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Diagnostic 131-Iodine Whole-Body Scan May Be Avoided in Thyroid Cancer Patients Who Have Undetectable Stimulated Serum Tg Levels After Initial Treatment

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The follow-up of differentiated thyroid cancer after total thyroidectomy and thyroid ablation is commonly based on serum Tg determination and 131-iodine (^{131}I) diagnostic whole-body scan (WBS) performed in the hypothyroid state, 6–12 months after thyroid ablation. Based on the greater sensitivity of Tg measurement, with respect to WBS, the diagnostic yield of diagnostic WBS has been questioned in patients who are off L-T_4 therapy and have undetectable Tg levels.

The aim of the present retrospective study was to evaluate the diagnostic relevance of ^{131}I WBS performed after thyroid remnant ablation, in patients with undetectable serum Tg and off thyroid hormone therapy. The study included 315 of 662 consecutive patients (47.6%) treated in our department between 1980 and 1990, who, at the first control WBS after thyroid ablation, had undetectable serum Tg levels in the hypothyroid state. There were 54 men (17%) and 261 women (83%), with a mean age of 40.9 ± 13.1 yr (range, 12–76), followed for a mean of 12 ± 2.8 (range, 9–19) yr.

The control WBS was negative in 225 (71.4%) patients and positive for persistent areas of thyroid bed uptake, frequently of very low significance, in 90 (28.6%). No local or distant metastases were discovered.

At the last follow-up visit (1999–2000), 281 (89.2%) patients showed complete remission, with undetectable serum Tg off L-T_4 and negative WBS. Persistent thyroid bed uptake, with undetectable levels of Tg, was observed in 29 patients (9.2%) studied during L-T_4 withdrawal. Only 2 patients (0.6%) experienced local recurrence (lymph-node metastases) during their follow-up.

In conclusion, our data suggest that the presence of undetectable levels of serum Tg off L-T_4 at the time of the first control WBS after initial treatment, is highly predictive of complete and persistent remission. With the exception of detecting persistent thyroid bed uptake in a minority of cases, the control WBS has never given information that could influence the following therapeutic strategy. On this basis, we propose that the diagnostic ^{131}I WBS may be avoided in patients with undetectable levels of Tg off L-T_4. These patients may be monitored with clinical examination, neck ultrasound, and serum Tg measurements on L-T_4. (*J Clin Endocrinol Metab* 87: 1499–1501, 2002)

IN MANY CENTERS, the therapeutic strategy for differentiated thyroid cancer is based on near-total thyroidectomy, followed by 131-iodine (^{131}I) ablation of residual thyroid (1–3). The subsequent follow-up of these patients includes a control ^{131}I whole-body scan (WBS) and serum Tg measurement in the hypothyroid state, within 1 yr after thyroid ablation. These tests are aimed at ascertaining the effectiveness of radioiodine ablation and excluding the presence of residual disease in the neck or at distant sites (4). Usually, serum Tg measurement off L-T_4 is superior to WBS in predicting the presence or absence of local or distant metastases. Detectable or elevated serum Tg levels correlate with persistent disease, whereas undetectable levels are usually associated with complete remission, provided that anti-Tg antibodies are not present in the circulation (5–9). Based on this assumption, the question arises as to whether the execution of routine WBS might be limited to patients with detectable serum Tg and avoided in those with undetectable serum Tg. In a recent study addressing this issue, Cailleux *et al.* (10) reported that a diagnostic WBS, after thyroid ablation, yields no additional information, with respect to the results of serum Tg off L-T_4. Measurable Tg levels allowed the selection of patients requiring diagnostic and/or therapeutic intervention. Based on this finding, we designed the present retrospective study, aimed to assess the utility of the first control WBS after initial treatment and its impact on the subsequent outcome in 315 consecutive patients with undetectable serum Tg and off L-T_4.

Abbreviations: cps, Counts per sec; ^{131}I, 131-iodine; WBS, whole-body scan.

Subjects and Methods

The study included 662 consecutive patients undergoing the first control ^{131}I WBS and serum Tg measurement in the hypothyroid state, 6–12 months after postsurgical ablation of residual thyroid with radioiodine (30–100 mCi), during the interval of 1980–1990. Patients with positive anti-Tg autoantibodies were excluded from the study. Serum Tg measurements, at that time, were detectable (>3 ng/ml) in 347 (52.4%) patients, who were considered affected by residual or metastatic thyroid tissue and are not the object of the study.

The other 315 (47.6%) patients had undetectable serum Tg (<3 ng/ml) and represent the study group. They were 54 men (17%) and 261 women (83%), with a mean age of 40.9 ± 13.1 (range, 12–76) yr. Histology was papillary thyroid carcinoma in 272 (86.3%) and follicular thyroid carcinoma in 43 (13.7%). According to the classification proposed by De Groot *et al.* (1), 195 (62.0%) patients had class I disease (tumor limited to the thyroid gland), 76 (24.2%) had class II (lymph node metastases), 17 (5.4%) had class III (tumor extending outside the thyroid capsule), and 27 (8.4%) had an undetermined class because of lack of information.

Subsequent follow-up ranged between 9 and 19 yr (mean, 12 yr). For all patients, follow-up consisted of yearly clinical and ultrasound examination, periodic ^{131}I WBS in hypothyroidism, and periodic serum Tg measurements before and after L-T_4 withdrawal.

Serum Tg measurements

At the time of the study (1980–1990), serum Tg was measured using a commercial immunoradiometric assay (Sorin Tg, Saluggia, Italy) with

a sensitivity of 3 ng/ml. In more recent years, serum Tg was measured by an immunometric assay (Immulite 2000 Thyroglobulin; Diagnostic Products, Los Angeles, CA) with a functional sensitivity of 1 ng/ml.

^{131}I WBS

^{131}I WBS was performed after adequate withdrawal of L-T_4 suppressive therapy (TSH > 30 μU/ml) with a tracer dose of 4–5 mCi ^{131}I. Up to 1995, WBS was performed using a rectilinear scanner, 48–72 h after a tracer dose of 4–5 mCi ^{131}I. The time of scan was correlated with the activity, expressed in counts per second (cps), and ranged between 50 and 150 min. Scan speed was 50 cm/min for ≤200 cps and 150 cm/min for 200–500 cps. For more than 500 cps, the scan speed was 200 cm/min. Since 1995, a one-head γ-camera (Apex SPX 4000; Elscint Italia, Milano, Italy) was used for WBS, with a high energy collimator. Scan speed was 10 cm/min, with a count total of at least 100,000 cpm. WBS, after therapeutic doses of ^{131}I (90–150 mCi), was performed 5–10 d after the administration of the dose.

Results

Soon after surgery, all patients (n = 662) underwent thyroid ablation with ^{131}I, at doses ranging from 30–100 mCi, followed by posttherapy WBS. Residual thyroid tissue in the thyroid bed, with or without abnormal areas of uptake outside the thyroid bed, was present in all cases. Six to 12 months later, all patients underwent the first control ^{131}I WBS and serum Tg measurement in the hypothyroid state. At this time, 315 patients (47.6%) had serum Tg less than 3 ng/ml. These patients are the object of the study. At the time of thyroid ablation, the posttherapy scan showed the presence of thyroid bed uptake in all cases, with the addition of cervical node metastases in 33 (10.5%) and distant metastases to the lungs in 4 (1.3%) patients.

As shown in Fig. 1, the control ^{131}I WBS, 6–12 months after thyroid ablation, was negative in 225 (71.4%) patients and was positive for residual uptake in the thyroid bed in 90 (28.6%). No patient had scintigraphic or clinical evidence of local or distant metastases. Of the 90 patients with thyroid bed uptake, 54 received a second course of radioiodine therapy for ablation of residual thyroid, and 7 received 2 additional courses. Twenty-nine patients were not retreated. During the subsequent follow-up, extending from 9–19 yr, 281 (89.2%) patients remained free of disease (undetectable serum Tg and negative ^{131}I WBS), and 29 (9.2%) were free of disease, with persistence of thyroid bed uptake and undetectable serum Tg. Only 2 patients (0.6%) experienced recurrent disease in cervical lymph nodes. In 1 case, lymph node metastases were discovered 2 yr after initial treatment by neck ultrasound, confirmed by fine-needle aspiration cytology, and treated by surgery. In the other case, lymph node metastases were suspected 9 yr after initial treatment because of elevated serum Tg off L-T_4 (58 ng/ml), and confirmed in a posttherapy scan performed after the administration of 100 mCi. The patient was successfully treated with 2 courses of radioiodine therapy. Three (1%) patients died from nonthyroidal causes (Fig. 2). It is worth noting that when the sensitivity of the Tg assay changed from 3 ng/ml to 1 ng/ml, all the patients who were negative with the older assay remained negative also with the new one.

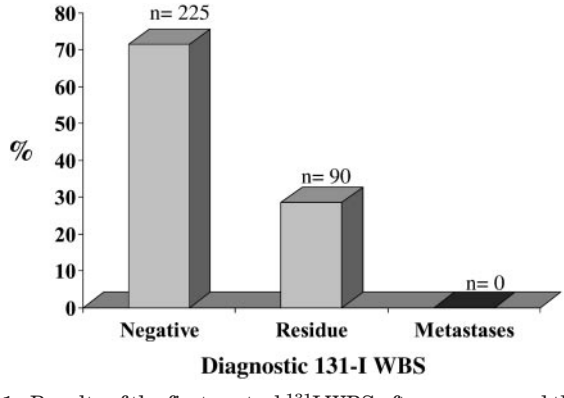

FIG. 1. Results of the first control ^{131}I WBS after surgery and thyroid ablation in 315 patients with undetectable (<3 ng/ml) serum Tg, off L-T_4.

Discussion

After initial treatment (near-total thyroidectomy and radioiodine thyroid ablation) for differentiated thyroid cancer, elevated levels of serum Tg, in the hypothyroid state at the time of the first control WBS, strongly suggest the presence of persistent disease that needs to be discovered and treated. In these cases, imaging with ^{131}I, after diagnostic or (preferably) therapeutic doses, may help localize the site of Tg production (11–14).

In the opposite situation, *i.e.* when serum Tg is undetectable, an undetectable serum Tg is highly predictive of disease-free status. In this case, the results of WBS do not add any valuable information, with the only exception being persistence of minor uptake in the thyroid bed in a minority of patients in whom the previous ablative dose of ^{131}I was not totally effective. This finding may or may not lead to a second course of radioiodine therapy but, in any case, will not influence the final outcome, as demonstrated by the observation that the 29 patients not retreated with radioiodine for persistent thyroid bed uptake had an excellent outcome, with spontaneous disappearance of thyroid bed uptake, at the last control WBS, in nearly one third of the cases (10 of 29). After a mean follow-up of 12 yr, we observed only 2 neck recurrences, accounting for 0.6% of all patients, both discovered by routine neck ultrasound.

Our results are in agreement with a similar study by Cailleux *et al.* (10), showing that in 210 patients with a Tg less than 1 ng/ml while hypothyroid, the control WBS was negative

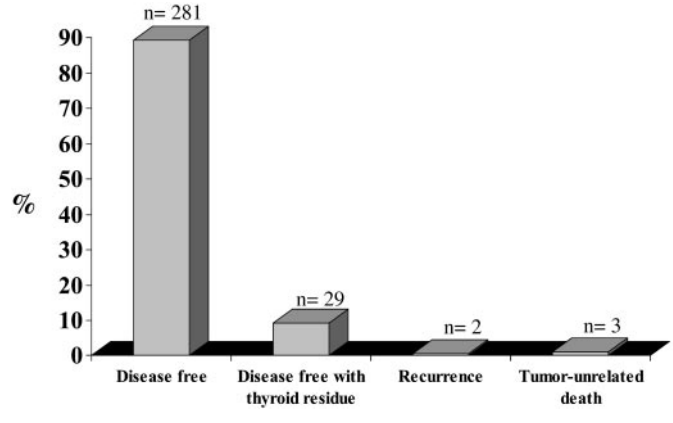

FIG. 2. Patients status during follow-up, based on clinical data, neck ultrasound, and the results of the last serum Tg and ^{131}I WBS during hypothyroidism.

in the large majority and positive in the thyroid bed in a small minority (15/210). In the subsequent follow-up, only 2 patients (0.9%) experienced recurrent disease more than 3 yr after initial treatment, detected by palpation and visible in the posttherapy ^{131}I WBS.

The results of Cailleux *et al.* and those of our report reinforce the concept that the finding of an undetectable serum Tg, off L-T_4, is highly predictive of complete remission and indicates the low usefulness of scanning patients with diagnostic doses of ^{131}I. The follow-up of such patients may be continued, with periodic serum Tg measurements on L-T_4, in addition to clinical and ultrasound examination. The recent introduction of recombinant human TSH (Thyrogen; Genzyme Transgenics Corp., Cambridge, MA) into clinical practice (15) will further facilitate follow-up, allowing measurement of stimulated-Tg values in all patients with undetectable basal Tg, or in selected cases. Diagnostic or therapeutic procedures will be limited to patients showing positive Tg responses to recombinant human TSH.

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References

1. **De Groot LJ, Kaplan EL, McMormick M, Strauss FH** 1990 Natural history, treatment and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 71:414–424
2. **Schlumberger M** 1998 Papillary and follicular thyroid carcinoma. N Engl J Med 338:297–306
3. **Mazzaferri EL, Jhiang SM** 1994 Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 97: 418–428
4. **Maxon HR, Smith HS** 1990 Radioiodine-131 in the diagnosis and treatment of metastatic well-differentiated thyroid cancer. Endocrinol Metab Clin North Am 19:685–718
5. **Pacini F, Pinchera A, Giani C, Grasso L, Baschieri L** 1980 Serum thyroglobulin concentration and 131-I whole-body scans in the diagnosis of metastases from differentiated thyroid carcinoma (after thyroidectomy). Clin Endocrinol (Oxf) 13:107–110
6. **Pacini F, Lari R, Mazzeo S, Grasso L, Taddei D, Pinchera A** 1985 Diagnostic value of a single serum thyroglobulin determination on and off thyroid suppressive therapy in the follow-up of patients with differentiated thyroid cancer. Clin Endocrinol (Oxf) 23:405–411
7. **Schlumberger M, Baudin E** 1998 Serum thyroglobulin determination in the follow-up of patients with differentiated thyroid carcinoma. Eur J Endocrinol 138:249–252
8. **Ozata M, Suzuki S, Miyamoto T, Liu RT, Fierro-Renoy F, De Groot LJ** 1994 Serum thyroglobulin in the follow-up of patients with treated differentiated thyroid cancer. J Clin Endocrinol Metab 79:98–105
9. **Spencer CA, LoPresti JS, Fatemi S, Nicoloff JT** 1999 Detection of residual and recurrent differentiated thyroid carcinoma by serum thyroglobulin measurement. Thyroid 9:435–441
10. **Cailleux AF, Baudin E, Travagli JP, Ricard M, Schlumberger M** 2000 Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid carcinoma? J Clin Endocrinol Metab 85:175–178
11. **Pacini F, Lippi F, Formica N, Elisei R, Anelli S, Ceccarelli C, Pinchera A** 1987 Therapeutic doses of iodine-131 reveal undiagnosed metastases in thyroid cancer patients with detectable serum thyroglobulin levels. J Nucl Med 28: 1888–1891
12. **Pineda J, Lee T, Ain K, Reynolds J, Robbins J** 1995 Iodine-131 therapy for thyroid cancer patients with elevated thyroglobulin and negative diagnostic scan. J Clin Endocrinol Metab 80:1488–1492
13. **Schlumberger M, Mancusi F, Baudin E, Pacini F** 1997 131I therapy for elevated thyroglobulin levels. Thyroid 7:273–276
14. **Pacini F, Pinchera A** 1999 Serum and tissue thyroglobulin measurement: clinical applications in thyroid disease. Biochimie 81:463–467
15. **Haugen BR, Pacini F, Reiners C, Schlumberger M, Ladenson PW, Sherman SI, Cooper DS, Graham KE, Braverman LE, Skarulis MC, Davies TF, DeGroot LJ, Mazzaferri EL, Daniels GH, Ross DS, Luster M, Samuels MH, Becker DV, Maxon 3rd HR, Cavalieri RR, Spencer CA, McEllin K, Weintraub BD, Ridgway EC** 1999 A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant of cancer. J Clin Endocrinol Metab 84:3877–3885