

# Management of Low-Risk Patients With Thyroid Carcinoma and Detectable Thyroglobulin on T4 After Thyroidectomy and Ablation With Iodine-131

## ABSTRACT

**Objective:** To evaluate the positive predictive value of detectable Tg during T4 therapy (Tg on T4) in patients with thyroid cancer after total thyroidectomy and remnant ablation, discussing the work-up in this situation and the empirical indication of  $^{131}\text{I}$ . **Patients and methods:** Initially, 234 low-risk patients [tumor  $\leq$  5cm, completely resected, no extensive extrathyroid invasion (pT4)] submitted to total thyroidectomy and ablation with  $^{131}\text{I}$  (3.7–5.5 GBq) who presented no ectopic uptake on RxWBS were studied. Of these, 23 patients with detectable Tg on T4 ( $>$  1ng/ml) during the first year after initial therapy were selected. **Results:** Metastases were detected by neck US in 7 patients, by chest CT in 2 and by US and CT in 3. Four of five patients with lung metastases upon CT had a positive RxWBS. Eleven patients with negative US and CT received a new  $^{131}\text{I}$  dose (without DxWBS), and RxWBS showed ectopic uptake in 3 patients. Among the patients with negative RxWBS, 7 remained free of apparent disease and Tg was declining (5 with undetectable Tg on T4 at the end of the study). One patient presented an increase in Tg and FDG-PET was positive for lymph node and bone metastases. **Conclusions:** All patients with Tg on T4  $>$  5ng/ml presented apparent disease. In these cases, even when US and CT are negative, the administration of a therapeutic dose of  $^{131}\text{I}$  (without DxWBS) and FDG-PET are recommended. Among patients with detectable Tg on T4  $\leq$  5ng/ml and negative US and CT, only 12% presented ectopic uptake on RxWBS. These cases could be followed up by monitoring Tg on T4, and RxWBS and FDG-PET should only be performed if this marker does not decrease after 1–2 years. (*Arq Bras Endocrinol Metab* 2007;51/1:99-103)

**Keywords:** Detectable Tg on T4; Radioiodine; Thyroid cancer

## RESUMO

### Manuseio de Pacientes com Carcinoma de Tireóide de Baixo Risco e com Tiroglobulina Detectável Durante T4 após Tireoidectomia e Ablação com $^{131}\text{I}$ do.

**Objetivo:** Avaliar o valor preditivo positivo da Tg detectável durante terapia com T4 (Tg sob T4) em pacientes com câncer de tireóide após tireoidectomia total e ablação dos remanescentes, discutindo o manuseio dessa situação e a indicação empírica de  $^{131}\text{I}$ . **Pacientes e métodos:** Inicialmente, foram estudados 234 pacientes de baixo risco [tumor  $\leq$  5cm, completamente ressecado, sem invasão extratireoideana extensa (pT4)] submetidos à tireoidectomia total e ablação com  $^{131}\text{I}$  (3,7–5,5 GBq) que não apresentaram captação ectópica com RxWBS. Desses, foram selecionados 23 pacientes com Tg detectável com T4 ( $>$  1ng/ml) durante o primeiro ano após a terapia inicial. **Resultados:** Metástases foram detectadas em 7 pacientes pelo US cervical, em 2 pela TC de tórax e em 3 pela US e TC. Quatro de 5 pacientes com metástases pulmonares à TC tiveram um RxWBS positivo; 11 pacientes com US e TC negativos receberam uma nova dose de  $^{131}\text{I}$  (sem DxWBS), e a RxWBS mostrou captação ectópica em 3 pacientes. Entre os pacientes com RxWBS negativo, 7 permaneceram livres de doença aparente e a Tg estava em declínio (5 com Tg indetectável sob T4 ao final do estudo). Um paciente apresentou aumento da Tg e o FDG-PET foi positivo para linfonodos e metástases ósseas. **Conclusões:** Todos os patients com Tg sob T4  $>$  5ng/ml apresentaram doença aparente. Nesses casos, mesmo quando a US e a TC são negativos, é recomendada a administração de dose terapêutica de  $^{131}\text{I}$  (sem DxWBS) e FDG-PET. Em pacientes com Tg detectável sob T4  $\leq$  5ng/ml, mas US e TC negativos, apenas 12% apresentaram captação ectópica com a RxWBS. Estes casos podem ser seguidos pelo monitoramento da Tg sob T4, e RxWBS e FDG-PET devem ser feitos apenas se esse marcador não diminuir. (*Arq Bras Endocrinol Metab* 2007;51/1:99-103)

**Descritores:** Tg detectável sob T4; Radioiodo; Câncer de tireóide

## artigo original

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Recebido em 12/04/06

Aceito em 26/05/06

THE IDENTIFICATION OF DETECTABLE levels of thyroglobulin (Tg) during the course of adequate TSH suppression shows a high specificity in the follow-up of patients with thyroid cancer after total thyroidectomy and ablation with <sup>131</sup>I. In these cases, some authors recommend the administration of a new therapeutic dose of <sup>131</sup>I, followed by post-treatment whole-body scan (RxWBS) (1,2). However, in the case of low-risk patients the frequency of metastases after total thyroidectomy and ablation with <sup>131</sup>I is relatively low in some centers (3,4), a minority of patients without apparent disease may present detectable levels of Tg during the first year after therapy but become negative for this marker during subsequent evaluations, and many metastases detected by RxWBS can be diagnosed by other imaging methods and treated surgically. Thus, the administration of a new <sup>131</sup>I dose (with RxWBS) to low-risk patients with detectable Tg on T4 after initial therapy should be discussed, especially when considering that even a <sup>131</sup>I dose of 3.7 GBq (100 mCi) can have adverse effects, including a higher risk of tumors (5).

The present study evaluated the positive predictive value of detectable Tg on T4 in low-risk patients after thyroidectomy and ablation with <sup>131</sup>I, discussing the work-up in this situation and the empirical indication of a new radioiodine dose.

## PATIENTS AND METHODS

The initial sample consisted of 234 consecutive patients (186 women and 48 men; age range: 13 to 78 years, mean: 47.2 years; 182 with papillary carcinoma and 52 with follicular carcinoma) seen at the Santa Casa de Belo Horizonte, Brazil, and considered to be at low risk for recurrence and mortality (6): tumor ≤ 5 cm (major diameter), completely resected, no extensive extrathyroid invasion (pT4), non-aggressive histological subtype. One-hundred-and-two patients had lymph node metastases (N1)

**Table 1.** TNM classification (8) of the patients studied.

TNM stage of the 234 initial patients			
	T1	T2	T3
N0	42	50	40
N1	24	34	44
TNM stage of the 23 selected patients			
	T1	T2	T3
N0	0	1	2
N1	3	6	11

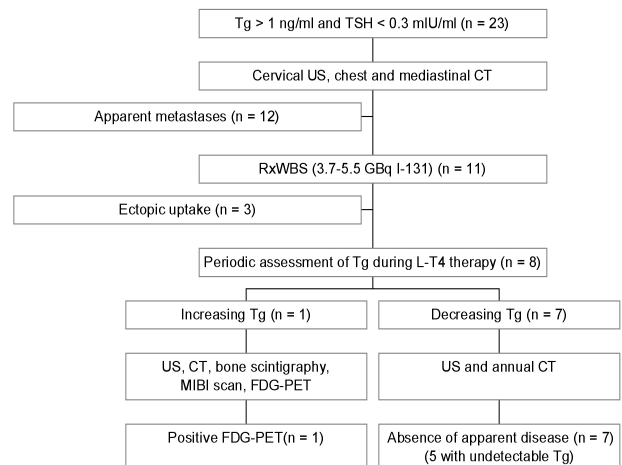
and 48 presented minimal extrathyroid invasion (pT3) (table 1). All patients underwent total thyroidectomy and ablation with <sup>131</sup>I (3.7–5.5 GBq, 100–150 mCi), with RxWBS showing no ectopic uptake, and were reassessed during the first year after therapy (6–12 months) by clinical examination and measurement of Tg during L-T4 therapy (TSH ≤ 0.3 mIU/l) (7) and antithyroglobulin antibodies (TgAb). Only patients without TgAb were included. Twenty-three patients (18 women and 5 men; age range: 16–72 years, mean: 46.5 years; 18 with papillary carcinoma and 5 with follicular carcinoma) with detectable Tg on T4 (> 1 ng/ml) were selected from the initial group (table 1). The investigation protocol of the patients is shown in figure 1. The study was approved by the Research Ethics Committee of our institution.

Tg was measured with an immunoradiometric assay (ELSA-hTG, CIS bio international, France) with a functional sensitivity of 0.8 ng/ml. TgAb were determined by a chemiluminescent assay (Chemiluminescent ICMA, Nichols Institute Diagnostics, San Juan Capistrano, CA) with a detection limit of 1 IU/ml and a reference value of up to 2 IU/ml. Based on the functional sensitivity of the assay, a Tg level > 1 ng/ml was defined as detectable.

RxWBS was performed after the administration of 3.7–5.5 GBq <sup>131</sup>I, after T4 withdrawal for 4 weeks and prescription of a low-iodine diet for 2 weeks. Anterior and posterior whole-body images were obtained 7 days after radioiodine administration.

Ultrasound (US) was performed with a linear, multifrequency transducer (7.5 to 10 MHz). Suspected lymph nodes (9) or cervical masses were submitted to diagnostic biopsy and to surgical excision in selected cases.

Chest and mediastinal computed tomography (CT) was performed on 10-mm sequential sections in the absence of an iodated contrast agent.



**Figure 1.** Investigation protocol and number of patients according to the result of the exams.

## RESULTS

The characteristics of the patients are listed in table 2 and the distribution of the patients according to the results of the investigation is shown in figure 1.

US revealed suspected lymph node metastases (9) in 10 patients, which were later confirmed by histological analysis. Seven patients were only treated surgically and achieved complete remission (negative stimulated Tg and US) and 3 (with associated lung disease) also received radioiodine, with two of them being in remission.

CT revealed lung micrometastases in 5 patients (3 with positive US). These patients received a new <sup>131</sup>I dose and RxWBS was positive in 4. The patient with negative RxWBS will receive a retinoic acid preparation (10), followed by a new attempt with <sup>131</sup>I.

Eleven patients with negative US and CT were submitted to empirical therapy with <sup>131</sup>I (3.7–5.5 GBq) and RxWBS showed ectopic uptake in 3 (cervical central and mediastinal, only mediastinal, pulmonary). Seven of the eight patients without metastases on US, CT and RxWBS did not develop apparent disease (mean follow-up of 24 months) and probably will not since Tg is declining (> 50%

decrease) in all of them (11), with Tg during L-T4 therapy being undetectable in 5. One patient presented an increase in Tg (from 8 ng/ml in the first assessment to 19 ng/ml after 2 years) and FDG-PET revealed lymph node and bone metastases in the mediastinum and femur. Surgical treatment and external radiotherapy were chosen in this case.

No difference was observed in Tg on T4 levels (mean) between patients with metastases and those without metastases on US and CT [8.3 versus 5.1 ng/ml (p ns)], but was higher in the patients with apparent disease in all imaging methods (US, CT, RxWBS and FDG-PET) [9.7 versus 3 ng/ml (p< 0.05)].

Of the 13 patients with detectable Tg ≤ 5 ng/ml, 4 had cervical metastases and one had pulmonary disease diagnosed by US and CT, respectively. Only one of the 8 cases submitted to empirical radioiodine therapy presented ectopic uptake (cervical central and mediastinal) on RxWBS. Among the 10 patients with Tg > 5 ng/ml, US was positive in 3, US and CT were positive in 3, and only CT was positive in 1. Among the 3 patients submitted to empirical radioiodine therapy, RxWBS revealed pulmonary ectopic uptake in one patient and mediastinal uptake in another, and

**Table 2.** Characteristics of the patients with detectable Tg on T4.

Patient	Age/Gender/ Histology	Tg on T4 (ng/ml)	US	CT	RxWBS (uptake)
1	56/F/papillary *	1.6	Negative	Negative	Negative
2	48/F/follicular *	2	Lymph nodes	Negative	—
3	29/M/papillary	2.2	Negative	Negative	Thyroid bed
4	52/F/follicular	2.5	Lymph nodes	Negative	—
5	50/M/papillary *	2.5	Negative	Negative	Negative
6	72/F/follicular	3	Negative	Negative	Negative
7	21/F/papillary *	3.2	Negative	Negative	Thyroid bed
8	58/F/papillary	3.5	Lymph nodes	Negative	—
9	35/M/papillary	3.5	Negative	Negative	Cervical and mediastinal
10	57/F/papillary	3.8	Lymph nodes	Negative	—
11	46/F/papillary	4	Negative	Negative	Negative
12	47/F/papillary	4.2	Negative	Lung metastases	Pulmonary
13	26/M/follicular *	4.5	Negative	Negative	Thyroid bed
14	32/F/papillary	5.4	Lymph nodes	Negative	—
15	42/F/papillary	5.5	Negative	Negative	Mediastinal
16	62/F/papillary	5.8	Lymph nodes	Lung metastases	Pulmonary
17	70/F/papillary	6.5	Lymph nodes	Negative	—
18	16/F/papillary §	8	Negative	Negative	Negative
19	66/M/follicular	8.5	Lymph nodes	Negative	—
20	53/F/papillary	12	Lymph nodes	Lung metastases	Pulmonary
21	32/F/papillary	18.5	Negative	Negative	Pulmonary
22	62/F/papillary	20	Lymph nodes	Lung metastases	Cervical and mediastinal
23	36/F/papillary	26	Negative	Lung metastases	Negative

\* Patients without apparent disease and with undetectable Tg on T4 at the end of the study.

§ Subsequent positive FDG-PET for bone and lymph node metastases.

subsequent FDG-PET showed lymph node and bone metastases in the case with negative RxWBS. These results suggest that the distinction of patients with Tg levels  $\leq 5$  ng/ml during suppressive therapy (12) seems to be relevant (table 3).

## DISCUSSION

In the present study, the positive predictive value of detectable Tg ( $> 1$  ng/ml) during suppressive therapy with L-T4 was 70% in low-risk patients (6) after total thyroidectomy and ablation with  $^{131}\text{I}$  (46% in patients with Tg  $\leq 5$  ng/ml and 100% if Tg  $> 5$  ng/ml).

No DxWBS was performed in the present series and we directly administered a therapeutic dose of  $^{131}\text{I}$  (followed by RxWBS) to patients with negative US and CT. DxWBS showed ectopic uptake in only 5 to 33% of patients with detectable Tg on T4 in other series (13-16). We therefore considered DxWBS to be of little value in this situation.

Direct administration of a therapeutic  $^{131}\text{I}$  dose to these patients would permit the detection of most cases of metastases, with a sensitivity of 75 to 93% (13-15). However, empirical therapy with radioiodine in all patients with detectable Tg on T4 (1,2) deserves further discussion. First, because a good part of these patients do not have metastases and would be exposed to high radioiodine activities without any benefit, with this percentage reaching 85% in very low risk patients (T1N0M0) (16). Second, because most patients with cervical metastases detected by RxWBS could be spared from radioiodine therapy since these metastases can be seen on US (17) and can be managed surgically. The care to avoid unnecessary exposure to radioiodine becomes important in view of the fact that even a dose of 3.7 GBq  $^{131}\text{I}$  is associated with adverse effects, including a higher risk of a second neoplasm (5).

We therefore suggest starting the work-up of patients with detectable Tg on T4 with neck US and chest and mediastinal CT. These easily available and noninvasive methods permit to identify most cases of lymph node (cervical and mediastinal) metastases and

a good part of lung metastases. The former patients would be referred for surgery (18), with a high chance of remission. For patients with lung micrometastases, a therapeutic radioiodine dose would continue to be indicated but previous knowledge about the presence of radiologically visible metastases might define a specific preparation with retinoic acid (10) or lithium (18). In addition, these methods are able to diagnose most metastases not apparent on RxWBS (13-15,17).

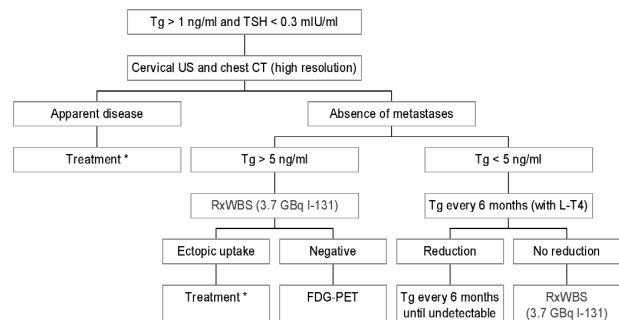
Finally, exclusion of patients with positive US and/or CT reduces the probability of finding apparent disease in the remaining group, especially in patients with Tg  $< 5$  ng/ml (only 12% in the present study). In this group, monitoring Tg during L-T4 therapy would discriminate patients without disease, who present declining Tg levels, from the minority of patients with metastases who would show an increase in Tg in subsequent measurements. It is possible that Tg remains unchanged in some cases with metastases maintained under TSH suppression; however, since these patients are at low risk, have no apparent disease (clinical examination, US and CT) and present no increase in Tg, we do not believe that a possible delay in the diagnosis would compromise the chance of cure in these specific cases. On the other hand, we support the recommendation of a therapeutic dose of  $^{131}\text{I}$  and even FDG-PET in patients with Tg  $> 5$  ng/ml during L-T4 therapy (12) and negative US and CT. A proposal for investigation is shown in figure 2.

## CONCLUSION

We concluded that low-risk patients with Tg on T4  $\leq 5$  ng/ml and negative US and CT could be followed up by monitoring Tg on T4 and RxWBS should be performed if this marker does not decrease after 1–2 years. Other studies with more patients and longer follow-up should be done to confirm our results.

**Table 3.** Positive predictive value considering any detectable Tg on T4 (n 23) versus only Tg  $\leq 5$  ng/ml (n 13).

Initial investigation	Detectable Tg	Tg $\leq 5$ ng/ml
Normal clinical exam	16/23 (69.5%)	6/13 (46%)
Negative US	6/13 (46%)	2/9 (22%)
Negative US and CT	4/11 (36.5%)	1/8 (12.5%)
Negative US, CT and RxWBS	1/8 (12.5%)	0/7 (0%)



**Figure 2.** Investigation suggested by the authors for patients with detectable Tg during L-T4 therapy.

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