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Prognostic value of serial serum thyroglobulin determinations after total thyroidectomy for differentiated thyroid cancer

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ABSTRACT. Serial weekly serum samples (for 3 weeks) were obtained from 42 patients with differentiated thyroid cancer (DTC, papillary no.=35, follicular no.=6, Hürthle cell no.=1) for serum thyroid hormone, TSH and TG before and after total thyroidectomy. Serum specimens were also obtained one month after radioiodine (^{131}I) therapy followed by suppressive dose of L-thyroxine (L-T_4, 2.5 µg/kg). The patients were subdivided into four groups: group I: the DTC was confined to a single solid nodule (no.=12); group II: thyroid malignancy invaded local cervical structures but there were no lymph node metastases (no.=8); group III: DTC with lymph node metastases (no.=6); and group IV: DTC with distant metastases (no.=16). In all group I patients serum TG remained undetectable in spite of elevated serum TSH levels at the 3rd week post-surgery (PS). Only one of group II patients had a detectable serum TG value of 5.2 ng/ml (3rd week PS). By contrast, 37.5% of group III patients had detectable serum TG levels, ranging from 3.4 to 16.8 ng/ml (3rd week PS). Lymph node metastases were detected in 5 of these patients by whole body scan (WBS) and removed surgically in 3. As expected, group IV patients had elevated serum TG values ranging 33.0-958.0 ng/ml and distant metastases were confirmed in all of them by WBS. From the calculations through univariate logistic regression comparing TG concentrations at the 3rd week PS from groups I and II *vs* groups III and IV, we obtained a cut-off value of 2.3 ng/ml with the following efficacy features: sensitivity=74.5%; specificity=95%; positive predictive value=92.3%; negative predictive value= 65.5%; and accuracy=73.8%. After ^{131}I and L-T_4 suppressive therapy, only 5 out of 36 patients of groups I, II and III had detectable serum TG levels (3.1-7.0 ng/ml) whereas serum TG was detectable in all group IV patients (ranging 2.5-8.6 ng/ml). We concluded that serum TG concentrations above 2.3 ng/ml at the 3rd week PS could be suggestive of lymph node or distant metastases in patients with DTC. Patients with serum TG above this limit could be considered at risk for metastatic disease and higher doses of diagnostic iodine-131 (^{131}I) may be indicated for actinic ablation.

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INTRODUCTION

Thyroid cancer is one of the most frequently occurring endocrine malignancies worldwide. Approximately 17,000 new cases are diagnosed yearly in the United States, but prevalence may be higher in other regions of the world (1-3). The majority of these lesions are papillary and follicular carcinomas, the incidence of the latter being relatively more elevated in areas of iodine deficiency (1, 4). The follow-up of thyroid cancer after total thyroidectomy typically includes a diagnostic iodine-131 (^{131}I) whole-body scan (WBS), and determination of the serum level of TG under stimulation with the rising endogenous TSH after surgery (5-9). An increased TG level, associated or not with a positive cervical thyroid scan, indicates the persistence of some thyroid remnant in the anterior cervical area or, alternatively, the presence of regional or distant metastases.

Considering an emergent body of knowledge (10, 11), we hypothesized that serum TG may be a predictive index of local and distant metastases in patients submitted to total thyroidectomy for differentiated thyroid cancer (DTC) as early as in the period immediately following this therapy.

Key-words: Thyroglobulin, thyroid cancer, thyroid surgery, metastases, radioiodine.

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PATIENTS AND METHODS

Patients

We included 42 patients submitted to total thyroidectomy because cytology was suggestive of cancer. Seven patients with confirmed thyroid cancer were not included in this study because they had positive anti-TG autoantibodies. The study cohort was formed by 32 female patients (76.2%) and 10 male patients (23.8%), aged between 23 and 87 yr (median: 42.5 yr). All patients gave their consent, after being informed of the purpose of this research project. Moreover, the project was approved by the Ethics Committee of the Hospital das Clinicas, University of Sao Paulo Medical School.

Pre-surgical data: Before surgery all patients underwent a complete thyroid workup including total T_4, total T_3, TSH, serum TG, serum anti-thyroperoxidase (anti-TPO) and anti-TG autoantibodies, thyroid scan and thyroid ultrasonographic studies. Sonographic examination were performed by one of the authors (E.T.) using a 7.5 MHz transducer (ALOKA SSD-500, Tokyo, Japan) in both longitudinal and transverse planes covering both lobes and isthmus. All thyroid nodules were evaluated by fine needle aspiration (FNA).

All patients had palpable single nodules that further ultrasound evaluation revealed to be multiple non-palpable thyroid nodules in nearly one third of the patients; the usually hypoechoic dominant nodule mean volume (±SE) was 12.7±9.8 ml (range: 0.9-411 ml). Some patients had evidence for lymph node and/or distant metastases. In 35 out of 42 patients the FNA yielded cytologic findings of papillary carcinoma, in 6 follicular neoplasm and in 1 patient Hürthle-cell neoplasm.

Post-surgical data: Blood specimens were collected after surgery at 7, 14 and 21 days for evaluation of thyroid function and serum TG concentrations. Between the 22nd and the 30th day the patients were admitted to the University Hospital for ^{131}I treatment (100-150 mCi of ^{131}I) followed by a ^{131}I WBS 4 to 7 days later to search for foci of uptake outside the thyroid bed. One month later serum thyroid hormone, TSH and TG were again evaluated while they were on suppressive dose of levothyroxine (L-T_4, 2.5 µg/kg).

During the period between surgery and ^{131}I therapy the patients were kept on a low-iodine diet and consumed only non-iodized salt. Serum TSH levels were above 35 µU/ml in all patients, before thyroid ablation with ^{131}I. Subsequently, the patients were instructed to start L-T_4 suppressive dose (2.5 µg/kg). Considering the clinicopathological features after thyroidectomy, results of WBS to detect or exclude metastases and the American Joint Commission on Cancer (AJCC) tumor-node-metastasis (TNM) classification system (12, 13), the patients without statistical difference, neither for age (mean±SD) nor for gender proportion between the groups, were allocated into four groups to compare the results of serum TG:

Group I (no.=12, 9 women and 3 men): the subjects presented single nodules with different sizes without lymph node metastases (T_2, N0, M0). Nine had papillary cancer (common histological type) and 3 had follicular cancer. Eight patients were classified as stage I and 4 patients as stage II;

Group II (no.=8, 7 women and 1 man): all the subjects presented papillary carcinoma (common histological type) and local invasion of cervical structures without metastases to local lymph nodes (T_4, N0, M0). In these patients post-surgical pathologic evaluation did not show invasion of suspicious regional lymph nodes identified and resected intraoperatively. Four patients were classified as stage I and 4 patients as stage III;

Group III (no.=16, 11 women and 5 men): thirteen had a final pathological diagnosis of papillary cancer (common histological type) and 3 follicular cancer. All patients had metastases to cervical lymph nodes (T_2, N1, M0). Ten patients were classified as stage I and 6 patients as stage III;

Group IV (no.=6, 5 women and 1 man): five patients presented with papillary cancer (4 with common histologic type and 1 with a follicular variant of the tumor; classified as papillary carcinoma because of the presence of typical "ground glass" nuclei) and 1 patient with Hürthle cell carcinoma. All patients had metastases (pulmonary, no.=5, and both lungs and bone, no.=1) (T_2, N0, M1). Three patients were classified as stage II and 3 as stage IV.

Evaluation of thyroid function

TSH, total T_4 and total T_3 were measured by immunoenzymometric assays (Stratus automated system, Baxter Diagnostics Inc., Deerfield, IL, U.S.A.) (normal ranges: TSH=0.4-3.5 µU/ml; total T_4=4-12 µg/dl; total T_3=80-200 ng/dl). Unaware of clinical data, serum TG was evaluated by IRMA (DYNOtest, BRAHMS Diagnostica, Berlin, Germany) with sensitivity of 0.2 ng/ml and the within-run and between-run coefficients of variation (CVs) of 9.0 and 10.0%, respectively. Normal

range: 0.5-15.5 ng/ml. Anti-TG was assayed by RIA (DYNOtest anti-TG, BRAHMS Diagnostica, Berlin, Germany) (14). The result was considered positive for values of anti-TG greater than 200 U/ml.

Ultrasonographic studies and cytological examination

Sonographic examination was performed using a 7.5 MHz transducer in both longitudinal and transverse planes covering both lobes and isthmus (ALOKA SSD-500, Tokyo, Japan). The ultrasonographic studies were performed by one of the Authors (E.T.). All thyroid nodules were evaluated by FNA.

Statistical analyses

Data were analyzed by usual descriptive statistics (mean, standard deviation, standard error, median and percentage). Kruskal-Wallis non-parametrical testing for independent samples and the Fisher exact test (2-tailed) were employed for comparison between groups. A TG level (cut-off point) that could be associated with an indication of extrathyroidal and/or extracervical metastases was obtained through a univariate logistic regression model, evaluating TG concentrations of groups I and II *vs* III and IV at the third week after surgery. Also, the following efficacy indexes related to that cut-off point were calculated: sensitivity, specificity, positive predictive value, negative predictive value and accuracy. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS for Windows, SPSS Inc., Chicago, IL, U.S.A.).

RESULTS

Serum thyroid hormone and TSH

There were no significant differences between total T_4, total T_3 and TSH concentrations both at the presurgical blood specimen and following 4 measurements after surgery and ^{131}I, for all patients in the 4 groups studied. Serum TSH in all patients in the 4 groups rose in function of time after surgery, and attained mean levels between 46.6 and 81.1 μU/ml (Table 1). After ^{131}I treatment and L-T_4 suppressive therapy all patients had undetectable serum TSH values.

Serum TG

The results are shown in Table 2 and Figure 1. All measurements for TG were performed blind using the same assay in order to eliminate the inter-assay variation. Before surgery group IV patients had a mean±SE of TG of 352.1±136.3 ng/ml (range: 46.7-906.0 ng/ml) that was significantly different ($p<0.0004$) as compared with the 3 other groups (Kruskal-Wallis test). As for groups I, II and III, there were no significant differences in serum TG mean concentrations before surgery.

In the following 3 weeks after surgery the situation remained the same, *e.g.* only the group of patients with distant metastases (group IV) had mean±SE TG concentrations that were significantly higher than the 3 other groups (Table 2). From the calculations through univariate logistic regression comparing TG concentrations at the 3rd week after surgery from groups I and II against groups III and IV, we obtained a cut-off value of 2.3 ng/ml. Thus, a TG level above 2.3 ng/ml could be a risk-indicator associated with local and/or distant metastases. This point presented the following efficacy indexes: sensitivity=74.5%; specificity=95.0%; positive predictive value=92.3%; negative predictive value=65.5% and accuracy=73.8%.

In addition, taking the TG values at the highest TSH concentration attained at the 3rd week after surgery we observed that, in group I, none of 8 stage I and 4 stage II patients had a TG value higher than 2.3 ng/ml. Similarly only 1 stage III out of 8 patients of group II (12.5%) subjects had serum TG values higher than 2.3 ng/ml. However, 6 of the 16 patients in

Table 1 - *Serum TSH levels in patients with differentiated thyroid cancer before and after surgery followed by radioiodine ablation (RAI).*

Groups of patients	Before surgery (μU/ml)	After surgery (days) (μU/ml) 7	14	21	After RAI+L-T_4* (μU/ml)
I	1.5±0.4 (0.05-4.3)	26.0±11.1 (0.09-132.8)	52.9±17.5 (0.8-216.0)	76.0±18.4 (6.7-250.8)	0.1±0.1 (0.05-0.3)
II	0.9±0.4 (0.05-2.9)	6.7±3.1 (0.05-24.4)	23.3±7.6 (3.8-67.9)	46.9±11.3 (16.4-118.0)	0.2±0.1 (0.03-0.8)
III	1.5±0.3 (0.05-3.6)	14.1±4.7 (0.05-70.5)	37.4±6.9 (0.6-102.0)	61.3±7.8 (14.8-116.0)	0.1±0.1 (0.03-1.6)
IV	1.9±0.3 (0.7-4.3)	29.2±12.4 (6.1-75.8)	55.0±15.1 (23.2-110.8)	81.1±15.3 (36.8-138.8)	0.1±0.1 (0.05-0.9)

Data are given as mean±SE and (range). *Thirty days after ablation (100-150 mCi) and suppressive dose of levothyroxine (L-T_4).

Table 2 - *Serum thyroglobulin levels in patients with differentiated thyroid cancer before and after surgery followed by radioiodine ablation (RAI).*

Groups of patients	Before surgery (ng/ml)	After surgery (days) (ng/ml) 7	14	21	After RAI+L-T_4* (ng/ml)
I	12.1±1.8 (2.2-16.5)	1.8±0.5 (0.5-6.4)	0.7±0.2 (0.5-2.6)	0.7±0.1 (0.5-2.0)	0.5±0.008 (0.5-0.6)
II	4.5±2.1 (0.5-18.0)	0.7±0.2 (0.5-1.8)	1.2±0.4 (0.5-3.5)	1.5±0.6 (0.5-5.2)	1.8±0.9 (0.5-7.7)
III	11.8±3.5 (0.5-50.0)	2.5±0.6 (0.5-8.2)	2.5±0.7 (0.5-11.8)	3.5±1.1 (0.5-16.8)	1.4±0.4 (0.3-7.0)
IV	352.1±136.3** (46.7-906.0)	463.6±136.3** (61.4-871.0)	294.1±141.5** (57.0-939.0)	251.0±146.3** (33.0-958.0)	5.5±1.2 (2.5-8.6)

Data are given as mean±SE and (range). *Thirty days after ablation (100-150 mCi) and suppressive dose of levothyroxine (L-T_4); **$p<0.05$ in comparison with the other groups.

group III (37.5%) had TG higher than 2.3 ng/ml, 4 stage I patients of them with TG values between 3.4 and 16.8 ng/ml and 2 stage III patients with 3.6 ng/ml and 8.1 ng/ml, respectively (Fig. 1, left panel). This was considered significant ($p<0.05$) when submitted to the Fisher exact test (2-tailed). As expected all 6 patients of group IV had elevated TG values at the 3rd week post-surgery (Table 2).

After ablation with ^{131}I all patients from group I (4 stage II and 8 stage I patients) had TG values of less than 1 ng/ml whereas in group II (1 stage I and 1 stage III; range: 3.3-7.7 ng/ml) and group III 3 patients (2 stage I and 1 stage III; range: 3.1-7.0 ng/ml) had detectable levels of TG. The mean±SE of TG (0.5±0.008 ng/ml) of group I was significantly lower (Kruskal-Wallis test) as compared with group IV (5.5±1.2 ng/ml) ($p<0.05$) although it did not differ from the two other groups (II: 1.8±0.9 ng/ml; III: 1.4±0.4 ng/ml). Two patients from group I, 1 from group II, 2 from group III and 1 from group IV became anti-TG antibody-positive following ^{131}I therapy.

After ^{131}I and under suppressive daily dose of L-T_4, all patients in group I (4 stage II and 8 stage I) had undetectable levels of TG. Two patients (1 stage I and 1 stage III) in group II had a TG concentrations of 3.3 ng/ml and 7.7 ng/ml, respectively, while 3 patients (2 stage I and 1 stage IV) in group III had TG values between 3.1 and 7.0 ng/ml. By contrast, all patients in group IV (3 stage II and 3 stage IV) had detectable TG concentrations ranging 2.5-8.6 ng/ml with a mean value±SE of 5.5±1.2 ng/ml (Table 2 and Fig. 1, right panel).

In Figure 1 the serum TG values at the 3rd week post-surgery and corresponding values after ^{131}I ab-

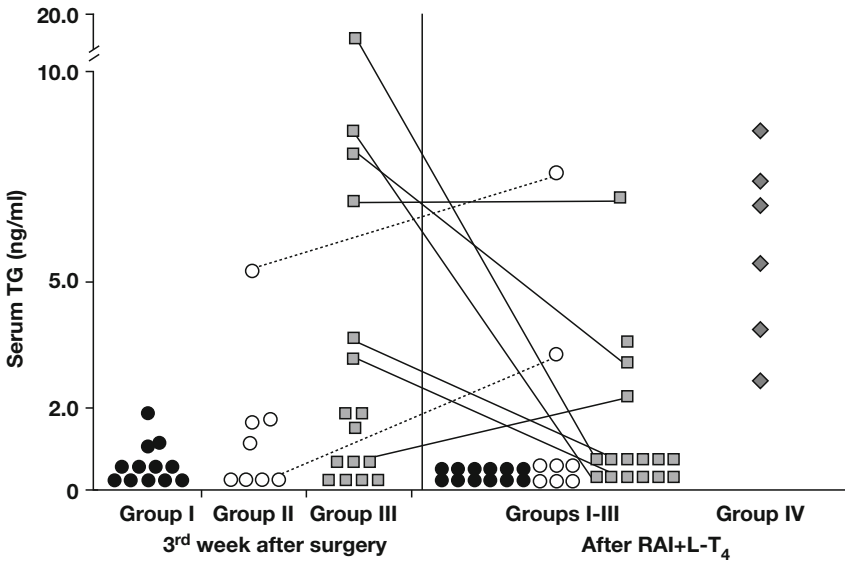

Fig. 1 - *The left panel shows TG levels at maximal TSH concentrations, attained at the 3rd week post-surgery. Note that group III (with lymph node metastases) had 6 patients with relatively elevated TG levels. The right panel depicts the TG levels one month after radioiodine ablation (RAI), followed by suppressive daily doses of levothyroxine (L-T_4). Note that all patients in group IV had detectable TG levels. Two patients in group II (○) increased their serum TG levels after ablation (respectively 5.2 to 7.7 ng/ml, and 0.5 to 3.3 ng/ml). In both patients the whole body scan indicated uptake only in the thyroid bed. Six patients in group III (■) had serum TG values >2.3 ng/ml at the 3rd week post-surgery. In one patient serum TG remained the same (7.0 ng/ml) and in 5 other patients serum TG decreased to lower values. Only one patient increased to a higher value.*

lation and L-T_4 are indicated individually. The 2 patients from group II (○) that had an increased serum TG value post-RAI had a WBS demonstrating uptake only in the thyroid bed. By contrast 5 patients from group III (■), with the highest serum TG values at the 3rd week post-surgery (3.6-16.8 ng/ml) had evidence for nodal metastases in the WBS performed after the therapeutic dose (Fig. 1).

DISCUSSION

TG is the main thyroid gland protein where it represents, approximately, 75% of all proteins. As a precursor of thyroid hormone, it is synthesized exclusively in the follicular cells of the thyroid. It has long been believed that TG is present only in the thyroid. About 40 yr ago it was demonstrated that TG is present in the systemic circulation as well, being released via lymph from the thyroid (15).

In thyroid oncology, TG has been used as a tumor marker for the detection of metastases or recurrence after total thyroidectomy in patients with DTC for about 18 yr (5-8, 10, 11). In order to determine the optimal timing of serum sampling for TG measurements, information on TG half-life is of essential importance. Like all glycoproteins, TG is eliminated through the liver (16). The data on serum TG half-life in the literature are scarse (16, 17) and the reported values vary greatly, ranging from 6 to 96 h. Following subtotal thyroidectomy, Feldt-Rasmussen *et al.* (17) were able to demonstrate that TG with different molecular sizes (ranging 100-600 kDa) were detected in the systemic circulation. Accordingly, for the heaviest TG molecule (19S) the mean disappearance rate was 4.3 days whereas the overall half-life of smaller molecules had a mean disappearance rate value of 3.7 h. More recently, Hocevar *et al.* (18) collected serum samples of patients with DTC (no.=6) and nodular goiter (no.=5) at 24, 48, 72 and 168 h after total thyroidectomy. All measurements were performed using the same assay in order to eliminate interassay variations. Serum TG levels were determined and TG half-life calculated by the use of one-compartment kinetic mode. Mean serum TG half-life was 65.2 h (SE=4.3 h) or, approximately, 2.7 days. Individual values ranged 36.9-86.6 h for serum TG half-life (1.5-3.6 days, approximately). These results and the previous work by Lo Gerfo *et al.* (16) suggest that serum TG sampling should be carried out about 3 weeks after total thyroidectomy, in order to be indicative of the presence or absence of metastatic or residual disease.

Based on these experiments, Ronga *et al.* (11) evaluated the diagnostic significance of serum TG measurements performed 40 days after total thyroidectomy for DTC, prior to the therapeutic use of ^{131}I. In 79 patients who later presented with lymph node (no.=32) or distant metastases (no.=47), serum TG at the 40th day post-thyroidectomy was significantly higher (mean: 250 ng/ml) than in 255 patients without metastases (mean: 15.9 ng/ml). Thus, an elevated serum TG level (>69 ng/ml) about 5 weeks post-total thyroidectomy has a 90% predictive value for the presence of DTC metastases.

In this paper we have presented our data on weekly serum TG determinations after total thyroidectomy for DTC. The patients were subdivided in 4 groups, based on the surgical and pathological findings. Thus, group I represented patients with DTC confined to a single solid nodule, whereas group IV patients had a confirmed diagnosis of distant metastases. Also, we included within this spectrum of malignancy patients with invasion of cervical structures by the tumor (but without lymph nodes metastases; group II) and patients with pathological confirmation of lymph node metastases (group III). As expected all patients (with one stage II patient exception) in group I had undetectable serum TG values 21 days after total thyroidectomy. One patient classified as stage III from group II had detectable levels of serum TG at the 3rd week post- surgery. This was interpreted as an evidence of residual thyroid tissue, possibly infiltrating local structures. After thyroid ablation and WBS there was no evidence for lymph node metastases. Group III patients had higher mean±SE serum levels of TG; in 6 of these patients serum TG ranged 3.4-16.8 ng/ml at the 3rd week post-surgery (Fig. 1). After thyroid ablation and WBS, 5 of them had evidence for lymph node metastases and in 3 of these 5 patients metastatic nodes were removed surgically.

As previously mentioned, all patients in group IV had evidence for distant metastases, which explained the higher levels of TG obtained at the 3rd week post-surgery.

After ^{131}I ablation, TG was undetectable in 31 patients (out of 36) from groups I, II and III while all patients with distant metastases (group IV) exhibited TG concentrations ranging 2.5 to 8.6 ng/ml. These detectable TG levels might be expected after thyroid ablation and L-T_4 therapy, because of the occurrence of distant metastases. More difficult to explain is the presence of detectable TG values in patients from group II (2 cases) and group III (3 cases) after ^{131}I therapy and L-T_4 suppressive doses. One explanation could be that the time after ablation (30 days) would be too short to evaluate the therapeutic effectiveness of the ^{131}I therapy.

In conclusion, we have demonstrated that in some patients with thyroid malignancy and lymph nodes metastases detectable TG values can be observed at the 3rd week after surgery. This fact may be indicative of the need for higher doses of ^{131}I in these patients in an attempt to eradicate the regional and distant metastases.

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