IN VITRO NUCLEAR MEDICINE

Critical Evaluation of Serum Thyroglobulin Levels and I-131 Scans in Post-Therapy Patients with Differentiated Thyroid Carcinoma: Concise Communication

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Serum thyroglobulin measurements by radioimmunoassay were performed in the follow-up of 68 patients with differentiated thyroid carcinoma undergoing I-131 total-body scans following surgery and/or I-131 therapy. Of 12 patients with distant metastases demonstrated by I-131 scan, thyroglobulin levels were elevated (>60 ng/ml) in nine (75%); the remaining 25% either ranged between 20 and 60 ng/ml or were below 20 ng/ml in spite of having functional metastases. Of six patients with only regional lymph-node metastases demonstrated by I-131 scan, only one (16%) had an elevated thyroglobulin level, while two fell in the 20–60 ng/ml range and three were below 20 ng/ml. Of the remaining patients with no metastatic disease demonstrable by I-131 scan, three (6%) had elevated thyroglobulin levels. These patients were subsequently found to have metastatic disease by other criteria. These results suggest caution in the use of thyroglobulin levels as a replacement for I-131 scans in the follow-up of differentiated thyroid carcinoma. Based on our study, however, the two methods complement each other to achieve maximum sensitivity and reliability.

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Thyroglobulin (Tg) determination in serum is a useful marker for the identification of recurrent or metastatic disease in patients with nonmedullary differentiated thyroid carcinoma who have undergone a total thyroidectomy (*1–4*).

Consequently, attempts have been made to correlate the serum Tg findings with the I^{-131} scan in the follow-up of these patients (*5*), and the results of these studies seem to indicate that Tg in serum has a sensitivity comparing favorably with the whole-body scan in the assessment of persistent or recurrent functional tumor after initial treatment (*6*).

Moreover, it has been suggested that serum Tg can predict total-body scan findings and can replace them in many patients (*7*).

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In this study, we attempt to see whether this statement applies to our population of posttherapy patients with differentiated thyroid carcinomas when a commercial thyroglobulin RIA kit* is used.

MATERIAL AND METHODS

For this study, 68 thyroid-cancer patients were selected from a group referred for follow-up with I-131 total-body scanning. Thirteen had had follicular carcinomas, five papillary, 48 mixed papillary-follicular, and two Hürthle-cell types. All had been treated with surgery and/or iodine-131, and all had been off thyroid-suppression medication for 6 wk.

The criterion for the selection of these patients was that they must have been found, by RIA, to be free from circulating thyroglobulin antibodies that might interfere with the Tg determination, as has been reported (*8,9*).

TABLE 1. Tg RIA KIT NMS-1041 PERFORMANCE CHARACTERISTICS (PROVIDED BY MANUFACTURER)

A. Sensitivity and range
6 ng/tube
(15 ng–1000 ng/ml)

B. Specificity
The following proteins were examined for cross reaction with anti-human-Tg rabbit serum: human AFP, hCK-B, hCG, hPL, hFSH, hTSH, hPAP, hMyoglobin. None of these showed any significant cross reaction.

C. Accuracy

Dose (ng/ml)	Runs	Mean (ng/ml)	% Recovery
150	7	146	97.3
125	7	122.8	98.3
500	7	510	102

D. Precision

a. Interassay variation

Dose (ng/ml)	Runs	Means (ng/ml)	s.d. (ng/ml)	CV %
15	7	14.6	1.9	13
125	7	122.8	8.1	6.6
500	7	51.9	10.2	10.2

b. Intra-assay variation

Dose (ng/ml)	Runs	Mean (ng/ml)	s.d. (ng/ml)	CV %
15	8	145	1.1	7.81
125	8	124	6.3	5.1
500	8	510	41.8	8.2

Expected values: Up to 60 ng/ml.

Every patient was given a thorough clinical evaluation, including chart review, physical examination of the neck, careful screening for iodine contamination, inquiry into current thyroid hormone intake, and (in women) possible pregnancy.

After obtaining written consent from each patient, 20 ml of whole blood were withdrawn and nonhemolized serum was immediately obtained and frozen until the in vitro procedures were performed. Immediately after the blood sampling, the patient received 1.0 mCi of sodium iodide (I-131) by mouth, and a 24-hr neck uptake and a total-body scan were performed with a dual-head rectilinear scanner, using a high-energy focused collimator. Gamma-camera views, at 6 and 18 cm from the neck and chest, were obtained using a pinhole collimator with a $^3/_{16}$ inch aperture. Pictures were taken until 200,000 counts had accumulated, or for 10 min, whichever occurred first.

The criteria of the interpretation of the I-131 total-body scans are as follows: normal when no abnormal uptake or radioactivity is present; abnormal if a discrete or ill-defined area of radioactivity is present in neck, chest, or elsewhere, not related to physiological concentration in the gastrointestinal or genito-urinary tracts. When there is abnormal uptake in the neck, a further decision is attempted according to the location of the abnormality: thyroid bed and thyroglossal tract when the location suggests functioning thyroid remnants, or metastatic to the neck when extrathyroidal radioactivity suggests functioning metastasis (lymph node or soft tissues). Distant metastases in lungs or bones are characterized by abnormal uptake in the chest or skeleton.

Each serum sample was screened by RIA† for circulating Tg antibodies.

Those samples without detectable Tg antibodies were selected for the study of Tg by RIA.* Performance characteristics provided by the manufacturer appear in Table 1. Other tests included: T_4 by RIA‡ with a normal range 4.5–12.0 μg/dl and a limit of detectability of 1.5 μg/dl; T_3 by RIA‖, with a normal range 80–200 ng/dl and a limit of detectability of 25 ng/dl; and HTSH by RIA‖, with a normal range of 1–5 μIU/ml. Serum protein-bound iodine (PBI) determinations were performed commercially, with a normal range 4.0–8.0 μg/dl.

All Tg determinations in serum were run in duplicate. The expected Tg values in a normal population, as pro-

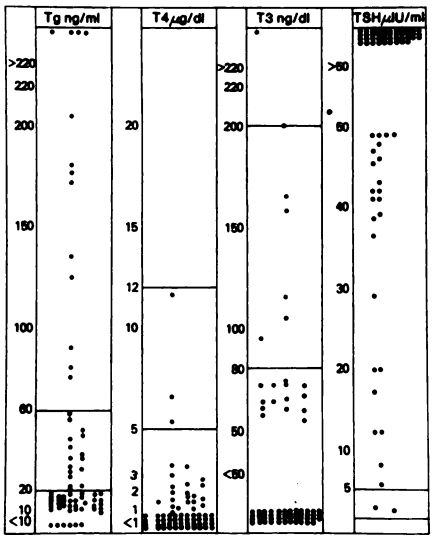

FIG. 1. Correlation of Tg levels with in vitro thyroid-function tests.

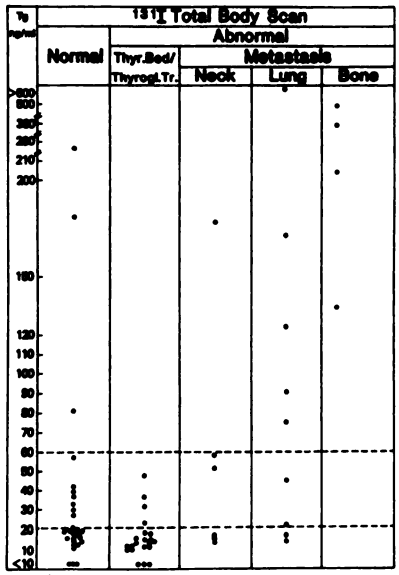

FIG. 2. Correlation of Tg levels with findings of I-131 total-body scans.

vided by the manufacturer, range up to 60 ng/ml.

To study the correlation between Tg in serum and the I-131 total-body scan, in a population of thyroidectomized patients, we have empirically defined three groups, according to the levels of Tg in serum:

(1) Patients with serum Tg values greater than 60 ng/ml (i.e., above the manufacturer's upper limit of normal).

(2) Those with Tg levels between 20 and 60 ng/ml.

(3) Those with Tg levels below 20 ng/ml.

RESULTS

Figure 1 shows the levels of Tg, T_4, T_3, and TSH. T_4 values were in the hypothyroid range in 65 patients (96%), of which 65% showed no T_4 by the assay used. The other three patients (4%) were in the euthyroid range. T_3 values were in the hypothyroid range in 61 patients (90%) with 69% below the lower limit of detectability. The T_3 was in the euthyroid range in six patients (9%), and in the hyperthyroid range in one. TSH levels were above the normal range in 66 patients (97%), of which 62% were above the upper limit of sensitivity of the method; only 2 patients (3%) were below the upper normal limit. One of these two cases had a T_3 level in the hyperthyroid range and showed a low T_4; the other had a normal T_3 with a subnormal T_4. In the patients with euthyroid T and T_4, the I-131 scan revealed thyroid-bed activity in two and in the others metastases in neck and lungs. The findings of nondetectable or hypothyroid T_4 and T_3 levels, associated with elevated TSH, indicated that the patients were, for the most part, well exposed to endogenous TSH stimulation. The few cases with euthyroid values suggest an endogenous source of thyroid hormone either from normally functioning thyroid-bed tissue or from functioning metastases. Accidental or surreptitious administration of thyroid hormones cannot be ruled out. In fact, the latter seemed to be the case for a patient with a T_3 value in the hyperthyroid range, a low T_4, and suppressed TSH, indicating possible exogenous intake of tri-iodothyronine.

Figure 2 shows the relationship between serum Tg and the findings in the I-131 scan.

Tg serum levels greater than 60 ng/ml. In this group, four patients had distant skeletal metastases. Five patients had lung metastases, one had neck metastases, none showed persistent activity in thyroid bed and/or thyroglossal tract, and three patients had normal findings in the I-131 scan. The last three had evidence of metastatic disease on routine chest radiograph, and lung biopsy confirmed thyroid metastases in two of them. These three patients (false negative by I-131 scan) were checked for possible inadequate TSH stimulation or iodine contamination; the TSH levels were elevated, ranging from 29 to >50 μIU/ml. The PBI was elevated in two of the three (11.3 and 30 μg/dl) and was subnormal in the third (2.5 μg/dl). As a further check for iodine contamination in the group of patients with normal I-131 scan, 15 additional patients had PBIs determined and all were in the subnormal range. Therefore, in those three patients with negative I-131 scans and metastatic disease in the lungs, inadequate TSH stimulation can be ruled out. Two of the three patients had an elevated PBI, indicating either exogenous iodine contamination or excessive circulating iodoproteins. The third case with subnormal PBI had a Hürthle-cell carcinoma, a tumor with nonfunctional metastases that retain the capacity to synthesize and release Tg but are unable to take up the iodine. This may reflect an abnormality of the TSH receptor, a peroxidase deficiency in the tumor, or other factors as discussed elsewhere (*10*).

TABLE 2. CORRELATION OF THYROGLOBULIN (Tg) IN SERUM WITH THE I-131 SCAN

Tg (ng/ml)	No. of pts.	I-131 total-body scan: Normal	Abnormal: Thyroid bed or thyroglossal tract	Abnormal: Metastasis: Neck	Abnormal: Metastasis: Lung	Abnormal: Metastasis: Bone
60	13	3 (23%)		1 (8%)	5 (38%)	4 (31%)
20–60	16	8 (50%)	4 (25%)	2 (12.5%)	2 (12.5%)	
20	39	18* (46%)	17 (44%)	3 (8%)	1 (2%)	

* Including one case read as equivocal in lung and later found to indicate fungal infection.

Tg serum levels between 20 and 60 ng/ml. In this group there were no patients showing metastases in the bones. There were two patients with lung metastases, two with regional lymph-node metastases (in one of them, the serum Tg level fell from 50 to 25 ng/ml after surgical removal of a 2- by 2-cm palpable lymph node), four with persistent uptake in thyroid bed and/or thyroglossal duct tract, and eight with a thyroid but otherwise normal I-131 scans.

Tg levels below 20 ng/ml. In this group none of the patients had bone metastases. Two of the patients appeared to have lung metastases. The first of these two (serum Tg - 18 ng/ml), had an I-131 scan interpreted as equivocal in the lung. The chest radiograph showed nodular densities, and a subsequent lung biopsy showed a fungal infection (*Allescheria boydii*), without malignant cells. In the second case with lung metastases, the abnormal diffuse uptake in both lungs in the I-131 scan had improved when compared with a study performed a year earlier. The chest radiographs of this patient, previously showing fine nodularities in both lung fields, had become normal 7 mo before the I-131 scan. This patient had a papillary-follicular thyroid carcinoma, treated with surgery (total thyroidectomy with bilateral modified neck dissections) and three oral doses of I-131 (one per year), for a total of 429 mCi.

There were three patients with neck metastases. In two of them there was minimal uptake in the neck; the third showed the neck abnormalities markedly improved when compared with a study performed a year earlier. There were 17 cases with abnormal activity in thyroid bed and/or thyroglossal tract, including three with nondetectable Tg. There were also 17 cases with normal I-131 scans, again including three with nondetectable Tg. Table 2 shows the distribution of Tg in serum contrasted with the I-131 scan findings. Table 3 shows the distribution of the I-131 scan findings against the Tg levels in serum.

Case reports. *Case 1.* A 53-yr-old white male; follicular carcinoma of the thyroid, metastatic to the cervical spine, soft tissue of the posterior neck, and lungs, diagnosed 1 yr before study and treated elsewhere with 100 mCi I-131, cervical laminectomy, and 3000 rad cobalt radiotherapy combined with chemotherapy. At the time of the study (Fig. 3), Tg = 360 ng/ml. At our hospital the patient received an additional 206 mCi of I-131, followed by another dose of 152 mCi 6 mo later, but the cervical spine disease progressed, resulting in quadriparesis.

Comment. This case typifies the correlation of Tg levels and I-131 in a case of metastatic thyroid cancer. The presence of follicular carcinoma with bone metastasis, in our experience, is associated with the highest Tg levels, and—as this patient illustrates—an unfavorable prognosis.

Case 2. A 76-yr-old, white female; papillary-follicular

TABLE 3. CORRELATION OF I-131 SCAN WITH SERUM THYROGLOBULIN (Tg)

I-131 scan	No. of pts	Tg (ng/ml) >60	Tg (ng/ml) 20–60	Tg (ng/ml) <20
Distant metastasis	12	9 (75%)	2 (17%)	1 (8%)
Neck metastasis	6	1 (17%)	2 (33%)	3 (50%)
Thyr. bed/thyrogl. tr	21	0	4 (19%)	17 (81%)
Normal	29	3 (10%)	8 (28%)	18* (62%)
TOTAL	68	13	16	39

* Including one case read as equivocal in lung and later found to indicate fungal infection.

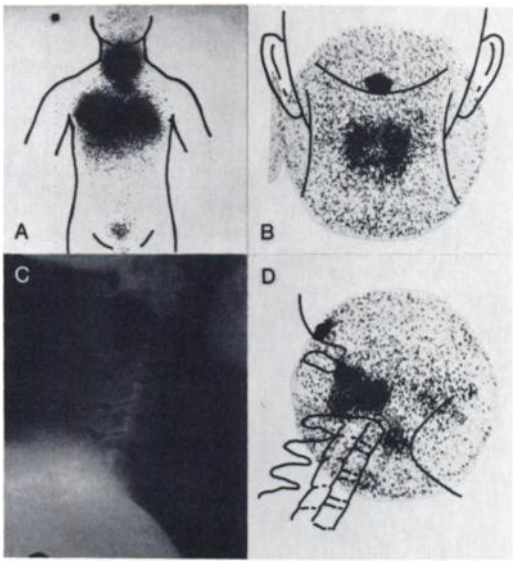

FIG. 3. A: rectilinear body scan, anterior view, obtained 24 hr after therapeutic dose of I-131, reveals widespread functioning thyroid tissue in neck and lungs. B: posterior camera view, 24 hr after 1.0 mCi of I-131, reveals abnormal uptake in upper cervical spine. C: lateral radiograph of cervical spine shows involvement and destruction of upper cervical vertebral bodies. D: corresponding lateral camera view, 24 hr after oral I-131 reveals abnormal uptake in upper cervical spine and neighboring structures, indicating functioning metastatic thyroid carcinoma.

carcinoma with invasion of adjacent muscle, diagnosed 8 yr before our study. Total dose of I-131 = 200 mCi. At the time of the study there was a mass in the neck 2 × 2 cm Tg = 50 ng/ml. Upon biopsy with excision of metastatic tumor, Tg fell to 25 ng/ml.

Comment. In this patient, only a minimal amount of tumor was present, apparently insufficient to elevate Tg above the normal range, though the decline following removal suggests that some Tg was produced. Iodine-131 uptake was also minimal and vanished after removal of metastatic disease (Fig. 4).

Case 3. A 41-yr-old, white male; papillary-follicular carcinoma metastatic to lymph nodes. Six months after total thyroidectomy and right paratracheal neck dissection, Tg = 22 ng/ml. A chest radiograph showed multiple nodular densities throughout both lung fields. Figure 5 shows an I-123 thyroid scan performed before surgery, and two I-131 scans at the time of the study.

Comment. Iodine-131 concentration was excellent in neck and lung metastases, but apparently the production of Tg was more like that from the normal thyroid gland than from a metastatic thyroid tumor.

DISCUSSION

All the cases with Tg levels greater than 60 ng/ml had metastatic disease, including the three cases with false-negative I-131 scans.

In the group with Tg levels between 20 and 60 ng/ml, the absence of patients with bone metastases supports

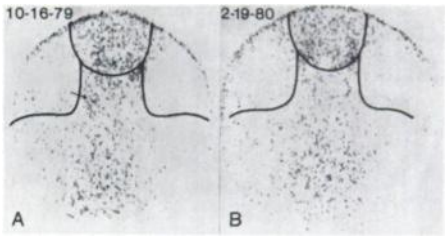

FIG. 4. A: camera view of chest and neck, 24 hr after oral I-131 demonstrates abnormal uptake corresponding to palpated neck mass. B: similar camera view after surgery, reveals clear neck and chest.

the impression of other investigators that bone metastasis produces the highest Tg levels. However, neck and lung metastases cannot be excluded (e.g., Cases 2 and 3, respectively). In addition, patients with only thyroid-bed activity may have neck metastases suppressed by the presence of normal thyroid tissue.

A word of caution applies to patients within the range 20–60 ng/ml but with a normal I-131 scan. Seven patients who had adequate TSH stimulation had subnormal PBI (ruling out iodine contamination) and, so far, had no clinical or radiological evidence of metastatic disease. Therefore, the follow-up of these patients is mandatory, due to threat of metastatic disease. Scanning with higher I-131 doses may be helpful.

In the group of cases with Tg levels less than 20 ng/ml, the finding of an abnormal chest radiograph may alert the physician to consider a diagnosis other than metastatic thyroid disease. The small amount of I-131, localized nonspecifically in the infectious fungal lesion, was responsible for the interpretation of an equivocal lung scan in one patient. In another patient, the abnormal I-131 lung scan, together with a low Tg, might be taken as a sign of healing (after surgery and I-131 treatment, with a total dose of 429 mCi), which is supported by the normalized chest radiograph. For patients who have already received large doses of I-131, the finding of a low serum Tg might suggest a more conservative approach to further treatment. However, more cases are needed with long-term correlation of both Tg and I-131 scan findings. Again, the low Tg associated with minimal or improved neck metastases suggests a good prognosis in these patients. Once more, in certain cases the low Tg levels with minimal neck activity might suggest a conservative approach with regard to I-131 treatment as long as their follow-up is not neglected.

Finally, the observed overlapping with this method, of nondetectability of Tg in serum in the athyroid cases as well as in those with residual thyroid activity, points to the need for performing both tests if the policy is to treat these cases with I-131 if the diagnostic scintiscan, after initial surgery, reveals residual thyroid-tissue activity (*11*).

Our study has been taken from a population of highly selected referrals to a cancer center, and may not nec-

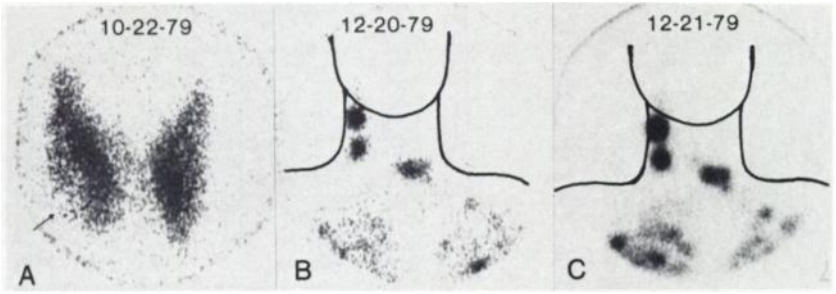

FIG. 5. A: thyroid scan at 4 hr after 100 μCi of oral I-123, reveals discrete uptake defect (area of low concentration of radionuclide) in lower portion of right lobe. B: postsurgical (see text) scintiphoto of neck and chest, 24 hr after oral I-131 (1 mCi), shows residual uptake in neck and scattered spots in both lungs. C: better view, 24 hr after 150 mCi of I-131.

essarily be representative of differentiated thyroid carcinomas in general. However, the conclusion from our study, correlating the Tg serum level with the I-131 total-body scan, is that we can obtain complementary information that helps us in the diagnosis (staging), prognosis, and management of patients with differentiated thyroid carcinomas—information superior to that obtainable from either method alone. We believe that 6 wk after a patient has completed the first stage for the management of differentiated thyroid carcinoma (near-total thyroidectomy with or without neck dissection), a sample of serum for Tg determination should be obtained, then an I-131 scan, and the results taken as a baseline for that particular case. Follow-up examinations can then provide guidelines for management.

In this study, as was mentioned, all the cases had been evaluated after being off thyroid suppression medication for 6 wk. We feel that although it would be of interest to establish the effect of the continuous thyroid suppression upon the Tg levels in this type of patient, with Tg tests alternating with the I-131 total-body scan, it will be difficult to accept a normal Tg level while the patient is on thyroid suppression as conclusive evidence of the absence of metastatic disease. The paper by Schlumberger and associates (*12*) indicates that Tg levels are higher after TSH stimulation in patients with differentiated thyroid cancer, and that Tg is suppressed by the administration of exogenous thyroid hormone. Therefore, it will be necessary to conduct careful periodic I-131 scanning in many patients. On the other hand, elevated Tg levels while the patient is taking thyroid hormones can be an indication for an I-131 total-body scan, performed after discontinuing thyroid hormone and with the patient under TSH stimulation (*7*). Thus we advocate the use of Tg levels as a complement to, and not as a replacement for, the I-131 total-body scan.

FOOTNOTES

*I-125 Tg RIA kit, Catalog No. 1041, Nuclear Medical Systems, Newport Beach, CA.

† Anti-thyroglobulin radioimmunoassay kit, CIS, Sorin, Italy.

‡ Ames Co., Elkhart, IN.

‖ Beckman Instruments, Fullerton, CA.

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REFERENCES

1. VAN HERLE AJ, ULLER RP: Elevated serum thyroglobulin: A marker of metastasis in differentiated thyroid carcinomas. *J Clin Invest* 56:272-277, 1975
2. LOGERFO P, COLACCHIO D, STILLMAN T, et al: Serum thyroglobulin and recurrent thyroid cancer. *Lancet* 1:881-882, 1977
3. SHAH D, DANDEKAR S, GANATRA RD: Thyroglobulin levels in serum and saliva of patients with differentiated thyroid carcinoma. *Proc Indian Acad Sci* 87B (Experimental Biology-3): 169-175, 1978
4. BOTSCH H, SCHULZ E, LOCHNER B: Serum-Thyreoglobulinbestimmung zur Verlaufskontrolle bei Schilbdrüzenkarzinom-Patienten. *Dtsch Med Wschr* 104:1072-1074, 1979
5. TANG FUI SC, HOFFENBERG R, MAISEY MN, et al: Serum thyroglobulin concentrations and whole-body radioiodine scan in follow up of differentiated thyroid cancer after thyroid ablation. *Br Med J* 2:298-300, 1979
6. PACINI F, PINCHERA A, GIANI C, et al: Serum thyroglobulin concentrations and I-131 whole body scans in the diagnosis of metastases from differentiated thyroid carcinoma (after thyroidectomy). *Clin Endocrinol* 13:107-110, 1980
7. CHARLES MA, DODSON LE, WALDECK N, et al: Serum thyroglobulin levels predict total body iodine scan findings in patients with treated well differentiated thyroid carcinoma. *Am J Med* 69:401-407, 1980
8. VAN HERLE AJ, ULLER RP, MATTHEWS NL, et al: Radioimmunoassay for measurement of thyroglobulin in human serum. *J Clin Invest* 52:1320-1327, 1973
9. SCHNEIDER AB, PERVOS R: Radioimmunoassay of human thyroglobulin: Effect of antithyroglobulin autoantibodies. *J Clin Endocrinol Metab* 47:126-137, 1978
10. SHLOSSBERG AH, JACOBSON JC, IBBERTSON HK: Serum thyroglobulin in the diagnosis and management of thyroid carcinoma. *Clin Endocrinol* 10:17-27, 1979
11. MAHESHWARI YK, HILL CS, HAYNIE TP, et al: I-131 therapy in differentiated thyroid carcinoma: M.D. Anderson Hospital experience. *Cancer* 47:664-671, 1981
12. SCHLUMBERGER M, CHARBORD P, FRAGU P, et al: Circulating thyroglobulin and thyroid hormones in patient with metastases of differentiated thyroid carcinoma: Relationship to serum thyrotropin levels. *J Clin Endocrinol Metab* 51: 513-519, 1980