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Editorial
Serum Thyroglobulin in the Management of Thyroid Cancer

Although the majority of thyroid adenocarcinomas can be removed surgically, there is often uncertainty as to the completeness of the resection and the presence of local or distant histologic metastases despite the absence of clinically detectable abnormalities. Radioiodine ^{131}I has been used as adjunctive therapy in the management of thyroid adenocarcinoma for more than 40 yr. There is mounting evidence indicating an increased rate of survival and a decreased tumor recurrence rate in patients who have received radioiodine therapy. Ablation with radioiodine of any residual thyroid tissue that has not been removed surgically appears to be well accepted management since complete ablation of normal thyroid tissue usually assures radioiodine uptake in remaining tumor deposits and tumor metastases (*1*).

The efficacy of radioiodine therapy with rare exception is related directly to tumor uptake and retention. Efficient uptake and response to therapy is observed in tumors that are of differentiated cell types such as papillary or follicular, whereas undifferentiated tumors and Hürthle cell and medullary carcinomas rarely concentrate radioactive iodine. Effective tumor uptake is ~0.5% of the dose per gram with a biologic half-life of ~4 days (*2*). From the administration of 5.55 GBq ^{131}I, a tumor will receive ~25,000 cGy or five times the absorbed dose that can be delivered by a course of external radiation therapy. Ablation of small thyroid remnants after near total thyroidectomy may be accomplished with the administration of 2.78 to 3.70 GBq ^{131}I. Repeat doses are given at intervals of 4–6 mo until no imaging evidence of residual thyroid or functioning tumor tissue is demonstrable.

The recurrence of tumor following radioiodine ablation of all functioning tumor tissue has been found in more than 50% of patients who had tumor metastases at the time of therapy and in 25% of patients who did not have metastases (*3*). Recurrences have been observed after 5 to 10 yr of negative diagnostic studies (*3,4*). In view of the possibility of late recurrence, all patients in whom total radioiodine ablation has been obtained should be followed for at least 10 yr to assure that they remain free of recurrent functioning tumor.

Although whole-body imaging with radioiodine is considered to be the most sensitive means of detecting recurrent disease, it is a formidable procedure requiring withdrawal of thyroid hormone and periods of symptomatic hypothyroidism. In recent years there have been numerous reports suggesting that the determination of serum thyroglobulin (Tg) may be as

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sensitive in the detection of recurrent thyroid cancer as whole-body imaging, and that it may supplement or even replace routine whole-body imaging in the management and followup of patients who appear to be in remission (*5–9*).

Thyroglobulin is a large glycoprotein that is found in normal thyroid gland follicular tissue. In the course of thyroid hormone secretion, small amounts of Tg may be secreted and may be detected in low concentration in the blood of most normal individuals by sensitive radioimmunoassays. Most differentiated thyroid carcinomas secrete Tg. Patients with bone and lung metastases have the highest Tg concentrations, while those with metastases in lymph nodes have the lowest. Medullary and anaplastic carcinomas and probably pure papillary carcinomas, i.e., those without follicular components, do not secrete Tg; whereas Hürthle cell carcinoma, a variant of follicular carcinoma, secretes Tg but does not concentrate radioiodine.

The assay for Tg is technically demanding and, until recently, was performed primarily in research laboratories. However, it is now performed by large research oriented commercial reference laboratories and several kits are available. Unfortunately the assay has not yet been standardized and each laboratory must determine its own range of normal values. Consequently, only samples analyzed in the same laboratory can be compared.

Circulating antibodies to Tg can interfere in the radioimmunoassays causing either falsely high or low results. Serum must be screened for the presence of anti-Tg antibodies and those that are positive are ordinarily rejected. Fortunately, only 13% of patients with thyroid cancer have been found to have such antibodies. However, according to the experience of Black et al. (*7*), thyroid antibodies do not present a significant problem in the correlation between Tg levels and the status of cancer.

It is clear that the serum Tg can be of great value in following patients with differentiated thyroid cancer who have had total thyroid gland removal. Serial monitoring of Tg can detect residual tumor tissue or metastases, or the recurrence of disease. There is considerable disagreement, however, as to whether serum Tg levels are reliable in patients who are receiving thyroid suppression therapy. It is well established that serum Tg is under the influence of the pituitary. The discontinuation of thyroid hormone replacement with concomitant elevation of endogenous thyroid stimulating hormone appears to enhance serum Tg levels primarily in patients with metastatic disease (*10, 11*).

On the other hand, Shepherd (*12*), and Black et al. (*13*) state that in most situations serum Tg can replace radioiodine scans and the need to withdraw thyroid suppression therapy. They believe that a scan should be performed only when serum Tg values obtained during thyroid suppression are elevated or when there is clinical evidence suggesting recurrence. Van Herle (*personal communication,* 1990), who devised the original assay for Tg, states that serum Tg values of less than 10.0 ng/ml in patients who are on thyroid suppression therapy are not suspicious for malignant disease, whereas values above 10.0 ng/ml may indicate tumor recurrence. In the latter instances, thyroid hormone should be withdrawn and radioiodine scans obtained.

Other investigators including Ronga et al. (*14*), whose report appears in this issue of *The Journal of Nuclear Medicine*, conclude that serum Tg performed during thyroid suppression therapy has a fairly good predictive value, but can be used only as a general guide in the follow up of thyroid cancer. According to Ronga, it is not possible to discriminate between patients with or without metastases based only on Tg levels obtained either during or after suppression therapy. When both the Tg and whole-body radioiodine scan were taken into consideration, sensitivity reached 95.7%, specificity, 100%, and accuracy, 96.7%. Sensitivity of diagnostic whole-body scan alone was 76.6% and the sensitivity of serum Tg was 83.3%.

Several groups have reported abnormally elevated serum Tg levels in patients with negative radioiodine scans (*6,7,11*). Routine determination of serum Tg may be of paramount importance in following the clinical course of such patients since some investigators believe that serum Tg may be a more sensitive indicator of disease than radioiodine scans (*6*). Pacini et al. (*15*) suggest that false-positive Tg results may be due to the presence of residual thyroid or metastatic tissue that is not detected in conventional radioiodine diagnostic scans, but can be visualized using therapeutic doses. On the other hand, Aiello and Manni (*16*) point out that serum Tg is not sufficiently sensitive to detect either normal or malignant thyroid tissue confined to the neck and is, therefore, less sensitive than the radioiodine scan, although it may be more sensitive in detecting the presence of distant metastases than the radioiodine scan. In this connection, Müller-Gartner and Schneider (*17*) report a small number of false-negative Tg results in patients with papillary histology or small lymph node metastases in the neck or mediastinum.

It is apparent that the most useful clinical application of the serum Tg assay is to monitor thyroid cancer patients who have received thyroid ablative therapy and who are receiving thyroid hormone suppression therapy. If the assay could detect tumor activity reliably under such conditions, it would obviate the hypothyroid morbidity associated with prolonged abstinence from thyroid suppression therapy that is required to perform radioiodine imaging. To assure this degree of reliability, an assay with substantial sensitivity and specificity performed in a laboratory with high technological capability is required. Since such assays and laboratories are or will be available in the future, it would appear to be the consensus that a Tg assay performed during thyroid suppression therapy has a good predictive value and can be used as a general guide in the follow-up of patients who have differentiated thyroid cancer.

The majority of investigators now

consider that serum Tg values below 10.0 ng/ml when assays are performed in most major reference laboratories in patients receiving thyroid suppression therapy are not suspect for malignant disease. Serum Tg values above 10 ng/ml may indicate tumor recurrence and require withdrawal of thyroid hormone and radioiodine scanning. If the radioiodine body scan is negative, other techniques should be used to attempt to localize metastatic or recurrent tumor tissue such as high resolution ultrasonography, radionuclide bone scan, and computed tomography. In all clinical studies, it is essential to know the thyroid ablative and thyroid hormone suppression state of the patient in order to interpret serum Tg values correctly. Most clinicians agree that the determination of serum Tg is of considerable value in monitoring patients with differentiated thyroid cancer and that this assay has substantially reduced the need for repetitive radioiodine body scans.

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