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Prognostic Value of Thyroglobulin after Thyroidectomy before Ablative Radioiodine Therapy in Thyroid Cancer

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Serum thyroglobulin (Tg) is a suitable marker for differentiated thyroid carcinoma after total thyroid ablation by surgery and ^{131}I therapy. Before the first ^{131}I treatment, Tg is not a reliable tumor marker since it can also originate from remnant tissue. It was hypothesized that the ratio of serum Tg to ^{131}I uptake in the thyroid bed could be used to correct Tg values for variations in remnant tissue. **Methods:** The hypothesis was evaluated in 111 patients with differentiated thyroid cancer (38 follicular/73 papillary). Tg and ^{131}I uptake in the thyroid bed were measured before the first ^{131}I therapy. The ratio of Tg to ^{131}I uptake was determined in four groups: Group A, tumor free (n = 81); Group B, lymph node metastases (n = 11); Group C, distant metastases (n = 11); Group D, later recurrence [during a mean follow-up of 56 mo; (n = 8)]. Wilcoxon two-sample test was performed to determine statistical significance between Group A and Groups B-D. **Results:** Significant differences in the Tg/^{131}I uptake ratios (median) between Group A (1.0 ng/ml/%) and Groups B (3.3 ng/ml/%), C (20.2 ng/ml/%) and D (3.3 ng/ml/%) were observed ($p < 0.01$). In tumor-free patients (Group A), there was no value higher than 5.7 ng/ml/%. Therefore, a higher ratio, observed in 14 of the 30 remaining patients, was indicative of metastases or later recurrence. **Conclusion:** The ratio of serum Tg to ^{131}I uptake in the thyroid bed might be used as a prognostic marker for thyroid cancer before implementing ablation with ^{131}I.

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Small amounts of serum thyroglobulin (Tg) can be found in the serum of most healthy people, but it can be elevated in several benign thyroid diseases (*1,2*) and in thyroid cancer (*3–10*). Since Tg is a normal tissue component, it can only be reliably used as a "tumor marker" after total thyroid ablation, such as after thyroidectomy and ablative ^{131}I therapy. In these cases, serum Tg is a very reliable marker for the local recurrence of thyroid cancer, lymph node metastases and distant-site metastases. Serum Tg has the advantage of high sensitivity (>90%) in detecting recurrence and/or metastases and can be used under TSH-suppressive thyroxine therapy (although the sensitivity of serum Tg also depends on TSH).

Scintigraphy with ^{131}I is used as a generalized "marker" for thyroid tissue as a result of its uptake and subsequent incorporation into tissue Tg, whether it be in the normal thyroid remnant or in thyroid cancers. Whole-body scintigraphy with ^{131}I is commonly used to detect the recurrence of thyroid carcinoma and/or metastatic lesions. The procedure requires thyroid hormone withdrawal to induce hypothyroidism and maximize uptake of ^{131}I and its subsequent incorporation into Tg. In some cases, whole-body scintigraphy fails to detect

TABLE 1
Tg/^{131}I Uptake Ratios (ng/ml/%) in Patients with Differentiated Thyroid Carcinomas

	Group no.			
	A*	B†	C‡	D§
Median	1.0	3.3§	20.2§	3.3¶
Range	0–5.7	0.3–61.3	0.1–78.5	0.3–19.9
25th percentile	0.3	1.5	4.1	1.5
75th prcentile	1.7	10.1	50.3	9.6
p value		0.0005	0.0001	0.0085

*No metastases and no recurrence.
†Lymph node metastases.
‡Distant metastases.
§Patients with recurrence.
¶Significantly different from Group A ($p < 0.01$).

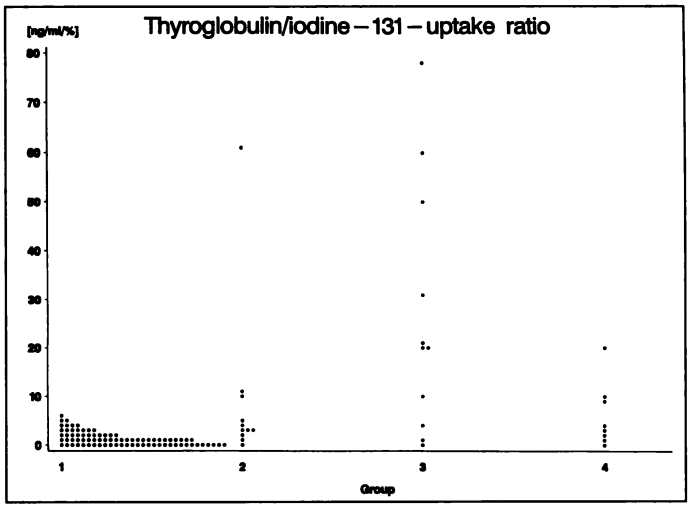

FIGURE 1. Thyroglobulin/^{131}I uptake ratios (ng/ml/%) in patients with differentiated thyroid carcinomas; Group A/1 no metastases and no recurrence; Group B/2 lymph node metastases; Group C/3 distant metastases; Group D/4: recurrence.

recurrence and/or metastases. This is particularly true in patients contaminated with high amounts of "cold" iodine and in oncocytomas. The therapeutic and diagnostic value of ^{131}I depends on the iodination of Tg. Several studies dealing with the comparison of Tg and whole-body scintigraphy have been published (*4,11–18*).

"Tumor-specific" Tg evaluation would improve the diagnostic assessment of patients after surgical ablation but before initiating ^{131}I therapy. In patients in whom remaining tissue may be malignant, further diagnostic evaluation can be initiated early and higher ^{131}I doses can be considered for the first treatment. Unfortunately, immediately after surgical ablation, serum Tg can be of limited value and elevated serum Tg levels are particularly evident after incomplete thyroidectomy (*19*). Surgical ablation could be expected to increase serum Tg by disruption of the thyroid structure.

The present studies were undertaken to evaluate the hypothesis that the ratio of serum Tg to ^{131}I uptake in the thyroid bed could be used during postsurgery conditions and before initiating ^{131}I therapy to detect thyroid cancer (residual or metastatic lesions), even in the presence of remnant thyroid tissue. With complete surgical ablation, ^{131}I uptake would be essentially background and any serum Tg would necessarily arise from the metastases. With remnant thyroid tissue, serum Tg could be expected to originate from the normal remnant plus tumor masses. In remnants with no tumor burden, serum Tg would be low and directly correlated to the mass of the thyroid remnant.

METHODS

Patients

In this study of thyroid cancer patients post-thyroidectomy, we evaluated serum Tg levels and compared those values to ^{131}I uptake in the thyroid bed (determined by upper thorax scintigraphy) before initiating ^{131}I therapy. Tg levels were determined by radioimmunoassay (RIA) or immunoradiometric assay (IRMA), as described previously (*8*) using Tg RIA or Dynotest Tg, respectively, both provided by Henning, Berlin, Germany. Patients with Tg-specific auto-antibodies or with inaccurate recovery-test results (lower than 80% or higher than 120%) were excluded from the study.

The ^{131}I treatment regimen of patients with highly differentiated thyroid cancer has been described elsewhere (*20,21*). Iodine-131 therapy is performed 4–5 wk after thyroidectomy with no replacement therapy during this time. TSH has to be higher than 30 μU/ml. Since iodine supplementation is low in Germany, no low-iodine diet is necessary before ^{131}I therapy. Mean iodine excretion in urine was 64 ± 35 (mean ± s.d.) μg/g creatinine in a subgroup of these patients with thyroid cancer. In our department, mean iodine excretion in the population without thyroid diseases is 83 ± 41 μg/g creatinine (unpublished results). Serum Tg levels were measured immediately before the first ^{131}I therapy (during the same day). Iodine uptake in the thyroid bed was measured scintigraphically 5 hr after oral administration of 74 MBq ^{131}I.

One hundred eleven patients with highly differentiated carcinomas were studied (38 follicular and 73 papillary). To achieve a sufficient follow-up period (for determination of later recurrence), patients included in this study were those who had undergone thyroidectomy and thus Tg measurement before 1989 (by RIA). Unfortunately, Tg could not be measured using the same technique in all patients. On the other hand, it is essential in differentiated thyroid cancer to allow a follow-up period of about 5 yr to record > 80% of recurrence (*22–24*). In the present study, the mean follow-up was 56 mo. For analytical purposes, the patients were retrospectively evaluated in four groups: Group A (n = 81), disease-free—no local recurrence or metastases (regional or distant); Group B (n = 11), lymph node metastases—regional lymph node metastases without distant metastases before the first ^{131}I therapy; Group C (n = 11), distant metastases—distant metastases without regional lymph node involvement before ^{131}I therapy; and Group D (n = 8), recurrence—local recurrence during follow-up with no known prestudy metastases. In addition, one patient had cervical lymph node metastases.

Tg/^{131}I uptake ratios were calculated for all patients. Initially, Kruskal-Wallis testing (chi square approximation) was used to test for the global hypothesis of no significant differences between the four groups. Subsequently, Wilcoxon two-sample testing (normal approximation, with continuity correction of 0.5) was performed to determine statistical significance between Group A and Groups B-D. The threshold for statistical significance was $p < 0.01$.

RESULTS

The results are shown in Table 1 and Figure 1. Tg/^{131}I uptake ratios in Group A ranged between 0 and 5.7 ng/ml/%. The values were significantly different ($p < 0.01$) compared to Groups B-D ($p < 0.01$). Individual values of thyroglobulin/^{131}I uptake ratio values are presented in Figure 1. The use of a threshold of 6 ng/ml/%, which seems to be optimal in this specific situation (to exclude false-positive results) resulted in sensitivity, specificity and positive and negative predictive values of 27%, 100%, 100%, 91% for lymph node metastases

(Group B), 73%, 100%, 100%, 96% for distant metastases (Group C) and 38%, 100%, 100%, 94% for recurrence (Group D), respectively.

DISCUSSION

Tg is a glycoprotein (660,000 Daltons) that is normally sequestered in the follicles of the thyroid gland and plays a central role in the synthesis and storage of thyroid hormones. In several benign thyroid diseases, Tg levels are increased, but in healthy subjects, Tg can also be found in the serum (*1,2,21*). The mechanisms by which Tg can arise in the circulation include transcellular transport from the lumen of the follicle through the basal lamella, aberrant synthesis/secretion or leakage through disruptions of the cell-to-cell junctions of the cells forming the thyroid follicles.

Since cell-to-cell junctions are frequently disrupted in a variety of disease states, including cancer, increases in Tg can be used as a serum marker related to thyroid disease. In patients with well-differentiated thyroid carcinoma, serum Tg is particularly useful in follow-up after thyroidectomy for thyroid cancer therapy and subsequent ^{131}I therapy (*3–10*).

A study published by Baskin in 1994 (*5*) proved that Tg levels are reliable in detecting recurrent thyroid cancer in patients who have undergone subtotal thyroidectomy and have been treated with only low doses of radioiodine (1.1 GBq). Tourniaire et al. (*19*) reported that Tg is also useful as a sensitive marker after unilateral thyroidectomy if a rise during follow-up is evaluated as suggestive of recurrence.

Although there is an overlap between the tumor-free patients and those with lymph node metastases, distant metastases and later recurrence, the results of the present study show that the Tg/^{131}I uptake ratio might serve as a prognostic marker also immediately after thyroidectomy but before radioiodine therapy. In contrast to a "screening" application, the identification of "high risk" patients (high probability of metastases or recurrence) is the main target of the prognostic evaluation before the first ^{131}I therapy. Since the Tg/^{131}I uptake ratio does not have to fulfill all criteria of a "classical" tumor marker, a threshold value, associated with a positive predictive value of 100% was chosen. Consequently, the sensitivity values are relatively low (27%, 73%, 38% for lymph node metastases, distant metastases and recurrence, respectively).

Iodine-131 uptake in the thyroid bed can be influenced by several factors, including TSH levels, the presence of remnant tissue masses, malignancy grade and the (rare) co-existence of distant metastases with high ^{131}I uptake, which significantly decreases the amount of available ^{131}I in the blood. One possible explanation for enhanced detection capabilities of the ratio could be that the serum Tg is proportional to the amount of remnant tissues mass (benign and normal cells) in patients without malignancy. In these patients, the iodination of Tg is not affected. The integrity of the remnant follicles is intact. Thus, the Tg is sequestered in the follicles and correlates with ^{131}I uptake. In patients with malignancy, iodination of Tg is decreased (with wide variability) in most cases. It might be expected that knowledge of additional information about Tg iodination (e.g. immunostaining) would lead to a better evaluation of this variability. Thus, while there is some local ^{131}I uptake, it is not strictly correlated to the Tg. For logistical reasons, we measured ^{131}I uptake already in the thyroid bed after 5 hr. Since, at this time, the amount of inorganic ^{131}I in the blood is still relatively high, later measurements might allow slightly clearer estimation of pure thyroid ^{131}I uptake.

CONCLUSION

Our results suggest that in differentiated thyroid carcinoma, ^{131}I uptake in the thyroid bed can be used to normalize Tg values for variations in the amount of remnant thyroid tissue after surgery and before ablative ^{131}I therapy. Therefore, the Tg/^{131}I uptake ratio might be considered a prognostic marker in this situation.

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