J Clin Endocrin Metab. First published ahead of print January 11, 2012 as doi:10.1210/jc.2011-1882

Outpatient Thyroid Remnant Ablation Using Repeated Low 131-Iodine Activities (740 MBq/20 mCi × 2) in Patients with Low-Risk Differentiated Thyroid Cancer

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Context: In low-risk differentiated thyroid cancer (DTC), postoperative ^{131}I remnant ablation should employ a minimum effective activity; reports increasingly suggest efficacy of low activities, *e.g.* 1110 MBq/30 mCi.

Objectives, Design, Patients, and Interventions: We retrospectively studied the ablation capability and diagnostic utility of the Minidose protocol, two 740-MBq/20 mCi outpatient administrations, 6–18 months apart, plus related diagnostic procedures, in 160 consecutive (near-) totally thyroidectomized low-risk DTC (pT1/N0-Nx) patients. Successful ablation comprised negative 740-MBq whole-body scintigraphy with cervical uptake below 0.1%, negative stimulated thyroglobulin (STg) (<1 ng/ml, negative thyroglobulin antibodies), and negative Doppler ultrasonography (performed around Minidose 2).

Setting: The study took place at a referral center.

Results: Minidose imaging found unsuspected nodal or distant metastases in nine of 160 patients (5.6%). Ablation success rates after one (two) 740-MBq activity (activites) were 75.9% (90.2%) in 145 (132) evaluable imaging-negative patients. Compared with thyroid hormone withdrawal, recombinant human TSH stimulation was associated with higher urinary iodine excretion/creatinine, lower cervical uptake, and more frequent ablation success after the first 740 MBq; success rates no longer differed significantly after both administrations. Patients with STg below 10 ng/ml at Minidose 1 were oftener ablated at Minidose 2 (odds ratio = 13.9, 95% confidence interval = 2.5–76.4, $P < 0.003$), attaining 92.0% final ablation success after recombinant human TSH preparation, suggesting that one 740-MBq activity should suffice in this subgroup. All 81 evaluable patients with prolonged follow-up (mean 41.8 ± 21.9 months after Minidose 1) had no evidence of disease at the last visit.

Conclusions: The Minidose outpatient ablation protocol is effective and diagnostically useful in low-risk DTC. **(*J Clin Endocrinol Metab* 97: 0000–0000, 2012)**

Management of low-risk differentiated thyroid cancer (DTC) patients currently provokes substantial debate, especially regarding the need for postsurgical radioiodine thyroid remnant ablation and, if such a need exists, which activity to use (1). Indeed, low-risk DTC usually is associated with approximately 5% 10-yr recurrence and

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2011-1882 Received June 28, 2011. Accepted December 13, 2011.

Abbreviations: CI, Confidence interval; DTC, differentiated thyroid cancer; OR, odds ratio; rhTSH, recombinant human TSH; STg, stimulated serum thyroglobulin; Tg, thyroglobulin; TgAb, Tg antibody; THW, thyroid hormone withdrawal; UC, urinary creatinine; UIE, urinary iodine excretion; US, ultrasonography; 740WBS, whole-body scintigraphy with 740 MBq.

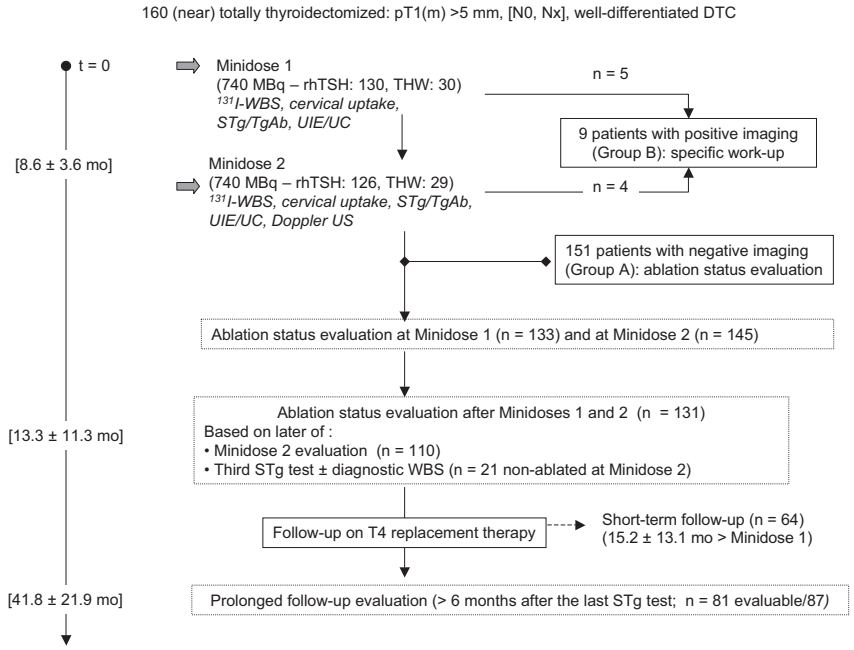

FIG. 1. Flow chart of the Minidose protocol. Each Minidose included a 740-MBq ^{131}I administration followed by WBS with cervical uptake measurement, STg/TgAb determination using a second-generation assay, and UIE/UC measurement; Doppler US was performed around Minidose 2. Minidose 1 was time zero of the study. Nine patients with positive Minidose imaging were treated separately (group B). The remaining 151 patients (group A) underwent ablation success evaluation. Patients with positive TgAb (18 at Minidose 1, six at Minidose 2, and two at the last visit) were excluded from the ablation success evaluation or prolonged follow-up evaluation for the times when they were TgAb positive. Immediately after the Minidose 2 procedure, 129 patients were followed on T_4 replacement therapy, whereas 22 patients not ablated at Minidose 2 entered follow-up after a last STg test some months after the Minidose 2 evaluation. Eighty-seven patients had prolonged follow-up (>6 months after the last STg test); data were evaluable in 81 of these patients.

2–3% disease-specific mortality (2, 3). Therefore, in this setting, recent American Thyroid Association guidelines emphasize applying the minimum effective ablation activity (4).

Although originally empirically chosen, 3.7 GBq (100 mCi) of ^{131}I traditionally has been the most common ablation activity. However, during the past decade, use of smaller activities has aroused considerable interest (5–7). Recent published papers (8–12) or meeting presentations (13, 14) suggest that 1.11–2.0 GBq (30–54 mCi) ^{131}I activities may be as effective as 3.7 GBq in eradicating remnant. Lately, improved surgical procedures frequently result in remnant volume less than 1 ml, corresponding to 48- to 72-h cervical uptake of less than 2%. These small remnant sizes probably explain lower activities' success.

In February 2001, we began using a Minidose protocol comprising two 740-MBq ^{131}I administrations, 6–18 months apart, plus related diagnostic procedures. This activity is permitted for outpatient therapy in many countries; we hypothesized that this regimen would successfully ablate most low-risk DTC patients. Our main rationales for ablation in such patients were to 1) eliminate postsurgical remnant, facilitating detection of recurrence throughout follow-up, and 2) identify individuals with occult metastases.

We now report a retrospective analysis regarding ablation outcomes in 160 consecutive low-risk patients referred to our department for the Minidose protocol. We also sought to identify ablation success predictors and to examine the protocol's ability to detect previously unknown lesions in this population. Additionally, we attempted to assess the impact of the TSH stimulation method and iodine load on ablation success.

Patients and Methods

Patients, patient instruction, and ethics

The study cohort included consecutive patients scheduled for the Minidose protocol meeting the following criteria: age at least 18 yr, well-differentiated papillary or follicular thyroid carcinoma or their oxyphilic variants, stage pT1/N0-Nx disease (15) and (near-) total thyroidectomy. We excluded patients with unifocal tumors smaller than 5 mm or insular, tall-cell or diffuse sclerosing histology. The study period was February 2001 to June 2011.

Because a single 3.7-GBq activity was the standard ablation regimen at most centers as of February 2001, the Minidose protocol was gradually phased into our practice, used in approximately 10% of our eligible patients in 2001, approximately 43% in 2003, approximately 88% in 2008, and more than 95% from 2009 on. The Minidose protocol was approved by our Ethics Committee, and the choice of using the Minidose protocol *vs.* other options was made by our Tumor Board before being submitted to the patient's approval.

Protocol, main study analyses, and endpoints

Figure 1 summarizes the Minidose protocol and study analyses. Patients with negative imaging at both Minidose procedures (151 of 160, group A) were included in two main analyses: 1) ablation success at Minidose 1, at Minidose 2, and after both Minidoses [*i.e.* at the later of Minidose 2 or a third stimulated serum thyroglobulin (STg) test some months later] and 2) disease status after prolonged follow-up (>6 months after the latest STg test). We evaluated ablation success at these times to determine the effects on thyroid remnant of surgery only (Minidose 1 evaluation), of the Minidose 1 activity (Minidose 2 evaluation) or of both Minidose activities, *i.e.* cumulative administration of ~1.48 GBq (~40 mCi) ("after both Minidoses" evaluation).

Ablation success at Minidose 2 also was the endpoint of a multivariate analysis to identify factors present at Minidose 1 independently predicting this outcome. The ultimate objective of

the multivariate analysis was to identify patient categories in which the Minidose 2 activity might be omitted.

Patients with positive imaging at either Minidose evaluation (nine of 160, group B) underwent an individualized work-up, because two 740-MBq activities given 6–18 months apart had not been reported to reliably destroy metastases. Because of this difference in disease management, group B patients were excluded from the previously described analyses.

Ablation success was defined as the combination of 1) no visible thyroid bed uptake on whole-body scintigraphy with 740 MBq (740WBS) or cervical uptake below 0.1% and 2) undetectable STg (<1 ng/ml). Patients were considered to be inevaluable for analyses involving evaluation times when they were antithyroglobulin antibody (TgAb) positive.

TSH stimulation

Minidose activities and STg tests were stimulated by recombinant human TSH (rhTSH) (Thyrogen; Genzyme, Cambridge, MA) or thyroid hormone withdrawal (THW). rhTSH was administered as two consecutive daily 0.9-mg im injections, with the ^{131}I activity given 24 h after the second injection. THW comprised T_4 withholding for 4 wk, with T_3 typically substituted for T_4 during the first 2 wk. The choice of TSH preparation shifted over time depending upon rhTSH availability and regulatory status. THW (rhTSH) stimulation was used at Minidose 1 in 51.9% (48.0%) of cases through 2005 and in 2.8% (97.2%) thereafter.

Iodine overload avoidance and urinary iodine excretion (UIE) testing

Patients were prescribed a low-iodine diet for at least 2 wk before receiving ^{131}I. Before each radioiodine administration, UIE after a single urination was determined by colorimetric assay with an approximately 80 nM/liter detection limit; urinary creatinine (UC) was codetermined to calculate the UIE/UC ratio.

Scintigraphy, cervical uptake measurement, and doppler ultrasonography (US)

The 740WBS (>250,000 counts) and cervical uptake measurement were performed 2–3 d (mean 66 ± 11 h) after radioiodine administration using γ-cameras with parallel high-energy collimators and external probes, respectively. To facilitate comparisons, uptake values were normalized to 72 h, taking into account ^{131}I physical decay and reported mean effective half-times in remnants of 104.0 h (rhTSH) or 63.9 h (THW) (16). All Doppler US was conducted by experienced ultrasonographers affiliated with our institution.

Thyroglobulin (Tg)/TgAb testing

We simultaneously determined STg and TgAb concentrations in serum samples obtained on the day of ^{131}I administration (THW stimulation) or on the day of 740WBS (rhTSH stimulation: sampling ~5 d after first injection). Of note, mean STg values at Minidose 1 did not statistically differ with rhTSH *vs.* THW stimulation ($P = 0.52$, data not shown). Overall, 92.7% of final ablation success determinations used rhTSH preparation. Nevertheless, we separately analyzed predictive factors for ablation success according to the Minidose 1 stimulation method.

Tg was measured using one of two commercial second-generation immunoassays (Kryptor from Thermo Fisher B.R.A.H.M.S., Hennigsdorf, Germany; Immulite 2000 TG from Siemens Medical Solutions Diagnostics, Los Angeles, CA). Both had lower detection limits (functional sensitivities) of 0.2 (0.8) ng/ml. For comparison with CRM-457-calibrated assays, B.R.A.H.M.S. assay values were multiplied by 1.92, per the manufacturer's recommendation. STg values below 1 ng/ml were considered negative.

TgAb was measured by sensitive immunometric assay (Immulite 2000 anti-TgAb; Siemens). Samples with TgAb titers over 40 IU/ml were considered TgAb positive.

Prolonged follow-up

Of 151 group A patients, 129 were planned to be followed on T_4 replacement every 1–2 yr with physical exam, TSH measurement, unstimulated Tg/TgAb testing, and, until two consecutive sonographs were negative, Doppler US. Twenty-two patients considered nonablated at Minidose 2 received an additional STg/TgAb test some months later, accompanied if requested by diagnostic ^{131}I WBS [mean activity, 400 MBq (10.8 mCi)].

Data on prolonged follow-up, defined as more than 6 months after the last available STg test, were evaluable in 81 patients (53.6% of group A); six additional patients with prolonged follow-up had inevaluable data due to positive TgAb (n = 2) or negative Tg with a persistent suppressed TSH level (n = 4).

No evidence of disease was defined as a normal clinical exam, negative follow-up Doppler US, and undetectable last unstimulated Tg/TgAb tests on T_4 replacement.

Statistics

Continuous variables are expressed as means ± SD and were compared between groups by the Student's *t* test or the protected least-significant difference Fisher *t* test (Mann-Whitney *U* test) if the variables were normally (nonnormally) distributed. Categorical variables are presented as proportions and were compared between groups with the χ^2 test or the Fisher exact test. Logistic regression analysis of factors potentially predicting ablation success at Minidose 2 was performed using multiple linear regression with StatView version 5.0 (SAS Institute, Inc., Cary, NC). The final model expressed the odds ratio (OR) and calculated 95% confidence intervals (CI). *P* values <0.05 were considered significant.

Results

Study cohort characteristics are presented in Table 1. Most patients (112 of 160, 70.0%) had a unifocal primary tumor at least 10 mm in diameter or multifocal primary tumors totaling at least 10 mm in diameter. Apart from proportion of rhTSH *vs.* THW use, we found no significant differences in key characteristics between patients given the Minidose protocol before 2006 (n = 52) or thereafter (n = 108), except a slightly increased mean unifocal tumor size in the later period (9.7 ± 3.3 *vs.* 12.5 ± 4.0 mm, $P < 0.0005$).

TABLE 1. Selected characteristics of 160 consecutive low-risk (near-) totally thyroidectomized patients entering the Minidose protocol

Variable	Value
Age (yr), mean ± SD (range)	50 ± 13 (19–81)
Female gender [% (n)]	83.8 (134)
Number of surgical procedures [% (n)]	
1	81.9 (131)
2	18.1 (29)
Primary tumor focality and diameter [% (n)]	
Unifocal, tumor diameter 5 to <10 mm	15.0 (24)
Unifocal, tumor diameter ≥10 mm	45.6 (73)
Multifocal, sum of tumor diameters <10 mm	15.0 (24)
Multifocal, sum of tumor diameters ≥10 mm	24.4 (39)
Previous node dissection [% (n)]	51.3 (82)
Nx status[a] [% (n)]	72.5 (116)
Dissected nodes, mean ± SD	7.9 ± 6.2
DTC histology [% (n)]	
Papillary	61.9 (99)
Follicular or papillary, follicular variant	30.6 (49)
Papillary or follicular, oxyphilic variant	7.5 (12)
Patients with TgAb ≤40 IU/liter at Minidose 1 [% (n)]	88.8 (142)
Patients with lymphocytic infiltration[b] and TgAb >40 IU/liter at Minidose 1 [% (n)]	6.9 (11)
Patients with DTC as the second primary malignancy[c] [% (n)]	11.3 (18)
STg (ng/ml) at Minidose 1, mean ± SD	12.0 ± 28.3
STg (ng/ml) at Minidose 1, mean ± SD	
Patients with positive nodes in Minidose imaging[d] (n = 7)	10.0 ± 10.1
Patients with distant metastasis in Minidose imaging (n = 2)	10.7 ± 10.1
Patients with negative Minidose imaging (n = 133[e])	12.1 ± 29.1
P among groups	0.97

[a] Nx, no lymph node dissection or dissection of fewer than six neck lymph nodes; N0, at least six nodes, all negative, dissected. Patients with N1a/N1b status at surgery were not included in the study.

[b] Includes lymphocytic/Hashimoto's thyroiditis (n = 10) or Graves' disease (n = 1).

[c] First primary malignancies: breast carcinoma (n = 7), melanoma (n = 3), lymphoma (n = 2), and miscellaneous (n = 6).

[d] Excludes 18 of 160 patients with TgAb over 40 IU/liter at this measurement point.

[e] Minidose imaging consisted of 740 MBq (20 mCi) ^{131}I WBS (both Minidose evaluation times) and neck Doppler US (Minidose 2 evaluation only).

Ablation success

The success rate after both Minidose administrations (Table 2) was 90.1% overall and 90.4% in patients with STg below 10 ng/ml at Minidose 1 (71.2% of our cohort evaluable after both Minidoses). Additionally, patients not ablated after both administrations had low mean cervical uptake (0.11%) and mean STg (1.65 ng/ml) that were only slightly above cutoffs. The ablation success rate after the two 740-MBq activities was 95.5% using lax criteria of STg below 2 ng/ml, negative TgAb, and cervical uptake below 0.2%.

About 10% of patients were ablated by surgery alone. The first 740-MBq activity had a strong ablative effect (Table 2). This effect was especially apparent when the activity was stimulated by rhTSH rather than THW (81.4 *vs.* 51.9% success rates after Minidose 1 administration, $P < 0.002$). The cervical uptake classification, mean percent cervical uptake, and mean STg concentration were all dramatically ($P < 0.0001$) modified at Minidose 2 *vs.* at Minidose 1 (Table 3).

As seen in Table 2, overall, the Minidose 2 activity only modestly increased the proportion of ablated patients from that attained by the Minidose 1 activity. However, the second administration appeared to have a more important effect in THW patients than in their rhTSH counterparts (52.0 *vs.* 13.0% relative increase in the ablation success rate), although a delayed response to the first 740 MBq cannot be excluded in the former subgroup. After both Minidose activities, an STg below 1 ng/ml was seen in 62.9% (91.5%) of evaluable patients receiving THW (rhTSH) at Minidose 1.

Impact of TSH stimulation method and iodine load on urinary iodine excretion and scintigraphic variables

Although 740WBS image grading was not significantly affected by the stimulation method, rhTSH patients had a higher (≥2.13 times) mean UIE/UC ratio and lower (≤0.46 times) mean cervical uptake than did THW patients at both Minidose administrations (Table 3).

Factors predicting ablation success at Minidose 2

Table 4 shows the relationship of selected factors with ablation status at Minidose 2. On univariate analysis, ablated patients tended to be younger and had lower mean cervical uptake at Minidose 1 ($P \leq 0.021$) compared with nonablated patients. rhTSH stimulation at Minidose 1 was significantly associated with ablation success at Minidose 2 ($P = 0.002$). However, the strongest predictor for ablation at Minidose 2 was STg below 10 ng/ml at Minidose 1 ($P < 0.0001$), which likely reflected smaller remnants. Other tested variables, including primary tumor diameter totaling less than 10 mm or multifocality, appeared to have no statistical relationship with ablation success at Minidose 2.

On multivariate analysis, we identified two independent factors predicting ablation success of a single 740-MBq administration: rhTSH stimulation (OR = 6.5, 95% CI = 1.7–24.4, $P < 0.006$) or STg below 10 ng/ml at Minidose 1 (OR = 13.9, 95% CI = 2.5–76.4, $P < 0.003$). The predictive value of a low cervical uptake (<1.00%) at Minidose 1 was no

TABLE 2. Overview of ablation success rates and variables related to nonablation in patients with negative Minidose imaging (group A, n = 151)

Assessment	At Minidose 1	At Minidose 2	After both Minidoses[a]
Intervention(s) evaluated	Primary surgery	Minidose 1	Minidoses 1 and 2
Months after Minidose 1, mean ± SD	0	8.6 ± 3.6	13.5 ± 11.4
Ablation success[b] rate			
% (n ablated/n evaluable[c])	10.5 (14/133)	75.9 (110/145)	90.2 (119/132)
THW patients[d]	0 (0/24)	51.9 (14/27)	78.9 (15/19)
rhTSH patients[d]	11.9 (14/109)	81.4 (96/118)	92.0 (104/113)
P, THW *vs.* rhTSH	0.10	<0.0015	0.076
If STg at Minidose 1			
<10 ng/ml	14.9 (14/94)	85.1 (80/94)	90.4 (85/94)
≥10 ng/ml	0 (0/39)	51.3 (20/39)	61.5 (24/39)
Reasons for nonablation [% (n)]			
Cervical uptake >0.1%	16.0 (19)	17.1 (6)	30.8 (4)
STg >1 ng/ml	3.3 (4)	48.6 (17)	61.5 (8)
Both	80.7 (96)	34.3 (12)	7.7 (1)
Characteristics of nonablated patients			
Cervical uptake (%), mean ± SD	1.23 ± 1.05	0.14 ± 0.11	0.11 ± 0.09
Cervical uptake, median (range)	1.05 (0.05–4.60)	0.10 (0.01–0.48)	0.07 (0.004–0.30)
STg (ng/ml), mean ± SD	13.4 ± 30.4	1.71 ± 1.37	1.65 ± 1.47
STg (ng/ml), median (range)	4.3 (0.2–260.0)	1.2 (0.2–5.37)	1.4 (0.19–5.0)
Success rates using lax criteria			
% (n ablated/n evaluable[c])	21.8 (29/133)	88.3 (128/145)	95.5 (126/132)
THW patients[d]	8.3 (2/24)	70.4 (19/27)	89.5 (17/19)
rhTSH patients[d]	24.8 (27/109)	92.4 (109/118)	96.5 (109/113)
P, THW *vs.* rhTSH	0.078	0.0013	0.176

[a] Overall success rate of the after-both-Minidoses evaluation is based on the later of either the Minidose 2 evaluation (n = 110) or a third STg test, aided by rhTSH (n = 22), some months after the Minidose 2 evaluation.

[b] Criteria (lax criteria) for ablation success comprised an STg below 1 (<2) ng/ml with negative TgAb and cervical bed uptake below 0.1% (<0.2%).

[c] Group A patients with positive TgAb (n = 18 at Minidose 1 evaluation, n = 6 at Minidose 2 evaluation) were excluded from analyses regarding evaluation times when this finding was present.

[d] Refers to the stimulation method at Minidose 1.

longer significant ($P = 0.39$), because STg and cervical uptake both reflected remnant size and were clearly correlated ($P < 0.0001$, Spearman rank correlation test).

In the subgroup of patients evaluable at Minidose 2 who had been given rhTSH at Minidose 1 (n = 118), a postablation STg below 10 ng/ml at Minidose 1 was highly predictive of ablation success (OR = 6.7, 95% CI = 1.2–36.0, $P < 0.028$). Similar findings were seen in the subgroup undergoing THW at Minidose 1 (n = 27); preablation STg below 10 ng/ml at Minidose 1 predicted ablation success at Minidose 2 (OR = 10.9, 95% CI = 1.1–117.2, $P < 0.048$).

Prolonged follow-up

None of 81 patients with evaluable prolonged follow-up data showed evidence of disease at the last assessment (mean ± SD follow-up was 41.8 ± 21.9 months, range 12.4–97.1 months after Minidose 1, 30.2 ± 21.9 months after the latest STg test). One THW patient died of a cerebral stroke 54.2 months after Minidose 1.

Detection of previously occult disease

As seen in Supplemental Table 1 (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org), in a cohort classified as postsurgically low-risk, Minidose imaging nevertheless detected metastases in 5.6% of patients (nine of 160). Five patients had positive mediastinal nodes (n = 3) or distant lesions (n = 2) that would not have been localized by US or identified by STg (Fig. 2, Supplemental Figs. 1–3). Notably, mean STg values at Minidose 1 did not differ between the nine group B patients and the 133 evaluable group A patients ($P = 0.97$, Table 1). However, three individuals had positive cervical nodes detected only by US, which, per our protocol, first was performed around Minidose 2.

Discussion

The present analysis demonstrates the ablative efficacy and diagnostic utility in a large series of low-risk DTC patients of the Minidose protocol of outpatient thyroid remnant ablation with two 740-MBq ^{131}I activities plus related surveillance procedures. The two main objectives of the protocol appear generally to have been met. First, in a great majority of patients, thyroid remnant, the main locus of Tg production and radioiodine uptake that could

TABLE 3. Scintigraphic and biochemical data at both Minidose procedures (group A, n = 151)

Variable	Minidose 1 (rhTSH, n = 123)	Minidose 2 (rhTSH, n = 136)	*P*, Minidose 1 *vs.* Minidose 2
Administered ^{131}I activity, [MBq (mCi)], mean ± SD	742 ± 29 (20.1 ± 0.8)	738 ± 69 (19.9 ± 1.9)	0.63
Urinary iodine: UIE /UC[a] *nM/mM), mean ± SD			
All patients[b]	183 ± 327	130 ± 86	0.075
THW patients[c]	98 ± 128 (n = 25)	55 ± 36 (n = 15)	
rhTSH patients[c]	209 ± 361 (n = 87)	142 ± 85 (n = 96)	
P, THW *vs.* rhTSH	<0.0001	<0.0001	
Cervical uptake[d] classification [% (n)]			
None visible	1.5 (2)	41.7 (63)	<0.0001
Faint, <0.1%	12.5 (17)	45.7 (69)	
Uptake ≥0.1%	86.0 (117)	12.6 (19)	
^{131}I uptake measurements[d] (%), mean ± SD			
All patients	1.09 ± 1.06	0.07 ± 0.08	<0.0001
THW patients[b]	1.58 ± 0.98 (n = 28)	0.13 ± 0.09 (n = 15)	
rhTSH patients[b]	0.97 ± 1.04 (n = 116)	0.06 ± 0.08 (n = 136)	
P, THW vs. rhTSH	<0.0009	<0.0001	
STg (ng/ml)	n = 133[e]	n = 145[e]	
Mean ± SD	12.1 ± 29.1	0.66 ± 0.92	<0.0001
Category [% (n)]			
Undetectable, <1 ng/ml	24.8 (33)	82.1 (119)	<0.0001
Low, 1 to <2 ng/ml	13.5 (18)	11.0 (16)	
Elevated, ≥2 ng/ml	61.7 (82)	6.9 (10)	

[a] UIE was normalized by UC, both obtained from a single urination; normal values for this ratio in France are 30–300 nM/mM.

[b] For technical reasons, UIE data were not available in 39 patients at either Minidose; additionally, one patient with iodine overload was excluded at Minidose 2.

[c] Refers to the TSH stimulation method for the given Minidose activity.

[d] For technical reasons, quantitative measurements of visible cervical uptake could not be obtained in 15 patients at Minidose 1.

[e] Excludes patients with TgAb over 40 IU/liter (n = 18 at Minidose 1, n = 6 at Minidose 2).

confound long-term diagnostic follow-up, was eradicated (Table 2).

Second, despite our cohort's reassuring initial pTNM classification, we identified previously occult disseminated disease in 5.6% of patients, and five of nine such cases would have been misdiagnosed based on Doppler US and Tg testing alone. Indeed, factors beyond primary lesion size, *e.g. BRAF* mutations (17), influence DTC aggressiveness. In our opinion, this situation justifies performing highly sensitive ^{131}I WBS to identify patients requiring modified treatment for cure. An improvement in our protocol would be to carry out Doppler US, ^{123}I diagnostic WBS, or both before Minidose 1. Doing so could help sooner identify patients in whom conventional 3.7-GBq therapy or surgical reintervention would be indicated or identify individuals already ablated by surgery and thus requiring no radioiodine therapy. In our anecdotal experience, two to four 740-MBq administrations failed to eradicate positive nodes in four of five patients; only small tumors with substantial ^{131}I uptake appeared to be successfully treated at this activity (Supplemental Table 1, Fig. 2, and Supplemental Figs. 1 and 3). These observations suggest that at low activity levels, remnant ablation and tumoricidal effects are separate goals of postoperative ^{131}I administration.

We believe that the success of the Minidose protocol in eradicating remnant relied on two principal factors. One factor was the relatively small remnant volumes in our cohort due to improved surgical techniques and greater recognition of the value of specialization in thyroid procedures. In a 509-patient prospective study of THW-aided ablation, Bal *et al.* (7) concluded that 555-MBq (15 mCi) or 740-MBq activities produced unacceptably low success rates (59.6 and 63.6%, respectively). However, their results may reflect only subtotal thyroidectomy, because mean cervical uptake was 9.1% at 48 h in their series *vs.* 1.09% at 72 h in ours.

Another factor explaining the ablation success of the Minidose protocol was the 6- to 18-month interval between radioiodine therapies. This interval allowed ample time for remnant cell die-off, presumably reducing target tissue volume and increasing absorbed dose delivery by the second Minidose activity. Additionally, the interval probably precluded thyroid stunning (18), likely a problem with iterative ^{131}I therapy administered at shorter intervals (19–21).

A limitation of our analysis was its retrospective, nonrandomized nature, including the changing frequency of Minidose protocol use over time. However, this last factor seems unlikely to have introduced any clinically relevant

TABLE 4. Relationship of selected factors with ablation status at Minidose 2 (group A)

Variable	n = 145[a]		*P*, univariate analysis
	Ablated, n = 110	Nonablated, n = 35	
Gender (%)			
Female (n = 120)	78.3	21.7	0.20
Male (n = 25)	64.0	36.0	
Age (yr), mean ± SD	47.6 ± 12.5	55.8 ± 12.2	0.002
Histological autoimmunity[b] (%)			
Absent (n = 106)	74.5	25.5	0.54
Present (n = 39)	79.5	20.5	
Tumor focality (%)			
Unifocal, tumor diameter 5 to <10 mm (n = 21)	61.9	38.1	0.19
Unifocal, tumor diameter ≥10 mm (n = 66)	83.3	16.7	
Multifocal, sum of tumor diameters <10 mm (n = 19)	68.4	31.6	
Multifocal, sum of tumor diameters ≥10 mm (n = 39)	74.4	25.6	
TSH stimulation method, Minidose 1			
Ablation status rates (%)			
THW (n = 27)	51.8	48.1	0.002
rhTSH (n = 118)	81.3	18.6	
Cervical uptake at Minidose 1[c] (%), mean ± SD	1.00 ± 1.07	1.33 ± 0.96	0.021
Ablation status rates (%)			
Uptake <1% at Minidose 1 (n = 70)	81.4	18.6	0.047
Uptake ≥1% at Minidose 1 (n = 59)	66.1	33.9	
STg level at Minidose 1 (ng/ml), mean ± SD (n = 133)[d]	9.4 ± 30.8	20.2 ± 21.9	<0.0001
Ablation status rates (%)			
STg <10 ng/ml at Minidose 1 (n = 94)	85.1	14.9	<0.0001
STg ≥10 ng/ml at Minidose 1 (n = 39)	51.3	48.7	
Cumulative activity, Minidose 1 + Minidose 2 (GBq), mean ± SD	1.48 ± 0.69	1.47 ± 0.98	0.73
UIE/UC[e] (nM/mM), mean ± SD at			
Minidose 1	183 ± 353	143 ± 135	0.55
Minidose 2	136 ± 87	113 ± 87	0.23

[a] Among the 151 patients with negative Minidose imaging, six with positive TgAb at Minidose 2 were excluded.

[b] Histological autoimmunity includes multifocal or diffuse foci of lymphocytic infiltrates according to the histological reports and regardless of the TgAb status.

[c] For technical reasons, quantitative measurements of visible cervical uptake could not be obtained in 15 patients at Minidose 1.

[d] Excludes patients with positive TgAb at Minidose 1.

[e] Only available in 107 of 145 patients (73.8%).

bias regarding outcome; tested patient characteristics were statistically similar before *vs.* after the Minidose protocol became routine in eligible patients, except the presurgical variable of unifocal primary tumor diameter (2.9 mm mean increase after the protocol became routine). These findings suggest that if anything, the Minidose protocol was applied to slightly lower-risk patients earlier in the study period. Nonetheless, higher ablation success rates were observed more recently (67.3% before 2006 *vs.* 83.9% thereafter, $P < 0.016$). Moreover, throughout the study, 100% of evaluable patients given the Minidose protocol had no evidence of disease after prolonged follow-up.

Despite these limitations and our relatively low number of THW-aided radioiodine administrations, our use of both rhTSH and THW produced several interesting comparative observations. First, rhTSH stimulation was associated with a significantly higher ablation success rate after the first Minidose activity than was THW, although this difference vanished after both activities (Table 2). This finding suggests that the time to ablation may be longer after THW stimulation. However, one cannot exclude a bias regarding remnant volume. Nor can one exclude bias from higher STg values attributable to THW, with its longer TSH elevation, being used to stimulate success assessment of the first Minidose activity in part of the THW group, but not the rhTSH group. Nevertheless, our data join a growing body of evidence of both the efficacy of lower ablative activities and the statistically not different final ablation success rates of rhTSH and THW stimulation (6, 9, 10, 12–14).

Second, we observed that rhTSH was associated with a significantly greater iodine excretion than was THW (Table 3), but the difference appeared not to influence ablation success. This iodine status discrepancy may chiefly be due to lower renal iodine clearance in the hypothyroid THW patients (22). Of interest, unlike other studies (6, 22–24), which had conflicting results regarding differ-

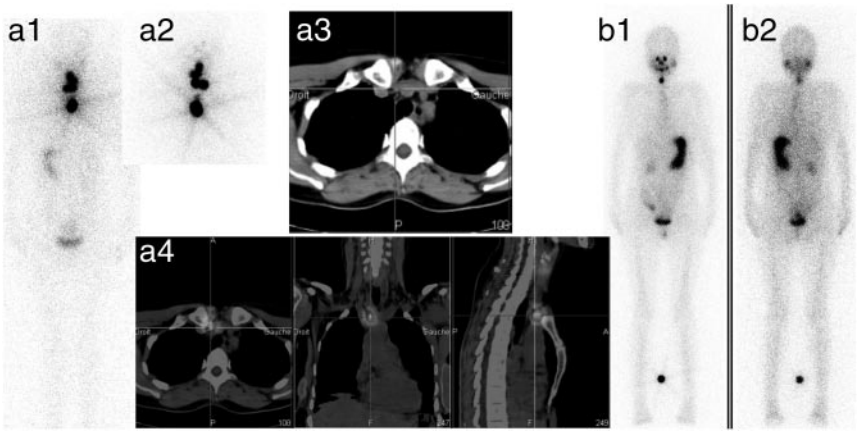

FIG. 2. Patient 3 in Supplemental Table 1: 44.1-yr-old woman with a pT1N0 papillary thyroid cancer (18 mm unifocal tumor, 11 negative nodes dissected). Panels a1 and a2, Anterior and posterior view 73 h after Minidose 1 activity administration (rhTSH; 699 MBq/18.9 mCi ^{131}I). STg was 7.6 ng/ml with negative TgAb. Panels a3 and a4, The WBS shows a large remnant with a cervical ^{131}I uptake of 1.02% and an additional focus corresponding to a positive upper mediastinal node, as evidenced by single-photon emission computed tomography/computed tomography fusion images. The node was too anatomically low for Doppler US detection, even after reperforming US aided by the ^{131}I WBS image. Panels b1 and b2, WBS after high-activity retreatment (THW-aided 3.7 GBq 6.8 months after Minidose 1); STg was 0.2 ng/ml. The WBS shows apparent destruction of the mediastinal node and most remnant tissue by the Minidose 1 activity. Only a small thyroglossal duct focus is visible (72-h uptake of 0.068%). Demonstration of a possible curative effect of the first 740 MBq, perhaps due to the high initial nodal uptake.

ences in iodine load and ablative efficacy, we normalized our UIE values to UC. Doing so increased the reliability of iodine load test results from a single urination, because UIE may vary hugely during the day.

Third, rhTSH use was associated with significantly lower mean cervical uptake than was THW, but this difference too had no relationship with ablation success. This observation conforms with other studies' findings of significantly (10, 25) or borderline significantly (9, 16, 26) lower uptake with rhTSH *vs.* THW. The uptake difference may be due to one or both of the higher blood residence time or the longer stimulation of the organification machinery in THW patients. We did not acquire data on ^{131}I kinetics, and conflicting results have been reported regarding remnant dosimetry (16, 25–27). In our opinion, those discrepancies may stem from the difficulty in reliably assessing small functional target volumes.

Regarding clinical practice, our analysis suggested that most low-risk patients with negative ^{131}I WBS and neck US after the first 740-MBq activity need receive only that activity. A postablation STg under 10 ng/ml at Minidose 1 (seen after 76.1% of rhTSH stimulations), a likely surrogate for small remnants, helped identify patients ablated at the Minidose 2 evaluation, *i.e.* by the Minidose 1 activity alone. In this subgroup, the high ablation success rate after the initial 740 MBq was little increased at the final evaluation (Table 2), and one STg determination or, possibly, a Tg determination using an ultrasensitive assay during T_4 replacement (28) should suffice to subsequently verify disease status. Such Tg testing could be performed at 6 months after Minidose 1 when rhTSH is used and 9 months when THW is used, because our data suggest that the latter method may be associated with a delayed response.

A second Minidose activity would appear to be helpful mostly in subtotally thyroidectomized patients, a status sometimes reflecting a surgeon's limited experience. Such patients will be selected at Minidose 1 as having higher cervical uptake and concomitantly higher STg values.

After a mean 41.8 ± 21.9 months after Minidose 1 administration, we observed no evidence of disease in our 81 evaluable patients with prolonged follow-up. However, given the typical indolence of low-risk DTC, this follow-up may well have been insufficient for all recurrences to manifest.

An important advantage of the Minidose protocol is that it avoids hospitalization, improving accessibility to ablation in nations with limited inpatient radioprotection facilities, and conferring pharmacoeconomic and patient quality-of-life benefits relative to inpatient ablation. We conservatively estimate that in our institution, a two-activity Minidose protocol costs approximately 2420 euros, favorably comparing to a single 1110-MBq administration, which in Europe entails a one-night hospitalization and thus costs approximately 4450 euros. Savings will be even greater using a modified Minidose protocol of only one 740-MBq activity (cost ~1350 euros). These advantages relative to higher activities of course would not apply in countries permitting outpatient administration of higher activities.

Regarding patient quality-of-life, hospitalization in a radioactive oncological environment is often disturbing (29) and may erroneously create fears that low-risk DTC is life-threatening. In our experience, the Minidose protocol had excellent acceptance, because activities were administered during routine visits. We have observed no undesired symptoms with our protocol other than mild, well-known side effects of TSH stimulation.

Use of an ^{131}I activity as low as 740 MBq limits public radiation exposure to less than 1 mSv/yr. Additionally, the mean patient blood absorbed doses associated with such activities, below 100 mSv (16), are not known to carry a significant risk of radiation-related second primary ma-

lignancies, an important concern with higher activities and low-risk DTC patients (30).

In conclusion, the Minidose protocol is effective, diagnostically useful, clinically well tolerated, and widely applicable in low-risk DTC patients. Extension of this protocol to pT2 N0-Nx patients should be considered, as should making the second Minidose activity optional in low-risk patients with postablation STg below 10 ng/ml after the first 740-MBq activity.

Acknowledgments

This work is dedicated to the Alliance patients in gratitude for their participation in an attempt to develop a simple ablation protocol that would be safe, effective, well tolerated, and feasible worldwide.

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This work was supported by Genzyme, the recombinant human TSH manufacturer, via a grant to the Association pour le Développement de la Recherche en Médecine Nucléaire in 2009. Editorial work on this paper by one of the authors (R.J.M.) was supported by a grant from Genzyme.

Disclosure Summary: R.J.M. is a consultant to Genzyme and is a shareholder in Sanofi Aventis, the parent company of Genzyme; the authors have no other conflicts of interest to declare.

References

1. **Mazzaferri EL** 2009 What is the optimal initial treatment of low-risk papillary thyroid cancer (and why is it controversial)? Oncology 23:579–588
2. **Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS, Sturgeon C** 2007 Extent of surgery affects survival for papillary thyroid cancer. Ann Surg 246:375–381; discussion 381–384
3. **Elisei R, Schlumberger M, Driedger A, Reiners C, Kloos RT, Sherman SI, Haugen B, Corone C, Molinaro E, Grasso L, Leboulleux S, Rachinsky I, Luster M, Lassmann M, Busaidy NL, Wahl RL, Pacini F, Cho SY, Magner J, Pinchera A, Ladenson PW** 2009 Follow-up of low-risk differentiated thyroid cancer patients who underwent radioiodine ablation of postsurgical thyroid remnants after either recombinant human thyrotropin or thyroid hormone withdrawal. J Clin Endocrinol Metab 94:4171–4179
4. **Cooper DS, Doherty GM, Haugen BR, Hauger BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM** 2009 Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 19:1167–1214
5. **Pacini F, Molinaro E, Castagna MG, Lippi F, Ceccarelli C, Agate L, Elisei R, Pinchera A** 2002 Ablation of thyroid residues with 30 mCi (131)I: a comparison in thyroid cancer patients prepared with recombinant human TSH or thyroid hormone withdrawal. J Clin Endocrinol Metab 87:4063–4068
6. **Barbaro D, Boni G, Meucci G, Simi U, Lapi P, Orsini P, Pasquini C, Turco A, Mariani G** 2006 Recombinant human thyroid-stimulating hormone is effective for radioiodine ablation of post-surgical thyroid remnants. Nucl Med Commun 27:627–632
7. **Bal CS, Kumar A, Pant GS** 2004 Radioiodine dose for remnant ablation in differentiated thyroid carcinoma: a randomized clinical trial in 509 patients. J Clin Endocrinol Metab 89:1666–1673
8. **Mäenpää HO, Heikkonen J, Vaalavirta L, Tenhunen M, Joensuu H** 2008 Low vs. high radioiodine activity to ablate the thyroid after thyroidectomy for cancer: a randomized study. PLoS ONE 3:e1885
9. **Lee J, Yun MJ, Nam KH, Chung WY, Soh EY, Park CS** 2010 Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. Thyroid 20:173–179
10. **Chianelli M, Todino V, Graziano FM, Panunzi C, Pace D, Guglielmi R, Signore A, Papini E** 2009 Low-activity (2.0 GBq; 54 mCi) radioiodine post-surgical remnant ablation in thyroid cancer: comparison between hormone withdrawal and use of rhTSH in low-risk patients. Eur J Endocrinol 160:431–436
11. **Pilli T, Brianzoni E, Capoccetti F, Castagna MG, Fattori S, Poggiu A, Rossi G, Ferretti F, Guarino E, Burroni L, Vattimo A, Cipri C, Pacini F** 2007 A comparison of 1850 (50 mCi) and 3700 MBq (100 mCi) 131-iodine administered doses for recombinant thyrotropin-stimulated postoperative thyroid remnant ablation in differentiated thyroid cancer. J Clin Endocrinol Metab 92:3542–3546
12. **Rosario PW, Xavier AC** 3 February 2011 Recombinant human thyroid stimulating hormone in thyroid remnant ablation with 1.1 GBq 131iodine in low-risk patients. Am J Clin Oncol 10.1097/COC.0b013e318201a41a
13. **Catargi B, Borget I, Deandris D, Zerdoud S, Bridji B, Bardet S, Rousseau A, Bastie D, Schvartz C, Vera P, Morel O, Benivsy D, Bournaud C, Bonichon F, Dejax C, Toubert ME, Benhamou E, Schlumberger M,** Comparison of four strategies of radioiodine ablation in patients with thyroid cancer with low-risk of recurrence: the randomized prospective ESTIMABL study on 573 patients. International Thyroid Congress, Paris, France, 2010 (Abstract P-1665)
14. **Mallick U, Harmer C, Clarke S, Moss L, Nicol A, Clarke P, Smellie J, McCready R, Farnell K, Franklyn J, John R, Nutting C, Yap B, Lemon C, Wadlsey J, Gerrard G, Roques T, Macias E, Whitaker S, Abdul-Hamid A, Alvarez P, Kadalayil L, Hackshaw A,** HiLo: Multicentre randomised phase III clinical trial of high vs low dose radioiodine, with or without recombinant human thyroid stimulating hormone (rhTSH), for remnant ablation for differentiated thyroid cancer. International Thyroid Congress, Paris, France, 2010 (Abstract OC-068)
15. **Fleming I, Cooper, JS, Henson, DE, Hutter, RVP, Kennedy, BJ** 1997 AJCC cancer staging manual. 5th ed. Philadelphia: Lippincott-Raven
16. **Hänscheid H, Lassmann M, Luster M, Thomas SR, Pacini F, Ceccarelli C, Ladenson PW, Wahl RL, Schlumberger M, Ricard M, Driedger A, Kloos RT, Sherman SI, Haugen BR, Carriere V, Corone C, Reiners C** 2006 Iodine biokinetics and dosimetry in radioiodine therapy of thyroid cancer: procedures and results of a prospective international controlled study of ablation after rhTSH or hormone withdrawal. J Nucl Med 47:648–654
17. **Elisei R, Ugolini C, Viola D, Lupi C, Biagini A, Giannini R, Romei C, Miccoli P, Pinchera A, Basolo F** 2008 BRAF(V600E) mutation and outcome of patients with papillary thyroid carcinoma: a 15-year median follow-up study. J Clin Endocrinol Metab 93:3943–3949
18. **Leger FA, Izembart M, Dagousset F, Barritault L, Baillet G, Chevalier A, Clerc J** 1998 Decreased uptake of therapeutic doses of iodine-131 after 185-MBq iodine-131 diagnostic imaging for thyroid remnants in differentiated thyroid carcinoma. Eur J Nucl Med 25:242–246
19. **Czepczyński R, Ziemnicka K, Baczyk M, Oleksa R, Ruchała M, Sowiński J** 2005 Fractionated dosage of radioiodine for the ablation of differentiated thyroid carcinoma. Thyroid 15:1261–1265
20. **Hung GU, Tu ST, Wu IS, Yang KT** 2004 Comparison of the effec-

tiveness between a single low dose and fractionated doses of radioiodine in ablation of post-operative thyroid remnants. Jpn J Clin Oncol 34:469–471

21. **Wu HS, Hseu HH, Lin WY, Wang SJ, Liu YC** 2005 Decreased uptake after fractionated ablative doses of iodine-131. Eur J Nucl Med Mol Imaging 32:167–173
22. **Löffler M, Weckesser M, Franzius C, Kies P, Schober O** 2003 Iodine excretion during stimulation with rhTSH in differentiated thyroid carcinoma. Nuklearmedizin 42:240–243
23. **Pacini F, Ladenson PW, Schlumberger M, Driedger A, Luster M, Kloos RT, Sherman S, Haugen B, Corone C, Molinaro E, Elisei R, Ceccarelli C, Pinchera A, Wahl RL, Leboulleux S, Ricard M, Yoo J, Busaidy NL, Delpassand E, Hanscheid H, Felbinger R, Lassmann M, Reiners C** 2006 Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: results of an international, randomized, controlled study. J Clin Endocrinol Metab 91:926–932
24. **Tala Jury HP, Castagna MG, Fioravanti C, Cipri C, Brianzoni E, Pacini F** 2010 Lack of association between urinary iodine excretion and successful thyroid ablation in thyroid cancer patients. J Clin Endocrinol Metab 95:230–237
25. **Vaiano A, Claudio Traino A, Boni G, Grosso M, Lazzeri P, Colato C, Davì MV, Francia G, Lazzeri M, Mariani G, Ferdeghini M** 2007 Comparison between remnant and red-marrow absorbed dose in thyroid cancer patients submitted to ^{131}I ablative therapy after rhTSH stimulation versus hypothyroidism induced by L-thyroxine withdrawal. Nucl Med Commun 28:215–223
26. **Taïeb D, Sebag F, Farman-Ara B, Portal T, Baumstarck-Barrau K, Fortanier C, Bourrelly M, Mancini J, De Micco C, Auquier P, Conte-Devolx B, Henry JF, Mundler O** 2010 Iodine biokinetics and radioiodine exposure after recombinant human thyrotropin-assisted remnant ablation in comparison with thyroid hormone withdrawal. J Clin Endocrinol Metab 95:3283–3290
27. **Freudenberg LS, Frömke C, Petrich T, Marlowe RJ, Koska WW, Brandau W, Eising EG, Knust EJ, Bockisch A, Jentzen W** 2010 Thyroid remnant dose: ^{124}I-PET/CT dosimetric comparison of rhTSH versus thyroid hormone withholding before radioiodine remnant ablation in differentiated thyroid cancer. Exp Clin Endocrinol Diabetes 118:393–399
28. **Schlumberger M, Borget I, Nascimento C, Brassard M, Leboulleux S** 2011 Treatment and follow-up of low-risk patients with thyroid cancer. Nat Rev Endocrinol 7:625–628
29. **Stajduhar KI, Neithercut J, Chu E, Pham P, Rohde J, Sicotte A, Young K** 2000 Thyroid cancer: patients' experiences of receiving iodine-131 therapy. Oncol Nurs Forum 27:1213–1218
30. **Sandeep TC, Strachan MW, Reynolds RM, Brewster DH, Scélo G, Pukkala E, Hemminki K, Anderson A, Tracey E, Friis S, McBride ML, Kee-Seng C, Pompe-Kirn V, Kliewer EV, Tonita JM, Jonasson JG, Martos C, Boffetta P, Brennan P** 2006 Second primary cancers in thyroid cancer patients: a multinational record linkage study. J Clin Endocrinol Metab 91:1819–1825