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Re-ablation I-131 activity does not predict treatment success in low- and intermediate-risk patients with differentiated thyroid carcinoma

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Abstract

Purpose: The aim of this study was to evaluate the efficacy of different radioactive iodine (I-131) activities used for re-ablation, to compare various combinations of treatment activities, and to identify predictors of re-ablation failure in low- and intermediate-risk differentiated thyroid carcinoma (DTC) patients.

Methods: The study included 128 consecutive low- and intermediate-risk patients with DTC with ablation failure after total thyroidectomy. Patient characteristics, T status, tumor size, lymph node involvement, postoperative remnant size on whole body scintigraphy, serum thyroglobulin (Tg), thyroid-stimulating hormone (TSH), anti-Tg antibody (TgAb), and Tg/TSH ratio were analyzed as potential predictors of the re-ablation success.

Results: Re-ablation was successful in 113 out of 128 patients (88.3%). Mean first I-131 activity was 2868 ± 914 MBq (77.5 ± 24.7 mCi), and mean second I-131 activity 3004 ± 699 MBq (81.2 ± 18.9 mCi). There was no association between the first, second, and cumulative activity with re-ablation treatment outcome. Treatment failure was associated with higher Tg levels prior to re-ablation (Tg2) (OR 1.16, 95% CI 1.05 - 1.29, P=0.003) and N1a status (OR 3.89, 95% CI 1.13 - 13.41, P=0.032). After excluding patients with positive-to-negative TgAb conversion, Tg2 level of 3.7 ng/mL predicted treatment failure with a sensitivity of 75.0 %, specificity of 80.5%, and a negative predictive value of 97.1%. Patients with positive-to-negative TgAb conversion had higher failure rates (OR=2.96, 95% CI 0.94 - 9.29).

Conclusions: Re-ablation success was high in all subgroups of patients and I-131 activity did not influence treatment outcome. Tg may serve as a good predictor of re-ablation failure. Patients with positive-to-negative TgAb conversion represent a specific group, in whom Tg level should not be used as a predictive marker of treatment outcome.

Keywords: radioactive iodine, radioiodine ablation, thyroglobulin, anti-Tg antibody.

Introduction

Patients with low- and intermediate-risk differentiated thyroid carcinoma (DTC) are selectively treated with postoperative radioactive iodine (I-131) ablation; however, the indication for I-131 therapy is the subject of an ongoing debate, and there is no consensus regarding optimal I-131 activity in this group of patients [1-7]. Following a single application of I-131, approximately 8-40% of patients require an additional application (re-ablation) due to ablation failure. Ablation activities for first and second ablation range from low (1110 MBq [30mCi]) to high (≥3700 MBq [100mCi]) [8-10].

The optimal I-131 activity used in the first ablation is still debated. While most studies have shown that I-131 activity is not correlated with ablation success, some authors still recommend higher I-131 activities, while others recommend lower activities for effective ablation [10-14]. Similarly, in patients with ablation failure, additional uncertainties pertain to the optimal second ablation activity and the optimal combination of activities used for the first and second ablation, especially when the potential risks of treatment must be balanced against treatment success [9,11-12] .

The aim of this study was to evaluate the efficacy of different I-131 activities used in re-ablation, to compare various combinations of treatment activities, and to identify predictors of re-ablation failure in low- and intermediate-risk DTC patients.

Patients and Methods

This cohort study included 740 consecutive low- and intermediate-risk patients with DTC, treated between the years 2005 to 2014. All patients were treated with total thyroidectomy, and if indicated, selective neck dissection. The TNM staging system was used to classify tumors into T1-3, N0-1, and M0. After primary surgical treatment, all patients received adjuvant I-131 therapy if remnant thyroid tissue was detected on whole body scintigraphy (WBS). Exclusion criteria were as follows: patients with tumors that invaded adjacent structures (category T4), residual disease in lymph nodes detected on WBS or by neck ultrasound (US), distant metastases confirmed by WBS, or other methods such as computed tomography, bone scan, chest X-ray, positron emission tomography (category M1), mixed tumors, and tumors ≤1 cm in diameter. In addition, patients with tumors >1 cm in diameter who had undetectable thyroglobulin (Tg) levels, or absent I-131-I uptake in the thyroid bed on WBS were excluded.

Four weeks after surgery, serum stimulated thyroglobulin (Tg1), thyroid-stimulating hormone (TSH1), and anti-Tg antibody (TgAb1) levels were measured. A stimulated TSH1 level of ≥ 30 mU/L was reached by omitting thyroid hormone replacement for 4 weeks. Neck US (US1) was performed in all patients, and pre-ablative diagnostic WBS (WBS1) was performed in patients with suspected remnant thyroid tissue. Activities between 1036 – 4625 MBq (28 – 125 mCi) were used in patients with indications for adjuvant I-131 ablation. Low I-131 activity was defined as an activity of 1036 – 1850 MBq (28 – 50 mCi), intermediate activity as 2775 MBq (75 mCi), and high activity as 3700 – 4625 MBq (100 – 125 mCi). All patients had post-therapy WBS performed following I-131 administration.

Six to eight months following initial I-131 administration, all patients (in a hypothyroid state) had serum levels of serum stimulated thyroglobulin (Tg2), thyroid-stimulating hormone (TSH2), and anti-Tg antibody (TgAb2) measured. Neck US (US2) and WBS (WBS2) were also repeated. Following the first application of I-131, criteria for the determination of the successful ablation included: 1) absence of I-131 accumulation in the thyroid bed on WBS2; 2) absence of I-131 accumulation in the cervical region on WBS2. These findings were compared with Tg2 and US2 findings, in order to estimate the thyroid mass remnant. Patients that did not fulfill these criteria were considered to have ablation failure and required a second ablation.

Ablation failure was detected in 139 out of 740 patients. The outcome of re-ablation was assessed six to nine months after the second application of I-131 using the same criteria already mentioned (Tg, US, and WBS). Eleven patients were excluded from further analysis; four patients had suspected residual disease in lymph nodes detected on WBS2, two patients developed neck lymph node metastases and required surgery, two patients had a high index of suspicion for distant metastasis, one patient had inaccessible data, and two patients did not have re-ablation outcome assessed. Re-ablation outcome was compared in groups with low-, intermediate-, and high I-131 activities. Patient characteristics, T status, tumor size, lymph node involvement, remnant size on WBS, Tg levels, thyroid-stimulating hormone (TSH) levels; anti-Tg antibody (TgAb) conversion, and Tg/TSH ratios were analyzed and correlated with re-ablation success.

Statistical analysis

Patient characteristics were assessed using descriptive statistics presented as mean ± standard deviation, and median. Independent continuous variables were compared using the Student t-test, dependent variables with pared t-test, and categorical variables using the Chi square test with Yates correction. Binary and multinominal logistic regression were used to analyze the association between all variables and treatment outcome, when appropriate. Logistic regression models was also used to adjust for confounding factors. Receiver operating characteristic (ROC) analysis was performed for independent predictors of treatment outcome, in order to establish cut-off values, and to determine sensitivity, specificity and positive- and negative predictive value. P value of <0.05 was considered statistically significant. The statistical analysis was done using SPSS Version 20.

Results

Patient characteristics

The final analysis included 128 patients, and these patients received re-ablation with low (1110 – 1850 MBq [30 – 50mCi]), intermediate (2775 MBq [75 mCi]) or high (≥3700 MBq [100 mCi]) activity of I-131. Out of these 128 patients, 29 were males, with a mean age of 46.2 ± 13.3 years, and 99 were females, with a mean age of 46.2 ± 12.0 years. There was no association between gender, age, and treatment outcome. Baseline characteristics of the study population are presented in Table 1 and Table 2.

Re-ablation

Re-ablation was successful in 113 out of 128 patients with ablation failure (88.3%), while re-ablation failure occurred in 15 patients (11.7%). Mean first I-131 activity was 2868 ± 914 MBq (77.5 ± 24.7 mCi), and mean second I-131 activity 3004 ± 699 MBq (81.2 ± 18.9 mCi), P=0.147. Cumulative activity after two I-131 applications was 5872 ± 1217 MBq (158.7 ± 32.9

mCi). When compared to the first I-131 activity, the second ablation activity was decreased in 51 patients (39.8%), increased in 68 patients (53.1%), and 9 patients were given the same I-131 activity (7.1%). Treatment failure occurred in 4 (44%) patients with unchanged I-131 activity, which was significantly higher compared to treatment failure in patients who received decremental (5/51, 9.8%) and incremental activity (6/68, 8.8%), P=0.014. Patients were divided based on I-131 activity in the first and second ablation into low-, intermediate-, and high activity-groups. The majority of patients were in the intermediate–intermediate, or high–high groups (Table 3). Although the sample size did not have sufficient statistical power, re-ablation failure rates were similar between the low–low and high–high group. In the logistic regression model there was no association between I-131 activity change and treatment outcome in the second ablation. Additionally, there was no association between the first, second, and cumulative activity with re-ablation treatment outcome.

Association of Tg and Tg/TSH ratio prior to re-ablation and treatment outcome

Compared to findings before the first ablation, TSH significantly increased from 84.8 ± 40.8 mU/L to 110.1 ± 48.6 mU/L, Tg decreased from 7.0 ± 9.7 ng/mL to 3.0 ± 4.6 ng/mL, and Tg/TSH ratio decreased from 0.115 ± 0.217 mg/U to 0.034 ± 0.071 mg/U prior to re-ablation (P value for all changes <0.001). A positive association was found between treatment failure and Tg2 levels (OR=1.16, 5% CI 1.05 - 1.29, P=0.003), as well as between treatment failure and Tg2/TSH2 ratio (OR=1.14, 95% CI 1.05 - 1.28, P=0.016). Twenty-six patients who were TgAb1-positive became TgAb2-negative (positive-to-negative TgAb conversion), while only one previously TgAb-negative patient became TgAb positive. Patients with positive-to-negative TgAb conversion had higher failure rates (OR=2.96, 95% CI 0.94 - 9.29), but the difference did not reach statistical significance (P=0.063). When all patients with negative TgAb2 were included in the analysis, Tg2 level of 1.5 had a sensitivity of 71.4% and a specificity of 71.6% in predicting treatment failure, while Tg2/TSH2 ratio of 0.0349 mg/U had a sensitivity of 57.1 % and a specificity of 82.4%. Tg2 alone had a slightly greater area under the curve (AUC) than Tg2/TSH2 ratio (0.725 vs. 0.706). After excluding patients with positive-to-negative TgAb conversion, AUC increased to 0.799 for Tg2, and to 0.779 for Tg2/TSH2 ratio (Figure 1).

A Tg2 level of 3.7 ng/mL predicted treatment failure with a sensitivity of 75.0 % and specificity of 80.5%. Treatment failure occurred in 95% of patients with Tg2> 11.8 ng/mL, while none of the patients with Tg2< 0.2 ng/mL had treatment failure. Tg2 had a positive predictive value of 27.3% and a negative predictive value of 97.1 %. On the other hand, Tg2/TSH2 ratio of 0.0349 mg/U had a sensitivity of 75.0% and specificity of 78%, which was inferior to the prognostic value of Tg2 alone.

Association of other factors and treatment outcome

Neither TSH levels, nor the change in TSH levels did not influence final outcome. There was no association between Tg1 level and Tg1/TSH1 ratio and final outcome. When primary disease characteristics were taken into account, only patients with N1a status had significantly higher risk of treatment failure when compared to N0 patients (OR=3.89, 95% CI 1.13 - 13.41, P=0.032), while tumor type, T status, tumor size, capsular invasion, and number of removed and positive lymph nodes were not found to be associated with re-ablation treatment outcome. Patients with N1a tumor status had a failure rate of 27.8% (5/18), while those with N0 status had 9% (9/100). There was no statistically significant difference between N1a and N1b, or between N0 and N1b status. No association between Tg2 levels and N status was found. Moreover, the positive association between N1a status and treatment failure was more significant after adjustment for Tg2/TSH2 ratio (OR=4.41, 95% CI 1.15 - 17.0, P=0.031), but it diminished after adjustment for Tg2 alone (OR=3.70, 95% CI 0.96 - 14.32, P=0.058).

Discussion

The optimal re-ablation treatment strategy has not been clearly defined; moreover, studies in this area are lacking because a significant proportion of patients has successful ablation following a single application of I-131, and only high-volume thyroid centers manage to collect enough data on patients with I-131 re-ablation for these studies to have sufficient statistical power. The most effective cost-benefit strategy, the rationale for re-ablation, as well as the re-ablation I-131 activity in these patients is still a subject of an ongoing debate [8-9,14]. Malick and colleagues concluded that low activity I-131 in post-thyroidectomy ablation using 1110 MBq (30 mCi) was effective [8]. However, the majority of the patients that required re-ablation were given intermediate to high activities of I-131 – 29 out of 30 patients received ≥ 2997 MBq (81 mCi) I-131, therefore, definite conclusions regarding the efficacy of low activity I-131 re-ablation cannot be made [8]. Our results are in accordance with a study by El-Refaei et al, which investigated treatment outcome after re-ablation using both low- and high I-131activities, and found no difference in overall treatment success between these two study groups [9]. Similarly, another study, concluded that although high I-131 activities used in the first application are significantly more effective in thyroid ablation than low- and intermediate activities, it is not the case in re-ablation [14]. Long-term side effects, including the possibility for secondary malignancies, as well as increased radiation exposure to medical staff, must be taken into consideration when using high activities [17,18]. Furthermore, when high activity I-131 is applied, the patient has to be hospitalized on two occasions. In comparison, low activity treatment can be applied on an outpatient basis.

A multidisciplinary approach is necessary in order to improve coordination, communication, and the decision-making process. In the present study, overall re-ablation treatment success was achieved in 88.3% of patients. Generally, the overall success of DTC treatment is highly dependent on the extent of primary surgery [15,16]. Since all patients underwent total thyroidectomy with or without neck dissection in a high-volume thyroid university hospital center, the extensiveness of the surgery could not affect the ablation outcome in our patients. Also, there was no association between gender, age, first-, second-, and cumulative I-131 activity, as well as changes in I-131 activity and treatment outcome. In comparison to the first ablation, higher success rates were observed following re-ablation, an interesting finding considering that a higher proportion of patients requiring re-ablation are radioresistent. This phenomenon could be explained by the smaller thyroid remnant, which was also indirectly correlated with lower Tg2, when compared to mean Tg1 levels in these patients (3.0 ng/mL vs. 7.0 ng/mL.

A positive association was found between treatment failure and Tg2 levels and Tg2/TSH2 ratio. When all patients with negative TgAb2 were included in the analysis, Tg2 alone had a slightly greater AUC than Tg2/TSH2 ratio. Although patients with positive-to-negative TgAb conversion had insignificantly higher failure rates, after exclusion of these patients AUC for both Tg2 and Tg2/TSH2 ratio increased (predicting value was again in the favor of Tg2). Thus, in this subgroup of patients, Tg and Tg/TSH ratio are even more potent predictive markers, and TgAb conversion should be taken into account when discussing optimal I-131 re-ablation activity in an individual patient. Since the predictive value of Tg2/TSH2 ratio was inferior to the prognostic value of Tg2 alone, and TSH alone was not found to have predictive value in these patients, this study proposes Tg as the main predictor of the treatment outcome in re-ablation. A Tg2 level of 3.7 ng/mL predicted treatment failure with a sensitivity and specificity of 75.0% and 80.5%, respectively.

Initial N tumor status was also evaluated as a potential predictor of treatment outcome. Patients with N1a status had a significantly higher risk of treatment failure compared to N0 patients (P=0.032) – those with N1a status had a failure rate of 27.8%, and those with N0 status 9%. This positive association improved after adjustment for Tg/TSH ratio (P=0.031), but it diminished after adjustment for Tg alone (P=0.058). The lack of statistically significant difference in treatment outcome between N1a and N1b, and between N0 and N1b status can be explained by the more extensive surgery that was done in cases of more extensive disease (patients with suspected N1b disease), according to the surgeon's clinical judgement. Tumor type, T status, tumor size, capsular invasion, and number of removed and positive lymph nodes were not found to be associated with (re-ablation) treatment outcome. Also, no association between Tg and N status was found.

This study evaluated I-131 re-ablation treatment outcome in patients with low- and intermediate-risk DTC. The results of the study are limited due to its retrospective design, and because long-term outcomes were not examined. In this group of patients, disease recurrence may occur even several decades after surgery and subsequent I-131 therapy. Moreover, secondary malignancies as a consequence of I-131 therapy should be taken into consideration when evaluating treatment outcome. There is also a possible clinical bias, since patients with more advanced disease generally receive higher activities of I-131 in both ablation and re-ablation, based on the attending physician's decision.

In conclusion, there are still no completed large clinical trials evaluating predictors of re-ablation outcome and optimal treatment strategies in these patients. Only high-volume thyroid medical centers have a potential to include sufficiently large patient populations who require re-ablation, and these patients have to be followed-up for decades in order to make definitive conclusions about the value of potential predictors for re-ablation treatment outcome. Thus, as a more practical approach, we propose using Tg, which was found to be the most reliable predictor of re-ablation treatment outcome in the present study. Since I-131 activity was not found to be correlated with treatment outcome, administration of high I-131 activities in re-ablation can be avoided, especially in a high–high activity treatment regimes and in patients with low Tg, without affecting treatment outcome.

Declaration of interest

The authors declare that they have no conflict of interest.

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Ethics

This study was carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors.

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Table 1. Continuous variables of the study population, divided based on treatment outcome. Variables labeled as 1 refer to values prior to first ablation, and 2 to values prior to re-ablation.

	Treatment outcome				
	Success (n=113)		Failure (n=15)		
	Mean	SD	Mean	SD	P value*
Age (years)	46.8	12.2	41.5	12.4	0.120
First I-131 activity (mCi)	77.7	24.1	75.7	29.6	>0.3
Second I-131 activity (mCi)	81.2	19.1	81.2	18.8	>0.3
Cumulative RAI activity (mCi)	158.9	31.9	156.9	41.0	>0.3
Δ I-131 activity (mCi)	3.6	29.6	5.5	27.9	>0.3
Δ I-131 activity (%)	19.5	62.7	29.7	74.3	>0.3
TSH1 (mU/L)	84.2	41.0	83.5	38.1	>0.3
TSH2 (mU/L)	108.6	47.4	118.8	47.8	>0.3
Δ TSH (mU/L)	24.5	32.6	35.3	27.3	0.222
Tg1 (ng/mL)	6.7	9.4	9.8	12.6	>0.3
Tg2 (ng/mL)	2.07	3.70	6.11	6.39	0.001
Δ Tg (ng/mL)	-4.34	8.11	-1.29	9.82	>0.3
Tg/TSH1 (mg/U)	.108	.208	.176	.291	>0.3
Tg/TSH2 (mg/U)	.021	.049	.080	.119	0.001
Δ Tg/TSH (mg/U)	-.082	.193	-.049	.257	>0.3
Removed lymph nodes	1.9	5.8	3.1	6.0	>0.3
Positive lymph nodes	.8	2.5	1.3	2.4	>0.3

*Student t-test; SD – standard deviation

Table 2. Categorical variables of the study population divided based on treatment outcome.

	Success N = 113	Failure N = 15	P value
Gender (male) % (n)	24.8 (28)	6.7 (1)	0.188
First I-131 activity (tertiles)			
Low % (n)	23.9 (27)	26.7 (4)	>0.3
Intermediate % (n)	41.6 (47)	26.7 (4)	>0.3
High % (n)	34.5 (39)	46.7 (7)	>0.3
Second I-131 activity (tertiles)			
Low % (n)	18.6 (21)	20.0 (3)	>0.3
Intermediate % (n)	46.0 (52)	40.0 (6)	>0.3
High % (n)	35.4 (40)	40.0 (6)	>0.3
Positive TgAb1 % (n)	26.5 (30)	46.7 (7)	0.132
Positive TgAb2 % (n)	9.7 (11)	6.7 (1)	>0.3
Seroconversion % (n)	18.6 (21)	40.0 (6)	0.086
Remnant size before 1. ablation			
Large % (n)	62.8 (59)	63.6 (7)	>0.3
Histopathology			
Papillary % (n)	95.6 (108)	100 (15)	>0.3
Follicular % (n)	4.4 (5)	0 (0)	>0.3
T status			
1a % (n)	41.7 (45)	35.7 (5)	>0.3
1b % (n)	29.6 (32)	42.9 (6)	>0.3
2 % (n)	5.6 (6)	14.3 (2)	>0.3
3 % (n)	23.1 (25)	7.1 (1)	>0.3
Thyroid capsule invasion % (n)	20.4 (23)	6.7 (1)	>0.3
N status			
0 % (n)	80.5 (91)	60.0 (9)	0.095
1a % (n)	11.5 (13)	33.3 (5)	0.038
1b % (n)	6.2 (7)	6.7 (1)	>0.3
1x % (n)	1.8 (2)	0 (0)	>0.3
Lymph node capsule invasion % (n)	1.8 (2)	0 (0)	>0.3

Table 3. The rate of treatment failure in patients divided in tertiles according to I-131 activity at first and second ablation.

I-131 activity (tertiles) First – second ablation	Number of patients	Treatment failure % (n)
Low – low	11	18.2 (2)
Low – intermediate	9	11.1 (1)
Low – high	10	9.1 (1)
Intermediate – low	6	0 (0)
Intermediate – intermediate	31	9.7 (3)
Intermediate - high	14	7.1 (1)
High – low	7	14.0 (1)
High – intermediate	18	11.1 (2)
High – high	21	19.0 (4)

Figure legend:

Figure 1. ROC curves for Tg2 (A) and Tg2/TSH2 ratio (B) when patients with positive to negative TgAb conversion were included into analysis. Increase of area under the curve was observed for Tg2 (C) and Tg2/TSH2 ratio (D) after patients with positive to negative TgAb conversion were excluded.