ORIGINAL PAPER

# Preoperative determination of serum thyroglobulin to identify patients with differentiated thyroid cancer who may present recurrence without increased thyroglobulin

## *Dosaggio preoperatorio della tireoglobulina per evidenziare la possibilità di recidivare del carcinoma tiroideo ben differenziato in assenza di aumento dei valori di tireoglobulina*

B. GIBELLI, P. TREDICI, C. DE CICCO[1], L. BODEI[1], M.T. SANDRI[2], G. RENNE[2], R. BRUSCHINI, N. TRADATI
Division of Head and Neck Surgery; [1] Division of Nuclear Medicine; [2] Division of Pathology and Laboratory Medicine, European Institute of Oncology, Milan, Italy

Key words

Thyroid cancer • Recurrence • Thyroglobulin • Follow-up

Parole chiave

*Carcinoma tiroide • Recidiva • Tireoglobulina • Follow-up*

Summary

Thyroglobulin is considered a reliable marker of recurrent disease in patients with well-differentiated thyroid carcinoma. However, some patients present recurrence with no increase in serum thyroglobulin. In the attempt to identify patients who might present recurrence with no such sign of the disease, thyroglobulin levels have been determined pre-operatively in 185 consecutive patients scheduled for primary treatment for well-differentiated thyroid carcinoma from June 1997 to May 2002 at the Head and Neck Division of the European Institute of Oncology. In 22 patients (11.9% of total), serum thyroglobulin was undetectable. In none of these 22 cases was thyroglobulin detected during follow-up, either during thyroxin suppressive therapy or during withdrawal for radioiodine scan. One of these low-thyroglobulin patients developed recurrent disease involving cervical lymph nodes, with positive radioiodine scan: thyroglobulin remained undetectable. On the contrary, in the patients with high or normal thyroglobulin presenting recurrence, the recurrence was indicated, in all cases, by increased thyroglobulin levels. From these findings it may be concluded that pre-operative assessment of serum thyroglobulin may identify patients who might present recurrence without increased thyroglobulin, and in whom standard follow-up by monitoring thyroglobulin serum levels is inadequate.

*Riassunto*

*Nei pazienti con carcinoma differenziati della tiroide il dosaggio della tireoglobulina (HTG) è normalmente considerato un marker attendibile di malattia, tanto che attualmente viene proposto il dosaggio, sia in condizioni basali che sotto stimolo con TSH ricombinante, come metodica esclusiva di follow-up per i tumori a basso rischio. È noto comunque che almeno il 10% dei pazienti con recidiva di malattia non presenta valori di HTG modificati. Nel tentativo di identificare i soggetti che potrebbero recidivare senza elevazione del marker sono stati valutati i valori di HTG preoperatoria in 185 pazienti operati per carcinoma differenziato della tiroide nella divisione di chirurgia cervicofacciale dell'Istituto Europeo di Oncologia da giugno '97 a maggio 2002. La HTG preoperatoria si presentava inferiore ai limiti di sensibilità del metodo in 22 pazienti (11,9% del totale) e in nessuno di questi fu possibile notare un'elevazione del marker neppure al momento della terapia radiometabolica. Un paziente di questo gruppo con HTG bassa sviluppò recidiva linfonodale ancora con HTG segnalate sempre dall'elevazione del marker. Da queste osservazioni sembra possibile suggerire che il dosaggio preoperatorio della HTG – metodica semplice e poco costosa – potrebbe identificare i pazienti in pazienti in condizione di recidivare senza aumento del marker, per i quali il follow-up esclusivamente biochimico è inadeguato.*

## Introduction

Thyroglobulin (TG), the most important protein produced by the thyroid, is a large (660 kDa) dimeric glycoprotein, secreted only by thyroid follicular cells. It provides a matrix for the synthesis of the thyroid hormones and a vehicle for their subsequent storage. The protein is confined to thyroid cells and, in normal conditions, only low levels (3-60 ng/mL) are present in serum. TG production shows no diurnal or seasonal variation and synthesis appears to be controlled by a dominant gene [1 2].

At steady-state, thyroid volume and thyroid stimulating hormone (TSH) are the main factors modulating

serum TG levels [1-6]. High serum TG concentrations may be due to an abnormally large thyroid, excessive thyroid stimulation, or physical damage to the thyroid. Serum TG concentrations generally increase in the presence of well-differentiated thyroid carcinoma (WDTC), to return to normal after tumour removal. However, TG levels may increase again in the presence of disease recurrence or metastases; indeed, according some authors serum TG evaluation is more sensitive than $^{131}$I whole body scan for detecting residual thyroid tissue [7 8].

However, the presence of circulating auto-antibodies to TG (TGAb) may interfere with the TG assay, causing false positive or false negative results [2 9-12]. The estimated prevalence of TGAb, in the general population, is about 10%, but rises to 23%-40% in patients with WDTC [13 14].

In the absence of elevated TGAb, serum TG has been shown to be an excellent marker of WDTC recurrence or residual disease after total thyroidectomy [2 9 11 12 15-21].

To avoid repeated withdrawal of thyroid replacement, sometimes resulting in symptomatic hypothyroidism, and, in any event, increasing the risk of tumour growth, serum TG assay alone is often used to monitor recurrence or residual disease However, optimum sensitivity (> 98%) [21-23] is achieved with whole body radioiodine scan associated with TG assay, following thyroid tissue stimulation by means of high TSH levels, either by thyroxin withdrawal, or as a result of administration of human recombinant TSH [18 19 24-34]. The disadvantage of TG as a marker of recurrence is that an estimated 4-10% of WDTC patients have undetectable serum TG even with clear evidence of metastases [1 4 10 13 34-36].

In the present study, serum TG levels were determined pre-operatively in patients with WDTC since it was hypothesized that pre-operative findings of low or undetectable serum TG would identify a subgroup in whom any cancer recurrence would not be accompanied by increased serum TG, and who would, therefore, require a follow-up schedule not relying only upon TG evaluation, either during thyroxin therapy or during TSH stimulation.

## Patients and methods

From June 1997 to May 2002, 185 consecutive patients (mean age 40.6 years, range 14-81) with a histological diagnosis of WDTC underwent surgery at the Head and Neck Division of the European Institute of Oncology, Milan, as primary treatment for their disease. Standard pre-surgical assessment included clinical evaluation, ultrasonography (US) of the thyroid and neck, fine-needle aspiration biopsy (FNAB) of the thyroid nodule, and FT3, FT4, TSH, TG and TGAb evaluation.

Serum levels of TG were assessed using the Immulite thyroglobulin assay (Medical Systems, Euro/DPC, UK). This is a sensitive two-site chemiluminescent immunoassay, based on ligand-labelled monoclonal antibody and separation by anti-ligand-coated solid phase. The lower limit of detection is 0.2 ng/ml, and the calibration range is up to 300 ng/ml. Intra-assay coefficient of variation (CV) is < 5.7%, and inter-assay CV < 8.8%. The assay is standardized against Certified Reference Material for human thyroglobulin (CRM 457) in compliance with the Community Bureau of Reference of the European Commission. Reference range is 0.83-68 ng/ml.

Following surgery, all patients received suppressive treatment with thyroxin to maintain TSH below 0.05 mU/l. Patients classified at high risk or with advanced disease, and submitted to total thyroidectomy, underwent total body $^{131}$I scan post-operatively and post-radioiodide therapy when required. Serum TG and TGAb levels were measured one month after surgery, every 6 months during TSH suppression, and repeated when thyroid replacement was withdrawn for $^{131}$I scan or therapy. The 6 monthly examination also included clinical check-up, neck US, and assessment of FT3, FT4, and TSH; with chest X-ray every year.

## Results

Of the 185 patients evaluated, 133 underwent total thyroidectomy and 52 hemithyroidectomy. Tumour stage, according to the UICC (1997) classification, is shown in Table I. Neck dissection was performed according to our protocol, depending on the presence of node metastases, extracapsular extension, tumour size, and age of the patient. Radioiodine therapy was administered after total thyroidectomy to patients with extracapsular tumour, intracapsular tumour > pT2, or positive lymph nodes. Serum TGAbs were present in 37.2% of patients at surgery.

Table I. Pathological diagnosis in 185 patients with well-differentiated thyroid cancer.

| Stage at surgery | pT4N0 | pT4N1 | pT3N0 | pT3N1 | pT2N0 | pT2N1 | pT1N0 | PT1N1 |
|---|---|---|---|---|---|---|---|---|
| N. patients | 34 | 39 | 7 | 4 | 41 | 11 | 38 | 11 |

Table II. Characteristics of 22 patients with low (< 2 µg/ml) pre-operative serum TG.

| | Age/sex | TNM | Histology | Surgery | TG pre | TG sp | TG $^{131}$I | TGAb | Follow-up (m) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 23/ F | T4N0 | Papillary ca. + CLT | Tot. | 0.1 | 0.1 | 0.2 | 921 | NED (27) |
| 2 | 37/ F | T4N1 | Papillary ca. | Tot. | 0.8 | 0.0 | 0.2 | N | NED (60) |
| 3 | 15/ F | T1bN0 | Papillary ca. | Tot. | 1.0 | < 0.2 | 5.5 | 163 | NED (18) |
| 4 | 40/ F | T2bN0 | Papillary ca. CLT | Tot. | 0.1 | 0.1 | 0.1 | 142 | NED (28) |
| 5 | 17/ F | T1bN1 | Papillary ca. + CLT | Tot. | 0.17 | 0.1 | 0.1 | 336 | NED (06) |
| 6 | 37/ F | T4N0 | Papillary ca. + CLT | Tot. | 0.1 | < 0.5 | 0.1 | 9070 | NED (28) |
| 7 | 48/ M | T4N1b | Papillary ca. | Tot. | 0.78 | < 1 | < 1 | 288 | NED (06) |
| 8 | 52/ F | T1N0 | Papillary ca. + CLT | Hemi. | 1 | < 0.5 | ND | N | NED (06) |
| 9 | 42/ F | T4bN1b | Papillary ca. | Tot. | 2.0 | 0.1 | 1 | N | NED (60) |
| 10 | 47/ F | T1bN0 | Papillary ca. + CLT | Hemi. | 0.63 | 0.5 | ND | 218 | NED (21) |
| 11 | 45/ F | T2aN0 | Papillary ca. | Hemi. | 0.2 | 0.9 | ND | 623 | NED (24) |
| 12 | 56/ F | T2N0 | Papillary ca. + CLT | Tot. | 1 | 1 | 0.1 | N | NED (59) |
| 13 | 37/ F | T2N0 | Papillary ca. + CLT | Hemi | 2 | 0.1 | ND | N | NED (29) |
| 14 | 64/ F | T4N0 | Papillary ca. | Tot. | 0.1 | < 0.1 | 0.1 | N | NED (49) |
| 15 | 59/ M | T3N0 | Papillary ca. | Tot. | 1.5 | 0.1 | 2.5 | N | NED (33) |
| 16 | 37/ F | T4N1 | Papillary ca. + tracheal inv. | Tot. | 0.7 | 0.1 | 0.5 | N | REC (31) NED (38) |
| 17 | 37/ F | T1N0 | Papillary ca. + CLT | Tot. | 0.59 | 0.5 | ND | 734 | NED (18) |
| 18 | 25/ F | T2N0 | Papillary ca. + ST | Tot. | 0.1 | 0.1 | ND | N | NED (10) |
| 19 | 63/ F | T2N0 | Papillary ca. | Tot. | 2.0 | 0.1 | ND | 1428 | NED (28) |
| 20 | 20/ F | T1N0 | Papillary ca. + CLT | Hemi | 1.6 | 0.5 | ND | 79 | NED (32) |
| 21 | 33/ M | T4N1 | Papillary ca. | Tot. | 0.70 | < 0.5 | < 1 | 511 | NED (06) |
| 22 | 46/ F | T4bN1 | Papillary ca. + oesophageal inv. | Tot. | 1.5 | 0.37 | 2.4 | N | NED (34) |

Histology: ca. = carcinoma; CLT = chronic lymphocytic thyroiditis; ST = sclerosing thyroiditis; Inv. = invasion;
Surgery: Tot. = total thyroidectomy; Hemi = hemi-thyroidectomy; TG pre = pre-surgery TG (ng/ml); TG sp = TG during T4 suppressive therapy (ng/ml); TG $^{131}$I = TG at $^{131}$I scan (ng/ml); ND = not done (hemithyroidectomy); TGAb = anti TG antibodies at time of surgery (U/ml); N = negative; Follow-up (m) = latest follow-up (months after surgery); NED = no evidence of disease; REC = recurrence.

We identified a group of 22 patients (19 female, 3 male), median age 40 years (range 15-64) with serum TG levels, prior to surgery, < 2 ng/ml, which was the lower sensitivity limit of the assay used at the beginning of the study (Table II). Eleven (50%) of these patients had TGAb above the normal range before surgery, but, in all cases, levels decreased slowly and none had elevated TGAb two years after surgery.
Of the 22 patients, 13 underwent radioiodine ablation therapy (two patients received two treatments). Mean ablation dose was 3700 MBq (range 2,200-5,550). I-131 total-body scans were performed before and after ablation, and 6 months later. Two years after primary surgery, patient 16 (Table II) developed recurrent disease involving the cervical lymph nodes with positive radioiodine scan; TG remained undetectable. She was submitted to neck dissection and a repeat dose of radioiodine and is, at present, free from disease. At present, all patients remain disease-free.

## Discussion

About 20-30% of patients with high risk or advanced (stage III or IV) WDTC, submitted only to surgery, develop local recurrences or distant metastases. In most cases, repeat surgery, associated with radioiodide therapy is successful. Most recurrences are diagnosed within 5 years of surgery, but due to the indolent clinical behaviour of these tumours, long-term follow-up (up to 40 years) is necessary [4 18 19 27 28 30 32 33 37 38]. In general, TG assay alone or combined with $^{131}$I scan is a highly sensitive marker of disease recurrence. However, less differentiated metastases tend to be associated with lower TG levels [13 17 25]. This may be due to reduced synthesis or release of normal TG, or production of an abnormal TG unrecognized by routine radioimmunoassay (RIA) methods or rapidly cleared from the plasma [13 25 34]. Furthermore, an estimated 4-8% of WDTC patients have undetectable serum TG even with clear evidence of metastases [1 4 13 34-36 39].

Table III. Follow-up protocol for patients with well-differentiated thyroid carcinoma.

| Low risk | High risk |
|---|---|
| | After surgery: $^{131}$I total body scan<br>plus $^{131}$I therapy if required |
| Thyroxin for substitutive therapy or TSH suppression | TSH suppression with thyroxin |
| Every 6 months for 3 years, then yearly for 7 years:<br>Clinical evaluation<br>US scan of neck<br>fT4, TSH, TG and TGAb assay<br>Thereafter (annually):<br>Clinical evaluation<br>TG assay | Every 6 months for 5 years, then yearly for 10 years:<br>Clinical evaluation<br>US scan of neck<br>fT4, TSH, TG, TGAb assay<br>Thereafter (annually):<br>Clinical evaluation<br>TG assay |
| | $^{131}$I total body scan 6 months after $^{131}$I therapy<br>then 1, 2, 3, 5 and 7 years later |
| Chest X-ray every 2 years for 10 years | Chest X- ray every year for 3 years then every 2 years |

It is important, therefore, to identify patients in whom recurrence may not be revealed by this method and to have sensitive and preferably low-cost means available to detect recurrent disease at an early stage, particularly with a view to performing conservative surgery.

The most frequent follow-up techniques used, in such cases, are X-ray, US, radioiodine scan, FNAB, and magnetic resonance imaging (MRI) [6 22 40 41]. Some Authors have attempted to detect thyroid cancer cells by polymerase chain reaction (PCR) amplification of TG mRNA [3 9 15 42-45] particularly since human recombinant TSH is expensive. PCR is highly sensitive but Takano et al. [45] found no difference in the expression of TG mRNA in patients with or without metastases, and TG mRNA has also been found in control blood [42 44 46]. These data indicate that PCR is not useful for detecting occult disease or for selecting patients at high risk of recurrence.

Other markers proposed for the diagnosis and follow-up of WDTC are NIS > (Na+/I- symporter), thyroid peroxidase and the TSH receptor [17, 47] and vascular endothelial growth factor [5 48] but none have proved sufficiently sensitive to reliably detect recurrent disease [49].

In the present investigation, the problem was approached by measuring serum TG levels pre-operatively and, indeed, 22 patients were identified with primary WDTC in whom serum TG had not been detected before treatment. TGAbs were present in 11 of these patients, at diagnosis, but following treatment TGAb decreased slowly in all cases. However, in none of these 22 cases was TG detected during follow-up, either during TSH suppressive therapy or during TSH withdrawal for radioiodine scan.

Only one of these patients has, so far, presented recurrence: she underwent neck dissection for lymph node metastasis. The metastasis proved to be well differentiated papillary thyroid carcinoma, contrary to the tendency for recurrences in low TG cases to be associated with dedifferentiation.

For those patients with TGAb, the latter explanation would be the most likely, but patients with low TG before surgery may be unable to produce TG or present a form not detected by the assay at present used. We are currently evaluating neoplastic and normal thyroid tissue from all TG negative patients in the attempt to establish the reasons for the negative titres, and we are studying one family (two sisters and their aunt: the aunt and one niece with papillary thyroid cancer and second niece with benign thyroid disease) in whom serum thyroglobulin was undetectable before surgery, in the absence of antibody, while both tumour tissue and normal thyroid tissue around the tumour stained regularly for TG.

Meanwhile, such patients should, in our opinion, be followed according to a "high-risk-of-recurrence" protocol (Table III) involving $^{131}$I total body scan, even though it seems clear that these patients are not at high risk of recurrence, simply because we cannot rely on an oversimplified protocol.

As immunoassays for TG become more sensitive, and in view of the excellent results obtained with recombinant TSH-stimulated TG monitoring with these assays, some Authors have proposed that this method alone may be sufficient in the follow-up of WDTC patients [10 11 16 39 50 51]. We would be against

this policy because of the persistence of false negatives [1 2 4 10 13 34-36]. Even when TG assay is combined with whole body scan, a few false negatives remain [39]. We hypothesized that pre-operative TG assay can identify TG-negative patients who, if they recurred, would not be picked up by regular TG assay. Clearly, the fact that only one of our TG-negative patients recurred – and remained TG-negative notwithstanding recurrence does not confirm this hypothesis. It is worthwhile emphasizing, however, that pre-operative TG assay is a simple and inexpensive procedure, available to all centres. Moreover, although TGAbs were present in half of these TG-negative cases, TGAbs became undetectable in all of these patients, within two years of surgery, despite the fact that TG remained undetectable.

We, therefore, suggest that pre-operative TG assay is a simple and worthwhile procedure that identifies a sub-group of patients requiring $^{131}$I total body scan, neck US, or possibly MRI, since TG assay is always likely to be negative. On the other hand, for low-risk WDTC patients with normal pre-operative TG levels, periodic TG assay may by sufficient for long-term follow-up.

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■ Address for correspondence: Dr. B. Gibelli, Divisione di Chirurgia Cervico-Facciale, Istituto Europeo di Oncologia, via Ripamonti 435, 20141 Milano, Italy. Fax + 39 02 57489491. E-mail: bianca.gibelli@ieo.it