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Long-Term Surveillance with Serum Thyroglobulin Might Not Be Worthwhile in Patients with Very-Low-Risk Differentiated Thyroid Cancer

Cord Sturgeon

Durante C, Montesano T, Attard M, Torlontano M, Monzani F, Costante G, Meringolo D, Ferdeghini M, Tumino S, Lamartina L, Paciaroni A, Massa M, Giacomelli L, Ronga G, PTC Study Group. Long-term surveillance of papillary thyroid cancer patients who do not undergo postoperative radioiodine remnant ablation: is there a role for serum thyroglobulin measurement? J Clin Endocrinol Metab 2012;97;2748-53, Epub June 7, 2012.

SUMMARY

Background

The postthyroidectomy, postablative stimulated serum thyroglobulin (Tg) level is a sensitive measure of disease burden for differentiated thyroid cancer (DTC). After radioiodine remnant ablation (RRA), it is expected that there should be no detectable Tg in patients who have been cured of cancer and remain disease-free. Because RRA is not routinely used for very-low-risk DTC, the authors wished to evaluate the usefulness of serum Tg measurement in patients who have not undergone RRA for low-risk DTC. The goal of this observational study was to determine the temporal trend of serum Tg levels in patients with low-risk DTC who did not undergo RRA.

Methods

In this multicenter retrospective study, Durante et al. examined the records of 290 patients with low-risk DTC who were treated with total or near-total thyroidectomy but were not given RRA; 287 of these patients had tumors smaller than 1 cm. None of the patients were known to have metastatic lymphadenopathy at the time of surgery. They compared this cohort with a group of 495 patients who did receive RRA. All patients were antithyroglobulin-antibody–negative. Unstimulated Tg levels from the final follow-up visit were recorded for each group. The lower limit of detection for Tg for most subjects was 1 ng/ml. A small subset of RRA-negative patients had highly sensitive assays (threshold sensitivity, 0.2 ng/ml) from the same lab using the same method, and from this group, yearly Tg levels were analyzed (n = 78).

Results

In the RRA-negative group the median tumor size was 4 mm, as compared with a median size of 12 mm in the group that underwent RRA. Only one recurrence was detected in the RRA-negative group, and no recurrences were detected in the RRA-positive group (not statistically significant). Serum Tg levels were >1.0 ng/ml in 5% (17 of 290) of the RRA-negative group and 1% (3 of 495) of the RRA-positive group. This difference was statistically significant. The median serum Tg level in the 17 patients in the RRA-negative group was 2.68 ng/ml. TSH was not suppressed in 46% of the RRA-negative group. In the subgroup of patients who had serum Tg measured with a highly sensitive assay, 60% (47 of 78) had undetectable levels (<0.2 ng/ml) at the first postoperative exam. After 5 years of follow-up, 79% of the patients (number not given) had undetectable serum Tg. In 98.7% (77 of 78) of patients the serum Tg either declined or remained stable over time.

Conclusions

The authors state that their goal was to determine whether Tg assays have any value in the follow-up of patients with DTC who do not undergo RRA after

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total thyroidectomy. They argue that it is difficult to interpret the serum Tg level in patients who have not had RRA after thyroidectomy. Furthermore, they state that cervical ultrasound has a higher diagnostic accuracy than serum Tg or 131I scanning. They concluded that because the serum Tg was below 1 ng/ml in 95% of patients who never underwent RRA (even though many patients did not even have a suppressed TSH) and because the serum Tg declined over time, the serum Tg may not be a reliable marker of disease burden in this population. Finally, the authors call for cost-effectiveness studies and other efforts to determine the proper use of serum Tg and cervical ultrasound in the long-term surveillance of patients with low-risk DTC.

ANALYSIS AND COMMENTARY

Recommendation 32 from the 2009 Revised ATA Guidelines states that RAI ablation is not recommended for patients with unifocal cancer <1 cm without other higher-risk features (1). The guidelines acknowledge that the follow-up of patients who have undergone surgery without RRA may be a challenge. In addition, the guidelines state that "Tg levels should be interpreted in light of the pretest probability of clinically significant residual tumor" and that the Tg trend over time should identify the patients with clinically significant recurrent disease.

This paper does a nice job of describing the long-term kinetics of serum Tg in patients with thyroid cancer who have an extremely low risk of recurrence. It is fascinating to see that the serum Tg levels decline over time in the vast majority of patients with low-risk thyroid cancer who did not get RRA. Although the median follow-up time was a respectable 5 to 6 years, there was only one recurrence identified in the 785 cases included in this study (0.13%). Durante et al. concluded that the serum Tg may not be a reliable marker of disease burden in this population because the serum Tg declined over time and it was below 1 ng/ml in 95% of patients who never underwent RRA. The results, however, should be carefully interpreted, as they may apply only to a small subset of patients with ultra-low-risk thyroid cancer. The median tumor size in the RRA-negative group was only 4 mm, and no subject had extrathyroidal extension or positive lymph nodes. No patients had evidence of vascular invasion or aggressive histology. Eighty percent of these cancers were incidentally found microcarcinomas, some as small as 0.5 mm. Finally, TSH values were not given for the RRA-positive cohort, and it is possible that they may have had a greater degree of TSH suppression.

In 2006, similar results were reported by Torlontano et al. (2). In their study 56% of patients with low-risk papillary thyroid microcarcinoma who did not undergo RRA had a stimulated Tg of <1 ng/ml. They compared ultrasound, whole-body radioiodine scanning and stimulated serum Tg and concluded that cervical ultrasound was the most effective screening tool.

Durante et al. state that they conducted this study to determine the role of serum Tg in the follow-up of patients with low-risk PTC who underwent thyroidectomy without RRA. They concluded that Tg might not be a reliable marker of disease burden in this population. It should be acknowledged, however, that it is possible to make a type II error when studying a finite population with an extremely low rate of clinically meaningful recurrence. In order to further test their hypothesis, the authors might have considered increasing the size of their cohorts, or adding a third group to their study composed of patients who underwent a total or near-total thyroidectomy for benign pathology and for whom postoperative TSH and serum Tg levels were followed.

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In conclusion, patients with well-differentiated microcarcinoma that do not have metastatic lymphadenopathy, vascular invasion, positive margins, extrathyroidal extension, or aggressive histology and who have undergone a total thyroidectomy probably have such a low risk of recurrent or persistent disease that it should call into question the intensity or even the necessity of long-term surveillance with ultrasound, serum Tg, and/or radioiodine scans. The authors appropriately call for studies that could identify the most optimal long-term surveillance strategy for these patients.

References

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