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Usefulness of repeated recombinant human thyrotropin-stimulated thyroglobulin test in the post-surgical follow-up of very low-risk patients with differentiated thyroid carcinoma

C. Cappelli[1], M. Rotondi[2], I. Pirola[1], E. De Martino[1], E. Gandossi[1], B. Agosti[1], E. Agabiti Rosei[1], L. Chiovato[2], and M. Castellano[1]

[1]Department of Medical and Surgical Sciences, Internal Medicine and Endocrinology Unit, University of Brescia, Brescia; [2]Unit of Internal Medicine and Endocrinology, Fondazione Salvatore Maugeri, I.R.C.C.S., ISPESL Laboratory for Endocrine Disruptors and Chair of Endocrinology, University of Pavia, Pavia, Italy

ABSTRACT. ***Background:*** **The European Thyroid Association (ETA) and the American Thyroid Association (ATA) guidelines identify subgroups of patients affected by thyroid carcinoma in whom, due to a low risk of recurrence, radioiodine ablation is not indicated. These patients are referred to as "very low-risk" according to the ETA consensus and "low-risk" patients according to the ATA guidelines. The recommended post-surgical follow-up of these patients is based upon periodical measurements of serum thyroglobulin (Tg) on levothyroxine therapy and neck ultrasound (US).** ***Aim:*** **To evaluate the usefulness of recombinant human (rh)-TSH Tg test and its repetition 2-3 yr afterwards in very low-risk patients.** ***Materials and methods:*** **We consecutively enrolled 32 patients with undetectable anti-Tg antibodies. Basal serum Tg levels was undetectable in all patients.** ***Results:*** **Following rhTSH serum Tg remained undetectable in 23 (71.9%) patients (UP) and was >1.0 ng/ml in 9 (DP). US and whole body scan, revealed lymph node metastasis in 4/9 DP patients. A second rhTSH stimulation test (36.9±3.5 months later) was performed in all UP and in 5 DP patients without proven recurrences. All the UP and 4/5 formerly DP patients showed undetectable Tg stimulation.** ***Conclusions:*** **Our results suggest that rhTSH Tg test may be helpful in very low-risk patients, given its ability to differentiate those who may be considered "free of disease" from those who require further investigation and treatment. Repeated rhTSH Tg tests may be indicated only in patients with detectable serum Tg at prior stimulation testing.**

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INTRODUCTION

Differentiated thyroid carcinoma (DTC) is the most frequent endocrine malignancy worldwide. Its incidence has been increasing in many countries over the last 20 years, mostly due to the earlier detection of small papillary cancers as a result of improved diagnostic accuracy) (1-5). Nearly 60-80% of newly diagnosed thyroid carcinomas are papillary microcarcinoma (size ≤10 mm) (PTMC) (5), carrying an excellent long-term prognosis, even if recurrences and/or metastasis have been reported (6-10).

The post surgical follow-up of DTC is aimed at the early detection of persistent or recurrent disease. In patients submitted to post-surgical radioiodine (^{131}I) ablation of thyroid remnants, serum thyroglobulin (Tg) measurement, after thyroid hormone withdrawal or after stimulation with recombinant human TSH (rhTSH), and neck ultrasound (US) investigation represent the gold standard procedure (10-15). The European Thyroid Association (ETA) and the American Thyroid Association (ATA) guidelines for the management of patients with DTC identify subgroups of patients in whom, due to a low risk of recurrence, radioiodine ablation is not indicated. These patients, defined as those bearing a unifocal microcarcinoma with favorable histology, no extension beyond the thyroid capsule and no lymph node metastases, are referred to as very low-risk according to the ETA consensus and low-risk patients according to the recently delivered ATA guidelines (10, 16). The recommended post-surgical follow-up of these patients is based upon periodical measurements of serum Tg on levothyroxine ($L\text{-}T_4$) therapy and neck US. However, the current guidelines do not provide precise recommendations regarding the levels of serum Tg which might be relevant for decision making. In a recent study, Torlontano et al. reported that in very low-risk patients with PTMC who did not receive radioiodine treatment following thyroidectomy, the measurement of serum Tg after rhTSH stimulation at 6-12 months after surgery is useful for identifying those patients with evidence of persistent disease (17).

Aim of this prospective study was to evaluate in patients bearing a very low-risk PTMC the usefulness of an rhTSH Tg test performed at the first post-thyroidectomy follow-up (6-12 months after surgery) and repeated 2-3 yr afterwards. This strategy could provide a tool for the early detection of persistent or recurrent disease, while reducing the number of false positive results observed after the first rhTSH test.

Key-words: Recombinant TSH, thyroglobulin, thyroid carcinoma, papillary thyroid cancer, very low risk patients.

Correspondence: C. Cappelli, M.D., Department of Medical and Surgical Sciences, Internal Medicine and Endocrinology Unit, University of Brescia. c/o 2^ Medicina Spedali Civili di Brescia, Piazzale Spedali Civili n°1, 25100 Brescia (Italy).

E-mail: cappelli@med.unibs.it

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MATERIALS AND METHODS

Patients

From January 2003 to December 2004, we consecutively enrolled 32 patients affected by PTMC with undetectable anti-Tg antibodies, who were classified as very low-risk in accordance with the European ETA consensus (10). All patients underwent near-total thyroidectomy performed by the same skilled surgical team. In detail, 18 patients were submitted to surgery for the suspicion of DTC, as assessed by fine needle aspiration cytology, whereas the remaining 14 patients were submitted to thyroidectomy for a multinodular non-toxic goiter. In the latter group, thyroid malignancy was incidentally discovered on histological examination. A classical papillary thyroid carcinoma was diagnosed in all patients. Fine sections of the surgical specimens excluded the presence of tumor multifocality. After surgery, all patients received L-T_4 aiming for a serum TSH level <0.4 μU/ml.

The first follow-up evaluation was performed within 6-12 months (mean 8.8±1.7 months) after surgery. Patients were submitted to physical examination and to neck US performed by the same physician. On day 1, blood samples were drawn for the determination of baseline serum TSH, Tg, and anti-Tg antibodies. Thereafter, patients received an injection of rhTSH (0.9 mg) (Genzyme Transgenics Corp., Cambridge, MA). On the following day, a second injection of rhTSH (0.9 mg) was administered. On day 3, 185 MBq (5 mCi) of ^{131}I were given. On day 5, a whole body scan (WBS) and a US neck examination were performed. Clinical examination, rhTSH Tg test and US were repeated at a second follow-up visit performed 36 months after the first one. Patients were defined as free of disease when stimulated serum Tg was <1.0 ng/ml and no evidence of disease at clinical examination, neck US or ^{131}I WBS was detected.

Methods

Serum TSH, Tg, and TgAb were measured using a chemiluminescent assay by an automated analyzer (Immulite 2000, DPC Cirrus, Los Angeles, CA, USA).

The Tg assay had a functional sensitivity of 0.9 ng/ml with an analytical sensitivity of 0.2 ng/ml. The interassay variability of the Tg assay in our laboratory was 3.9%. TgAb were considered negative when <20 IU/ml. The normal range for TSH was 0.4-4.5 mIU/l.

All patients were submitted to neck US investigation using an ultrasonographic scanner (LOGIQ General Electirc, Milwaukee, WI) equipped with a 10-14 MHz linear transducer. Neck US was performed by a specifically trained endocrinologist (CC) who was blinded as to the patients' Tg status. WBS was performed using a double-head-γ camera, equipped with high-energy collimators and thick crystals (GCA 901; Toshiba, Tokio, Japan).

Statistical analysis

Data are expressed as mean±SD. Comparisons between groups and differences between proportions were calculated using analysis of variance test for quantitative variables and χ^2 test for categorical variables, as appropriate. All data analyses were performed using SPSS version 11.5 (SPSS, Inc., Chicago IL).

RESULTS

Baseline

Anthropometric and clinical characteristics of investigated patients are reported in Table 1. No difference in gender, body mass index, and TSH values was found between subjects with incidental (I-PTMC) and non-incidental (NI-PTMC) thyroid cancer. The 18 NI-PTMC subjects submitted to surgery for the suspicion of malignancy were significantly younger than I-PTMC (p=0.012) and had significantly greater tumor size (p<0.001). On L-T_4, basal serum Tg levels (i.e. before rhTSH) were <1.0 ng/ml ("undetectable", according to our functional sensitivity limit) in all patients.

Table 1 - *Clinical characteristics of the patients.*

	Patients with incidental PTMC	Patients with non-incidental PTMC	*p*
Gender (F/M)	10/4	(13/5)	ns
Age (yr)	59.7±9.5	49.9±10.6	0.012
BMI (kg/m^2)	26.9±2.4	26.3±3.1	ns
Tumor size (mm)	2.2±1.1	7.4±2.1	<0.001
TSH (mU/l)	0.12±0.14	0.23±0.26	ns

PTMC: papillary thyroid microcarcinoma; F: female; M: male; BMI: body mass index.

Early follow-up

After rhTSH stimulation, Tg levels remained undetectable in 23 (72 %) patients (UP); in the other 9 patients (DP), stimulated serum Tg was ≥1.0 ng/ml (mean 3.5±2.2 ng/ml), without significant difference between I-PMTC and NI-PTMC (4 and 5 patients, respectively) (Fig. 1). Mean serum TSH increased to 55.6±7.6 mIU/l in the whole group of 32 patients, without significant difference between UP [55.2±8.0 mIU/l (range 48.4-72.3, median 56.5)] and DP subjects [56.5±6.6 (range 41.2-64.4, median 58.0)].

Neck US was negative for recurrence in 29 patients and positive in 3, whereas rhTSH-stimulated WBS revealed radioiodine uptake (RAIU) limited to thyroid bed, ranging from 0.1% to 9.8% (a finding which is compatible with variable amounts of residual thyroid tissue in not ablated patients) in 31 patients and positive lymph node uptake in 1 patient. In detail, both neck US and WBS were negative for recurrence or metastasis in UP, whereas among the 9 DP patients, neck US and/or WBS showed small lymph node metastases (all confirmed by cytology) in 4 (44.4%). US showed lymph node recurrence in 3 patients with negative WBS, whereas in 1 patient WBS was able to detect a pathological lymph node that had been missed by US (Fig. 1); in the latter case, a second neck US based upon the positive result of WBS was able to identify the small metastatic lymph node (diameter 4.7 mm) located near to the right internal jugular that had been missed at the first US evaluation. These 4 patients were submitted to high dose ^{131}I (100 mCi) and post-treatment WBS showed pathological lymph node uptake in all cases.

The remaining 5 DP patients with negative findings at both imaging techniques showed a non statistically significant trend toward lower stimulated Tg levels as compared to those with recurrences [1.74±0.45 ng/ml (range 1.1-2.3) *vs* 5.70±5.68 ng/ml (range 2.2-14.2), p=0.158].

Second follow-up

A second rhTSH stimulation test was performed at follow-up (36.9±3.5 months after the first one) in all UP and in the 5 DP patients without evidence of recurrent or

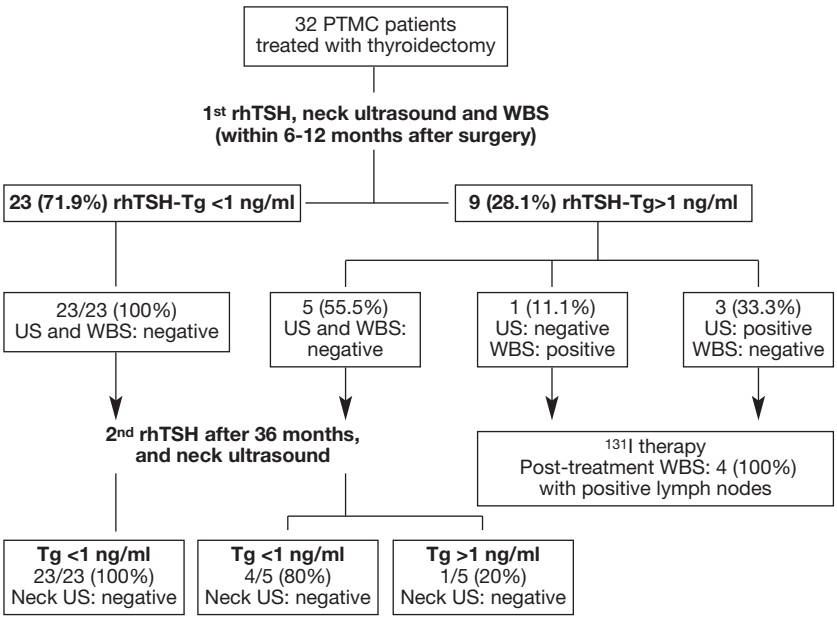

Fig. 1 - *Results of the first and second recombinant human (rh)-TSH stimulation tests. PTMC: papillary thyroid microcarcinoma; WBS: whole body scan; Tg: thyroglobulin; US: ultrasound; ^{131}I: radioiodine.*

metastatic disease at US or WBS (Fig. 1). All these 28 patients presented undetectable pre-stimulation Tg values. Twenty-seven out of the 28 presented undetectable Tg also after the second stimulation test, including the 23 patients who were found UP after the first test and 4 out of the 5 formerly DP. One additional patient, resulting DP at the first challenge, maintained measurable Tg levels after the second stimulation test (2.0 ng/ml and 1.9 ng/ml, respectively). A 50 mCI dose of ^{131}I was administered to this patient and the subsequent WBS showed uptake only in the thyroid bed.

Subsequent follow-up

All the subjects, including the 4 ^{131}I treated patients, are attending regular follow-up, carried out by means of basal serum Tg measurement and neck US while on L-T_4 substitution/suppressive therapy. To date, at 49.7±11.2 months after surgical treatment, none of the patients exhibits clinical or ultrasonographic signs of recurrent or metastatic disease.

DISCUSSION

The prognostic value of serum Tg measurement after thyroidectomy and before ablation with radioiodine was investigated, but discordant results were reported (18-22). Current guidelines from the most authoritative scientific societies, both in Europe (10) and United States (16), consider rhTSH Tg test and neck US examination as the appropriate tools for early detection of recurrence and/or metastases in DTC patients. With the exception of a single recent report (17) there are no data on the use of the rhTSH-stimulated serum Tg measurement in patients bearing a very low-risk DTC who did not perform ^{131}I ablation of post-surgical thyroid remnant. At this regard, ETA Consensus state only that in this category of patients "rhTSH is usually not recommended. Follow-up is based on serum Tg determination during L-T_4 treatment plus neck ultrasound".

The results of our study suggest that the rhTSH Tg test may be helpful also in patients with very low-risk thyroid cancer not submitted to radioiodine ablation, given its ability to differentiate those who may be considered "free of disease" from those who require further investigation and treatment. When performed within 6-12 months after thyroidectomy, measurable serum Tg levels (i.e.: above 1 ng/ml) 5 days after rhTSH administration were found in all subjects bearing lymph node metastasis (sensitivity = 100%, specificity = 82%). Stimulated serum Tg was always undetectable in subjects with no evidence of metastasis at US/WBS during a 4-yr follow-up [negative predictive value (NPV) =100%]. In comparison, the sensitivity, specificity and NPV of unstimulated serum Tg plus US-based follow-up was 75%, 100%, and 96.5, respectively. On the other hand, in our study WBS alone had a very low sensitivity (25%), thus confirming also in this type of patients that WBS is of little, if any value in the follow-up of thyroid cancer patients.

A few points deserve a specific consideration. Lymph node metastases were detected by neck US and/or by rhTSH-stimulated ^{131}I WBS (185 MBq) in 4 (44.4%) out of 9 patients with measurable serum Tg; these patients showed a trend toward higher Tg levels as compared to patients without lymph node metastasis, although statistical significance was not reached. In our study, the incidence of metastasis was higher than that reported by Torlontano et al. (12.5% *vs* 3.8%) (17), but in accordance with other recent data (23-25).

Five out of 32 patients showed a positive early rhTSH Tg test, lower as compared to those with recurrences (1.74±0.45 *vs* 5.70±5.68 ng/ml, respectively) with no evidence of recurrent/metastatic disease at imaging. In

agreement with patients, we decided to not treat them with high-dose ^{131}I (100 mCi) taking in account the favorable histology of the tumor, the absence of imaging suggestive for recurrent or metastatic disease and the very low stimulated Tg values. In fact, this relatively high (15.7%) proportion of "false positive" responses at rhTSH Tg test is most likely attributable to the presence of residual thyroid tissue, as indicated by the presence of a statistically significant correlation between neck RAIU and stimulated serum Tg levels in the whole group of patients ($r=0.49$, $p<0.001$) and the finding that all those with undetectable serum Tg had neck RAIU levels ≤0.6% (data not shown). This data underlined the high performance in term of low thyroid remnant amount obtained by our surgical team also for benign disease, allowing the use of rhTSH stimulation test also in not ablated patients. In the subgroup of patients with a positive rhTSH-Tg test at first examination, the second rhTSH stimulation demonstrated normalization (undetectable stimulated Tg values) in 4 patients (80%). This phenomenon could be attributed to a progressive atrophy of thyroid tissue remnants on long term L-T_4 therapy and/or to a cytotoxic effect of the previous diagnostic radioiodine administration (185 MBq ^{131}I). In the fifth patient, serum levels of Tg remained measurable and unchanged from the first to the second stimulation with rhTSH (2.0 ng/ml and 1.9 ng/ml, respectively), with no imaging evidence of recurrent or metastatic disease. An even higher proportion of negative imaging (32 out 35 DP) was observed in a previous study on very low-risk patients (17); interestingly, all patients in this series remained free of disease after a follow-up of 23±14 months.

Another intriguing observation in the present study is the finding of positive WBS in 1 rhTSH+ patient who had a negative neck US investigation. We should point out that performing a diagnostic WBS at follow-up was a widely adopted practice in 2003, when our study was designed, but this procedure is not indicated by current guidelines (10, 16). In fact, data from the literature are consistent in declaring the superior accuracy of stimulated serum Tg and US, as compared to WBS (10, 15, 16, 26, 27). In this particular case, a second neck US examination based upon the results of the WBS was able to detect a metastatic lymph node (diameter 4.7 mm) adjacent to the right internal jugular vein, missed at the first US examination. This finding underscores the risk that even experienced US operators (28, 29) may fail to diagnose metastatic lymph nodes and suggest to perform rhTSH Tg test prior to neck US investigation, to elicit greatest attention by the operator in DP.

As far as the prognostic value of repeating a second rhTSH Tg test a few years after thyroidectomy, the results of our study extend to very low risk patients the previously reported observations (5, 12, 27) in ^{131}I ablated low-risk patients. Both our and previous studies suggest that a second stimulation test should be avoided in UP patients at first evaluation, while this procedure might be of some utility in formerly DP with negative imaging, mainly because patients who revert to undetectable Tg status can be addressed to a less intensive follow-up.

We must also consider some limitations of this study, mainly consisting of the relatively small number of patients and the rather short follow-up period. However, a substantial agreement with previous studies performed in low-risk patients strengthens our data interpretation.

In conclusion, our results suggest that performing rhTSH Tg stimulation test in the early follow-up of patients with very low-risk thyroid cancer may be an helpful tool for differentiating patients who are free of disease from those who require further investigation and treatment. Thus, ETA criteria of "cured disease" would be extended to this category of patients who have not undergone remnant radioiodine ablation. We suggest to perform rhTSH Tg stimulation test before neck US evaluation. Repeated rhTSH Tg tests may be indicated only in patients with detectable serum Tg (>1.0 ng/ml) at prior stimulation testing.

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