Low postoperative nonstimulated thyroglobulin as a criterion to spare radioiodine ablation

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Abstract

This study evaluated the recurrence rate in patients with papillary thyroid carcinoma (PTC) who had low nonstimulated thyroglobulin (Tg), measured with a second-generation assay, after total thyroidectomy and who were not submitted to ablation with ¹³¹I. The objective was to define whether low postoperative nonstimulated Tg can be used as a criterion to spare patients with PTC from therapy with ¹³¹I. This was a prospective study including 222 patients with PTC (except for microcarcinoma restricted to the thyroid and tumor with extensive extrathyroid invasion (pT4), aggressive histology, extensive lymph node (LN) involvement, or known residual disease). After thyroidectomy, all patients had non-stimulated Tg <0.3 ng/ml, negative antithyroglobulin antibodies (TgAb) and neck ultrasonography (US) showing no anomalies. Because of this finding, the patients were not submitted to ablation with ¹³¹I. The time of follow-up ranged from 15 to 102 months (median 62 months). Of the 222 patients, 217 (97.7%) continued to have nonstimulated Tg <0.3 ng/ml and negative US. Tg was undetectable in the last assessment in 185 of these patients and detectable in 32. Five patients (2.2%) exhibited an increase in Tg, and LN metastases were detected in 4 (structural recurrence). One patient progressed to an increase in Tg, but disease was not detected by the imaging methods (biochemical recurrence). The results obtained here suggest that patients with PTC who have low nonstimulated Tg (measured with a second-generation assay and in the absence of TgAb) and negative neck US after thyroidectomy do not require ablation with ¹³¹I.

Key Words

- ▶ papillary thyroid carcinoma
- ▶ postoperative nonstimulated thyroglobulin
- ▶ radioiodine
- ▶ recurrence

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Introduction

In patients with papillary thyroid carcinoma (PTC) submitted to total thyroidectomy with complete tumor resection, ablation of thyroid remnant with ¹³¹I is not required in patients with microcarcinoma restricted to the thyroid with nonaggressive histology (Cooper *et al.* 2009, Rosario *et al.* 2013, Lepoutre-Lussey *et al.* 2014, Perros *et al.* 2014). In contrast, adjuvant therapy with ¹³¹I has been recommended when the histological data (tumor size,

extrathyroid invasion, histologic subtype, vascular invasion, lymph node (LN) involvement) suggest a higher risk of recurrence (Cooper *et al.* 2009, Rosario *et al.* 2013, Lepoutre-Lussey *et al.* 2014, Perros *et al.* 2014). The need for radioiodine is controversial in the remaining patients. In these individuals, when postoperative-stimulated thyroglobulin (Tg) is low (in the absence of anti-Tg antibodies (TgAb)), post-therapy whole-body scanning (RxWBS)

rarely detects persistent disease (Nascimento *et al.* 2011, Rosario *et al.* 2011, Furtado *et al.* 2015) and the risk of recurrence is very low (about 1% in 5 years), even without the administration of radioiodine (Vaisman *et al.* 2010, Rosario *et al.* 2012, Orlov *et al.* 2015). In fact, many authors recommend low postoperative-stimulated Tg as a criterion to spare these patients from therapy with ^{131}I (Vaisman *et al.* 2010, Nascimento *et al.* 2011, Rosario *et al.* 2011, 2012, 2013, Schlumberger *et al.* 2011, Orlov *et al.* 2015).

Only two studies correlated postoperative non-stimulated Tg, measured with a second-generation assay, with the RxWBS results and both demonstrated the absence of metastases on this imaging method in patients with low Tg (Giovannella *et al.* 2008, Rosario *et al.* 2015a). Little information is available about the rate of recurrence in patients with low nonstimulated Tg after thyroidectomy who were not submitted to radioiodine therapy because of this finding. In previous studies involving patients not submitted to ablation of thyroid remnant who had low postoperative nonstimulated Tg, most patients had microcarcinoma restricted to the thyroid and nonaggressive histology (Durante *et al.* 2012, Ibrahimpasic *et al.* 2012, Nascimento *et al.* 2013, Angell *et al.* 2014); thus, there was already no indication for radioiodine. Taking together all of these series, the number of patients with non-T1aN0-NxM0 stage tumors was only about 100 (Durante *et al.* 2012, Ibrahimpasic *et al.* 2012, Nascimento *et al.* 2013, Angell *et al.* 2014). Furthermore, all of these series were retrospective studies. In two of them, neck ultrasonography (US) for the exclusion of small LN metastases was not performed in all patients (Nascimento *et al.* 2013, Angell *et al.* 2014).

This prospective study evaluated the recurrence rate in patients with PTC who had low nonstimulated Tg, measured with a second-generation assay, and negative neck US after total thyroidectomy and who were not submitted to ablation with ^{131}I because of this finding.

Materials and methods

The study was approved by the Research Ethics Committee of our institution.

Design

This was a prospective study. The selection criteria and follow-up protocol of the patients were predefined and rigorously followed.

Patients

Patients consecutively seen at our institution from 2006 to 2014, who met the following criteria, were first selected: diagnosis of PTC, submitted to total thyroidectomy with apparently complete tumor resection, and no signs of persistent disease after surgery. The patients were not submitted to elective central compartment LN dissection. Patients with a tumor ≤ 1 cm (uni- or multifocal) restricted to the gland (T1aNxM0) and nonaggressive histology (Rosario *et al.* 2004a, 2007) and patients with the noninvasive encapsulated follicular variant of papillary carcinoma (E-FVPTC; Rosario *et al.* 2014a), who clearly would not benefit from ablation with ^{131}I , were excluded. Patients with one of the following characteristics were also excluded because of a higher risk of recurrence: extensive extrathyroid invasion (pT4); aggressive histological subtype (e.g., tall-cell, columnar-cell, diffuse follicular variant) or vascular invasion; LN metastases detected by preoperative US or during intraoperative inspection by the surgeon (clinical N1 (cN1)) if > 3 positive L, or LN > 1.5 cm, or LN exhibiting macroscopic extranodal tumor invasion; or combination of a tumor > 4 cm, minimal extrathyroid invasion, and LN metastases (cN1).

Therapy with levothyroxine (L-T4) was initiated immediately after surgery, adjusting the dose to maintain thyrotropin (TSH) < 2 mIU/l. Serum Tg and TgAb were measured during L-T4 use 3–6 months after thyroidectomy. Neck US was performed on the same occasion. The 391 patients selected were evaluated; 44 patients (11.2%) with positive TgAb, 119 patients (30.4%) with Tg > 0.3 ng/ml, and 6 patients (1.5%) with positive neck US were excluded. Finally, 222 patients (56.7%) had Tg < 0.3 ng/ml with TSH < 2 mIU/l, negative TgAb, and US showing no anomalies, and because of this finding, they were not submitted to ablation with ^{131}I .

Follow-up

The patients were maintained on 0.3–2 mIU/l TSH and were followed up by clinical examination, measurement of Tg and TgAb at intervals of 6–12 months, and annual neck US. An increase in Tg was defined as two consecutive measurements of Tg ≥ 0.3 ng/ml (interval 3–6 months) or one measurement ≥ 1 ng/ml, with TSH < 2 mIU/l. Imaging methods other than US (chest and mediastinal computed tomography (CT), fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT, RxWBS with ^{131}I) were performed when nonstimulated Tg converted to levels ≥ 1 ng/ml. The time of follow-up ranged from 15 to 102 months (median 62 months).

Imaging methods

US was performed with a linear multifrequency transducer for morphological analysis (B-mode) and for power Doppler evaluation. All suspected lesions apparent on the scans (Rosario *et al.* 2005, 2014b) were evaluated by US-guided fine-needle aspiration biopsy. RxWBS was obtained 7 days after ^{131}I administration (3.7 GBq) with L-T4 withdrawal for 4 weeks. Chest and mediastinal CT with contrast was performed on 5 mm sequential sections. FDG-PET/CT was carried out after stimulation with recombinant human TSH.

Assays

Chemiluminescent assays were used for the measurement of Tg (Access Thyroglobulin Assay, Beckman Coulter, Fullerton, CA) and TgAb (Immulate 2000, Diagnostic Products Corporation, Los Angeles, CA, USA) (reference value of up to 40 IU/ml) or ARCHITET Anti-Tg, Abbott Laboratories, IL, USA (reference value of up to 4.11 IU/ml). Patients with TgAb were excluded (Rosario *et al.* 2004b). The functional sensitivity obtained with the second-generation Tg assay at our laboratory was 0.1 ng/ml (Rosario *et al.* 2015b). We used this cut off to define undetectable serum Tg (i.e., ≤ 0.1 ng/ml).

Statistical analysis

Fisher's exact test and the χ^2 test were used for statistical analysis. A *P*-value < 0.05 was considered significant.

Results

Characteristics of the patients

The characteristics and risk classification of the patients are shown in Tables 1 and 2 respectively.

Follow-up

Among the 222 patients, 217 (97.7%) continued to have nonstimulated Tg < 0.3 ng/ml, negative TgAb, and neck US without anomalies. Serum Tg was undetectable in the last assessment in 185 of 217 patients (85.2%) and detectable in 32 patients (14.7%) (range 0.12–0.28 ng/ml; median 0.2 ng/ml).

Five of the 222 patients (2.2%) exhibited an increase in nonstimulated Tg, and LN metastases were detected in four (by neck US in three patients and by FDG-PET/CT in one patient (structural recurrence)). After surgery, two patients

Table 1 Characteristics of the patients studied

Number of patients studied	222
Gender	
Female	181 (81.5%)
Male	41 (18.5%)
Age (years)	
18–78 (median: 49)	
Tumor size	
Range	0.6–5 cm
≤ 1 cm ^a	34 (15.3%)
> 1 cm and ≤ 2 cm	88 (39.6%)
> 2 cm and ≤ 4 cm	85 (38.3%)
> 4 cm	15 (6.7%)
Minimal extrathyroid invasion (pT3)	68 (30.6%)
Multicentricity of the tumor	70 (31.5%)
TNM classification	
T1bNxM0	60 (27%)
T2NxM0	49 (22%)
T3NxM0	83 (37.4%)
T1N1M0	18 (8.1%)
T2N1M0	12 (5.4%)

^aAll with extrathyroid invasion (pT3) or clinically apparent lymph node metastases (cN1).

were free of disease (undetectable nonstimulated Tg, negative TgAb, US without anomalies), and two patients continued to have detectable nonstimulated Tg but < 1 ng/ml and no apparent tumor detected by the imaging methods. One patient progressed to an increase in serum Tg, but no tumor was detected by US or CT (biochemical recurrence). After receiving 3.7 GBq ^{131}I and RxWBS showing uptake only in the thyroid bed, serum Tg had already declined by more than 70%. The characteristics of the five patients with recurrence are shown in Table 3.

Recurrence (LN metastases) was observed in two (1.3%) of the 153 patients with undetectable initial Tg. Among the 69 patients with detectable initial Tg (range 0.15–0.29 ng/ml; median 0.22 ng/ml), recurrences were diagnosed in 3 (4.3%) (LN metastases in two and biochemical recurrence in the other).

The frequency of tumor recurrence according to the initial risk classification is shown in Table 2.

Discussion

First, we highlight some characteristics of the present study. This was a prospective study including a large number of patients. To our knowledge, this is so far the first prospective study that evaluated tumor recurrence in patients with low postoperative nonstimulated Tg, who were not treated with ^{131}I because of this result. In contrast to previous studies in which most of the patients had

Table 2 Risk classification of the patients studied

Risk classification	Risk	N	Recurrence	P-value
American Thyroid Association (Cooper <i>et al.</i> 2009)	Low	124	2 ^a (1.6%)	0.65
British Thyroid Association (Perros <i>et al.</i> 2014)	Intermediate	98	3 (3%)	
European Thyroid Association (Lepoutre-Lussey <i>et al.</i> 2014)	Low	109	1 (1%)	0.37
	High	113	4 ^a (3.5%)	
All patients		222	5 ^a (2.2%)	

^aOnly one patient exhibited biochemical recurrence (Tg elevation without apparent disease on the imaging methods).

microcarcinoma restricted to the thyroid (Durante *et al.* 2012, Ibrahimpasic *et al.* 2012, Nascimento *et al.* 2013, Angell *et al.* 2014), these patients and those with noninvasive E-FVPTC (Rosario *et al.* 2014a) were excluded from the present study because there is consensus that ablation of thyroid remnant is not necessary in these cases. More than half the patients were older than 45 years and 2 of 3 had a multicentric tumor > 1 and ≤ 4 cm (T1b-2Nx), tumor > 4 cm or with extrathyroid invasion (T3Nx), or clinically apparent LN metastases (T1-2cN1). Additionally, the patients were not submitted to elective LN dissection of the central compartment, and it is possible that 1 of 3 cN0 patients had clinically not apparent metastases (pN1) and that up to 40% of these patients had five or more affected LN (Scherl *et al.* 2014). Finally, the median follow-up time was 5 years, and it is known that 3 of 4 recurrences occur in these first years (Brassard *et al.* 2011, Durante *et al.* 2013). The rate of recurrence was the same (3 of 112 (2.6%)) when only patients with a follow-up time > 5 years were analyzed.

Even when measured with a second-generation assay, undetectable or low nonstimulated Tg can be achieved in many patients submitted to total thyroidectomy (Giovannella *et al.* 2008, Durante *et al.* 2012, Nascimento *et al.* 2013, Angell *et al.* 2014, Rosario *et al.* 2015a, 2015b). In these patients, two studies have shown that RxWBS did not reveal persistent disease in any case after the administration of ¹³¹I (1.1–3.7 GBq; Giovannella *et al.* 2008, Rosario *et al.* 2015a). A third study (Robenshtok *et al.* 2013)

showed uptake outside the thyroid bed in 12% of patients with undetectable postoperative nonstimulated Tg, but the Tg assay was not a second-generation assay, and 14 of 17 patients exhibited findings indicating a high risk of persistent disease (4 with important LN involvement (> 10 LN or LN > 3 cm), 9 with an aggressive histological subtype associated with vascular and/or extrathyroid invasion, and 1 with classical PTC > 1 cm associated with vascular invasion and LN metastases). Furthermore, postoperative US was not performed in that study. We believe that the combination of neck US increases the sensitivity in detecting persistent LN metastases after thyroidectomy, as occurs after therapy with ¹³¹I (Iervasi *et al.* 2007, Rosario & Purisch 2008, Castagna *et al.* 2011a, Chindris *et al.* 2012).

The fact that RxWBS was negative for metastases in these patients suggests that therapy with ¹³¹I does not provide any benefit (Nascimento *et al.* 2011, Rosario *et al.* 2011). However, to define whether low postoperative nonstimulated Tg, measured with a second-generation assay, can indeed be used as a criterion to exclude therapy with ¹³¹I, it was necessary to evaluate the risk of recurrence in the absence of this treatment, which was the objective of our study. The rate of tumor recurrence was only 2% in the present series. Serum Tg was undetectable in the last assessment in 85% of patients without recurrence and Tg continued to be < 0.3 ng/ml in the remaining patients. Additionally, neck US remained negative in all of these patients. These results make unlikely the long-term

Table 3 Characteristics of the patients with recurrence

Sex	F	F	F	M	F
Age (years)	38	50	58	32	48
TNM classification	T3NxM0	T3NxM0	T2NxM0	T2N1M0	T3NxM0
Postoperative nonstimulated Tg (ng/ml)	UND	UND	0.25	0.18	0.21
Interval between surgery and recurrence (months)	60	48	48	30	36
Tg at time of recurrent disease (ng/ml)	0.56	2.4	1.6	5.6	2
Site of recurrence	Cervical LN	Cervical LN	Cervical LN	Cervical LN	Unknown
Positive imaging method	US	US	US	FDG-PET	None

F, female; M, male; UND, undetectable.

occurrence of a relevant number of additional recurrences (Brassard *et al.* 2011). The rate of recurrence was low (~3%) even in patients classified as intermediate (Cooper *et al.* 2009, Perros *et al.* 2014) or high risk (Lepoutre-Lussey *et al.* 2014). This finding suggests that the importance of histological data as predictors of recurrence risk is minimized after complete tumor resection and when low Tg is achieved. This idea is supported by the low risk of recurrence in patients initially classified as intermediate risk but with an excellent response to thyroidectomy followed by radioiodine (Tuttle *et al.* 2010, Castagna *et al.* 2011b, Rosario *et al.* 2015c).

Elective dissection of the cervical LNs was not performed in the present study. Indeed, there is no consensus about the need for this procedure. We believe that, for the selection of patients who can be spared from ablation with ¹³¹I based on postoperative Tg, the absence of LN metastases can be demonstrated by US and perioperative examination (cN0) and does not require confirmation by elective dissection of the central neck compartment (Rosario *et al.* 2011, 2012). Supporting this view, in previous studies in which ¹³¹I therapy was not performed because of the finding of low postoperative stimulated Tg, the patients were also not submitted to elective dissection of the LN and yet the rate of recurrence was very low (no LN dissection or ¹³¹I therapy) (Vaisman *et al.* 2010, Rosario *et al.* 2012, Orlov *et al.* 2015).

The results obtained here suggest that patients with PTC (except for tumor with extensive extrathyroid invasion (pT4), aggressive histology, extensive LN involvement, or known residual disease) who have low non-stimulated Tg, measured with a second-generation assay and in the absence of TgAb, and negative neck US after thyroidectomy do not require ablation with ¹³¹I.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

Study design: G F Mourão, P W Rosario. Study conduct: G F Mourão. Data management: G F Mourão, P W Rosario. Data analysis: G F Mourão, P W Rosario. Data interpretation: G F Mourão, P W Rosario. Manuscript writing: all authors. Manuscript review and approval: all authors.

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