

Outcome of Differentiated Thyroid Cancer with Detectable Serum Tg and Negative Diagnostic ^{131}I Whole Body Scan: Comparison of Patients Treated with High ^{131}I Activities Versus Untreated Patients

F. PACINI, L. AGATE, R. ELISEI, M. CAPEZZONE, C. CECCARELLI, F. LIPPI, E. MOLINARO, AND A. PINCHERA

Department of Endocrinology and Metabolism, Section of Endocrinology, University of Pisa, 56124 Pisa, Italy

Detectable serum Tg levels associated with negative diagnostic ^{131}I whole body scan are not infrequently found in patients with differentiated thyroid cancer. Several researchers have shown that in these patients the administration of high ^{131}I activity (100 mCi or more) increases the sensitivity of a posttherapy diagnostic ^{131}I whole body scan performed a few days later and allows the detection of neoplastic foci not seen with diagnostic doses of ^{131}I . Empirical radioiodine treatment has also been advocated by some researchers, but its therapeutic effect is controversial.

In our institute, positive serum Tg/negative diagnostic ^{131}I whole body scan patients were not treated with high ^{131}I activities before 1984; afterward, almost all patients with positive serum Tg/negative diagnostic ^{131}I whole body scan patients were treated with radioiodine, and a posttherapy diagnostic ^{131}I whole body scan was performed. In the present retrospective study we compared the outcome of these two groups of patients, 42 treated and 28 untreated, followed for mean periods of 6.7 ± 3.8 and 11.9 ± 4.4 yr, respectively. In the treated group the first posttherapy diagnostic ^{131}I whole body scan was negative in 12 patients and positive in 30 patients. ^{131}I treatment was further administered only in the latter group.

At the end of follow-up in treated patients a complete remission (normalization of serum Tg off L-thyroxine and negative diagnostic ^{131}I whole body scan) was observed in 10 patients (33.3%). In 9 cases (30%) posttherapy diagnostic ^{131}I whole body scan became negative, and serum Tg was reduced but still detectable; in 11 patients (36.6%) serum Tg was de-

tectable, and posttherapy diagnostic ^{131}I whole body scan was positive. The resolution of ^{131}I uptake in lung metastases was observed in 8 of 9 cases (88.8%) and in cervical node metastases in 11 of 18 cases (61.1%). In patients treated only once because the posttherapy diagnostic ^{131}I whole body scan was negative ($n = 12$), 2 patients (16.7%) were in apparent remission, 7 (58.3%) had detectable Tg values without evidence of disease, 2 (16.7%) showed lymph node metastases in the mediastinum, and 1 patient (8.3%) died because of lung metastases.

Of the 28 untreated patients, none with radiological evidence of disease, serum Tg off L-thyroxine therapy became undetectable in 19 cases (67.9%), significantly reduced in 6 cases (21.4%), and unchanged or increased in 3 patients (10.7%), 1 of whom developed lung metastases 14 yr after the diagnosis.

In summary, our results indicate that in patients with detectable serum Tg and negative diagnostic ^{131}I whole body scan, treatment with high doses of ^{131}I may have therapeutic utility in patients with lung metastases and, to a lesser extent, in those with lymph node metastases. However, in view of the frequent normalization of Tg values in untreated patients, we believe that treatment with ^{131}I should be considered according to the result of the first posttherapy scan. If positive in the lung, ^{131}I treatment should be continued up to total remission; surgical treatment should be preferred in patients with node metastases, and no treatment should be used in those with thyroid bed uptake or no uptake. (*J Clin Endocrinol Metab* 86: 4092–4097, 2001)

SERUM Tg LEVELS off L-thyroxine therapy are usually well correlated with the results of diagnostic ^{131}I whole body scan (WBS) in the postsurgical follow-up of differentiated thyroid cancer. Undetectable Tg levels are found in patients with WBS^- , suggesting complete remission, whereas detectable or elevated Tg concentrations are associated with the presence of ^{131}I uptake in local or distant metastases (1–6).

Several large series have shown that in 10–15% of the patients detectable serum Tg levels are found despite WBS^- (4, 7, 8). In these cases, the discrepancy is mainly due to metastases able to produce Tg but having iodine uptake too

low to be visualized on diagnostic scans, either because the mechanism of iodine trapping is defective or because the mass of neoplastic tissue is small. In this situation several researchers (8–10) have shown that the administration of high ^{131}I activity (100 mCi or more) increases the sensitivity of a WBS performed a few days later and allows the detection of neoplastic foci not seen with diagnostic doses of ^{131}I .

Evidence of therapeutic effect with this treatment modality has been provided by some researchers (8, 10), but its impact on the final outcome of the disease remains uncertain, mainly due to the lack of long-term controlled studies including patients left untreated.

In our institution, positive serum Tg (Tg^+)/ WBS^- patients were not treated with high ^{131}I doses before 1984. Afterward, almost all patients with Tg^+ / WBS^- were treated with radioiodine based on our initial finding that this procedure was

Abbreviations: AbTg, Anti-Tg autoantibodies; cps, counts per sec; CT, computed tomography; NMR, nuclear magnetic resonance; Tg^+ , detectable serum Tg levels; WBS^- , negative diagnostic ^{131}I whole body scan.

beneficial (9). We report here the comparison of these two groups of patients, treated and untreated, with regard to the behavior of serum Tg and the long-term outcome of the disease. We are aware that the study is not randomized, but the two groups are unselected, and we believe that the study may give new insight into the controversial issue of the management of Tg⁺/WBS⁻ patients.

Subjects and Methods

Patients

Seventy patients affected by papillary differentiated thyroid cancer (52 females and 18 males), aged 14–75 yr, were suitable for this study. All patients had been treated with near-total thyroidectomy during 1969 to 1995, followed by thyroid ablation with ¹³¹I therapy. Thyroid ablation was preceded by a diagnostic WBS, and a posttherapy WBS was not routinely performed. Serum Tg measurement was an integral part of the follow-up. The first Tg measurement was obtained 3–4 months after thyroidectomy and subsequently at any clinical control on L-thyroxine therapy and off L-thyroxine any time the patient was scheduled for WBS.

At some point of the subsequent follow-up (1–22 yr after initial treatment; mean, 4.0 ± 3.8 yr), always after thyroid ablation, these patients showed detectable/elevated serum Tg values off L-thyroxine in the absence of circulating anti-Tg autoantibodies (AbTg), and negative diagnostic WBS performed with a tracer dose of 5 mCi of ¹³¹I. This eventuality was mainly observed during the first year after initial treatment (probably representing persistent disease) and only sporadically during follow-up after a period of time with undetectable serum Tg levels (probably representing recurrence of disease after a disease-free interval). No clinical or radiological evidence of local or distant disease [by ultrasound, chest x-ray, and lung computed tomography (CT) scan] was documented. Other patients, with radiological evidence of local or distant metastases, were assigned to appropriate treatment and were not included in this series. Circulating TSH measurement and urinary iodine excretion were used to rule out a mistake in withdrawing L-thyroxine therapy or iodine contamination as the cause of negative WBS.

Twenty-eight (40%) of the 70 patients, seen before 1984, were not treated with therapeutic doses of radioiodine. The other 42 (60%) patients, seen after 1984, were treated with at least 1 therapeutic dose of ¹³¹I (90–150 mCi), followed by posttherapy WBS. This posttherapy WBS was negative in 12 and positive in 30 patients. The therapeutic procedure was not repeated in the 12 negative patients, whereas further ¹³¹I treatments and posttherapy WBS were performed in positive patients. The procedure was discontinued when serum Tg off L-thyroxine became undetectable or when the posttherapy scan was negative, even if serum Tg was still detectable. In summary we have a group of 28 Tg⁺/WBS⁻ patients never treated with high ¹³¹I doses (untreated group), a group of 30 patients submitted to several treatment courses of radioiodine (treated group), and a group of 12 patients treated only once because the posttherapy scan was negative.

The epidemiological and clinical data of the study groups are shown

in Table 1. Among the 42 patients treated with ¹³¹I (32 women and 10 men; mean age, 39.1 ± 15.7 yr; range, 14–75 yr), the tumor stage at the time of diagnosis according to the Tumor-Node-Metastases classification (11) was stage 1 in 6 patients (14.3%), stage 2 in 24 (57.1%), and stage 3 in 10 (23.8%); in 2 (4.8%) patients it was not possible to ascertain the stage. Among 28 patients not subjected to ¹³¹I treatment (20 women and 8 men; mean age, 37.3 ± 12.4 yr; range, 14–60 yr), 11 (39.3%) patients had stage 1, 10 (35.7%) had stage 2, and 7 (25.0%) had stage 3 disease. The postsurgical ¹³¹I ablation dose was not different in treated or untreated patients (67.5 ± 33.9 and 69.7 ± 30.2 mCi, respectively).

The outcome of treated and untreated groups was assessed after mean follow-up periods of 6.7 ± 3.8 and 11.9 ± 4.4 yr, respectively, by serum Tg measurement, WBS, and radiological evaluation [neck ultrasonography, chest x-ray, CT scan, or nuclear magnetic resonance (NMR) imaging]. The longer period of follow-up in untreated patients is due to the above-mentioned different therapeutic strategy applied in patients with Tg⁺/WBS⁻ diagnosed before 1984 compared with that given to patients diagnosed thereafter.

¹³¹I WBS

Total body scan was performed using a rectilinear scanner. In all cases the conventional WBS was performed 48–72 h after administration of a tracer dose of 5 mCi ¹³¹I. The time of scan was correlated with the activity expressed in counts per sec (cps) and ranged between 50–150 min. Scan speed was 50 cpm for 200 cps or less and 150 cpm for 200–500 cps. For more than 500 cps the scan speed was 200 cpm. Since 1995 a one-head γ -camera (Apex SPX 4000, Elscint Italia, Milano, Italy) was used, with a high energy collimator and a sensitivity of 160 cpm/ μ Ci. The scan speed was 10 cm/min, with total counts of at least 100,000 cpm. WBS after therapeutic doses of ¹³¹I (90–150 mCi) was performed 5–10 d after administration of the dose.

As the empirical treatment with ¹³¹I reported in this study started in 1984, most patients were studied with the same apparatus (rectilinear scanner). Only a minority of the scans were performed with the more sensitive γ -camera introduced in 1995.

Measurement of serum Tg

Starting in 1974, serum Tg became a routine test in thyroid cancer patients. Serum Tg was measured by home-made RIA, with a functional sensitivity of 1.5 ng/ml, up to 1980 and by commercial immunoradiometric assay (HTGK, Sorin Biomedica, Saluggia, Italy), with a functional sensitivity of 3 ng/ml, after 1980. These cut-off values correlated well with remission or persistence of disease (12). As circulating AbTg interfere in Tg assays producing false results, we routinely screen all patients for serum AbTg by passive hemagglutination (Thyroid Test Kit, Fujizaki, Pharmaceutical Co., Tokyo, Japan) (13). Patients with positive autoantibodies were not included in this analysis.

Statistics

The Mann-Whitney U test was used for the analysis of serum Tg in different groups. The χ^2 test was used for the analysis of epidemiological

TABLE 1. Epidemiological and clinical data of Tg⁺/diagnostic WBS⁻ patients

| | Treated | | Untreated | P |
|--------------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------|
| | Posttherapy WBS+ | Posttherapy WBS- | | |
| No. of patients | 30 | 12 | 28 | |
| Age (yr) | 35.8 ± 15.9 (range, 14–75) | 47.2 ± 12.1 (range, 29–65) | 37.3 ± 12.4 (range, 14–60) | NS |
| Sex (F/M) | 25/5 | 7/5 | 20/8 | NS |
| TNM classification | | | | |
| Stage 1 | 6 | 11 | 9 |] NS |
| Stage 2 | 24 | 10 | 15 | |
| Stage 3 | 10 | 7 | 4 | |
| Stage x | 2 | 0 | 0 | |
| ¹³¹ I ablative dose (mCi) | 66.2 ± 34.5 (range, 30–150) | 70.8 ± 33.2 (range, 30–110) | 69.7 ± 30.2 (range, 30–120) | NS |
| Follow-up (yr) | 6.7 ± 3.8 | 6.5 ± 3.7 | 11.9 ± 4.4 | ^a |

^a P < 0.0001 vs. posttherapy WBS+; P = 0.0006 vs. posttherapy WBS-.

and clinical features of different groups. *P* < 0.05 was considered significant.

Results

Serum Tg at the first evidence of detectable Tg values and negative diagnostic WBS

As shown in Table 2, mean serum Tg values off L-thyroxine therapy were 62.1 ± 44.1 ng/ml (range, 7-207 ng/ml) in treated patients and 39.7 ± 54 ng/ml (range, 4-195 ng/ml) in untreated patients (*P* = 0.003, by Mann-Whitney U test). During L-T₄ suppressive therapy, Tg values were detectable in 12 of 30 treated patients (mean, 14.9 ± 12.9 ng/ml; range, 4-38 ng/ml) and undetectable (<3 ng/ml) in the other 18 cases. In untreated patients Tg values were detectable in 4 of 28 cases (mean, 11.2 ± 8.5 ng/ml; range, 3-22 ng/ml).

Results of the first posttherapy ¹³¹I WBS in the treated group (n = 42)

After administration of a therapeutic dose of ¹³¹I (90-150 mCi) areas of radioiodine uptake in the posttherapy scan were present in 30 cases (Fig. 1): thyroid bed in 3 cases (10%), cervical nodes in 18 cases (60%), and lung with or without cervical nodes in 9 cases (30%). Posttherapy WBS was negative in 12 patients. These 12 patients were no longer treated with radioiodine. The relationship between the results of the posttherapy WBS and the individual values of serum Tg both off and on L-thyroxine is shown in Fig. 2.

Outcome of treated patients with positive posttherapy WBS (n = 30)

The mean period of follow-up in this group was 6.7 ± 3.8 yr; during this period the patients were subjected to further radioiodine treatment, posttherapy WBS, and serum Tg measurement both off and on L-thyroxine therapy.

As shown in Fig. 3, patients were treated with cumulative ¹³¹I doses ranging between 90-500 mCi (mean, 256.8 ± 117.9 mCi). The mean number of radioiodine courses was 3 (range, 1-6). As summarized in Table 3, at the end of follow-up, the normalization of serum Tg off L-thyroxine (Tg undetectable) with negative WBS was observed in 10 patients (33.3%), including 1 patient with thyroid residue, 6 patients with lymph node metastases, and 3 patients with lung metastases at the time of the first posttherapy scan. The normalization of posttherapy WBS was observed in 9 patients (30%) in whom serum Tg was still detectable although reduced; in 11 patients (36.6%) both serum Tg and posttherapy WBS were abnormal, with evidence of radioiodine uptake in cervical nodes (9 cases) and in the lungs (2 cases). The individual changes in serum Tg off L-thyroxine at the end of follow-up

with respect to initial values are depicted in Fig. 4. Together, the normalization of serum Tg off L-thyroxine or the disappearance of uptake was observed in 8 of 9 patients (88.8%) with lung metastases and in 11 of 18 (61.1%) with cervical node metastases.

Outcome of untreated group (n = 28)

In this group the mean period of follow-up was 11.9 ± 4.4 yr. Patients were assessed by serum Tg measurement, diagnostic WBS, and radiological evaluation (neck ultrasonography, chest x-ray, CT scan, or NMR). At the end of the study serum Tg off L-thyroxine therapy was undetectable in 19 cases (67.9%), significantly reduced in 6 cases (21.4%), and unchanged or increased in 3 cases (10.7%). As shown in Table 4, these data were further analyzed, subdividing the 28 pa-

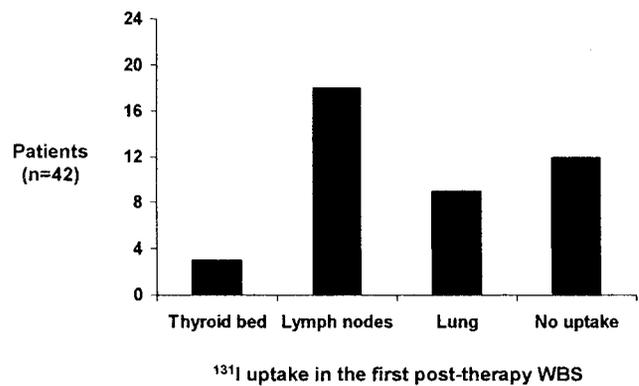


FIG. 1. Results of posttherapy ¹³¹I WBS in 42 Tg⁺/WBS⁻ patients at the time of the first treatment with high ¹³¹I activities.

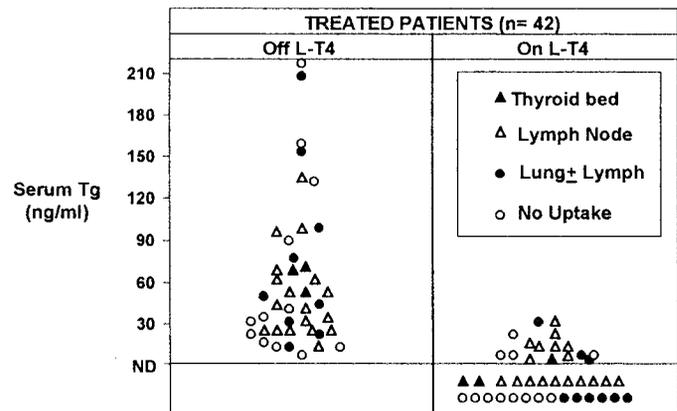


FIG. 2. Relationship between the results of the ¹³¹I posttherapy WBS and the individual values of serum Tg both off and on L-T₄ before therapy. N.D., Not detectable.

TABLE 2. Mean and median serum Tg values off and on L-thyroxine therapy in treated and untreated patients

| | Treated (n = 30) | | Untreated (n = 28) | |
|-------------------|--------------------------|-------------------------------------|--------------------------|------------------------------------|
| | Off L-thyroxine (n = 30) | On L-thyroxine (detectable, n = 12) | Off L-thyroxine (n = 28) | On L-thyroxine (detectable, n = 4) |
| Mean ± SD (ng/ml) | 62.1 ± 44.1 ^a | 14.9 ± 12.9 | 39.7 ± 54.0 ^a | 11.2 ± 8.5 |
| Median (ng/ml) | 55 | 9 | 9.5 | 10 |
| Range (ng/ml) | 7-207 | 4-38 | 4-195 | 3-22 |

^a *P* = 0.003, by Mann-Whitney U test.

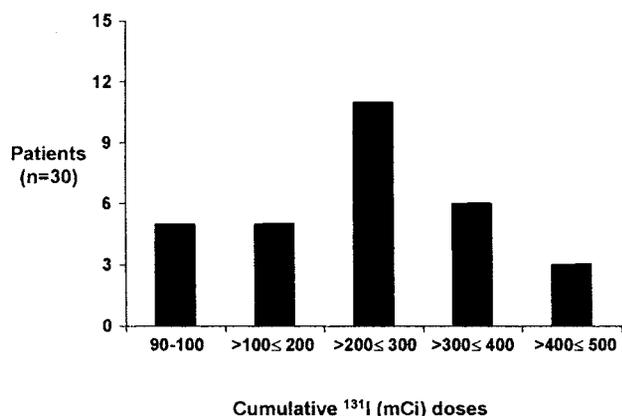


FIG. 3. Cumulative ¹³¹I doses (mCi) administered in treated patients with positive posttherapy WBS (n = 30).

TABLE 3. Results of posttherapy WBS and serum Tg at the last control off L-thyroxine in treated patients (n = 30)

| Site of uptake at the 1st posttherapy WBS | Last control off L-thyroxine | | | |
|---|------------------------------|------------------|-------------|---------|
| | Undetectable Tg ^a | Detectable Tg | | |
| | | Post-therapy WBS | | |
| | | Negative | Lymph nodes | Lung |
| Thyroid bed, n = 3 | 1 | 2 | | |
| Lymph nodes, n = 18 | 6 | 5 | 6 | 1 |
| Lung (±nodes) n = 9 | 3 | 2 | 3 | 1 |
| Total, n = 30 (%) | 10 (33.3) | 9 (30) | 9 (30) | 2 (6.7) |

^a ¹³¹I therapy was not administered because Tg became undetectable, and diagnostic WBS was negative.

tients into 2 groups according to the initial Tg values (>10 ng/ml, 14 patients; ≤10 ng/ml, 14 patients). In those with Tg levels greater than 10 ng/ml, the last control Tg became undetectable in 7 cases (50%), decreased in 6 cases (42.9%), and increased in 1 case (7.1%). In patients with Tg levels of 10 ng/ml or less, the last control Tg became undetectable in 12 cases (85.7%) and unchanged or increased in 2 cases (14.3%). Lung macrometastases were discovered in 1 of these patients by CT scan, 14 yr after diagnosis. Diagnostic WBS remained negative in all patients.

Outcome of patients with negative posttherapy WBS at the first and only treatment course (n = 12)

In this cohort of patients with negative posttherapy WBS at the time of the first radioiodine treatment, the mean period of follow-up was 6.5 ± 3.7 yr. At the end of follow-up, 2 patients (16.7%) were in apparent remission (undetectable Tg and no evidence of disease), 7 (58.3%) had detectable serum Tg concentrations without evidence of disease, 2 (16.7%) had evidence of lymph node metastases in the mediastinum detected by CT scan, and 1 patient (8.3%) developed lung metastases, which caused her death (Table 5).

Discussion

Serum Tg levels are usually undetectable in patients without residual disease during the postsurgical follow-up of differentiated thyroid carcinoma. On the contrary, the find-

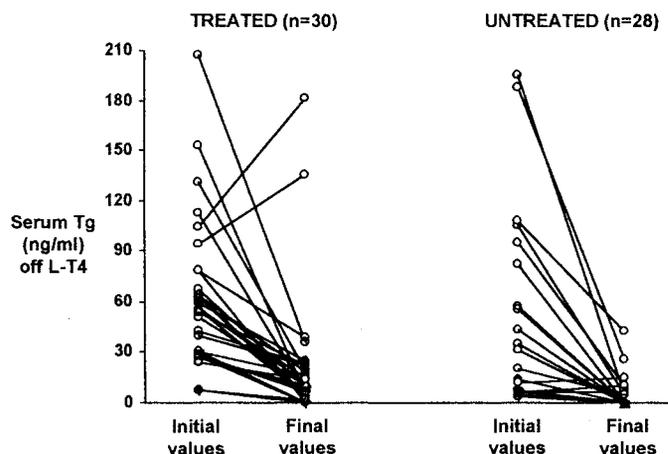


FIG. 4. Individual changes in serum Tg off L-T₄ at the end of follow-up with respect to initial values in ¹³¹I-treated and untreated patients.

TABLE 4. Results of serum Tg off L-thyroxine therapy at the last control in untreated patients (n = 28)

| Initial Tg | Tg at the end of follow-up ^a | | |
|-------------------------|---|-----------|--------------|
| | Unchanged or increased | Decreased | Undetectable |
| Tg >10 ng/ml, n = 14 | 1 | 6 | 7 |
| Tg >3 <10 ng/ml, n = 14 | 2 ^b | | 12 |
| Total, n = 28 (%) | 3 (10.7) | 6 (21.4) | 19 (67.9) |

^a Diagnostic WBS was negative in all.

^b Lung metastases were discovered in one patient by CT scan, 14 yr after the diagnosis.

TABLE 5. Final status of 12 patients who had negative posttherapy WBS at the first and only treatment with ¹³¹I

| | |
|--------------------------|---|
| Undetectable Tg (n = 2) | |
| No evidence of disease | 2 |
| Detectable Tg (n = 10) | |
| No evidence of disease | 7 |
| Local relapse | 2 |
| Dead for lung metastases | 1 |

ing of detectable/elevated serum Tg levels is the most reliable evidence of persistent or recurrent disease (7, 12, 14).

Serum Tg levels are usually well correlated with the results of WBS; however, in some cases serum Tg levels may be found in patients with no evidence of residual or metastatic thyroid tissue, including negative diagnostic WBS. Several large series have found this discrepancy in 10–15% of patients (4, 7, 8). In particular, some studies (8–10, 15) have clearly shown that the administration of high ¹³¹I activity (100 mCi or more) increases the sensitivity of a posttherapy WBS and allows the detection of neoplastic foci not seen with diagnostic doses of ¹³¹I. The therapeutic effect of this treatment is not fully demonstrated and is sometimes questioned.

In our study we addressed this issue by reviewing the outcome of two groups of patients with Tg⁺/WBS⁻, one of whom was treated with high ¹³¹I activities and one who was left untreated.

From the diagnostic point of view, our results show the high sensitivity of posttherapy ¹³¹I WBS in Tg⁺/WBS⁻ patients. Visible uptake limited to the thyroid bed occurred in

a minority of cases (three patients) and was interpreted as persistent thyroid residue. Its association with detectable serum Tg off L-thyroxine should not be surprising, especially if persistent residual thyroid tissue is abundant and TSH stimulation is important, as in our cases. From the clinical point of view, we believe that these residues do not represent a matter of concern for the patients' outcome and probably should not be treated with additional doses of radioiodine. Support for this hypothesis has been provided by Cailleux *et al.* (16), who in addition showed that metastatic disease may be discovered by scanning the patients after they received the ablative dose. However, the possibility that thyroid bed uptake may be due to residual or recurrent tumor rather than to normal thyroidal tissue should always be considered.

Our results indicate that the administration of a high ¹³¹I dose in Tg⁺/WBS⁻ patients is effective in curing lung metastases and, to a lesser extent, lymph node metastases. At the end of the follow-up, lymph node metastases were cured in 11 of 18 cases (61.1%). The complete resolution of ¹³¹I uptake in lung metastases was observed in 8 of 9 cases (88.8%), associated with serum Tg normalization in 3 cases and with serum Tg decline in the others. In these cases we cannot prove that the resolution of ¹³¹I uptake demonstrates effective treatment rather than loss of iodine-trapping ability. We favor the first possibility based on the consideration that our cases of lung metastases were all of the micronodular diffuse type, not visible on chest x-ray, those usually reported as having the best prognosis after radioiodine treatment. Furthermore, in one case the resolution of ¹³¹I uptake correlated with the results of CT scan, which converted to negative after treatment. In the other cases, the CT scan was negative from the beginning.

Similar results have been reported in previous studies (8, 10, 17). Schlumberger *et al.* (8) showed the complete remission of lung metastases demonstrated by posttherapy WBS in 20 of 23 patients with differentiated thyroid carcinoma when chest x-ray was normal. Pineda *et al.* (10) reported therapeutic effectiveness of ¹³¹I treatment in 14 patients with elevated Tg and negative WBS as assessed by a significant reduction of serum Tg to 5 ng/ml or less and by normalization of previously positive posttherapy WBS. Fautorechi *et al.* (17) concluded that treatment with high doses of ¹³¹I in Tg⁺/WBS⁻ patients, allows the detection of abnormal uptake in posttherapy WBS, particularly micrometastases. In their experience aggressive macrometastases with negative diagnostic WBS do not show significant uptake after therapeutic doses of ¹³¹I.

Despite the above reports, the use of high ¹³¹I activities in Tg⁺/WBS⁻ patients has been questioned by some researchers, mainly due to the lack of control studies (18, 19).

Although retrospective and not randomized, our study included a control group of untreated Tg⁺/WBS⁻ patients. The outcome of this group was good. Serum Tg dropped to undetectable levels in nearly two thirds of the patients and decreased in the others, and no evidence of disease has been documented in all but one who developed lung metastases 14 yr after the diagnosis. However, as a posttherapy scan was never performed in this group, we cannot exclude the possibility that other patients might have also had lung micrometastases that never progressed to the clinical stage. This

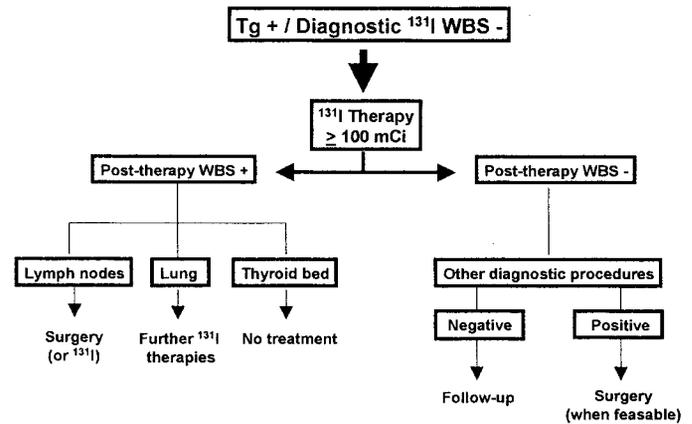


FIG. 5. Proposed protocol for the management of Tg⁺/WBS⁻ patients.

event probably occurred in the above-mentioned patient who developed lung macrometastases and in one patient in the group treated only once who died of lung disease.

A possible comment regarding the spontaneous drop of serum Tg in untreated patients is that they might have less severe disease as the source of serum Tg: residual thyroid tissue rather than metastases. This possibility is in agreement with the observation that mean serum Tg levels off L-thyroxine therapy in the untreated group at the beginning of the study were significantly lower than those in treated patients. The spontaneous reduction of serum Tg in these patients might be due to the long-term effect of L-thyroxine suppressive therapy. Together, the above considerations suggest strict selection criteria in deciding which patients should be treated with ¹³¹I to effectively treat tumor cells and not a mathematical number of Tg.

The following protocol (Fig. 5) seems to us a rational proposal for the management of Tg⁺/WBS⁻ patients. Each patient presenting with Tg⁺/WBS⁻ should undergo one treatment with high doses of ¹³¹I, followed by posttherapy WBS. If posttherapy WBS is positive for lymph node metastases, two alternatives, both effective, may be considered: surgery, possibly using the surgical probe-guided approach suggested by Travagli *et al.* (20) or repeated administration of ¹³¹I therapy. If lung metastases are detected, radioiodine treatment should be continued until complete remission, defined as normalization of serum Tg off L-thyroxine and/or normalization of the posttherapy scan. Thyroid uptake in the thyroid bed should not be treated.

If posttherapy WBS is negative, the patient should not be subjected to further treatment and followed with the traditional diagnostic methodologies (neck ultrasonography, chest x-ray, CT scan, or NMR) or with alternative scintigraphic methods employing radioactive tracers different by ¹³¹I (^{99m}Tc-tetrafosmin, ^{99m}Tc-Sestamibi, or fluorine-18 fluorodeoxyglucose-positron emission tomography), which have been indicated as useful alternatives in selected cases (21–23).

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Address all correspondence and requests for reprints to: Dr. F. Pacini, Department of Endocrinology and Metabolism, Section of Endocrinology, University of Pisa, Via Paradise, 2-56124 Pisa, Italy.

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References

1. Pacini F, Pinchera A, Giani C, Grasso L, Baschieri L 1980 Serum thyroglobulin concentration and ¹³¹I whole body scans in the diagnosis of metastases from differentiated thyroid carcinoma (after thyroidectomy). *Clin Endocrinol (Oxf)* 13:107–110
2. Pacini F, Pinchera A, Giani C, et al. 1980 Serum thyroglobulin in thyroid carcinoma and other thyroid disorders. *J Endocrinol Invest* 3:283–292
3. Charles MA, Dodson Jr LE, Waldeck N, et al. 1980 Serum thyroglobulin levels predict total body iodine scan findings in patients with treated well differentiated thyroid carcinoma. *Am J Med* 69:401–407
4. Ashcraft MW, Van Herle AJ 1981 The comparative value of serum thyroglobulin measurements and iodine 131 total body scans in the follow-up study of patients with treated differentiated thyroid cancer. *Am J Med* 71:806–814
5. Schneider AB, Line BR, Goldman JM, Robbins J 1981 Sequential serum thyroglobulin determination ¹³¹I scan and ¹³¹I uptakes after triiodothyronine withdrawal in patients with thyroid cancer. *J Clin Endocrinol Metab* 53:1199–1206
6. Galligan JP, Winship J, van Doorn T, Mortimer RH 1982 A comparison of serum thyroglobulin measurements and whole body ¹³¹I scanning in the management of treated differentiated thyroid carcinoma. *J Med Aust NZ* 12:248–254
7. Pacini F, Ceccarelli C, Elisei R, et al. 1988 Serum thyroglobulin determination in thyroid cancer. A ten year experience. In: Nagataki S, Torizuka K, eds. *The thyroid* 1988. Amsterdam: Elsevier; 685–689
8. Schlumberger M, Arcangioli O, Piekarski JD, Tubiana M, Parmentier C 1988 Detection and treatment of lung metastases of differentiated thyroid carcinoma in patients with normal chest x-ray. *J Nucl Med* 29:1790–1794
9. Pacini F, Lippi F, Formica N, et al. 1987 Therapeutic doses of iodine-131 reveal undiagnosed metastases in thyroid cancer patients with detectable serum thyroglobulin levels. *J Nucl Med* 28:1888–1891
10. Pineda JD, Lee T, Ain K, Reynolds JC, Robbins J 1995 Iodine-131 therapy for thyroid cancer patients with elevated thyroglobulin and negative diagnostic scan. *J Clin Endocrinol Metab* 80:1488–1492
11. Sobin LH, Wittekind CH, eds 1997 UICC TNM classification of malignant tumours, 5th ed. New York: Wiley & Sons
12. 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
13. Mariotti S, Pisani S, Russova A, Pinchera A 1982 A new solid-phase immunoradiometric assay for anti-thyroglobulin autoantibody. *J Endocrinol Invest* 5:227–233
14. Barsano CP, Skosey C, DeGroot LJ, Refetoff S 1982 Serum thyroglobulin in the management of patients with thyroid cancer. *Arch Intern Med* 142:763–767
15. Schlumberger M, Mancusi F, Baudin E, Pacini F 1997 ¹³¹I therapy for elevated thyroglobulin levels. *Thyroid* 7:273–276
16. Cailleux AF, Baudin E, Travagli JP, Ricard M, Schlumberger M 2000 Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid cancer? *J Clin Endocrinol Metab* 85:175–178
17. Fautorechi V, Hay ID 2000 Treating the patients with differentiated thyroid cancer with thyroglobulin-positive iodine-131 diagnostic scan-negative metastases: including comments on the role of serum thyroglobulin monitoring in tumor surveillance. *Semin Nucl Med* 30:107–114
18. Wartofsky L, Sherman L, Gopal J, Schlumberger M, Hay ID 1998 Therapeutic controversy: the use of radioactive iodine in patients with papillary and follicular thyroid cancer. *J Clin Endocrinol Metab* 83:4195–4203
19. McDougall IR 1997 ¹³¹I treatment of ¹³¹I negative whole body scan, and positive thyroglobulin in differentiated thyroid carcinoma: what is being treated? *Thyroid* 7:669–672
20. Travagli JP, Cailleux AF, Ricard M, et al. 1998 Combination of radioiodine (¹³¹I) and probe-guided surgery for persistent or recurrent thyroid carcinoma. *J Clin Endocrinol Metab* 83:2675–2680
21. Lind P, Gallowitsch HJ, Langsteger W, Kresnik E, Mikosch P, Gomez I 1997 Technetium-99m-tetrafosmin whole-body scintigraphy in the follow-up of differentiated thyroid carcinoma. *J Nucl Med* 38:348–352
22. Almeida-Filho P, Ravizzini GC, Almeida C, Borges-Neto S 2000 Whole-body Tc-99m sestamibi scintigraphy in the follow-up of differentiated thyroid carcinoma. *Clin Nucl Med* 25:443–446
23. Alnafisi NS, Driedger A, Coates G, Moote DJ, Raphael SJ 2000 FDG PET of recurrent or metastatic ¹³¹I-negative papillary thyroid carcinoma. *J Nucl Med* 41:1010–1015