Original article

Value of the negative PET-FDG in the middle term follow-up of differentiated thyroid cancer in patients with negative $^{131}$I-Na scan and elevated thyroglobulin serum levels

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OBJECTIVE: This study has aimed to analyze the evolution of patients diagnosed with differentiated thyroid carcinoma (DTC) with a negative $^{131}$I-Na whole body scan (WBS), high levels of serum thyroglobulin (Tg) and negative $^{18}$F-fluorodeoxyglucose positron emission tomography (PET-FDG) study.

Material and methods: Twenty-three patients diagnosed and treated for DTC were studied retrospectively. Patients were aged between 23 and 83 and had shown, between January 2001 and December 2002, negative WBS, Tg values in a range of suspected recurrence or metastasis (Tg $>$ 2 ng/mL with thyroid hormone withdrawal) and a negative PET-FDG study. The patients were monitored clinically, radiologically and analytically for a minimum period of 4 years. After this, a new evaluation was made of their state of disease with a control WBS, also observing the evolution of Tg. All WBS were performed with a 185 MBq diagnostic dose of $^{131}$I-Na.

RESULTS: In 18/23 patients, Tg decreased and in 5 it increased. Four patients (17%) were free of active disease (negative WBS Tg $<$ 2 ng/mL). A total of 16 patients (70%) were free of disease according to the WBS but had elevated Tg. Three patients (13%) had disease and high levels of Tg, two of them with positive WBS and the third with positive $^{99}$mTc-MIBI scan and CT.

CONCLUSIONS: Most patients with a negative WBS, high Tg serum levels and negative PET-FDG had good evolution, with descending Tg levels, normal levels even being reached in a significant percentage of them.

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Valor de la PET-FDG negativa en el seguimiento a medio plazo del carcinoma diferenciado de tiroides en pacientes con rastreo con $^{131}$I-Na negativo y cifras de tiroglobulina elevadas

Resumen

Objetivo: Pretendemos analizar la evolución de los pacientes diagnosticados de carcinoma diferenciado de tiroides (CDT) con un rastreo de cuerpo completo con $^{131}$I-Na (RCC) negativo, una tiroglobulina sérica (Tg) elevada y una tomografía por emisión de positrones con $^{18}$F-fluorodeoxiglucosa (PET-FDG) negativa. Material y métodos: Se estudiaron retrospectivamente a 23 pacientes diagnosticados y tratados de CDT, con edades comprendidas entre los 23 y 83 años, que entre enero de 2001 y diciembre de 2002 presentaron, un RCC negativo con valores de Tg en un rango de sospecha de recurrencia o metástasis (Tg $>$ 2 ng/mL con supresión de tratamiento hormonal) y una PET-FDG negativa. Tras un seguimiento clínico, radiológico y analítico de estos pacientes durante un periodo mínimo de 4 años, se vuelve a evaluar el estado de enfermedad con un RCC de control, observando a su vez la evolución de la Tg. Todos los RCC se realizaron con dosis diagnósticas de 185 MBq de $^{131}$I-Na.

Resultados: En 18 de los 23 pacientes la Tg descendió y en 5 ascendió. Cuatro pacientes (17%) estaban libres de enfermedad (RCC negativo y Tg $<$ 2 ng/mL). Diecisésis pacientes (70%) estaban libres de enfermedad según el RCC pero con cifras elevadas de Tg. En 3 pacientes (13%) se observó enfermedad y cifras elevadas de Tg, 2 con RCC positivo y el tercero con $^{99}$mTc-MIBI y TC positivos.

Conclusiones: La mayoría de los pacientes con RCC negativo, Tg elevada y PET-FDG negativa muestran una buena evolución, descendiendo los niveles de Tg e incluso alcanzando valores de normalidad en un porcentaje significativo de ellos.

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Introduction

The follow-up of patients with differentiated thyroid cancer (DTC) after total thyroidectomy and ablation of postsurgical remnants with radioactive iodine remains controversial, being based on serum Tg determinations combined with cervical ultrasound. WBS with $^{131}$I-Na is recommended in moderate and high risk patients with negative imaging studies and elevated Tg levels in order to detect possible disease recurrence as well as lesions with $^{131}$I-Na uptake early and thereby administer new therapeutic doses. In turn, elevated Tg levels due to withdrawal of hormone replacement therapy is more sensitive than WBS in the detection of tumor tissue.\(^2\) Thus, negative WBS with elevated Tg levels is not sufficient to exclude disease. PET-FDG has been demonstrated to be a very useful technique for the detection of distant metastasis of different tumors,\(^3\) and despite the slow growth of metastasis in DTC, PET-FDG is indicated for the detection of local or metastatic recurrence in cases with negative scans and elevated Tg levels within a range indicating the presence of disease ($\text{Tg} > 2 \text{ ng/mL}$). Tg levels greater than 10 ng/mL in patients receiving hormone replacement treatment and presenting a positive PET-FDG study have an impact clinical impact, allowing tumor extension and localization to be established and facilitating therapeutic decision making.\(^4,13\)

Nonetheless, when PET-FDG is negative in these cases, expectations are frustrated. Patients must continue to be closely controlled and should undergo other less specific tests. Moreover, the clinical relevance of this finding is uncertain and only the study of the evolution of the patient provides better knowledge as to its significance. The aim of this study was to analyze the evolution of patients diagnosed with DTC with negative WBS with $^{131}$I-Na, elevated serum Tg levels and a negative PET-FDG study.

Material and methods

Patients

We retrospectively studied 23 consecutive patients, 7 males and 16 females belonging to the area of the Hospital Universitario Virgen del Rocío of Sevilla with ages between 23 and 83 years (mean age of 51.22 years). These patients had undergone total thyroidectomy and posterior ablation of thyroidal remnants (none presented distant disease according to the pretreatment WBS) with a dose of 3.7 GBq of $^{131}$I-Na. All the patients fulfilled the following inclusion criteria:

- Diagnosed with and treated for DTC.
- Negative WBS with radioactive iodine performed one year post-ablation (carried out from January 2001 to December 2002).
- Tg values within the range of suspicion of recurrence or metastasis ($\text{Tg}>2\text{ ng/mL}$ with withdrawal of hormone replacement treatment).
- Negative PET-FDG study.
- Follow-up during a minimum period of 4 years (until December 2008) according to the DTC protocol\(^{14}\) (Fig. 1).

Exclusion criteria:

- Patients with elevated antithyroglobulin antibodies (TgAb).

With the clinical histories we analyzed the age, genre, tumor histopathology, TSH and Tg levels at the time of the initial scan and at the control scan, the results of the latter scan and those of other diagnostic tests performed according to the follow-up protocol\(^{14}\) as well as the time of evolution of each patient (Table 1).

Whole body scan with $^{131}$I-Na

For the present study we denominated the initial scan as that performed one year post-ablation and the control scan was that carried out after the follow-up period of each patient. These studies were undertaken with a large field gamma camera, whole body and high energy collimator, after the administration of an oral diagnostic dose of 185 MBq of $^{131}$I-Na and previous withdrawal of hormone treatment for 4 weeks to achieve TSH stimulation, which was above 30 µIU/ml in all cases and with ioduria below 10 mcg/dl.

A WBS was performed and anterior and posterior sectorial projections of areas of interest 54 h post-administration. All the initial WBSs were negative.

We considered the last scan performed prior to December 2008 during the usual follow-up of each patient as the control.

Serum determination of thyroglobulin and antithyroglobulin antibodies

A blood sample was obtained from each patient prior to the administration of the diagnostic dose of radioactive iodine in both the initial and control scans with previous withdrawal of thyroxin for 4 weeks. A commercial kit was used for the determination by radioimmunoassay (BRAMS\(^{®}\), analytical and functional sensitivity of 0.05 ng/mL and 0.3 ng/mL, respectively). Abnormal values of Tg were considered as those greater than 2 ng/mL without hormone replacement treatment.

With regard to the evolution of the Tg values a variation was considered if the control values differed from the initial values with a margin of ±15%.

Patients presenting the elevated TgAb serum levels in either of the two determinations, which could, therefore, influence the Tg values, were excluded from the study.

Positron emission tomography with 18F-fluorodeoxyglucose

After previous fasting of at least 6 h, PET-FDG was performed in a high resolution whole body ECAT HR+ (Siemens\(^{®}\)) tomograph 60 min after the administration of an intravenous dose of 370 MBq of $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) until June 2007, after which time the procedure was undertaken in a PET-TAC Biograph-16 (Siemens\(^{®}\)) tomograph.

Prior to the study all the patients were administered 50 mg of tetrazepam (Myolastan\(^{®}\)), 0.25 mg/kg of furosemide and hydration (250 cc i.v. physiological saline). The PET-FDG study was acquired from the temporal lobe until the upper third of the femur and the emission images were obtained in 2D with and without correction by transmission, with iterative reconstruction (2 iteraciones, 8 subconjuntos) in coronal, axial and sagittal planes for the ECAT HR+; and low dose CT images (without oral or intravenous contrast) and 3D PET with and without correction of attenuation, with iterative reconstruction (4 iteraciones/8 subconjuntos) in coronal, axial and sagittal planes with the Biograph-16. The studies were qualitatively and quantitatively examined by 3 specialists independently, quantifying the size and the standardized uptake value (SUV) of each lesion thereby facilitating the decision as to whether the study was pathologic or not.
Clinical evolution

The clinical evolution of three patients was followed during a period of between 4 and 7 years (mean follow-up of 5.04 ± 0.92 years) considering this to be sufficiently significant to evaluate any change. During this time the patients underwent periodical clinical-radiological and analytical tests according to the findings and within the established protocol (Fig. 1).

After this follow-up period, patients were considered to be free of disease when the last WBS was negative and the Tg levels were below 2 ng/dL, with no evidence of disease in other diagnostic tests. Patients were considered free of active disease when the last WBS was negative but the Tg remained above 2 mg/dL, with the remaining diagnostic tests being negative. Lastly, the presence of disease was considered with the presence of evidence of local or distant recurrence (lymph node or systemic metastasis) in either the last scan or in the other diagnostic tests.

Statistical analysis

Descriptive statistical analysis was performed of the quantitative variables studied (TSH and Tg levels and time of evolution), calculating the arithmetic mean, typical deviation and statistical range. The qualitative variables were analyzed calculating the percentage. The evolution of Tg values was studied using the Student’s t-test for unpaired data. Statistical significance was considered with a p value less than 0.05. The statistical analyses were performed using the SPSSv.17 software.

Results

The mean, typical deviation and statistical range of the Tg and TSH values in the initial and control scans are shown in Table 2.
Table 1
Description of the study variables.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Genre</th>
<th>Histologic type</th>
<th>Initial scan</th>
<th>Follow-up time (years)</th>
<th>Control scan</th>
<th>Tg evolution</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>Male</td>
<td>Papillary</td>
<td>150</td>
<td>19.6</td>
<td>6</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>Male</td>
<td>Papillary</td>
<td>213.6</td>
<td>20.4</td>
<td>6</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>Female</td>
<td>Papillary</td>
<td>120.6</td>
<td>8.39</td>
<td>5</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>Male</td>
<td>Papillary</td>
<td>135.1</td>
<td>9.47</td>
<td>4</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>Female</td>
<td>Papillary</td>
<td>40.6</td>
<td>6.85</td>
<td>6</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>Female</td>
<td>Follicular</td>
<td>65.1</td>
<td>26.8</td>
<td>5</td>
<td>Tg (ng/mL)</td>
<td>LNM/PM</td>
</tr>
<tr>
<td>7</td>
<td>62</td>
<td>Female</td>
<td>Follicular</td>
<td>51.7</td>
<td>25</td>
<td>5</td>
<td>Tg (ng/mL)</td>
<td>Ascent</td>
</tr>
<tr>
<td>8</td>
<td>73</td>
<td>Female</td>
<td>Papillary</td>
<td>60</td>
<td>30.2</td>
<td>4</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
<tr>
<td>9</td>
<td>64</td>
<td>Female</td>
<td>Papillary</td>
<td>127</td>
<td>19.6</td>
<td>5</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>Female</td>
<td>Papillary</td>
<td>60</td>
<td>38.0</td>
<td>5</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
<tr>
<td>11</td>
<td>39</td>
<td>Female</td>
<td>Papillary</td>
<td>147</td>
<td>32.19</td>
<td>4</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
<tr>
<td>12</td>
<td>32</td>
<td>Female</td>
<td>Papillary</td>
<td>239</td>
<td>14.6</td>
<td>7</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
<tr>
<td>13</td>
<td>42</td>
<td>Male</td>
<td>Papillary</td>
<td>60.1</td>
<td>12.5</td>
<td>4</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
<tr>
<td>14</td>
<td>39</td>
<td>Female</td>
<td>Papillary</td>
<td>74.7</td>
<td>42.7</td>
<td>4</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
<tr>
<td>15</td>
<td>23</td>
<td>Female</td>
<td>Papillary</td>
<td>147</td>
<td>32.19</td>
<td>4</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
<tr>
<td>16</td>
<td>37</td>
<td>Female</td>
<td>Papillary</td>
<td>55.9</td>
<td>24.1</td>
<td>6</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
<tr>
<td>17</td>
<td>83</td>
<td>Female</td>
<td>Follicular</td>
<td>67.9</td>
<td>15.9</td>
<td>6</td>
<td>Tg (ng/mL)</td>
<td>Ascent</td>
</tr>
<tr>
<td>18</td>
<td>67</td>
<td>Male</td>
<td>Papillary</td>
<td>64.5</td>
<td>12.8</td>
<td>4</td>
<td>Tg (ng/mL)</td>
<td>Ascent</td>
</tr>
<tr>
<td>19</td>
<td>68</td>
<td>Male</td>
<td>Papillary</td>
<td>65.6</td>
<td>17.6</td>
<td>4</td>
<td>Tg (ng/mL)</td>
<td>Ascent</td>
</tr>
<tr>
<td>20</td>
<td>49</td>
<td>Female</td>
<td>Papillary</td>
<td>67.4</td>
<td>17.14</td>
<td>6</td>
<td>Tg (ng/mL)</td>
<td>LNM/recurrence</td>
</tr>
<tr>
<td>21</td>
<td>46</td>
<td>Female</td>
<td>Follicular</td>
<td>115</td>
<td>26.6</td>
<td>6</td>
<td>Tg (ng/mL)</td>
<td>Ascent</td>
</tr>
<tr>
<td>22</td>
<td>61</td>
<td>Male</td>
<td>Follicular</td>
<td>62.7</td>
<td>228.3</td>
<td>4</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
<tr>
<td>23</td>
<td>45</td>
<td>Female</td>
<td>Papillary</td>
<td>44</td>
<td>40.92</td>
<td>5</td>
<td>Tg (ng/mL)</td>
<td>Descent</td>
</tr>
</tbody>
</table>

TSH: thyroid-stimulating hormone; Tg: thyroglobulin; LNM: lymph node metastasis; PM: pulmonary metastasis.

After the follow-up 4 out of the 23 patients (17.39%) were found to be free of disease versus 3 out of the 23 patients (13.04%) in whom disease was detected using morphofunctional tests (being detected in the control WBS in 2 of the 3 patients and by positive CT and scintigraphy with \(^{99m}\)Tc-MIBI in the remaining patient). The 16 remaining patients (69.57%) showed no evidence of active disease, that is, elevated Tg levels but no localization of tumoral foci in the morphofunctional tests.

On the other hand, a decreasing trend in Tg values (Table 3) was observed in 18 of the 23 patients (78.26%), with statistically significant differences between the final and initial values (Fig. 2) (mean of initial Tg 37.76 ± 51.8 ng/dL; mean of control Tg 13.56 ± 21.85 ng/dL; \(p = 0.004\)). Of these 18 patients, 2 (11.1%) presented disease in the study with morphofunctional tests (one with lung metastasis and another with lymph node and pulmonary metastasis). To the contrary, 4 of the 18 patients (22.2%) were disease free and the remaining 12 (66.7%) showed no evidence of active disease. Lastly, the 2 patients diagnosed with active disease in the morphological tests presented a histological follicular variant of DTC while the remaining 16 patients presented a papillary variant (Table 1).

In the remaining 5 of the 23 patients studied, we observed a trend to an increase in Tg values (Table 3) with no statistically significant differences between the initial and control determinations (Fig. 3) (mean initial Tg 19.49 ± 6 ng/dL; mean control Tg 70.45 ± 54 ng/dL; \(p = 0.087\)). On detailed analysis of the

Table 2
TSH and Tg levels at the time of the initial and control scans.

<table>
<thead>
<tr>
<th></th>
<th>Initial scan</th>
<th>Control scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td>TSH (mU/mL)</td>
<td>92.34 ± 55.01</td>
<td>32.4–239</td>
</tr>
<tr>
<td>Tg (ng/mL)</td>
<td>34.05 ± 46.07</td>
<td>6.85–228.3</td>
</tr>
</tbody>
</table>

Table 3
Evolution of Tg values and the state of the disease (number of patients).

<table>
<thead>
<tr>
<th>Tg</th>
<th>With disease</th>
<th>Without active disease</th>
<th>Without disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓</td>
<td>2</td>
<td>12</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>↑</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>16</td>
<td>4</td>
<td>23</td>
</tr>
</tbody>
</table>

Fig. 2. Variation in Tg values in patients with descending levels. Statistically significant differences were observed \((p = 0.004)\) between the initial and control serum Tg determinations.
Fig. 3. Variation in Tg values in patients with ascending levels. No statistically significant differences were found ($p=0.087$).

Evolution of these 5 patients during the follow-up we observed that:

- One patient presented new negative scan and PET-FDG during the follow-up although the Tg values showed an increasing trend.
- Another patient presented a positive scan and was treated with a therapeutic oral dose of $^{131}$I-Na after which the WBS became negative, albeit with elevated Tg levels.
- Two patients showed bone metastases in the control PET-FDG, with both undergoing surgery, confirming the anatomopathology of the lesion and becoming negative in the posterior PET-FDG (Fig. 4).
- The last patient with local recurrence in the WBS who received an oral therapeutic dose of $^{131}$I-Na, continued with the disease and remained in follow-up.

It should be mentioned that all these patients presented a follicular variant of DTC except the last who had a papillary variant (Table 1).

Discussion

The detection of recurrence of DTC at a cervical, lymph node or distant level is very important since it has been demonstrated to be associated with a greater morbidity and mortality. The determination of serum Tg levels in the absence of circulating TgAb, and the WBS are the tests most generally used in the follow-up of operated patients and those submitted to ablation of remnants with radioiodine. On detection of lesions in the WBS the next step is treatment with doses of $^{131}$I-Na. In the case of a negative scan, that is, in which no lesions with uptake of radioiodine are visualized, the determination of Tg values indicated the status of the patient.

Thus, if the Tg values are greater than 2 ng/dL without hormone replacement treatment and without circulating TgAb, the presence of tumoral recurrence is considered. Several studies have demonstrated the efficacy of PET-FDG in the localization of lesions which do not take up $^{131}$I-Na, with sensitivities of 60–94% and specificities of 25–90%. The use of PET-FDG also has a potential clinical impact after the localization of the lesion, with these patients benefiting from the different lines of treatment available such as new therapeutic doses of radioiodine or surgical excision of the lesions detected.

It has also been demonstrated that the level of Tg at the time of the WBS is related to the probability of recurrence. Thus, in one study Schlüter et al. established that with Tg values below 10 ng/ml only 11% of PET examinations showed pathological findings indicative of the presence of recurrence of metastasis of DTC, while with Tg values between 10 and 20 ng/ml 50% were

Fig. 4. (A) PET $^{18}$F-FDG study of a patient presenting a hypermetabolic lesion in the zone of the mandible, compatible with bone metastasis. (B) PET-TAC with $^{18}$F-FDG after surgery remaining without evidence of active disease.
positive and with values above 100 ng/mL the probability of detecting disease rose to 93%. Likewise, in the study by Ruiz Franco-Baux et al., in patients with Tg values above 10 ng/dL PET-FDG studies were profitable since this level was predictive of positivity and would facilitate selection of the patients in whom this study could be performed more efficiently.

However, from 30 to 40% of the patients with negative scans and elevated Tg levels are PET-FDG negative.\textsuperscript{8–12} Helal et al.\textsuperscript{8} studied the clinical impact of PET-FDG in patients with elevated Tg levels after empirical treatment with radiodiode whose posterior WBS was negative but without PET findings in 10 of the 37 patients studied. Neither did Muros et al.\textsuperscript{11} find lesions in the PET-FDG in 4 of the 10 patients studied. Bertagna et al.\textsuperscript{12} studied 52 patients, 18 of whom were negative and only 3 had elevated Tg levels. In all these studies a wait-and-see therapeutic attitude was adopted since all coincided in that no treatment would be effective.

Lastly, Schlüter et al.\textsuperscript{9} studied 64 patients, 20 of whom had negative PET-FDG studies and of these only 15 presented elevated Tg levels. Of these 15 patients, disease was detected by other morphofunctional techniques (MR, CT and/or WBS) in 4, who, based on the findings, accordingly underwent treatment with radiodiode or surgery. The 11 remaining patients did not receive any treatment. Nonetheless, in these patients only one Tg determination was performed, with no mention of the evolution of these levels nor the clinical state of the patients. On the observation of the evolution of the Tg determinations in our study, we attempted to establish a relationship between this trend and the possibility of presenting recurrence to thereby predict the need to include these patients in some treatment arm.

In this respect the only study in the literature which we found to evaluate the negative results of PET-FDG after an established follow-up period, albeit secondarily, was that of Salvatore et al.,\textsuperscript{13} who concluded that negative PET-FDG combined with Tg determinations may be a useful tool in the short-term prognosis of these patients. This last study involving a total of 45 patients differed from ours in that it included 28 patients with positive WBS and elevated Tg, 9 with negative WBS and positive PET-FDG and only 8 patients with a negative WBS and negative PET-FDG, while we report a group of 23 patients with the 3 premises. In addition, the Tg value considered to be elevated was of 1.5 ng/dL in a single determination at the time of the WBS, while we established a Tg value of 2 ng/dL and found a evolutive trend in this value over time, disputing the use of a precise, single, absolute value as the prognostic element of response in this disease. Finally, Salvatore et al.\textsuperscript{13} reported a middle follow-up period of 156 months with a minimum of 8 months versus our middle term follow-up of 60 months and a minimum of 48 months. This provides more validity to our results since DTC is a carcinoma of slow evolution and a short follow-up may not be sufficient.

We did not find any study analyzing the evolution of Tg values as a predictor of follow-up of patients with negative PET-FDG. We reviewed 23 patients with these 3 conditions (negative WBS, elevated Tg and negative PET-FDG) and followed their evolution over at least 4 years to evaluate disease outcome. In 18 of the 23 patients, Tg values showed a descending trend over time demonstrating an evolution toward disease stability since only 2 of these patients (11%) presented recurrence of DTC. The future Tg determinations in these patients will probably continue to descend until they are classified as values at which the patient may be considered completely disease free. This, together with the fact that the benefits of empiric treatments, gene therapy or the use of drugs for redifferentiation\textsuperscript{17} remain to be demonstrated, suggest that Tg may be a good marker for direction related to the evolution of these patients and thereby avoid unnecessary procedures.

Nonetheless, more randomized studies with a long follow-up are required.

Finally, in our study we observed that an ascending evolution in serum Tg levels carries a worse prognosis with a high probability of recurrence (80% according to our data) making the detection of elevations in this marker in the clinical follow-up and morphofunctional images of the patients necessary.

Conclusions

- A negative PET-FDG study together with a reduction in Tg levels seems to be an indicator of favorable disease evolution over a period of at least 4 years.
- On obtention of a negative PET-FDG study in patients with a negative WBS and elevated Tg levels, the probability of the development of active disease over time is low and the patients should therefore be followed with controls of Tg values.
- With a descending trend in Tg values in posterior determinations, the probability of the detection of tumor foci is even lower and may represent a trend toward normality (Tg < 2 ng/dL).
- If the trend is toward ascending Tg values, the probability of obtaining a positive study rises and a new morphofunctional study would be indicated.

Conflict of interest

The authors declare no conflict of interest.

References