Is Stimulated Thyroglobulin Before Radioiodine Therapy a Useful Tool in Predicting Response to Initial Therapy in Patients with Differentiated Thyroid Carcinoma?

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ABSTRACT

Thyroglobulin (Tg) is an important tool to evaluate the persistence and recurrence risk in differentiated thyroid cancer (DTC). We aimed to evaluate the correlation between pre-radioiodine therapy stimulated Tg (pre-RAI Tg) levels and the first response to treatment evaluation, and to establish a cut-off pre-RAI Tg threshold for predicting an initial excellent response. Retrospective cohort study of DTC patients who underwent total thyroidectomy and radioiodine therapy. Response to therapy was evaluated 6 to 24 months after initial therapy, and patients were classified as: excellent response (ER); indeterminate response (IndR) and incomplete response (IncR). Total patients: 166 among which 85.5 % female with mean age of 47.6 ± 13 years. The ER had a significantly lower pre-RAI Tg in comparison to IndR ($p < 0.001$) and IncR ($p < 0.001$), and pre-RAI Tg were different between the IndR and IncR ($p = 0.02$). A cut-off pre-RAI Tg value at 7.55ng/ml was obtained by receiver operating characteristics curve for differentiating ER from IndR and IncR. The area under curve was 0.832 (95 % CI 0.76–0.91). In multivariate analysis, ATA low-risk (RR 1.61, 95 % CI 1.06–2.43, $p = 0.025$) and Tg below 7.55ng/ml (RR 2.17, 95 % CI 1.52–3.10, $p < 0.001$) were associated with ER. After a median of 7.4-year follow-up, 124 (74.7 %) patients were allocated into ER, 22 (13.2 %) into IndR, and 20 (12 %) into IncR. In conclusion, pre-RAI Tg predicts first evaluation of treatment response. Pre-RAI Tg cut-off was a key predictor of initial excellent response to therapy and may be an important tool in the follow-up of DTC patients.

Introduction

Papillary thyroid carcinoma (PTC) represents 85–90 % of differentiated thyroid carcinoma (DTC), and it is considered a neoplasm of indolent behavior with a 5-year survival rate of 98.1 % [1]. However, persistence or recurrence is a condition related to this tumor, requiring long-term follow-up [1]. The estimated risk of persistent and/or recurrent disease varies among the cohorts studied, being between 0–14 % in patients with excellent response to initial treatment [2–4].

Postoperative thyroglobulin (Tg) has an important role in indicating the need of radioactive iodine therapy (RAI), to evaluate initial response to treatment and define response on long-term follow-up [1, 5, 6]. The evaluation of stimulated Tg (s-Tg) immediately before RAI (pre-RAI Tg) is used as an early marker to predict clinical recurrence, to detect distant metastasis, and also to predict

the results of radioiodine whole-body scintigraphy (WBS) after RAI [7, 8]. Several studies have demonstrated a wide range of pre-RAI Tg cut-offs, between 2.8 and 38.1 ng/ml to predict persistent and/or recurrence on follow-up, with variable sensitivity and specificity, and variable thresholds [6, 8–10]. Recently, it has been proposed that values of pre-RAI Tg ≥ 10 ng/ml have shown better sensitivity and specificity to predict persistent/recurrent disease and survival related to DTC [11–13].

Identifying patients with excellent response to the initial therapy enables having less follow-ups and consequently decreasing the psychological and economic impact on the patients and their families [1, 14, 15]. Indeed, parameters in favor of excellent response or long-term remission are necessary to individualize the management of each patient. The first evaluation of initial treatment response allows to guide thyrotropin (TSH) goals and to better accommodate the subsequent long-term follow-up [1, 4, 14, 16, 17]. Even though several studies have tried to identify the Tg cut-off in different points during follow-up, there is no agreement on what would be the best value of Tg to predict initial response to therapy and/or disease progression over time [9]. Considering a possible role of pre-RAI Tg to predict initial excellent response, we expected to achieve a pre-RAI Tg cut-off value that allows to guide a possible de-escalation in the follow-up of DTC patients.

Therefore, the objective of this study was to determine the correlation between the pre-RAI Tg level and the first evaluation of response to initial therapy. Furthermore, we aimed to define a cut-off level for pre-RAI Tg as a predictor of excellent initial response therapy, as well as assessing long-term disease status in patients with DTC.

Patients and Methods

Study population

A retrospective cohort of 353 DTC patients who underwent total thyroidectomy (TT), with or without lymph node dissection, followed between 2011 and 2022, were first assessed. Data for this study were collected from the Endocrine Division of Irmandade da Santa Casa de Misericordia de Porto Alegre, a tertiary care, university teaching hospital in Southern Brazil. Patients were treated under the Brazilian public health system. All patients were older than 18 years, both sexes, and their AJCC/UICC TNM staging for metastasis were M0/Mx at diagnosis. We excluded 24 patients who had positive antithyroglobulin antibodies (TgAb), 9 patients that had M1, 43 patients with incomplete record files, 71 patients that were not submitted to radioiodine therapy and 40 patients who had no stimulated thyroglobulin assessed before radioiodine therapy (**Fig. S1**). The study was approved by the ethics committee of the institution.

Laboratory analysis

During the study period, serum Tg were measured by chemiluminescence (Immulite 2000, Siemens) and electrochemiluminescence (ElecsysTgII, COBAS Roche). Functional sensitivities varied from 0.2 ng/ml to 0.1 ng/ml. Anti-thyroglobulin antibodies (TgAb) were measured using the electrochemiluminescence immunoassay and by chemiluminescence. Serum TSH levels were measured with a chemiluminescence assay (normal range 0.55–4.78 μUI/ml).

Follow-up protocol, risk stratification, response to treatment and outcomes

Patients submitted to TT, with or without lymphadenectomy, and RAI therapy were included. For the evaluation of the initial risk of recurrence, all patients were classified into low, intermediate, and high risk [1]. They were also staged as AJCC/UICC TNM staging 8th edition [18]. The status of the disease was defined by clinical examination, serum Tg, TgAb, and imaging evaluation (Neck US/WBS/other) when indicated. All s-Tg measurements were obtained after thyroid hormone withdrawal (THW) for a period of at least 4 weeks, with TSH levels > 30 μIU/ml. TSH, Tg and TgAb serum measurements were performed no more than 7 days before RAI therapy.

The response to initial therapy was evaluated between 6 to 24 months after completing the initial therapy in agreement with 2015 ATA guidelines [1]; then, patients were classified into three groups. As (i) excellent response (ER): no abnormal findings on imaging, stimulated Tg < 1 ng/ml or basal Tg < 0.2 ng/ml, (ii) Indeterminate response (IndR) – nonspecific finding on imaging and stimulated Tg ≥ 1.0 to < 10 ng/ml, or basal Tg ≥ 0.2 to < 1.0 ng/ml, or stable/declining TgAb over time. (iii) Incomplete response (IncR): biochemical incomplete response – negative imaging and stimulated Tg ≥ 10 ng/ml, or basal Tg ≥ 1 ng/ml, or rising TbAb over time, and structural incomplete response – abnormal finding in imaging. These last two responses were analyzed as a single group together, despite knowing that biochemical incomplete patients perform better outcomes in the long term than structural incomplete response patients, because both groups have a similar pattern of follow-up.

Follow-ups with Tg, TgAb, TSH were assessed every 6 to 12 months, according to disease status. Neck US and/or WBS were also performed to search for metastases. Other imaging exams were performed to search for pulmonary and/or cervical metastases in high-risk patients or those with higher Tg or ascending Tg patterns. Structural incomplete disease was defined as positive image results, cytology or histology, and/or unequivocal ectopic uptake on post-therapy WBS or FDG-PET/CT. Patients with confirmed structural disease were submitted to additional therapy according to clinical indication. The duration of follow-up was defined as initiating at the date of surgery up to the last medical visit.

The primary outcome of this study was excellent response after initial therapy. Secondary outcomes were to assess the response to the therapy re-staging system at the final follow-up.

Statistical analysis

The characteristics of our population are described as mean ± standard deviation (SD) or median and percentiles 25 and 75 (P25–75) for continuous variables and absolute numbers and percentages for categorical variables. Categorical variables were compared between groups by chi-square (χ^2) using adjusted standardized residuals. Continuous variables were compared between groups by Kruskal–Wallis, Mann–Whitney, and ANOVA tests. Bonferroni adjustments were used for multiple comparisons. Receiver operating characteristic (ROC) curve (area under the curve and corresponding 95 % CI) was used to obtain a cut-off for s-Tg before RAI to predict excellent response to initial therapy. The Youden's index was

used to choose the cut-off. For the evaluation of excellent response, the variables with p-values < 0.20 and age group (clinical relevance) were selected, in order to calculate uni and multivariate risks. For uni- and multivariate analysis, the sample was divided in two groups: excellent response and incomplete response/indeterminate response. Data analysis was performed using Statistical Package for Social Sciences (SPSS) software, version 25.0 (IBM Corp., Armonk, NY). Statistic tests were two-sided, and levels of significance were 0.05.

Results

Baseline characteristics of DTC patients

We evaluated 166 patients with DTC who underwent TT and RAI. The mean age of the patients was 47.6 ± 13 years, 113 (68.1 %) patients were < 55 years of age, and 85.5 % were women. Histologic analysis demonstrated mostly papillary thyroid carcinoma (PTC) (88.6 %), and most of the patients were classified as AJCC/UICC TNM stage I disease (86.7 %), with median tumor size of 2.0cm (1.3–3.5cm). The ATA Risk Stratification was low in 52 patients (31.3 %), intermediate in 80 patients (48.2 %), and high in 34 patients (20.5 %). The median radioiodine dose was 100 mCi (30–100 mCi) and the cohort was followed for a median of 7.4 years (3.5–10 years).

Response to initial therapy

▶ **Table 1** shows the baseline and clinical-pathological characteristics according to the initial response to therapy assessment. From the 166 patients followed, on the first evaluation of response to therapy the mean time was 15.8 months (± 7.6 months) after initial therapy, 103 (62 %) had excellent response(ER) to therapy, 39 (23.4 %) had indeterminate response (IndR) and 24 (14.4 %) had incomplete response (IncR) – of these 11 (6.6 %) patients had biochemical incomplete response and 13 (7.8 %) patients had structural incomplete response. The prevalence of female sex was higher in the ER group when compared to IndR and IncR (91.3 %; 79.5 % and 70.8 %, respectively; p = 0.018). AJCC/UICC TNM stage was also different between groups: the percentage of patients with TNM stage I was 91.3 % in ER, 84.6 % in IndR and 70.8 % in the IncR group (p = 0.026). The ATA low-risk prevalence was higher in the ER group compared to IndR and IncR groups (39.8 %, 20.5 % and 12.5 %, respectively; p < 0.001). The median of pre-RAI Tg was 4.1 ng/ml (1.15–13.7 ng/ml). The median pre-RAI Tg was 3.46 ng/ml (1.04–12.3 ng/ml) using chemiluminescence assay (n = 112) and it was not different from the other samples (n = 54), median pre-RAI Tg of 5.90 ng/ml (1.29–18 ng/ml) (p = 0.288). Pre-RAI Tg levels were significantly correlated with stimulated Tg (s-Tg) and basal Tg (b-Tg) measures in the initial evaluation of therapy response, Spearman's rho: 0.65 (p < 0.001) and 0.56 (p < 0.001), respectively. Pre-RAI Tg was significantly different between all groups. The median value in patients with ER was 2.3 ng/ml (0.5–5.7 ng/ml); IndR was 11.0 ng/ml (2.3–18.0 ng/ml), and in IncR was 37.0 ng/ml (13.5–86.2 ng/ml) (p < 0.001). Histological type, tumor size, radioiodine initial dosing, age at diagnosis and follow-up time were also evaluated, but had no significant difference between groups.

Predictive value of stimulated thyroglobulin levels before RAI in initial response to therapy

We demonstrated that the levels of pre-RAI Tg are significantly different between patients according to initial response to therapy (▶ **Table 1**). When we compared the pre-RAI Tg between each group of response to therapy, we observed that the ER group had a significantly lower pre-RAI Tg in comparison to IndR (p < 0.001) and IncR (p < 0.001). In addition, there is a significant difference in pre-RAI Tg levels between the IndR and IncR patients (p = 0.02). ▶ **Fig. 1** shows the difference in Tg values of pre-RAI Tg among the groups according to first dynamic risk stratification.

Considering the correlation of pre-RAI Tg levels with the first evaluation of response to treatment, we decided to search what would be the best cut-off that predicts ER. To avoid the effect of different assays to calculate a specific serum Tg value cut-off, we evaluated 112 patients in which the pre-RAI Tg was measured by the same methodology (chemiluminescence). ROC curve analysis demonstrated that pre-RAI Tg was predictive of excellent response. We found the cut-off value of 7.55 ng/ml (area under the curve = 0.832, 95 % CI 0.76–0.91), with sensitivity of 80.0 % and specificity of 73.0 %, positive predictive value (PPV) of 85.7 % and negative predictive value (NPV) of 64.3 % (▶ **Fig. 2**). This cut-off value was valid for low-risk (PPV = 91.9 %), intermediate-risk (PPV = 75.5 %), and high-risk (PPV = 76.9 %) when applied to all patients (▶ **Table 3**).

Clinicopathological factors associated with initial excellent response status

Applying univariate and multivariate logistic regression analysis, we identified few factors as predictors of initial response to therapy. In the univariate analysis, female sex (RR 1.77; 95 % CI 1.04–3.0, p = 0.03), ATA Initial risk stratification low (RR 2.23, 95 % CI 1.39–3.6, p = 0.001) and intermediate (RR 1.77, 95 % CI 1.09–2.88, p = 0.021) and the Tg under the cut-off value of 7.55 ng/ml (RR 2.49, 95 % CI 1.75–3.55, p < 0.001) were all predictors of excellent response. In the multivariate analysis, only ATA low risk (RR 1.61, 95 % CI 1.06–2.43, p = 0.025) and Tg below the cut-off value of 7.55 ng/ml (RR 2.17, 95 % CI 1.52–3.10, p < 0.001) were associated with an excellent response to treatment (▶ **Table 2**).

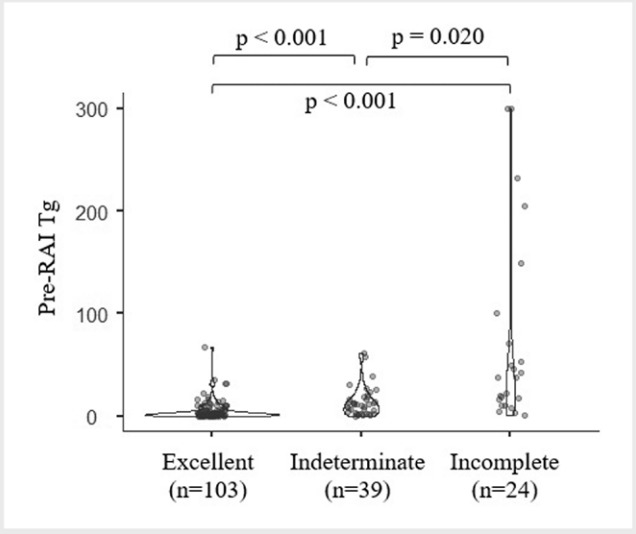
Disease status of DTC patients at last evaluation

After a median follow-up of 7.4 years (3.5–10 years), 124 (74.7 %) patients were allocated in the excellent response group, 22 (13.2 %) patients in the indeterminate response group, and 20 (12 %) patients in the incomplete disease group, where 7 (4.2 %) patients in biochemical incomplete response and 13 (7.8 %) patients in structural incomplete response (▶ **Fig. 3**). From the initial assessment on response to therapy, 99 (96.1 %) patients remained in the excellent response group in follow-up, and only 4 (3.9 %) patients were reclassified to the indeterminate group. Among patients with an initial indeterminate response, 13 (33.3 %) remained in the same classification at last visit, 23 (59 %) patients were reclassified to excellent response; and, of those, 15 patients had no additional therapies and 8 patients received additional lymphadenectomy and/or RAI therapy and 3 (7.7 %) patients changed status to incomplete response. Two of these patients presented biochemical incomplete response and 1 patient had structural incomplete disease (cervical

▶ **Table 1** Baseline clinical-pathological characteristics of the cohort subdivided according to initial response to therapy.

		Initial response therapy						
		Excellent		Indeterminate		Incomplete response		
		n	%	n	%	n	%	p
n		103	62	39	23.4	24	14.4	
Sex	Female	94	91.3	31	79.5	17	70.8	0.018
Histology	Pappilary	92	89.3	36	92.3	19	79.2	0.410
	Follicular	9	8.7	2	5.1	3	12.5	
	Oncocytic cell Carcinoma	2	1.9	1	2.6	2	8.3	
TNM stage	I	94	91.3	33	84.6	17	70.8	0.026
	II–IV	9	8.7	6	15.4	7	29.2	
ATA Initial risk assessment	Low	41	39.8	8	20.5	3	12.5	<0.001
	Intermediate	50	48.5	22	56.4	8	33.3	
	High	12	11.7	9	23.1	13	54.2	
Tumor size (cm)	Median|p25–75		2.0|1.2–3.2		2.0|1.3–3.4		3.0|1.8–5.1	0.063
RAI initial dosing (mCi)	30–50	33	32	11	28.2	2	8.3	0.065
	100–200	70	68	28	71.8	22	91.7	
Age	Median|p25–75		50.9|38–57.8		42.8|32.6–55.9		48.8|43.9–63.5	0.147
Age	<55	67	65	29	74.4	17	70.8	0.542
	>55	36	35	10	25.6	7	29.2	
Pre-RAI Tg (ng/ml)	Median|p25–75		2.3|0.5–5.7		11.0|2.3–18.0#		37|13.5–86.2#$	<0.001
Follow-up (years)	Median|p25–75		7.8|3.9–10		6.8|2.8–10.2		5.6|2.9–10.8	0.978

TNM: AJCC: American Joint Committee on Cancer staging 8th edition; ATA: 2015 American Thyroid Association guideline; RAI: Radioactive iodine therapy; pre-RAI Tg: Pre-radioiodine therapy thyroglobulin. # Significantly different from Excellent; $ Significantly different from Indeterminate (post-hoc Bonferroni adjustments, p<0.05).



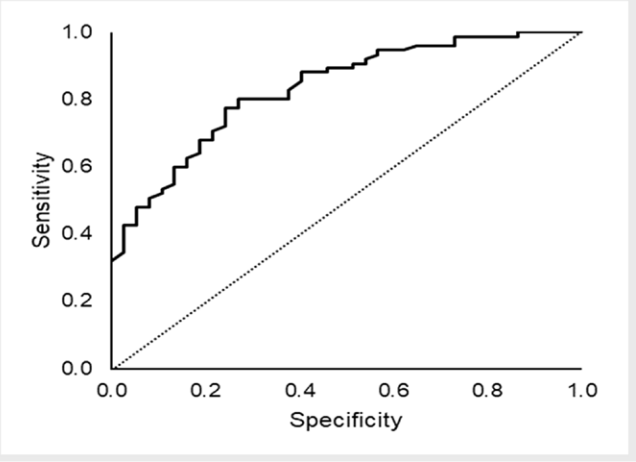
▶ **Fig. 1** Violin plot of stimulated thyroglobulin before radioiodine therapy according to response to therapy group.

lymph node disease). From the 24 patients with incomplete response at the initial evaluation, 17 (70.8 %) patients remained in the same classification, 2 (8.3 %) patients were reclassified to the excellent response, both of them were patients with biochemical incomplete response (only 1 patient received additional RAI therapy) and 5 (20.8 %) patients were reclassified to indeterminate group in the last evaluation, 3 of them received additional therapy, lymphadenectomy and/or RAI.

Discussion

In this study, we demonstrated that the Tg levels immediately before radioiodine therapy (pre-RAI Tg) had a correlation with the first assessment of response to initial therapy in DTC patients. As expected, patients with ER have lower pre-RAI Tg than patients with IndR and IncR. Interestingly, pre-RAI Tg levels also were significantly different between IndR and IncR groups. In clinical practice, the main challenge is to manage patients with indeterminate response, given that most patients remain with no evidence of disease, while

up to 20 % of them develop biochemical or structural disease [1, 19]. In our sample of patients with IndR, 92.3 % of those cases were free of disease at last evaluation. These findings reinforce that pre-RAI Tg is an important tool when making decisions regarding the follow-up of patients with DTC.



▶ **Fig. 2** Receiver operating characteristic (ROC) curves for differentiating ER (excellent response) from IndR (indeterminate response) + InCR (incomplete response).

An excellent response (ER) to therapy with its very low risk of recurrence should lead to re-evaluation of intensity of diagnostic surveillance procedures and treatment [1]. We demonstrated that a pre-RAI Tg cut-off ≤ 7.55 ng/ml has a very significant accuracy to predict ER to therapy in the initial assessment. This cut-off value was reliable for patients with low-risk and intermediate to high-risk of recurrence. In this way, other studies have shown that values below 10ng/mL have a better NPV for no evidence of biochemical or structural disease on long-term follow-up [8, 20]. Recently, Tian et. al. corroborated these results that a pre-RAI Tg ≤ 10.1 ng/ml is a factor to predict a disease-free status, validated to all ATA initial risk categories [13]. The determination of such a specific cut-off value of pre-RAI Tg – rather than the consideration of a "value < 10 ng/ml" – can be very useful in the initial management of DTC patients. Similar studies that evaluated the role of pre-RAI Tg in predicting ER response after initial therapy have determinate values of cut-off between 3.3 to 8.55 ng/ml [12, 21–24]. These differences between the studies may be affected by differences in patient populations, by the timing of the serum Tg determination and/or by preparation mode for remnant ablation (thyroid hormone withdrawal or recombinant human TSH) and variability in serum Tg depending on the method used. Moreover, our study not only defines an accurate cut-off value of pre-RAI Tg for predicting an excellent response applicable across all initial ATA risk categories but also contributes to identifying patients who may not warrant further evaluation. Furthermore, our study provides a more defined initial

▶ **Table 2** Univariate and multivariate logistic regression analysis for initial excellent Response.

Uni and multivariate analysis													
		ER		IndR/IncR		Uni				Multi			
		n	%	n	%	p	RR	95 % CI		p	RR	95 % CI	
Sex	Female	94	66.2	48	33.8	0.035	1.77	1.04	3.00	0.128	1.37	0.91	2.07
	Male	9	37.5	15	62.5		1				1		
TNM Stage	I	94	65.3	50	34.7	0.076	1.60	0.95	2.67	0.480	1.18	0.74	1.90
	II–IV	9	40.9	13	59.1		1				1		
ATA Initial risk assessment	Low	41	78.8	11	21.2	0.001	2.23	1.39	3.60	0.025	1.61	1.06	2.43
	Intermediate	50	62.5	30	37.5	0.021	1.77	1.09	2.88	0.134	1.38	0.91	2.09
	High	12	35.3	22	64.7		1				1		
Pre-RAI Tg	≤ 7.55	81	81.8	18	18.2	0.000	2.49	1.75	3.55	0.000	2.17	1.52	3.10
	> 7.55	22	32.8	45	67.2		1				1		
RAI initial dosing (mCi)	30–50	33	71.7	13	28.3	0.086	1.23	0.97	1.56	0.468	1.08	0.87	1.35
	100–200	70	58.3	50	41.7		1				1		
Age	> 55	36	67.9	17	32.1	0.267	1.15	0.90	1.46	0.290	0.90	0.75	1.09
	< 55	67	59.3	46	40.7		1				1		
Tumor size (cm)	Median (p25–75)		2.0 (1.2–3.2)		2.3 (1.5–4.0)	0.306	0.96	0.90	1.03				

TNM: AJCC: American Joint Committee on Cancer staging 8th edition; ATA: 2015 American Thyroid Association guideline; pre-RAI Tg: Pre-radioiodine therapy thyroglobulin; RAI: Radioactive iodine therapy.

outcome compared to others where the purpose of pre-RAI Tg (diagnostic or prognostic) was not well-defined.

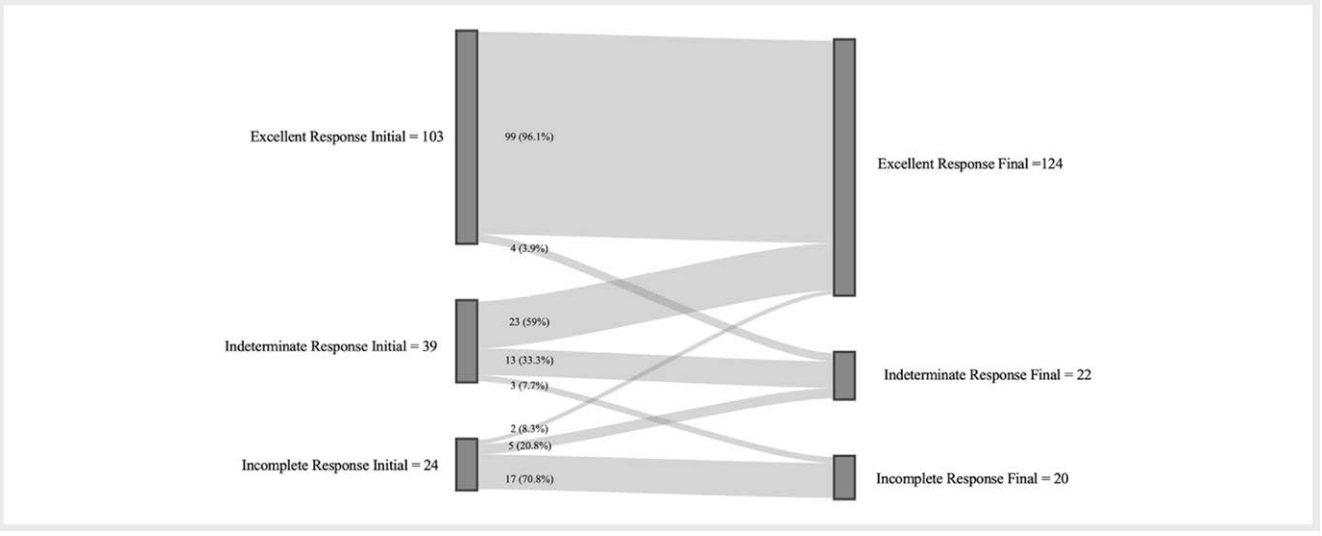
Although a high NPV of pre-RAI Tg for long-term remission in low-to-intermediate-risk DTC patients has been reported previously, we observed a high NPV in high risk (90.5 %) patients compared to low (53.3 %) and intermediate (58.1 %) risk patients, an effect of the higher sensitivity and lower prevalence of ER to therapy among high-risk patients. Of note, 20.1 % of patients were classified as high risk for recurrence indicating a cohort that included many patients with advanced disease. Together these results follow in the same direction, supporting that lower pre-RAI Tg level is a reliable tool on evaluating patients who will have a good response to initial therapy, helping in decision making about patient early and long-term follow-up.

Our study focused on other prognostic factors associated with an initial ER identifying patients which require less intensive follow-up. In fact, levels of pre-RAI Tg ≤ 7.55 ng/ml had the best sensitivity and specificity to predict ER to initial therapy, having even a stronger correlation to ER than female sex and ATA initial risk evaluation, establishing good prognostic factors in DTC. Indeed, initial risk evaluation has an important role on the treatment plan and also in planning for long-term follow-up, pre-RAI Tg levels can guide the next step of evaluation of initial therapy [20, 21, 23, 24]. In fact, serum Tg measured 6 to 12 months after the first RAI can be correlated with pre-RAI Tg in low-risk patients and can predict persistent or recurrent disease in the earliest postoperative time [11, 25]. We observed a significant correlation between pre-RAI Tg with b-Tg and s-Tg measures in the initial assessment of therapy response. In patients with intermediate risk undergoing TT and RAI therapy, ATA recommendations are unclear regarding assessment of initial response therapy by b-Tg or s-Tg [1]. In our sample, in which practically half of patients are classified as intermediate risk, a pre-RAI Tg ≤ 7.55 ng/ml was an independent factor associated with ER. In these patients, where initial evaluation of therapy has the greatest impact on treatment and follow-up, an ER decreases the estimated risk of recurrence from 20–30 % to < 5 %, leading to less intensive follow-up and no need for TSH suppression [1, 3]. In intermediate risk patients, we observed a pre-RAI Tg in patients with ER [pre-RAI Tg 1.95 ng/ml (0.6–9.5)] lower than patients with IndR [pre-RAI Tg 8.4 ng/ml (1.8–21.4)] and IncR (pre RAI Tg 27.8 ng/ml (5.1–129.5)] (data not shown). In fact, previous studies demonstrate that in the evaluation of response to initial therapy, with the non-stimulated Tg, 56 % of intermediate-risk patients had ER to therapy, of whom none had disease at the end of follow-up [26]. Like these results, 88.7 % of our intermediate risk patients were also free of disease at last evaluation. In the same way, in low or intermediate-risk patients a s-Tg may not be necessary when b-Tg defines the response as excellent [27]. Thus, these data together suggest that low or intermediate risk DTC patients with a pre-RAI Tg ≤ 7.55 ng/ml may be initially evaluated only based on b-Tg together with neck US.

At first evaluation, an ER was observed in 78.8 % of patients who are low, 62.5 % intermediate and 35.2 % high initial risk patients. The risk of recurrence in long term follow-up of patients with initial ER is low (1–2 %) [1]. In addition, most of the DTC patients who were considered to be disease free after the initial treatment generally remained with this status at long-term follow-up [28]. At the

▶ **Table 3** Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of pre-RAI Tg cut off = 7.55 ng/ml for low, intermediate, and high-risk patients.

Cut-off 7.55 ng/ml	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All (n = 166)	78.6	71.4	81.8	67.2
Low Risk	82.9	72.7	91.9	53.3
Intermediate Risk	74.0	60.0	75.5	58.1
High Risk	83.3	86.3	76.9	90.5



▶ **Fig. 3** Sankey curves of response to therapy in the first evaluation and in long-term follow-up.

last evaluation we observed that, in our sample of DTC patients with ER, the majority of patients (96.1 %) remained in the same category. Structural persistent/recurrent disease was detected in 7.8 % of DTC patients initially and 84.6 % remained in the same category at the final follow-up. This prevalence was less frequent than other studies that showed 13 to 26 % of structural persistent/recurrent disease in 10 years follow-up [3, 13, 17]. Of note, the majority of the patients in the present study were stage I and 120 (83.3 %) of them were at a low or intermediate initial risk of recurrence, which are known to have an excellent prognosis [29]. In this way, our data reinforce the role of pre-RAI Tg levels as a predictor of ER in long-term prognosis.

There are some limitations to this study. It is a retrospective design study at a single tertiary referral center. According to previous recommendations many patients at low initial risk received radioiodine ablative or adjuvant, which nowadays, would not have been submitted to this therapy. On the other hand, the data reflect real-life clinical practice, in which different Tg measurement methodologies, with distinct functional sensitivities over time may have enhanced the external validity of our findings. The fact that all assays used in this cohort had functional sensitivities < 0.5 ng/ml or less allowed us to retrospectively analyze the results using the evidence-based cut-off value recommended by the ATA [1]. In addition, this study included patients followed for a long time at the same institution, being evaluated by the same professionals, and being submitted to the same follow-up and investigation protocol.

In conclusion, our results suggest that stimulated thyroglobulin levels immediately before radioiodine therapy predict first response therapy evaluation. The pre-RAI Tg was a key predictor of initial excellent response to therapy and can be a tool to promote a patient-centered care chronogram allowing the improvement of the patient's quality of life and reducing the costs of follow-up, especially in the public health system.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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