+bilateral	38 (15.7%)
Ipsilateral only	2 (0.8%)
Controlateral only	1 (0.4%)
LN metastases	
Presence in neck compartment	106 (43.8%)
Central only	47 (44%)
Central and lateral	40 (37.7%)
Lateral only	19 (17.9%)
Absent	86 (35.5%)
Unknown (no neck dissection)	49 (20.2%)

LN, lymph node; CND, cervical neck dissection.

Postablation WBS results

Reviewing of postablation WBS was concordant with routine reports in 237 (98%) cases and discordant in only 5 (2%). After consensus reviewing, two initially abnormal WBS and two initially suspicious WBS were considered normal and one initially abnormal WBS was considered suspicious.

WBS was normal in 231 cases with a mean uptake in the thyroid bed of 0.3% (range 0.01–2.87). It disclosed foci of uptake outside the thyroid bed in 11 patients, which were considered abnormal in 7 (3%) and suspicious in the 4 (1.6%) other cases (Fig. 1).

All abnormal foci of iodine uptake were found in patients with pN1 tumors and were located in previously dissected neck compartments: in the central compartment in five cases and in the lateral neck compartment in two (Table 2). n-US, performed in six cases, was normal in five and falsely positive in one. A second ^{131}I treatment was administered after THW in all these seven patients after a mean time of 8.7 months (range 5–12 months). Stimulated Tg level remained undetectable and n-US was normal in all six cases in whom it was performed. The second WBS was normal in four cases, and showed persistent abnormal foci of iodine uptake in the neck in the three other cases. These patients were then followed up on L-T_4 treatment for a median follow-up of 48 months (range 14–77), and one patient experienced a cutaneous recurrence 14 months after the initial treatment. This patient had a pT3N1 tumor, a normal second WBS, and an undetectable Tg level on L-T_4 treatment at the time of recurrence.

Suspicious foci of ^{131}I uptake were located in the neck in two patients with both normal n-US (in the central neck compartment in one and in the lateral neck compartment in the other one); they were located in the lungs in one case with severe mucoviscidosis and in bone in one case. Tumors were pN0 in two cases and pN1 in two cases (Table 2). A second ^{131}I treatment was administered to two of these four patients 4.5 and

Table 2 Clinical characteristics of patients with (A) and (B) at the time of ^{131}I ablation

Sex/age at diagnosis	**Initial treatment**	**Pathology**	**pTN**	**Tumor size** (mm)	**Number of metastatic lymph node/number of metastatic lymph node with ECE**	**Multifocality** (yes/no)/ **bilaterality** (yes/no)	**Type of TSH stimulation/activity of radioactive iodine** (GBq)	**Postablation WBS results** (location of iodine uptake)
(A) Abnormal WBS or abnormal neck US								
F/43	TT+central and ipsilateral ND	Papillary	pT1N1	07	11/0	Yes/no	THW/4.1	Abnormal (neck: central)
F/28	TT+central and ipsilateral ND	Papillary	pT3N1	54	9/2	Yes/yes	THW/3.6	Abnormal (neck: central)
M/46	TT+central and ipsilateral ND	Papillary	pT1N1	07	8/2	No/no	THW/3.8	Abnormal (neck: lateral compartment)
F/33	TT+central and ipsilateral ND	Papillary	pT1N1	15	1/0	Yes/no	THW/3.9	Abnormal (neck: lateral compartment)
M/53	TT+central and ipsilateral ND	Papillary	pT4N1	65	1/1	No/no	THW/3.9	Abnormal (neck: central)
M/52	TT+central ND	Papillary	pT3N1	28	1/0	No/no	THW/3.8	Abnormal (neck: central compartment)
M/51	TT+central and bilateral ND	Papillary	pT3N1	55	9/1	Yes/no	THW/3.7	Abnormal (neck: central and lateral compartments)
F/36	TT+central lymph node picking	Papillary	pT1N1	20	2/0	Yes/yes	THW/3.8	Abnormal neck US
(B) Suspicious WBS								
F/33	TT+central and bilateral ND	Papillary	pT4N1	08	22/13	No/no	THW/3.8	Suspicious (lung)
F/56	TT+central and ipsilateral ND	Papillary	pT1N1	12	18/0	Yes/no	THW/3.9	Suspicious (neck – lateral compartment)
F/52	TT+central and ipsilateral ND	Papillary	pT1N0	11	0/0	Yes/no	THW/3.8	Suspicious (bone)
M/48	TT+central and ipsilateral ND	Follicular (oncocytic)	pT1N0	17	0/0	No/no	THW/3.9	Suspicious (neck – central compartment)

M, male; F, female; TT, total thyroidectomy; ND, neck dissection; TC, thyroid cancer; ECE, extracapsular extension; THW, thyroid hormone withdrawal; TgAb, thyroglobulin antibodies; US, ultrasonography.

8.5 months after the first ^{131}I treatment, and the WBS remained suspicious in the patient with lung uptake. These four patients were then followed on L-T_4 for a median of 18 months (range 6–50 months), and no recurrence occurred.

Initial n-US

Initial n-US performed at the time of ^{131}I ablation was available in 184 patients (76%). It was falsely positive in five (2.7%) cases, abnormal in one (0.5%), and suspicious in one (0.5%). The patient with abnormal n-US had a pT1N1b thyroid cancer (TC) with a normal WBS (Table 2). The patient with suspicious n-US had a normal WBS and a persistent suspicious lymph node with microcalcifications that remained stable in size over a period of 3 years without any morphological modification.

Risk factors for abnormal WBS or abnormal n-US

Risk factors for abnormal WBS or abnormal n-US are shown in Table 3. All patients with abnormal WBS or abnormal n-US had initial lymph node metastases. It was therefore not possible to test the significance of this variable. Among pN1 patients, WBS or n-US was abnormal in 33% (3/9) of the patients with a tumor size above 40 mm and in 5% (5/99) of the patients with a tumor size of 40 mm or less ($P=0.002$).

Follow-up

Besides the 11 patients with abnormal ($n=7$) or suspicious ($n=4$) postablation WBS and the patient with a normal WBS but abnormal n-US, there were 230 patients with normal WBS among which a follow-up of 6 months or more was available for 203 (mean follow-up: 4.0 years; range 0.5–10.4; median 3.5 years) (Fig. 1). TSH-stimulated serum Tg level at 6–18

Table 3 Risk factors for abnormal posttherapeutic whole body scan (WBS) or neck ultrasonography

	Persistent disease	Univariate analysis		Multivariate analysis	
	Yes/total	OR (95% CI)	*P*	OR (95% CI)	*P*
Age					
<45 years	4/103	1 (ref)	0.66		
45 years	4/139	0.7 (0.2; 3.0)			
Sex					
Male	4/54	1 (ref)		1	
Female	4/188	0.3 (0.1; 1.1)	0.07[a]	0.4 (0.1; 1.7)	0.19
Tumor size (mm)					
≤20	4/156	1 (ref)			
20–40	1/67	0.6 (0.1; 5.3)	0.63		
>40	3/17	8.3 (1.7; 40.6)	0.009[a]	7.3 (1.5; 35.9)	0.01[b]
Bilaterality					
No	6/172	1 (ref)	0.82		
Yes	2/69	0.83 (0.2; 4.2)			
Multifocality					
No	3/125	1 (ref)	0.42		
Yes	5/117	1.8 (0.4; 7.7)			
Extension beyond the thyroid capsule					
No	4/161	1 (ref)			
Yes	4/81	2.0 (0.5; 8.4)	0.32		
Initial surgery					
No neck dissection	1/48	1 (ref)			
Neck dissection	7/194	1.8 (0.2; 14.6)	0.60		
Aggressive variant					
No	8/227	–[b]	–[b]		
Yes	0/15				
Metastatic LN					
N0–Nx	0/136	–[b]	–[b]		
N1	8/106				

OR, odd ratio; LN, lymph node.
[a]Variables used for multivariate analysis.
[b]Statistical significance, however, no test is possible for the variables pN1 and aggressive variant in the absence of event in one of the group.

months after ablation was measured in 175 patients, either after THW in 18 cases (10%) or after rhTSH injections in 157 cases (90%). It was undetectable in the absence of TgAb in 173 (99%) cases, undetectable with TgAb in 1, and detectable at a level of 1.2 ng/ml in the remaining patient. n-US performed at 6–18 months after ablation in 156 patients was normal in 152 (97%), falsely positive in 3 (2%), and remained suspicious for malignancy in the patient who already had a suspicious n-US at the time of ablation and has been described earlier.

During the 4 subsequent years, 2 (1.0%) recurrences occurred among the 203 patients, 24 and 44 months after initial surgery (Fig. 1). Both had an aggressive variant of DTC and were classified as poorly differentiated pT3N0 follicular TC and oncocytic cell pT3N1 follicular TC respectively (Table 4). Both had an elevated serum Tg level on L-T_4 treatment at the time of recurrence. Recurrence was located in the neck in one case and in bone in the other case.

Furthermore, three patients were classified as suspicious of recurrence because of suspicious findings on n-US or TgAb (Table 4). In one case, n-US performed during follow-up remained suspicious for malignancy, as it was at the time of ablation and at the work-up 6–18 months after ablation with an undetectable Tg/L-T_4 level in the absence of TgAb. In one case, TgAb, already present at 6–18 months after ablation, stayed at a stable level during follow-up with an undetectable serum Tg level and a normal n-US. In the last case, TgAb became positive during follow-up, 80 months after initial treatment with a slowly increasing level from 6.1 to 43.6 UI/ml during a 12-month subsequent follow-up with a normal n-US.

Finally, the patient with a 1.2 ng/ml rhTSH–Tg level at 6–18 months after ablation had a second rhTSH–Tg level measurement that was undetectable in the absence of TgAb with a normal n-US.

Table 4 Clinical characteristics of patients with recurrence or suspicion of recurrence

Sex/age at diagnosis	Initial treatment	Pathology	pTN	Tumor size (mm)	Number of metastatic lymph node/number of metastatic lymph node with ECE	Multifocality (yes/no)/bilaterality (yes/no)	Type of TSH stimulation/activity of radioactive iodine (GBq)	Status at last follow-up
M/74	TT+central and ipsilateral ND	Follicular TC (oxyphil variant)	pT3N1	30	3/2	No/no	THW/3.8	Recurrence in bone
F/52	TT+central ipsilateral and controlateral ND	Follicular TC (poorly differentiated variant)	pT3N0	30	0/0	Yes/yes	THW/3.79	Recurrence in neck
M/34	TT+central and ipsilateral ND	Papillary	pT1N1	8	4/0	No/no	rhTSH/3.77	Suspicious neck LN on US
F/43	TT+central and ipsilateral ND	Papillary	pT1N0	19	0/0	Yes/yes	THW/3.82	Positive TgAb
F/53	TT+central and ipsilateral ND	Papillary	pT3N0	46	4/0	No/no	THW/3.59	Positive TgAb

M, male; F, female; TT, total thyroidectomy; ND, neck dissection; TC, thyroid cancer; ECE, extracapsular extension; THW, thyroid hormone withdrawal; TgAb, thyroglobulin antibodies; US, ultrasonography.

Risk factors for recurrence or suspicion of recurrence

The only risk factor in the univariate analysis was an aggressive histological variant of DTC ($P=0.01$; Table 5).

Survival

Five patients died during follow-up, none of them of thyroid cancer.

Table 5 Risk factors for recurrence or suspicion of recurrence

	Recurrence	Univariate analysis	
	Yes/total	OR (95% CI)	*P*
Age			
<45 years	2/86	1 (ref)	
45 years	3/117	1.1 (0.2–6.8)	0.91
Sex			
Male	2/44	1 (ref)	
Female	3/159	0.4 (0.1–2.5)	0.33
Tumor size (mm)			
≤20	2/128	1 (ref)	
20–40	2/57	2.3 (0.3–16.7)	0.41
>40	1/11	6.6 (0.5–78.7)	0.14
Bilaterality			
No	3/144	1 (ref)	
Yes	2/58	1.7 (0.3–10.3)	0.58
Aggressive histological variant			
No	3/190	1	
Yes	2/13	11.3 (1.7; 75.0)	0.01[a]
Multifocality			
No	3/107	1 (ref)	
Yes	2/96	0.7 (0.1–4.5)	0.74
Extension beyond the thyroid capsule			
No	2/137	1 (ref)	
Yes	3/66	3.2 (0.5–19.7)	0.20
Initial surgery			
No neck dissection	0/34	[b]	[b]
Neck dissection	5/169		
Metastatic LN			
N0–Nx	2/111	1 (ref)	
N1	3/92	1.8 (0.3–11.2)	0.51

OR, odd ratio. LN, lymph node.
[a]denotes statistical significance.
[b]OR cannot be calculated in the absence of any event.

Discussion

Postoperative administration of radioactive iodine allows a highly sensitive WBS that may detect persistent disease and facilitates follow-up by improving the specificity of serum Tg measurement by destroying any thyroid remnants. Some studies reported a benefit of postoperative radioactive iodine therapy for recurrence-free survival in patients with tumors larger than 1 or 1.5 cm, or with neck lymph node metastases, or with aggressive pathological variants of DTC (DeGroot *et al*. 1990, Mazzaferri 1997, Taylor *et al*. 1998, Jung *et al*. 2007, Jonklaas *et al*. 2010). However, the efficacy of adjuvant radioactive iodine therapy for improving survival and recurrence-free survival is still controversial in low-risk patients, and only nonrandomized studies are available (Samaan *et al*. 1992, Sanders & Cady 1998, Hay *et al*. 2002, Kim *et al*. 2004).

The definition of cure or 'free of clinically detectable disease' at 8–12 months after postoperative radioactive iodine treatment is based on an undetectable stimulated serum Tg level with a normal n-US. Therefore, the usefulness of radioactive ablation of thyroid remnants in patients who already have an undetectable postoperative stimulated serum Tg level can be questioned, in particular when n-US does not show any abnormality (Cailleux *et al*. 2000, Mazzaferri & Kloos 2002, Pacini *et al*. 2002, Torlontano *et al*. 2004, Toubeau *et al*. 2004, Rosario *et al*. 2011, Vaisman *et al*. 2010). These patients represent almost one-fourth of thyroid cancer patients treated with radioiodine in our institution, in accordance with the one-third (30%) reported in consecutive patients and one-half (57%) reported in selected patients with either no metastatic lymph node or no metastatic neck lymph node outside the central compartment (Rosario *et al*. 2011, Tala Jury *et al*. 2010, Vaisman *et al*. 2010).

Therefore, we focused on the number of abnormal findings on postablation WBS and n-US. These were found in only 3% of the patients, who were all initially N1 patients, consistent with the normal WBS found in all N0 patients with postoperative undetectable stimulated Tg level (Rosario *et al*. 2011). Indeed, the routine use of preoperative n-US should limit the frequency of postoperative abnormal n-US. Furthermore, subsequent clinical recurrence was rare (1%) and occurred only in two patients who had aggressive histological variants. Whether this low rate is linked to intrinsic cancer characteristics or to the beneficial effect of adjuvant radioactive iodine therapy cannot be determined because our study was retrospective and all patients were given ^{131}I. However, the two patients with recurrence had aggressive histological variants known to poorly respond to ^{131}I treatment, and both had elevated Tg level under L-T_4 treatment at the time of recurrence. This result is consistent with a prospective study on 59 low-risk DTC patients with undetectable postoperative Tg level, which reported the absence of recurrence after a mean follow-up of 3.3 years in the absence of ^{131}I ablation (Vaisman *et al*. 2010). Interestingly, among all patients with normal WBS, Tg level on L-T_4 remained undetectable in all patients, except in these two latter patients who did relapse.

Our data also suggest that there is no need for TSH-stimulated serum Tg measurement at 6–18 months after ablation when it was already undetectable at the time of ablation. In fact, this stimulation did not afford any significant data in our patients. These results are in accordance with previous studies that reported a limited value of repeated rhTSH–Tg measurement in patients with previously negative rhTSH–Tg

(Kloos & Mazzaferri 2005, Castagna *et al*. 2008, Crocetti *et al*. 2008). The results slightly differ from a study that recommends to repeat an rhTSH–Tg measurement 3 years after an undetectable rhTSH–Tg level measured 1 year after radioactive ablation in whom the results of the postoperative n-US are unknown (Klubo-Gwiezdzinska *et al*. 2010).

Two patients were considered as suspicious for recurrent disease because TgAb became detectable during follow-up, but no recurrence has been identified yet, and this may be related to a change of TgAb assay during the follow-up, emphasizing the importance of using the same assays over time (Spencer & Wang 1995, Schlumberger *et al*. 2007).

These results, therefore, suggest that when postoperative TSH–Tg level is undetectable and n-US is normal, ^{131}I ablation could be avoided in patients without lymph node metastasis at initial surgery and in the absence of aggressive histological DTC variant. Indication of ^{131}I administration should be tailored not only on pTNM staging and histological subtypes but also on postoperative stimulated Tg level (Fig. 2). The results also clearly emphasize the importance of lymph node staging for the indication of ^{131}I treatment, even though prophylactic neck dissection remains a matter of debate (Bonnet *et al*. 2009, Cooper *et al*. 2009, Vaisman *et al*. 2010). Of note, our results are even strengthened by the fact that half of the patients of this study were initially operated in nonspecialized center.

We also found that despite a mean interval of time of 87 days between surgery and ablation, n-US was informative as long as strict ultrasound criteria are used for the suspicion of malignancy. False-positive n-US is more frequent than true positive. This might be related to the short postoperative interval of time when postoperative lymphoceles or inflammatory hypervascularized hypertrophic lymph nodes are frequent.

Besides the fact that all patients were given radioactive iodine treatment, we are aware of the limitations of this study. First, it is a retrospective study. However, prospective studies on ablation in DTC are still scarce, and we studied all patients who were treated in our institution, thus avoiding a selection bias. Second, n-US at 6–18 months after ablation was only available in 75% of the patients. This is essentially

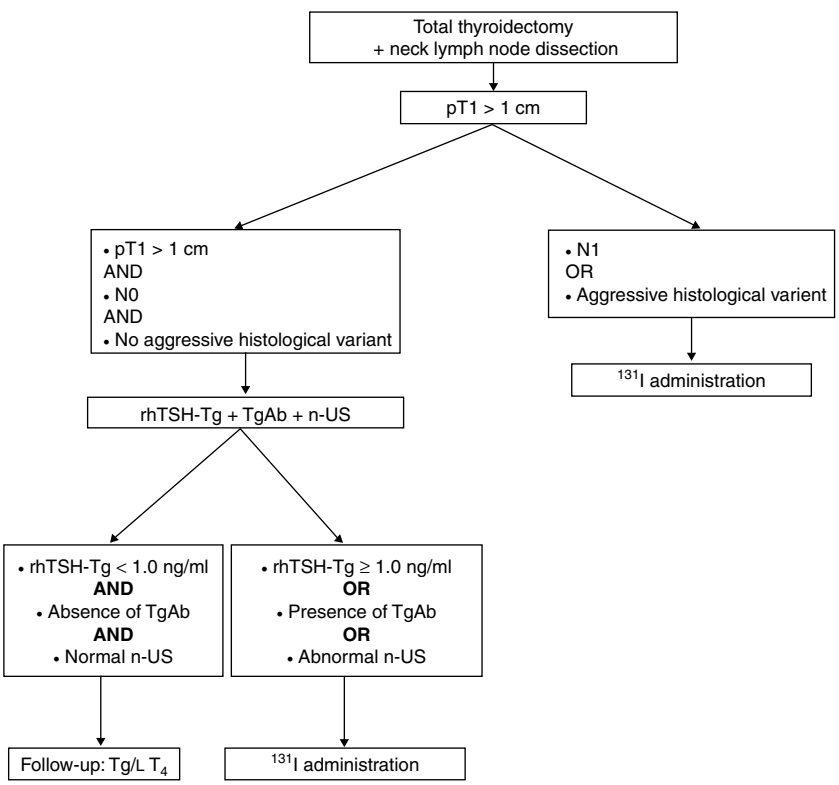

Figure 2 Flowchart for radioactive iodine administration decision based on pTNM, histopathological subtype, and stimulated postoperative Tg level in DTC above 1 cm of size. Tg, thyroglobulin; TgAB, thyroglobulin antibody; n-US, neck ultrasonography; N1, lymph node metastases; rhTSH, recombinant human thyrostimulin hormone; L-T_4, levothyroxine.

due to patients treated in 2001, when assessment of cure was based on stimulated serum Tg level and diagnostic WBS (Cailleux *et al*. 2000). Third, stimulated Tg levels at 6–18 months after ablation were only available in 86% of the cases, but serum Tg remained undetectable on L-T_4 treatment during the subsequent follow-up in all patients except in the two patients who did relapse. Fourth, the mean follow-up of the study is only 4 years, but most relapses are known to occur within 5 years after initial treatment (Mazzaferri & Kloos 2001). Furthermore, given the very high negative predictive value of an undetectable stimulated serum Tg level at 6–18 months after ablation, the number of further recurrence in the cohort is expected to be low (Cailleux *et al*. 2000, Mazzaferri & Kloos 2002, Pacini *et al*. 2002, Torlontano *et al*. 2004, Toubeau *et al*. 2004).

In conclusion, undetectable postoperative stimulated serum Tg level in the absence of TgAb at the time of ablation is frequent. In these patients, the stimulated Tg at 6–18 months after ablation does not afford any further information. Our results suggest that ^{131}I ablation indications could be tailored according to postoperative stimulated serum Tg level and may be avoided in the absence of lymph node metastases in patients without an aggressive histological variant of TC.

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

The authors are indebted to Catherine Martin for secretarial assistance.

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Received in final form 14 December 2010
Accepted 23 December 2010
Made available online as an Accepted Preprint
23 December 2010