Second Radioiodine Treatment: Limited Benefit for Differentiated Thyroid Cancer With Locoregional Persistent Disease

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Objectives: Radioactive iodine (RAI) treatment is often indicated after total thyroidectomy in differentiated thyroid cancer (DTC). However, its role in biochemical or locoregional persistent DTC is unclear. We aimed to investigate the effect of a second RAI treatment in patients with incomplete response to initial treatment and no evidence of distant metastases.

Methods: Patients who underwent at least two RAI treatments over a 20-year period at a tertiary hospital were identified. Thyroglobulin levels and neck imaging were compared before and 1 to 2 years after RAI retreatment and evaluated at the last visit.

Results: The cohort included 164 patients (103 female; mean age, 46.6 ± 17 years). Of 114 patients retreated without prior reoperation, 53 had structural disease. At 1 to 2 years after RAI retreatment, 10 of the 41 patients with sufficient data had structural progression, 5 resolution/shrinkage, and 26 stable disease. Stimulated thyroglobulin (stTg) measured 93.7.1 ± 108 ng/mL before and 102.2 ± 124 ng/mL after retreatment (P = NS). The other 61 patients had biochemical-only persistence. Their stTg levels decreased from 41.9 ± 56 to 24.6 ± 54 ng/mL (P = 0.003). The 50 patients who underwent neck reoperation before RAI retreatment showed no substantial change in stTg; 21 (42%) still had imaging findings 1 to 2 years later. At final follow-up, despite additional treatment in 63/164 patients (38.4%), only 56/164 (34.1%) had no evidence of disease.

Conclusions: This comprehensive study showed limited benefit of second RAI treatment in DTC patients with biochemical or locoregional structural persistent disease. Prospective studies are needed to distinguish patients for whom repeated RAI may be indicated to avoid unnecessary exposure. (***J Clin Endocrinol Metab*** **103: 469–476, 2018)**

For more than half a century, radioactive iodine (RAI) and thyroxine treatment have been the mainstays of therapy for patients with differentiated thyroid cancer (DTC) after initial total thyroidectomy (1). However, the rapidly increasing detection of small and even microscopic DTC lesions has led to a paradigm shift toward the selective use of RAI (2). RAI is still regularly recommended after thyroidectomy in patients categorized as high risk according to the American Thyroid Association (ATA) guidelines, but it is no longer routinely indicated for remnant ablation or as adjuvant therapy in ATA low- and intermediate-risk patients (2).

At the same time, however, up to 30% of patients with DTC who are treated by total thyroidectomy and remnant RAI ablation have persistent or recurrent disease in the thyroid bed or neck lymph nodes (3). According to the 2015 ATA guidelines, these patients are classified as structural incomplete responders (2). This state may be

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Abbreviations: ATA, American Thyroid Association; BIR, biochemical incomplete response; DTC, differentiated thyroid cancer; NED, no evidence of disease; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; RxWBS, posttherapy whole-body RAI scan; SIR, structural incomplete response; stTg, stimulated thyroglobulin; Tg, thyroglobulin; TSH, thyrotropin.

associated with substantial morbidity, emotional distress, and long-term mortality (4–7). Although bulky or invasive locoregional recurrences usually warrant reoperation (8–12), the management remains unclear for patients with indolent, low-volume neck disease or a combination of elevated thyroglobulin (Tg) levels with negative imaging studies (13, 14). This last situation, termed biochemical incomplete response, may appear in 15% to 20% of DTC patients after initial treatment (2).

Repeated RAI doses have been found to be beneficial in patients with iodine-avid distant metastases. It has been suggested that repeated administration of RAI may also be considered in patients with an incomplete biochemical or structural locoregional response to initial treatment (2). However, only a few studies have investigated the effect of a second RAI treatment in these patients.

In the current study, we evaluated the short- and long-term impact of a second RAI treatment in an institutional cohort of DTC patients with incomplete structural/biochemical response to initial treatment and no evidence of distant metastases.

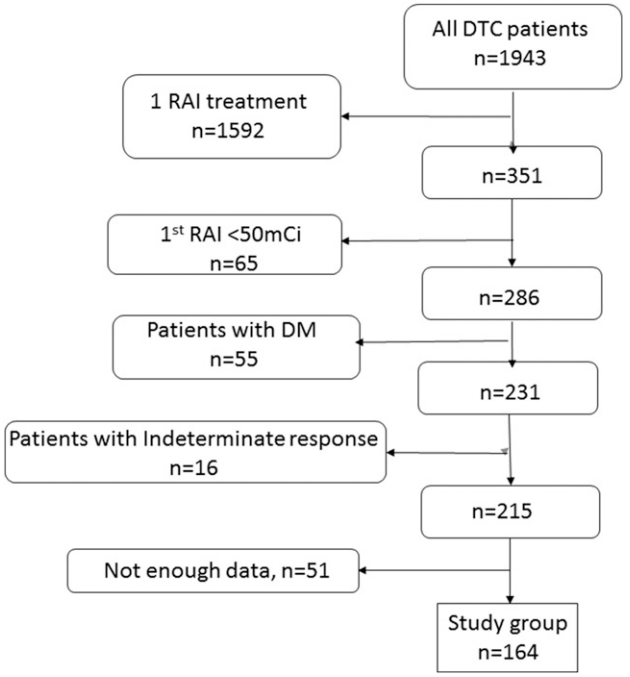

Figure 1. Flowchart of patient selection for the study.

Patients and methods

Definitions

1. An incomplete structural and biochemical response to initial thyroidectomy and RAI treatment was retrospectively categorized according to the 2015 ATA guidelines (2).
2. An elevated Tg level 1 to 2 years after the second RAI dose and at the end of follow-up was defined as suppressed Tg >1 ng/mL or stimulated Tg (stTg) >10 ng/mL or rising Tg antibody level. The stTg level was analyzed when the thyrotropin (TSH) concentration was >30 mIU/L.
3. Structural progression was defined as a ≥3-mm increase in the size of a known neck lesion or identification of new metastatic foci. Shrinkage was defined as a decrease of ≥3 mm in the size of a known lesion.

Patients and setting

The Rabin Medical Center Thyroid Cancer Registry was searched for all patients diagnosed with DTC between 1991 and 2013 who underwent at least two RAI treatments after total thyroidectomy.

Exclusion criteria (Fig. 1) were as follows.

1. RAI activity of <50 mCi at the initial treatment. This criterion was intended to exclude patients in whom a large thyroid remnant was observed on postoperative radioisotope scanning. In the era when this scan was regularly performed before RAI therapy, our institutional regimen consisted of a small ablative first RAI dose followed by scheduled RAI adjuvant therapy within 6 months.
2. Evidence of distant metastases on posttherapy whole-body RAI scans (RxWBSs), computed tomography scans of the chest, abdomen, and/or brain, and/or 18F fludeoxyglucose positron emission tomography performed before the second RAI dose.
3. An indeterminate response to initial thyroidectomy and RAI remnant ablation according to the definition in the ATA guidelines (2). This pertained to patients with nonspecific imaging abnormalities and patients with nonstimulated Tg values that were detectable but <1 ng/mL and TSH-stimulated Tg values between 1 and 10 ng/mL. Because these biochemical or structural findings do not necessarily represent residual disease (2), patients in this category were excluded from the analysis.
4. Insufficient data for analysis (Fig. 1).

Eligible patients were divided into those with a biochemical incomplete response (BIR) or a structural incomplete response (SIR) as defined by the ATA (Supplemental Fig. 1). The SIR group was further divided into those with or without neck reoperation before the second RAI treatment.

Follow-up protocol and data analysis

All patients were on a low-iodine diet for 2 weeks before RAI administration. An RxWBS was performed 7 days after RAI administration and evaluated by an experienced nuclear physician. All patients underwent regular follow-up, including measurements of serum basal Tg and/or stTg and neck ultrasonography performed by an expert radiologist. Those with a clinical suspicion of locoregional recurrence were further assessed by computed tomography scans of the neck and/or 18F fludeoxyglucose positron emission tomography, as needed.

Data on Tg levels and neck imaging findings before and 1 to 2 years after the second RAI treatment, as well as at the end of follow-up, were retrospectively collected from the medical files. Tg levels both under thyroxine treatment and on TSH stimulation (>30 mIU/mL), when available, were recorded in addition to the presence and titer of Tg autoantibodies. Tg levels before and 1 to 2 years after the second RAI treatment were compared for each patient under the same conditions (stimulated/nonstimulated with a similar TSH level). We also evaluated the

presence of structural evidence of locoregional persistent/recurrent DTC at the same time points and compared the size of the structural findings. In the patients with a structurally incomplete response who underwent reoperation before the second RAI administration (group B), the Tg values represented measurements made between the second neck surgery and the second RAI dose. However, because the second RAI treatment was often administered empirically, most of the patients did not undergo neck imaging between the two treatment modalities. Therefore, in this group, the imaging results acquired after the second RAI dose reflect the combined results of both the second neck surgery and the second RAI treatment.

Laboratory measurements of Tg and TSH

Levels of TSH, Tg, and antithyroglobulin antibodies were measured by chemoluminescence assay (Immulite 2000, Siemens Corp, Los Angeles, CA). The functional sensitivity for the thyroglobulin assay was 0.9 ng/mL and the analytical sensitivity was 0.2 ng/mL.

Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables are presented as means and standard deviations or as medians with ranges.

Categorical variables were compared between groups with the χ^2 test, and continuous variables, with Student *t* test or one-way analysis of variance, as appropriate. Paired *t* test was used to compare Tg levels before and after the second RAI treatment.

Analyses were generated using IBM SPSS Statistics for Windows, version 24.0.1 (IBM Corp., Armonk, NY). A *P* value <0.05 was considered statistically significant.

Results

The cohort included 164 patients: 103 females and 61 males; mean age, 46.6 ± 17 years at diagnosis; 151 had papillary thyroid carcinoma (PTC) or PTC follicular variant. Patients were followed for a median duration of 10 years from diagnosis (mean, 11.3 ± 7.2 years) and 7.4 years from the second RAI treatment (mean, 7.4 ± 5.1). Sixty-one patients were categorized as having a BIR to initial treatment (group A), and 103 as having a SIR to initial treatment, according to the ATA criteria (Supplemental Fig. 1). Of the SIR patients, 50 underwent neck reoperation before the second RAI treatment (group B) and 53 did not (group C) (Supplemental Fig. 1). In 46 of the 50 patients in group B, the medical files documented the performance of fine needle aspiration before the second neck surgery with results compatible with DTC. In all 50 patients in this group, the final pathological report of the excised neck lesion revealed DTC. In group C, fine needle aspiration results compatible with DTC were documented in 36 of the 53 patients. In the remaining 17 patients, neck imaging findings included microcalcifications in 12 lesions and hypervascularity in 5 and were defined as suspicious for thyroid cancer by an expert radiologist.

The clinical characteristics of the patients are shown in Table 1, and data on Tg level and imaging findings before and after the second RAI administration are shown in Tables 2 and 3. There were no statistically significant differences in clinical characteristics at baseline between patients who received the second RAI treatment because of a biochemical or a SIR, with or without neck reoperation. Overall, 94 patients (57.3%) had tumor–node–metastasis stage I/II and 98 (59.8%) presented with neck lymph node metastases. Positive uptake was found in 133 patients (81.1%) on RxWBS after the first RAI treatment, but in 88 (53.7%) after the second RAI administration (Table 1).

Death from disease occurred in one patient (1.6%) with BIR and six (5.8%) with SIR. The sole patient in the BIR group who died was diagnosed with distant metastases during follow-up.

Group A: BIR to initial treatment

Sixty-one patients were included in group A. Data on basal nonstimulated Tg levels both before and 1 to 2 years after the second RAI treatment were available for 51 patients; data on stTg were available for 31 patients. There was a substantial decrease in mean stTg level at 1 to 2 years after the second RAI treatment (Table 2).

Before receiving the second RAI treatment, all group A patients had a stimulated and/or suppressed Tg level compatible with the definition of BIR to total thyroidectomy and initial RAI treatment. At 1 to 2 years from the second RAI treatment, 44 of the 60 patients with complete data (73.3%) still had an elevated Tg level (Table 3). Comparison with the level before the second RAI revealed a more than 20% increase in Tg in 10 patients, stable level in 18, and a more than 20% decrease in 16. Within 2 years after the second RAI dose, 9/58 patients with available data in group A (15.5%) had positive locoregional imaging findings (Table 3).

Group B: SIR to initial treatment and neck reoperation before the second RAI treatment

Fifty patients were included in this group. The largest diameter of the neck metastatic lesions measured 20.9 ± 8.1 mm (median, 20; range, 8 to 45); only one patient had a subcentimeter nodule. There was no substantial difference in mean stimulated or nonstimulated Tg levels between baseline and 1 to 2 years after the second RAI dose (Table 2). Of the 44 patients with available data, an elevated Tg level was measured before the second RAI treatment in 31 (70.4%), and 1 to 2 years after the second RAI treatment, in 21 (47.7%) (Table 3). Within 2 years after neck reoperation and a second RAI dose, 21/44 patients (47.7%) still had positive locoregional imaging findings (Table 3).

Table 1. Clinical Characteristics of 164 DTC Patients With a BIR or SIR to Initial Total Thyroidectomy and RAI Treated With a Second RAI Dose

Clinical Characteristics	Tg-positive, Imaging-Negative (N = 61)	Imaging-Positive (N = 103)		*P* Value
		After Neck Reoperation (N = 50)	No Neck Reoperation (N = 53)	
Female sex, n (%)	38 (62.3%)	31 (62%)	34 (64.2%)	NS
Age at diagnosis, y				
Mean	43.9 ± 18.1	45.9 ± 16.7	50.3 ± 16.3	NS
Median (range)	46 (16-77)	49 (16.7-74)	54 (20-79)	
Histologic type, PTC/PTCFV	55 (90.2%)	45 (90%)	51 (96.2%)	NS
Tumor AJCC/UICC stage I/II, n (%)	29/58 (50%)	22/43 (51.2%)	27/50 (54%)	NS
Cervical LN metastasis, n (%)	35/59 (61%)	32/44 (72.7%)	31/50 (62%)	NS
AJCC/UICC TNM stage I/II, n (%)	38/60 (63.3)	28/47 (59.6)%	28/53 (52.8%)	NS
First RAI dose (mCi)				NS
Mean	134 ± 30	130 ± 32	134 ± 30	
Median (range)	150 (60–180)	150 (60–180)	150 (50–200)	
Neck uptake in posttreatment WBS				
First RAI, n (%)				NS
Any uptake	50 (82)	39 (78)	44 (83)	
Thyroid bed	30 (49.2)	22 (44)	29 (54.7)	
Second RAI dose (mCi)				
Mean	160 ± 24	161 ± 24	161 ± 25	NS
Median (range)	150 (88–200)	150 (100–250)	150 (100–200)	
Neck uptake in posttreatment WBS				
Second RAI, n (%)				NS
Any uptake	32 (52.5)	29 (58)	27 (50.9)	
Thyroid bed	18 (29.5)	14 (28)	10 (18.9)	
Follow-up from diagnosis (y)				
Mean	10.5 ± 5.9	12.3 ± 7.4	11 ± 8.1	NS
Median (range)	9 (2–37)	11 (1–40)	9 (2–40)	
Follow-up from second RAI ()				
Mean	7.4 ± 4.7	7.6 ± 4.9	7.2 ± 5.8	NS
Median (range)	7 (1–34)	7 (1–19)	6 (1–34)	

Abbreviations: AJCC, American Joint Committee on Cancer; LN, lymph node; NS, not significant; PTCFV, PTC follicular variant; TNM, tumor–node–metastasis; UICC, Union for International Cancer Control; WBS, whole body scan.

Group C: SIR to initial treatment with no neck reoperation before the second RAI treatment

In the 53 group C patients, no statistically significant change in mean stimulated or nonstimulated Tg levels was found 1 to 2 years after the second RAI treatment (Table 2).

Forty-four of the 47 patients with data (93.6%) still had positive neck imaging findings 1 to 2 years after the second RAI treatment (Table 3). Among this subgroup, measurements of the largest diameter of the neck metastatic lesions were available in 42 patients before the second RAI treatment and in 47 patients 1 to 2 years later. Mean neck lesion size at baseline measured 11.6 ± 5.1 mm (median, 10; range, 4 to 28 mm), which was significantly smaller than the mean size of neck lesions in group B (20.9 ± 8.1 mm, $P < 0.001$). The maximal lesion diameter

Table 2. Thyroglobulin Levels in 164 DTC Patients Before and 1 to 2 Years After a Second RAI Treatment

Patient Group by Response to Initial Treatment[a]	No. Patients	Tg Level (ng/mL), Mean ± SD		*P* Value
		Before Second RAI	1–2 Y After Second RAI	
BIR	61			
Basal Tg	51	3.0 ± 3.9	3.1 ± 4.8	0.85
Stimulated Tg	31	41.9 ± 56	24.6 ± 54	0.003
SIR, neck reoperation	50			
Basal Tg	30	5.6 ± 14	2.6 ± 5.3	0.14
Stimulated Tg	15	68.3 ± 115	35.2 ± 77	0.15
SIR, no neck reoperation	53			
Basal Tg	40	6.5 ± 12.5	10.3 ± 24	0.08
Stimulated Tg	12	93.7 ± 108	102.0 ± 124	0.73

[a]Initial treatment consisted of total thyroidectomy and adjuvant RAI.

Table 3. Patients With Biochemical and Structural Residual DTC Before and 1 to 2 Years After a Second RAI Dose

Patient Group, by Response to Initial Treatment[a]	Elevated Tg Level, N (%)[b]		Structural Neck Disease, N (%)	
	Before Second RAI	After Second RAI	Before Second RAI	After Second RAI
BIR	61/61 (100)	44/60 (73.3)	0/61 (0)	9/58 (15.5%)
SIR, neck reoperation	31/44 (70.4)	21/44 (47.7)	50/50 (100)[c]	21/44 (47.7)
SIR, no neck reoperation	39/46 (84.8)	42/47 (89.4)	53/53 (100)	44/47 (93.6)

[a]Initial treatment consisted of total thyroidectomy and adjuvant RAI.

[b]Suppressed Tg >1 ng/mL or stTg >10 ng/mL.

[c]Findings before the neck reoperation.

measured >15 mm in 9/42 patients. After the second RAI administration, neck lesions measured 14.7 ± 10 mm (median, 13; range, 0 to 59 mm). In only three group C patients with neck lesions measuring 6 to 10 mm were these nodules no longer demonstrated on repeated neck imaging after the second RAI treatment. Of the remaining 44 patients with documented structural persistence 1 to 2 years after the second RAI treatment, 10 showed locoregional structural progression, 2 showed a decrease in nodular size, and 26 had stable disease. In the remaining six patients, the data were insufficient for comparison.

Status at last follow-up visit

Overall, 63 patients (38.4%) received additional treatments after the second RAI dose. Data on the therapeutic modalities used and disease outcomes are shown in Table 4. At the last follow-up, there was no evidence of disease (NED) in 56/164 patients (34.1%). In 74 patients (45.1%), imaging studies were positive for locoregional disease. An elevated Tg level was detected in 89 patients (54.3%), of whom 32 had no structural findings: 21 (33.3%) in group A, 8 (16%) in group B, and 3 (5.7%) in group C. Of the 61 patients with a Tg-positive/imaging-negative status before the second RAI dose (group A), 21 (34.4%) received further treatments. However, 37 (60.6%) still had an elevated Tg level at the last follow-up visit. Moreover, although none of the patients had structural findings before the second RAI dose, 17 (27.9%) had positive findings on neck ultrasound at last follow-up (Table 4).

Of the 50 patients who underwent reoperation before the second RAI dose (group B), 22 (44%) had no biochemical and/or structural evidence of disease at the last follow-up. In group C, only 20.8% of the patients were disease-free at the last follow-up despite the administration of further therapies in 43.4%. Structural findings were still found on neck imaging in 70%.

Table 5 shows the association of positive/negative uptake on RxWBS after the second RAI dose with NED at last follow-up as well as the additional treatments administered to the patients. Only in group C was the proportion of patients with positive uptake and NED at last follow-up higher than the proportion of patients with no uptake, but most of them received additional treatments after the second RAI dose.

Discussion

In the current study, we demonstrated that a second RAI dose has limited value in patients with DTC who have an

Table 4. Additional Treatments and Disease Status at Last Follow-Up Visit in 164 DTC Patients After a Second RAI Treatment

Treatment and Outcome After Second RAI	Tg-Positive, Imaging-Negative (n = 61)	Imaging-Positive, After Neck Reoperation (n = 50)	Imaging-Negative, No Neck Reoperation (n = 53)
Additional treatment[a]			
Any	21 (34.4%)	19 (38%)	23 (43.4%)
RAI	19 (31.1%)	14 (28%)	13 (24.5%)
Surgery	7 (11.5%)	11 (22%)	19 (35.8%)
External radiation	3 (4.9%)	6 (12%)	6 (11.3%)
Disease status			
No disease	23 (37.7%)	22 (44%)	11 (20.8%)
Elevated Tg level[b]	37 (60.6%)	21 (42%)	31 (58%)
Structural findings	17 (27.9%)	20 (40%)	37 (70%)

[a]Some patients had more than one type of treatment.

[b]Suppressed Tg >1 ng/mL or stTg >10 ng/mL.

Table 5. Proportion of Patients With No Evidence of Disease at Last Follow-Up and Data on Additional Treatment Modalities Administered According to Uptake at the Second RAI Treatment

	Group A RAI Uptake, n (%)		Group B RAI Uptake, n (%)		Group C RAI Uptake, n (%)	
	Positive, 31	Negative, 28	Positive, 27	Negative, 19	Positive, 27	Negative, 21
Status at last follow-up						
NED	12 (38.7)	11 (39.2)	12 (44.4)	10 (52.6)	9 (33.3)	2 (9.5)
NED no additional treatments	9 (29)	7 (25)	8 (29.6)	7 (36.8)	2 (7.4)	0 (0)
Additional treatments						
Any	11 (35.5)	9 (32.1)	9 (33.3)	7 (36.8)	15 (55.6)	7 (33.3)
RAI	9 (29)	7 (25)	8 (29.6)	5 (26.3)	11 (40.7)	1 (4.7)
Surgery	3 (9.7)	4 (14.3)	8 (29.6)	3 (15.8)	12 (44.4)	7 (33.3)
External radiation	0 (0)	2 (7.1)	6 (22.2)	0 (0)	3 (11.1)	2 (9.5)

incomplete response to the initial treatment. In our cohort, only a minority of patients with an incomplete biochemical or locoregional structural response to primary therapy were reclassified as NED at the end of follow-up, even though a substantial proportion of them received additional treatments.

Currently, there are no prospective, randomized, controlled clinical trials demonstrating improved outcomes after a second RAI treatment in DTC patients with locoregional residual disease.

Yim *et al.* (15) retrospectively evaluated 45 Korean patients with DTC and persistent serum Tg elevation after reoperation for locoregional recurrence. The patients who received an empirical second RAI treatment showed no outcome benefit compared with untreated patients. Only 15% of patients in the treatment group had a >50% decrease in Tg level from baseline. The results of the current study are in accordance with these findings. In our cohort, of the 103 patients given a second RAI dose because of SIR to initial treatment, 50 had undergone revision surgery before the second RAI dose (group B). No substantial decrease in Tg level was found, and structural findings were still demonstrated in 48% after 1 to 2 years.

In another study by Yim *et al.* (16) evaluating the efficacy of the first reoperation in 83 patients with locoregional recurrent/persistent PTC, the biochemical remission rate was 51%. Only 18 of these patients (21.7%) received a second RAI treatment after reoperation. In our cohort, despite the administration of a second RAI dose after reoperation in all group B patients, and additional therapies in a substantial portion of the patients, 42% had Tg levels compatible with BIR at the last follow-up visit.

In the current study, as in the first report by Yim *et al.* (15), the second RAI activity in group B patients was administered empirically after neck reoperation. Thus, it may be assumed that improvements in neck structural findings, when they occurred, were attributable largely to the surgery and not to the second RAI dose. In a recent retrospective multicenter study from Italy and Switzerland investigating the effect of additional RAI administration in DTC patients with negative imaging studies after neck reoperation, the authors found no association between this treatment and improved overall or progression-free survival in the whole cohort of 113 patients (64 treated with RAI). However, subgroup analysis revealed better progression-free survival in patients with an elevated Tg level after receiving the RAI retreatment (17).

The results of the second RAI dose in patients with residual/recurrent structural disease who did not undergo neck reoperation (group C) were particularly disappointing. Of the 53 patients, only 5 (9.4%) showed a reduction in lesion size. The disappearance of a visible metastatic neck lesion was noted in only three patients with subcentimeter lesions 1 to 2 years after the second RAI dose. Despite the high proportion of patients who received additional treatments, only 21% of this group were disease-free at the last follow-up, and most of the remainder had both structural and biochemical evidence of residual disease. However, an inclusive analysis should refer to the small size of the neck lesions in this group (median, 10 mm). It has been shown that small thyroid bed nodules identified after total thyroidectomy rarely show clinically substantial structural progression (18). In the current study, patients with nonspecific unbiopsied structural findings compatible with an "indeterminate response to therapy" were excluded. Yet, it is still possible that in some of the patients in group C, the small neck lesions were benign or clinically insignificant and could have been followed with no need for the second RAI administration.

Our results are in accordance with previous studies showing that despite the administration of additional treatments, most patients classified as having a SIR to the initial treatment will have evidence of persistent disease at the final follow-up (2, 6, 8). Although patients in group B had significantly larger metastatic neck lesions at baseline than patients in group C, the proportion of patients who

were disease-free at the last follow-up was twice as high in group B than group C. Thus, although surgery might be curative for macroscopic neck lesions, the benefit of RAI without prior reoperation for smaller lesions is questionable and is often associated with the persistence of structural findings with diverse clinical significance.

The current study also included 61 patients with BIR to initial therapy (group A). Despite the generally good correlation between Tg levels and findings on RxWBS (19, 20), 15% to 20% of patients are scan-negative and Tg-positive (21). Previously, it was common practice to administer an empiric dose of ^{131}I to these patients with a goal of tumor localization and treatment (22, 23). Furthermore, the lack of visible uptake does not exclude some possible effect of RAI treatment at a microscopic level. Now, radioiodine diagnostic scanning has mostly been displaced by more sensitive neck ultrasonography (21, 24). Nevertheless, in a recent survey of ATA members regarding practice trends in DTC, most reported administering empiric RAI treatment in patients with persistent detectable Tg and negative imaging findings (25). Chao (21), in an overview of 17 clinical trials, found that most patients with BIR to initial treatment had a decrease in serum Tg level after a second RAI administration. Yet, a substantial portion of patients who received no specific treatment also showed spontaneous normalization or a substantial decrease in serum Tg (21). In the current study, group A patients showed a statistically significant decrease in Tg level 1 to 2 years after the second RAI dose. However, in most (73.3%), Tg levels were still above normal. Our study was self-controlled and lacked a control group, as have most of the studies in this field so far (21). Nevertheless, our results are in agreement with a comparative study of 39 patients with elevated stTg levels and negative imaging studies (26). These authors found that 36% of patients in the treatment group and 32% of patients in the control group had structural recurrence (26). Accordingly, in the current study, 27.9% of the patients with BIR to initial treatment had structural recurrence at the last follow up.

Our study does not include data on diagnostic WBS before the second RAI dose because this procedure in no longer routinely performed in our institution. However, RAI uptake was found in the majority of patients on the first posttreatment scan but not after the second one. A negative RxWBS after a second RAI treatment has been reported in most patients (15, 17), although the association with disease-related outcomes has not been analyzed. We found no association between positive RAI uptake after the second RAI treatment and long-term outcomes. Only in patients with a SIR who received a second RAI dose without prior reoperation (group C) was there a stronger association of positive rather than of negative uptake after the second treatment with a higher rate of NED at the last follow-up. However, this outcome was achieved after additional treatments in most patients and therefore cannot be attributed specifically to the second RAI dose.

It has been reported that SIR to initial therapy is associated with a worse clinical outcome than BIR (6, 8). Our data show that this distinction persists also after the administration of a second RAI treatment, with SIR more likely to be associated with structural disease at final follow-up and more disease-specific mortality.

The strengths of the current study are the inclusion of patients with biochemical and/or SIR to initial treatment, which provided an overview of the effect of a second RAI treatment in the management of different DTC patient subgroups followed for relatively long periods. The availability of neck ultrasonography data in most of our patients made it possible to compare the structural findings before and after administration of the second RAI dose. The limitations of the study include its retrospective design and the absence of a control group of patients with DTC who were not treated with repeated RAI for incomplete response to initial therapy. Thus, we cannot exclude that patients' outcomes would have been worse had they not received the second RAI dose. Specifically, most patients in groups A and B had no structural evidence of disease at the last follow-up, and a contributory role of the second RAI dose cannot be ruled out. Additionally, because most patients were treated in the era when diagnostic whole body scans were not routinely performed before administration of RAI therapy, our results might have been different if the patients had been selected for a second treatment based on a positive diagnostic scan.

In conclusion, this comprehensive institutional study shows no clear impact of a second RAI treatment in DTC patients with biochemical or structural regional incomplete response to initial thyroidectomy and RAI therapy. Although we cannot exclude a therapeutic effect of the second RAI dose, our data may aid in establishing realistic expectations of patients and physicians regarding this treatment. Prospective studies are needed to identify patients for whom repeated RAI treatment may be indicated to spare the remainder unnecessary exposure.

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