SUMMARY

**Background:** Serum thyroglobulin (Tg) is the marker of differentiated thyroid cancer after initial treatment and TSH stimulation increases its sensitivity for the diagnosis of recurrent disease.

**Aim:** The goal of the study was to compare the diagnostic value of seven methods for serum Tg measurements for detecting recurrent disease both during l-T4 treatment and after TSH stimulation.

**Methods:** Thyroid cancer patients who had no evidence of persistent disease after initial treatment (total thyroidectomy + radioiodine ablation) were studied at 3 months on l-T4 treatment (Tg1) and then again at 9-12 months after l-T4 withdrawal or recombinant human TSH stimulation (Tg2). Sera with anti-Tg antibodies or with an abnormal recovery test were excluded from Tg analysis with the corresponding assay. The results of serum Tg determination were compared to the clinical status of the patient at the end of the follow-up.

**Results:** Thirty recurrences were detected among 944 patients. A control RI-131 total body scan had a low sensitivity, a low specificity, and a low clinical impact. Assuming a common cut-off for all Tg assays at 0.9 ng/ml, sensitivity ranged from 19-40% and 68-76% and specificity ranged from 92-97% and 81-91% for Tg1 and Tg2, respectively. Using assays with a lower functional sensitivity at 0.2-0.3 ng/ml, sensitivity was 54-63% and specificity was 89% for Tg1. Using the two methods with the lowest functional sensitivity at 0.02 and 0.11 ng/ml resulted in a higher sensitivity for Tg1 (81% and 78%), but at the expense of a loss of specificity (42% and 63%); finally, for these two methods, using an optimized functional sensitivity according to receiver operating characteristic (ROC) curves at 0.22 and 0.27 ng/ml resulted in a sensitivity at 65% and specificity at 85-87% for Tg1.

**Conclusions:** Using an assay with a lower functional sensitivity may give an earlier indication of the presence of Tg in the serum of patients on l-T4 treatment and may be used to study the trend in serum Tg without performing any TSH stimulation. Serum Tg determination obtained after TSH stimulation still permits a more reliable assessment of cure and patient’s reassurance.

**COMMENT**

Present collaborative study was carried out in 27 hospital centers in France, and encompassed the prospective enrolment of 944 patients with a differentiated thyroid cancer, after initial surgery and complementary remnant ablation with RI-131. The first Tg sample (Tg1) was measured 3-4 months later, under l-T4 treatment; the second Tg sample (Tg2) was obtained 9-12 months after the initiation of l-T4 treatment, after TSH stimulation. TSH stimulation was achieved by either rhTSH...
injection (n = 504) or l-T4 withdrawal (n = 440). These two subgroups of patients did not differ in clinical or cancer characteristics: mean age of 47 years; 76-79% of women; 87-88% of papillary carcinomas, and similar overall TNM subclasses. The first important result of present study was the low frequency of recurrences after complete surgical excision of the tumor and when no focus of RI-131 uptake was seen outside the thyroid bed on initial post-ablation total body scan: 30 recurrences in 944 patients (< 3%). Furthermore, two thirds of the recurrences occurred in the thyroid bed or in neck lymph nodes.

Tg1 and Tg2 determinations were carried out using one of the following kits: Tg-Kryptor, Immulite-Tg, Thyro, Tg Advantage, Dyno Test Tg-Plus, Tg Access, and e-Iason TgCa. Each kit was calibrated against an international Tg Standard (CRM 457). The second important result of present study was to confirm the existence of a large method-to-method variability among the 7 kits. For instance, for a serial dilution of the CRM standard Tg to 1 ng/ml, the calculated values ranged from 0.4 to 1.8 ng/ml, depending on the kit used. Assuming a common cut-off of serum Tg at 0.9 ng/ml, the results were similar with all kits. During l-4 treatment (Tg1), the sensitivity for tumor detection ranged from 19-40% and rose to 68-76% after TSH stimulation (Tg2), whereas the specificity was high in both conditions (> 80%). The third important result of present study was to clearly confirm the interest of TSH stimulation for the follow-up of such patients and also that serum Tg determination is an excellent marker when obtained after TSH stimulation.

Finally, lowering the functional sensitivity of Tg determinations to 0.2-0.3 ng/ml improved the sensitivity without reducing the specificity of detection. Lowering the sensitivity of the test even further improved sensitivity yet again, but at the expense of a decreased specificity. The fourth important result of present study was to show that the use of Tg assays with an improved functional sensitivity (0.2-0.3 ng/ml) may indicate earlier the presence of circulating Tg in the serum of patients under l-T4 treatment.

The authors concluded that serum Tg determinations at 9-12 months obtained after TSH stimulation still permits a more reliable assessment of cure. In turn, the certainty of cure permits patient’s reassurance, decreased daily l-T4 dosage (to avoid subclinical hyperthyroidism), and limitation of later follow-up to an annual clinical examination on l-T4 treatment with serum TSH and Tg determinations, keeping in mind that the rate of recurrence is low in such patients and that the majority of them will have negative test with any method. (Daniel Glinoer, M.D.; Ph.D.)

See Figure below