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ORIGINAL ARTICLE

Biochemical persistence in thyroid cancer: is there anything to worry about?

Pitoia Fabián · Abelleira Erika · Tala Hernán · Bueno Fernanda · Urciuoli Carolina · Cross Graciela

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Abstract To evaluate the outcome of differentiated thyroid cancer (DTC) patients with biochemical persistence of disease (BP) after initial treatment (total thyroidectomy with or without lymph node dissection (LND) and thyroid remnant ablation). BP was defined as suppressed thyroglobulin (Tg) levels <1 ng/ml and rhTSH-stimulated thyroglobulin (St-Tg) >1ng/ml, with no evidence of structural disease. Structural persistence/recurrence (SPR): clinically identifiable disease. We reviewed 278 records of DTC patients. Tg-Ab positive patients ($n = 73$) were excluded and 32 were included in the analysis (median age 45 years, range 18–77 years); risk of recurrence ATA was: low in 38 %, Intermediate in 47 %, and high in 15 % of patients. All subjects had Tg levels <1 ng/ml under thyroid hormone therapy. Patients were divided into three groups: Group 1: St-Tg 1–2 ng/ml, $n = 6$; Group 2: St-Tg 2–10 ng/ml, $n = 17$; Group 3: St-Tg > 10 ng/ml, $n = 9$. In 5/32 (16 %) patients, SPR was observed after a median follow-up of 6 years (range 2–23 years). In Group 1: all patients were considered with no evidence of disease after a median follow-up of 2 years (range 1–2.5 years). In Group 2: 13/17 (76.5 %) patients continued with only a BP after a median follow-up of 4 years (range 2–10 years) and 4/17 (23.5 %) patients with intermediate risk of recurrence had a structural persistence (lymph nodes metastasis) diagnosed between 1 and 3.5 years after initial assessment. Following LND, all of them remained with BP after a median of 2 years (range 1.5–5 years). In Group 3: 8/9 (89 %) patients had BP after a median follow-up of 7 years (range 2–23 years) and 1/9 (11 %) had a SPR diagnosed 28 months after initial assessment, LND was indicated but he continued with BP, 5 years after the second surgery. Most patients with DTC and BP present an indolent course of the disease. In these patients the diagnosis of the structural recurrence did not change the outcome because all of them continued with BP.

Keywords Thyroid · Cancer · Risk of recurrence · Biochemical · Thyroglobulin

P. Fabián (✉) · A. Erika · B. Fernanda · U. Carolina · C. Graciela
División of Endocrinología, Hospital de Clínicas, University of Buenos Aires, Córdoba 2351, 5th floor, Buenos Aires, Argentina
e-mail: fpitoia@intramed.net

T. Hernán
Clínica Alemana de Santiago, Universidad del Desarrollo, Santiago, Chile

Introduction

The follow-up of patients with papillary and follicular thyroid carcinoma after total thyroidectomy and radioiodine remnant ablation (RRA) is mainly based on serum thyroglobulin (Tg) level assessment and neck ultrasonography (US) [1, 2]. By using the American Thyroid Association (ATA) and Latin American Thyroid Association (LATS) risk of recurrence prognostic systems to risk stratify patients treated with total thyroidectomy and RRA at a single thyroid cancer specialty center, we have recently confirmed the utility of the ATA system and for the first time, demonstrated the clinical utility of the LATS system [3]. Thus, the ATA risk stratification system has now been validated in cohorts of differentiated thyroid cancer patients in Argentina [3], Brazil [4], Italy [5], and New York [6] confirming its clinical applicability across a wide spectrum of patients and health care systems.

Approximately 20 % of patients who are clinically with no evidence of disease and undetectable Tg under thyroid

hormone therapy—whatever the risk of recurrence—will present Tg levels above 2 ng/ml after recombinant human thyrotropin (rhTSH) or thyroid hormone withdrawal (THW) [7–13]. Structural persistence/recurrence (SPR) may be identified on imaging studies in about 1/3 of these patients [7–13]. But the clinical significance of minimally detectable serum Tg levels is still unclear, especially when this situation occurs after TSH stimulation [3–6].

Therefore, the aim of the present study was to evaluate the outcome of patients with differentiated thyroid cancer in medium/long-term follow-up who, after initial treatment (total thyroidectomy with or without neck dissection and RRA) have been diagnosed with biochemical persistence. Biochemical persistence (BP) was defined as suppressed Tg levels <1 ng/ml and rhTSH-stimulated Tg (St-Tg) >1 ng/ml without the evidence of structural disease found on ultrasound (US) and fine needle aspiration biopsy (FNAB) and/or other imaging modalities.

Materials and methods

Patients

We retrospectively reviewed our database containing 535 file records of patients with DTC who had been followed up from January 2001 to December 2012. We included patients treated with total thyroidectomy (either with or without lymph node dissection, $n = 278$) and RRA in whom response to initial therapy was assessed after 8–15 months with a diagnostic whole body scan according to the risk of recurrence, and neck ultrasound together with rhTSH-St-Tg measurement. Patients should have had at least 24 months of follow-up after this initial response to therapy assessment and St-Tg should have been performed always after rhTSH administration [1]. From 535 DTC patients evaluated at our center, 257 were excluded because of the following criteria: 156 had a follow-up less than 1 year, 73 had detectable anti-thyroglobulin antibody (Tg-Ab), 16 were older than 80 years at diagnosis and follow-up less than 16 months, and 12 were treated with hemithyroidectomy without RRA. With these criteria, 278 DTC patients were included in the study. Patients were classified according to the ATA risk of recurrence classification [1].

RRA protocol

Our ablation protocol used fixed radioiodine activities based on the extent of initial disease. Patients typically received 3.70 GBq (100 mCi) ^{131}I for Low risk (ATA) disease, 5.55 GBq (150 mCi) for Intermediate risk (ATA) disease, and 7.40 GBq (200 mCi) for T4 and M1 patients. A low iodine diet was prescribed from 1 week before radioiodine administration through 2 days afterward. One hundred and seventy one patients were prepared after THW and the remaining 107 patients were ablated after the use of rhTSH. Patients prepared on THW received radioiodine after at least 3 weeks without thyroid hormone from the time of thyroidectomy reaching all of them TSH levels above 50 mIU/l.

Patients prepared with rhTSH (Thyrogen ®—Genzyme, A Sanofi Company) received radioiodine on day 3 after two consecutive intramuscularly 0.9 mg doses of rhTSH. Post-therapy whole body scan (WBS) was performed 5–7 days after therapeutic RAI administration.

Clinical management during follow-up

After this initial approach, patients were followed-up according to the ATA guidelines. Clinical status in response to initial therapy was assessed using rhTSH-stimulated Tg and neck US in all patients including diagnostic WBS in intermediate and high-risk patients (150 MBq [4 mCi] activity). St-Tg and WBS were performed 8–15 (mean 12 ± 3) months after ablation. Neck US using an 11 MHz linear array transducer was performed every 6 months after ablation. Patients with stimulated or unstimulated Tg > 1 ng/ml, suspicious neck US findings, or both during follow-up underwent morphological or functional imaging or both, including computed tomography (CT) ($n = 56$ [20 %]) or 18-fluorodeoxyglucose positron emission tomography (FDG-PET) ($n = 27$ [10 %]). All ultrasonographically suspicious nodules ≥1 cm in diameter underwent fine needle aspiration with measurement of Tg in the aspirate.

After ablation, all patients were kept on a suppressed TSH level until February 2006 when thyroid hormone therapy was adjusted in all patients according to the ATA recommendations for each risk of recurrence group [3].

Subsequent follow-up was assessed by using unstimulated Tg levels and neck US every 6 months in all patients. Those patients with BP [St-Tg > 1 ng/ml at the first assessment (8–15 months)] were followed-up as follows: for the low risk patients a new St-Tg were performed every 11–28 months; for the intermediate and high risk patients a St-Tg was associated to a diagnostic WBS every 14–26 months.

Biochemical persistence

BP was defined as suppressed Tg levels <1 ng/ml and St-Tg > 1 ng/ml at the first assessment (8–15 months) after initial treatment, with no evidence of structural disease.

According to the St-Tg level, we arbitrarily divided these patients into three groups: Group 1: St-Tg levels between 1 and 2 ng/ml (all low risk ATA patients), $n = 6$; Group 2: St-Tg levels between 2 and 10 ng/ml, $n = 17$

(6 low risk, 10 intermediate risk, 1 high risk); Group 3: St-Tg levels > 10 ng/ml, $n = 9$ (5 intermediate risk, 4 high risk).

The endpoint of the study was the assessment of the clinical status at time of last follow-up after initial assessment [median 6 years (range 2–23 years)]. Patients with persistent disease at the time of last follow-up were classified as either, biochemical (suppressed and/or stimulated Tg > 1 ng/ml in the absence of structural disease) or structural persistent/recurrent disease (lymph node metastasis confirmed by fine-needle aspiration biopsy with positive cytology, and/or distant metastasis confirmed by biopsy and/or imaging).

Those patients with low or intermediate risk received only the first RAI dose (remnant ablation), and the 5 patients with high risk received a second RAI dose (3 due to a T4 tumor and 2 due to a diffuse lung metastasis, median cumulative RAI therapy of 300 mCi, 6–12 months after remnant ablation).

Thyroglobulin and TgAb measurement

Samples for Tg and TgAb measurement were performed on the day of radioiodine administration. Tg and TgAb levels were assessed in one of two reference laboratories from Argentina using one of two commercial immunometric assays; the same laboratory and assay were used throughout a patient's follow-up. Tg assays comprised the Elecsys Tg Electrochemiluminescence Immunoassay (Roche Diagnostics GmbH, Mannheim, Germany), which has a functional sensitivity of 0.5 μg/l, or the Immulite 2000 Tg Chemiluminiscence Assay (Siemens Corp., Los Angeles, CA, USA), with a functional sensitivity of 0.9 μg/l. TgAb assays comprised the Elecsys Anti-Tg Electrochemiluminescence Immunoassay (RSR Ltd., Pentwyn, Cardiff, UK), or the Immulite 2000 Anti-TG Ab chemiluminescent immunometric assay method (Siemens). For both TgAb assays, values >20 IU/ml were considered to be positive, and to render Tg measurements non interpretable.

Statistical analysis

Data are expressed as mean ± SD and median (range). Categorical comparisons were made using Chi-square testing with the Fischer's exact test when appropriate. Analysis was performed using SPSS software (version 15.0.0: SPSS, Inc., Chicago, IL, USA). p values ≤ 0.05 were considered to be statistically significant.

Results

From the 278 included subjects, 32 (11.5 %) had a biochemical persistence as best response to initial treatment. The median follow-up since the time of the first St-Tg was 6 years (range 2–23 years). As can be observed in Table 1, the majority of patients were classic PTC (91 %), 81 % were female and 85 % had a low or intermediate ATA risk of recurrence.

Lymph node dissections had been performed in 56 % of the patients ($n = 18$) as part of the initial treatment. From these 18 patients, 14 (78 %) had ultimately confirmed nodal involvement. It was N1a alone for 8 patients and N1a+N1b for the remaining 6 subjects.

The diagnosis of SPR during the subsequent follow-up was observed in 5/32 (16 %) patients.

In Group 1, six patients had initial St-Tg levels between 1.5 and 1.9 ng/ml; at the end of the follow-up (median

Table 1 Characteristics of the 32 patients with BP after initial treatment

$n = 32$ patients	
Sex	
F/M	26 (81 %)/6 (19 %)
Median age (range)	45 years, range 18–77 years
Papillary thyroid cancer	32 (100 %)
Variant	
Classic	29 (91 %)
Follicular	2 (6 %)
Tall cell	1(3 %)
Bilateral tumor	39 (23 %)
Multifocal tumor	48 (28 %)
Neck dissection performed	18 (56 %)
Absence of LN metastasis	4 (22 %)
Presence of LN Metastasis	14 (78 %)
Central	5 (36 %)
Central and lateral	13 (74 %)
No neck dissection	14 (44 %)
M1 patients (lungs diffuse uptake)	2 (6 %)
ATA risk of recurrence	
Low	12 (38 %)
Intermediate	15 (47 %)
High	5 (15 %)
Median radioiodine activity for RA (mCi)	150 (range 100–150 mCi)
Median cumulative activity (mCi)	150 (range 100–400 mCi)
Clinical status at final follow-up	
NED	6 (19 %)
Biochemical persistent disease	21 (65 %)
Persistent/recurrent disease	5 (16 %)
Follow-up in months (median (range)	6 years (range 2–23 years)

M male, *F* female, *AJCC* American Joint Committee On Cancer 7th Edition, *ATA* American Thyroid Association, *LN* lymph node, *M1* systemic metastatic disease, *RA* remnant ablation, *mCi* miliCuries

2 years (range 1.8–2.5 years), St-Tg levels became undetectable in all of them and they were considered with no evidence of disease.

In Group 2 (Fig. 1), 13/17 patients (76.5 %) continued with only a BP after a median follow-up of 4 years (range 2–10 years). Four patients with intermediate risk of recurrence from these 17 subjects of Group 2 (23.5 %) had a structural persistence (lymph nodes metastasis) diagnosed between 1 and 3.5 years after initial assessment. Neck lymph node metastases in these four subjects were clinically detected by US/FNAB and were subsequently confirmed by lymph node dissection (1–4 affected lymph nodes from 15 to 43 lymph nodes obtained in the LN dissection).

All the four patients remained with biochemically persistent disease once the surgical procedures were done, after a median post re-surgical interventions follow-up of 2 years (range 1.5–5 years).

Considering the outcome of St-Tg levels in the Group 2: seven patients (41 %) had a mild decrease in the stimulated-Tg levels (from a mean of 7 ± 2 ng/ml to a mean of 3 ± 1.7 ng/ml, $p = 0.04$), 8 (47 %) had a stable stimulated Tg levels, and the remaining two patients (12 %) had a slight increase (from a mean of 4 ± 2 ng/ml to a mean of 5 ± 1.7 ng/ml, $p = 0.4$) (Table 2).

In Group 3 (Fig. 2), 8/9 (89 %) patients remained with only a BP after a median follow-up of 7 years (2–23 years). One patient with lung metastasis, who received a cumulative radioiodine dose of 400 mCi was considered with no evidence of disease 23 years ago, a new St-Tg performed 10 years later showed a BP with a negative diagnostic WBD.

Only one patient of Group 3 with intermediate risk of recurrence (11 %) had a SRP diagnosed 28 months after initial treatment. A modified lymph node dissection was performed, but this patient continued with BP (St-Tg level of 7 and 8 ng/ml performed in two different occasions: 3 and 5 years after this second surgery, respectively).

Considering the outcome of St-Tg levels in Group 3: Five patients (56 %) had a mild decrease in the stimulated Tg levels (from a mean of 18 ± 4 ng/ml to a mean of 12 ± 3 ng/ml, $p = 0.02$), 3 (33 %) had a stable stimulated Tg levels and the remaining patient (23 %) had an increase of Tg from 15 ± 4 to 24 ± 5 ng/ml after 1 year

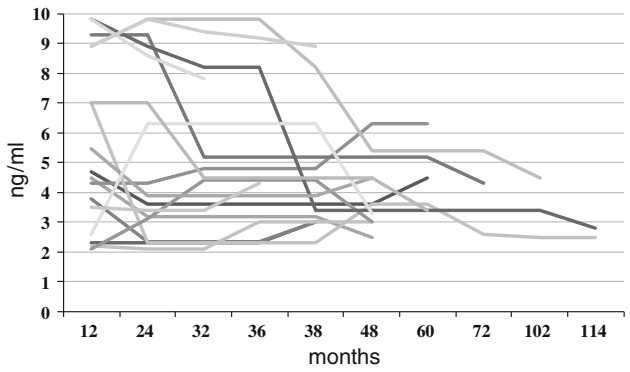

Fig. 1 Outcome of rhTSH-stimulated serum thyroglobulin levels in patients of Group 2 (Tg levels between 2 and 10 ng/ml)

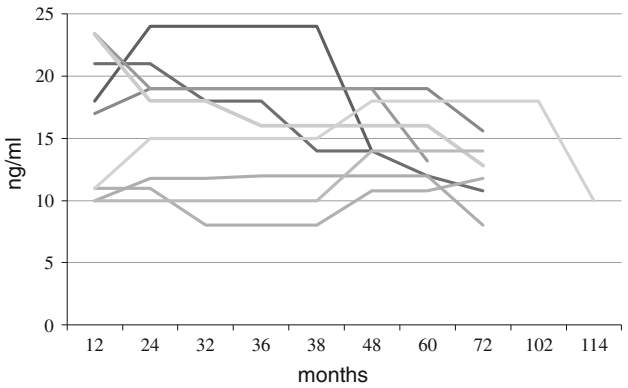

Fig. 2 Outcome of stimulated serum thyroglobulin levels in patients of Group 3 (Tg > 10 ng/ml)

Table 2 Clinical status observed in 32 patients with BP at follow-up

	Clinical status at follow-up (*n*, %)				
	St-Tg < 1	St-Tg decrease but still detectable	Stable St-Tg	St-Tg increase	Structural recurrence
Group 1 ($n = 6$) (St-Tg 1–2 ng/ml)	6 (100 %)	0	0	0	0
Group 2 ($n = 17$) (St-Tg 2–10 ng/ml)	0	7 (41 %)	8 (47 %)	2 (12 %)	4 (23 %)
Group 3 ($n = 10$) (St-Tg > 10 ng/ml)	0	5 (56 %)	3 (33 %)	1 (11 %)	1 (11 %)

These outcomes across the rows are not mutually exclusive

of follow-up. This was the patient who was diagnosed with the SPR.

Discussion

Thyroglobulin is a specific tumor marker when total thyroidectomy is performed and remnant ablation is indicated. Most differentiated thyroid cancer cells synthesize Tg, although there may be differences in the molecular conformation of this tumor-derived Tg [14]. The presence of detectable Tg after total thyroidectomy and remnant ablation may indicate one of the following three situations: the presence of normal thyroid remnant not completely ablated after the first radioiodine dose, persistence, or recurrence of the disease [1, 2]. The likelihood of finding structural disease is usually associated to the serum Tg level: the higher the Tg level, the larger the risk [14]. Patients with rhTSH-Tg levels <2 ng/ml are rarely associated to structural or progressive disease, while patients with rhTSH-Tg >2.0 ng/ml are more likely to have structural persistent disease [7–14].

When Tg is detectable—either on suppression or after TSH stimulus—and no structural findings are detected on neck US and/or other imaging methods, patients may be classified as having BP. It has been shown that 11–19 % of ATA low risk patients, 21–22 % of ATA intermediate risk patients, and 16–18 % of ATA high-risk patients had biochemical persistent disease during follow-up [3–6]. Usually, the ATA high risk patients are less likely to have BP than the ATA low and intermediate risk groups because the ATA high risk group has a lot more structural persistent disease and is less likely to have an excellent response [3–6]. Also, very few high risk patients achieve a suppressed Tg <1 ng/ml, and therefore would have been excluded from this study.

In this retrospective study, we refer specifically to those patients who had this situation at their first control during follow-up, in which response to therapy was assessed. We used strict criteria to define biochemical persistence: rhTSH-stimulated Tg > 1 ng/ml, absence of TgAb, and absence of any evidence of structural disease on neck US and/or any other imaging study. St-Tg was always performed after rhTSH stimulation, which homogenized the evaluation of the results. Our definition of BP includes what in other studies has been defined as acceptable response to therapy (St-Tg between 1.0 and 10 ng/ml and non specific or small finding on imaging) and biochemical incomplete response to therapy (St-Tg > 10 ng/ml with no structural disease) [3–6]. The aim of our study was to evaluate the clinical outcome and rhTSH-Tg trend of these patients followed with repeated St-Tg, neck US and other imaging methods.

By using these criteria, all patients who had the first St-Tg between 1–2 ng/ml had an undetectable St-Tg during their follow-up ($n = 6$) and all patients with St-Tg > 2 ng/ml persisted with detectable rhTSH-Tg during their follow-up. However 12 (37 %) had a decrease in mean St-Tg levels (Table 2).

Several previous studies have also demonstrated that many patients with a BP have a gradual decline in serum Tg levels over time without additional therapy [4, 15–24]. As it was previously postulated, it is probable that the outcome of these patients from this "incomplete or acceptable" response to therapy to a status of no evidence of disease could be related to the simply passage of time [4]. In this cited study, a 100 % 5-year survival and 34 % of spontaneous resolution of the non-stimulated-Tg values over time was observed [4].

Therefore, if serum Tg levels can continue to decline for many years after RRA, then an early assessment of response to therapy or new St-Tg assessments during follow-up could lead to excessive evaluations and treatments in patients with low-level Tg values that are likely to resolve or continue without changes over time without additional therapies [24]. That is why many authors are now recommending postponing the moment to define the response of initial treatment by the end of the second year [24, 25].

It was also recently reported that the doubling time of Tg measured under thyroid hormone therapy could be a potent dynamic factor to predict survival, distant metastasis, and loco-regional recurrence in patients with papillary thyroid cancer [26]. Even though this investigation was performed with Tg levels measured under thyrotropin suppression, the data can probably be applied to the trend in rhTSH-Tg levels over time [26]. The most important information extrapolated to our study is that patients with BP with a still detectable but declining Tg over time have a very good prognosis in terms on survival and recurrence. On the other hand, patients with stable or slowly increasing Tg levels, possibly have a less favorable but still a good prognosis in terms on survival and recurrence.

We conclude that clinical outcomes in patients with BP after initial treatment are very good; only 16 % of patients with BP developed structurally identifiable disease over the first 4 years of follow-up. Regarding St-Tg over time, 19 % of patients had undetectable stimulated-Tg and 65 % continued to have persistently abnormal stimulated-Tg values without structural correlate. The detection of overt clinical disease and subsequent surgical therapeutic intervention in our patients did not change the outcome, because all of them continued with biochemical persistence.

Conflict of interest None.

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