

Follow-Up Regimen of Differentiated Thyroid Carcinoma in Thyroidectomized Patients After Thyroid Hormone Withdrawal

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For differentiated, nonmedullary thyroid carcinoma, postsurgical ablation of thyroid remnants and treatment of residual tumor and metastases with ^{131}I is a potentially curative therapy. The aim of this study was to optimize the diagnostic protocol for the follow-up of thyroidectomized patients. **Methods:** Two hundred fifty-four patients (187 females, 67 males; mean age, 45 y; range, 8–83 y) were studied retrospectively for a mean follow-up period of 2.7 y (range, 1–12.5 y). An evaluation study consisted of a low-dose ^{131}I diagnostic procedure under hyperthyroid conditions (thyroid-stimulating hormone $> 30 \mu\text{U/mL}$), ^{201}Tl scintigraphy, and measurement of thyroglobulin (Tg) under hypothyroid conditions. A total of 254 preablation studies (1 study per patient) and 586 follow-up studies (average number of studies, 2.3 per patient) were evaluated. **Results:** Before ablation, low-dose ^{131}I screening was useful to estimate the size of the thyroid remnant. Low Tg levels ($< 10 \text{ pmol/L}$) indicated the absence of metastases. After ablation, undetectable Tg levels indicated the absence of tumor recurrence. When Tg levels were high ($> 10 \text{ pmol/L}$), local recurrence or metastases were always observed, providing the basis for additional high-dose ^{131}I therapy. In these patients, ^{201}Tl imaging did not provide a significant contribution to patient management. In the case of autoantibodies against Tg, both low-dose ^{131}I screening and ^{201}Tl scintigraphy may be advocated to allow an aggressive diagnostic work-up. **Conclusion:** Tg plays a key role in follow-up and in making decisions to treat patients with differentiated thyroid carcinoma. The role of ^{201}Tl imaging is very limited. In patients with negative low-dose ^{131}I screening, ^{201}Tl scintigraphy can be considered when Tg is elevated or cannot be evaluated because of autoantibodies against Tg. Under such circumstances, administration of a therapeutic ^{131}I dose without ^{201}Tl imaging can be considered.

Key Words: thyroid carcinoma; diagnosis; therapy; ^{131}I ; ^{201}Tl ; thyroglobulin

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Thyroid cancer is a relatively rare cancer type. In the United States, the annual incidence rate is 5 per 100,000, with an annual mortality rate of 0.4 per 100,000 (1). Radical

thyroidectomy is the primary treatment of choice. After surgery, ablation of thyroid remnants and treatment of residual tumor and metastases with ^{131}I is a potentially curative therapeutic approach for differentiated, nonmedullary thyroid carcinoma (approximately 75%–85% of all thyroid carcinomas). However, several diagnostic strategies can be applied for planning ^{131}I treatment. In routine clinical practice, low-dose ^{131}I imaging under hypothyroid conditions; nonspecific tumor imaging with, for example, ^{201}Tl ; and measurement of thyroglobulin (Tg) levels are used. In this study, we reviewed the patients referred to our center for post-thyroidectomy evaluation. The aim of this study was to optimize the diagnostic protocol for the follow-up of thyroidectomized patients.

MATERIALS AND METHODS

Patient Population

After the introduction of routine Tg measurement in 1987, a total of 285 patients with papillary and follicular thyroid cancer were referred to the nuclear medicine department after total thyroidectomy during 1987–1997. Thirty-one patients were excluded from this retrospective survey: 21 patients who never received an ablative ^{131}I dose and 10 patients who were lost to follow-up. The study population of 254 patients consisted of 187 (74%) females and 67 (26%) males (mean age, 45 y; range, 8–83 y). Histologically, 62% had papillary or mixed papillary-follicular carcinoma, 31% had follicular carcinoma, and 7% had Hürthle cell-type carcinoma. After thyroidectomy, no thymomimetics were administered initially. Four to 6 wk after total surgical thyroidectomy, thyroid remnants were ablated in all of these patients with a treatment dose of ^{131}I standardized to a radiation dose of at least 30,000 cGy (dose range, 1100–7400 MBq ^{131}I). The mean duration of the follow-up period was 2.7 y (range, 1–12.5 y). Four weeks before a follow-up study, levothyroxine (T_4) substitution was replaced by liothyronine (T_3) for a period of 2 wk. At least 2 wk before the study, patients were taken off all thyroid hormone medication to ensure a hypothyroid condition with an elevated thyroid-stimulating hormone (TSH) level (TSH $> 30 \mu\text{U/mL}$), as measured by a fluoroimmunoassay (Delfia hTSH; Pharmacia, Woerden, The Netherlands; normal range, 0.4–4 $\mu\text{U/mL}$). No low-iodine diet was used.

Evaluation of Patients

An evaluation study consisted of a low-dose ^{131}I diagnostic procedure (scintigraphic imaging and shielded whole-body counter

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measurements) under hypothyroid conditions (TSH > 30 μ U/mL), a ^{201}Tl imaging procedure, and measurement of Tg under hypothyroid conditions.

A total of 840 evaluations were performed: 254 preablation studies (1 study per patient) and 586 follow-up studies (average number of studies, 2.3 per patient).

^{131}I Measurements and Scintigraphic Imaging

Immediately after intravenous injection of 35–75 MBq Na^{131}I and after 2 and 7 d, the iodine uptake in the neck was measured with a lead-shielded collimated probe connected to an AccuSpec-NaI-Plus system (Canberra Industries, Meriden, CT). Furthermore, whole-body retention and a whole-body scan were recorded using a shadow-shielded whole-body counter connected to an AccuSpec-NaI-Plus system (Canberra Industries). These results are expressed as percentage of the administered ^{131}I dose.

Areas with increased ^{131}I concentration as established with the whole-body counter were further evaluated with scintigraphic imaging. Two days after injection of the diagnostic ^{131}I dose, planar scintigraphic images were recorded using a single-head γ camera (Orbiter; Siemens Medical Systems, Hoffmann Estates, IL) or a dual-head whole-body γ camera (MultiSpect II; Siemens Medical Systems) equipped with high-energy collimators.

After completion of the radioiodine studies, 75 MBq ^{201}Tl -chloride were injected intravenously. Five minutes after injection, whole-body scintigraphic images (planar and occasionally SPECT) were recorded using a single-head γ camera (Orbiter; Siemens Medical Systems) or a dual-head whole-body γ camera (MultiSpect II; Siemens Medical Systems) equipped with low-energy, all-purpose collimators. The remaining ^{131}I activity in the body did not cause problems with interpretation of the ^{201}Tl images, except in 5 patients with relatively large thyroid remnants in whom Compton scatter of ^{131}I interfered with optimal interpretation of the ^{201}Tl images of the neck.

Two to 4 d after ^{131}I thyroid remnant ablation and after each subsequent high-dose ^{131}I treatment, images of the whole body were recorded as described.

Tg Measurements

Tg levels (IRMA-mat Tg; Byk-Sangtec Diagnostica, Dietzenbach, Germany) were measured before each injection of a diagnostic ^{131}I dose. The normal value of this assay is <3 pmol/L (detection limit of the assay) in patients without thyroid tissue. Because it was shown in a previous study (2) that patients not receiving thyromimetics may have a Tg level between 3 and 10 pmol/L without evidence of recurrent or metastatic thyroid carcinoma, 3 groups were defined: Tg < 3 pmol/L, Tg > 3 but < 10 pmol/L, and Tg > 10 pmol/L. In some patients, Tg levels could not be estimated accurately because of the presence of autoantibodies against Tg.

Presence or Absence of Local or Metastatic Tumor

As gold standards for determining the presence or absence of malignant thyroid tissue, various modalities were adopted. When available, histologic evaluation of detected focal lesions was used. When this was not possible, the combination of Tg measurement and scintigraphic imaging after high-dose ^{131}I therapy was used, given the high diagnostic accuracy of Tg measurement and the high sensitivity of post-therapy ^{131}I scintigrams (3,4). Additionally, clinical follow-up, CT scanning, and sonography were considered as supportive evidence for the absence or presence of disease.

RESULTS

Preablation

In all patients, a thyroid remnant was identified by low-dose ^{131}I scanning, necessitating ^{131}I ablation. In 6 patients, additional metastatic lesions were identified on postablation scintigrams. These lesions were also visible on ^{201}Tl scintigraphy. ^{201}Tl imaging showed a noniodine-accumulating metastasis in only 1 patient after high-dose ^{131}I therapy in the scapula. In this patient, the Tg level was grossly elevated (>1000 pmol/L). Overall, this resulted in sensitivities of the low-dose ^{131}I screening of 97% and of ^{201}Tl imaging of 100% in the preablation phase.

When Tg levels were <10 pmol/L before ablation, metastases were never present (96 patients, 38%). In the remainder of the population, either Tg levels were >10 pmol/L or autoantibodies against Tg were present. In these patients, distant metastases (25 patients, 10%) or iodine-accumulating remnants in the thyroid bed (133 patients, 52%) were present.

Follow-Up After ^{131}I Ablation Therapy

When Tg levels were <3 pmol/L after ^{131}I ablation (155 patients, 61%), a minimal remnant in the thyroid bed was visualized by the low-dose ^{131}I screening in 7 patients. ^{201}Tl scintigraphy did not contribute to the diagnostic process. In fact, in 34 patients, ^{201}Tl scintigraphy revealed abnormal uptake that could not be attributed to a local recurrence or to metastases (specificity, 78%). In 1 of these patients, there was also faint ^{131}I uptake in the neck, which was interpreted as iodine-concentrating tissue. Because this could not be confirmed by the post-therapeutic ^{131}I scan, this was considered to be insignificant.

In 13 patients, Tg levels were intermediate (between 3 and 10 pmol/L). In 4 of these patients, some ^{131}I -concentrating tissue was identified in the neck on the subsequent post-therapy ^{131}I scans. These lesions were detected by low-dose ^{131}I in 1 patient and by ^{201}Tl scintigraphy in 3 patients (sensitivity of low-dose ^{131}I screening and ^{201}Tl imaging, 75%). ^{201}Tl scintigraphy showed unsubstantiated uptake in the neck in 2 patients (specificity, 84%).

When Tg levels were >10 pmol/L (38 patients, 15%), pathologic uptake could always be evaluated on the post-therapy ^{131}I scintigram, indicating distant metastases in 22 of the 38 patients. In 18 of the 38 patients, ^{201}Tl scintigraphy showed additional lesions compared with low-dose ^{131}I screening (2 distant metastases and 16 lesions in the neck), whereas low-dose ^{131}I screening showed additional distant metastases in 2 patients compared with ^{201}Tl scintigraphy. Overall, both neck and distant lesions (as visualized on the post-therapy ^{131}I images) were missed with low-dose ^{131}I screening in 25 patients and with ^{201}Tl scintigraphy in 9 patients. On a patient basis, sensitivity of low-dose ^{131}I screening was 84%, and sensitivity of ^{201}Tl imaging was 92%.

In the remaining 48 patients (19%), autoantibodies against Tg were detected, making the test unreliable. In most

patients (n = 28), no tumor recurrence or metastases were detected. In 12 patients, radioiodine accumulation was found in the neck, which may be attributed in part to a thyroid remnant and in part to residual or recurrent tumor. Five other patients had both a local recurrence and distant metastases, and in 3 additional patients distant metastases were present. Low-dose ^{131}I screening revealed neck lesions in 4 patients, which were not detected by ^{201}Tl scintigraphy. Conversely, ^{201}Tl scintigraphy showed additional neck lesions in 6 patients and distant metastases in 4 patients. On a patient basis, sensitivity of low-dose ^{131}I screening was 75%, and sensitivity of ^{201}Tl imaging was 91%.

DISCUSSION

In the preablation phase, ^{201}Tl imaging had a very limited contribution to patient management because high-dose ^{131}I therapy was necessary, providing an exquisitely sensitive postablation ^{131}I scintigram. However, preablation low-dose ^{131}I screening could be advocated to estimate the significance of the thyroid remnant, especially when it is the institution's policy to consider further surgery in the case of large thyroid remnants. Determination of initial Tg levels could be helpful to estimate the chance of primary metastasized carcinoma. Metastases were excluded when Tg was undetectable. However, undetectable Tg did not indicate that there was not a thyroid remnant for which high-dose ^{131}I ablation was indicated. In this phase, high Tg levels (>10 pmol/L) did not discriminate between patients with remnants in the thyroid bed and those with metastasized carcinoma.

In the follow-up after ablation, Tg becomes a valuable tumor marker, both during thyromimetic substitution and especially after withdrawal of replacement therapy. When Tg was undetectable after TSH stimulation, there was no evidence of local tumor recurrence or metastases. Repeated Tg measurements appeared to be sufficient for follow-up in these cases. However, in the few patients with faint ^{131}I uptake in the thyroid bed and undetectable Tg, incomplete ablation of thyroid tissue was most likely. A local tumor remnant could not be totally excluded in those cases, although this was unlikely given the follow-up data. Three strategies were considered: administration of a second high ^{131}I dose to eradicate any radioiodine-concentrating thyroid tissue (this is the preferred regimen in our institution), careful follow-up of these patients by repeated low-dose ^{131}I screenings and Tg measurements under hypothyroid conditions over several years, and follow-up of the patients by serial Tg while they are receiving replacement therapy. The latter 2 follow-up regimens would delay the second ^{131}I therapy until there was evidence of progression. There was no role for ^{201}Tl imaging in these patients.

When Tg levels were slightly elevated (between 3 and 10 pmol/L), a more difficult situation was present. Because Tg was still detectable, it was difficult to imagine that the patient was free of benign or malignant (or both) thyroid tissue. Similar to the group of patients with undetectable Tg

levels, ^{131}I -concentrating tissue was identified on the post-therapy ^{131}I scans in 4 of 12 patients in this group. Given the detectable Tg and the presence of ^{131}I -concentrating tissue, we preferred to treat these patients at least once with an additional high ^{131}I dose, although careful follow-up may also be advocated (3). ^{201}Tl scintigraphy was of little help to patient management in this category, although this study cannot provide a definitive answer because the group was small and no histologic verification of the neck lesions was available.

When Tg levels were clearly elevated (>10 pmol/L), there was always pathologic ^{131}I uptake on the post-therapy scans. ^{201}Tl imaging could be helpful in those patients whose low-dose ^{131}I screening was negative, thus preventing treatment initiation solely on the basis of an abnormal laboratory parameter. In these cases, lesions could be identified with ^{201}Tl scintigraphy before high-dose ^{131}I therapy was administered (4). However, because aggressive treatment is currently advocated (high-dose ^{131}I even when imaging procedures are negative), it can be argued that ^{201}Tl imaging can also be abolished in these patients. Patients with elevated Tg levels should be treated with high-dose ^{131}I at least once to obtain a potential therapeutic benefit (negative follow-up scans and decreasing Tg levels) (5,6). However, an improvement of clinical outcome in the long term remains to be established (7). In these cases, ^{201}Tl imaging may provide a visual basis for additional ^{131}I therapy. When such visualization is considered to be superfluous, ^{131}I therapy can be initiated directly. Besides being therapeutically beneficial, another advantage of high-dose ^{131}I therapy is the post-therapy ^{131}I scintigram that can direct the clinician to metastatic sites. Alternative treatment (external-beam radiation therapy or surgery [or both]) can then be considered.

The category of patients with persisting autoantibodies against Tg was highly interesting. In follow-up, serial measurement of autoantibody titers itself may be a marker for (tumorous) thyroid tissue, especially when autoantibodies persist over years (8). Furthermore, it has been shown that these patients are more at risk for local spread into the neck (9). In this series, a local recurrence or distant metastases (or both) were eventually diagnosed in a clinically significant percentage of the patients with autoantibodies (at least 8 of the 48 patients with autoantibodies against Tg). This observation warrants an aggressive diagnostic and therapeutic approach. Low-dose ^{131}I screening and ^{201}Tl scintigraphy were complementary in these patients. Therefore, a regimen including both modalities can be advocated. At least one high-dose ^{131}I treatment can also be considered for the same reasons as for the patients with elevated Tg levels and an otherwise negative work-up.

The limited role of ^{201}Tl scintigraphy is in agreement with the findings of several other authors (4,10,11). However, some authors did consider ^{201}Tl scintigraphy a useful diagnostic adjunct (12–14). Recently, a potential role of the late ^{201}Tl scan (2 h after injection) has been suggested as a predictor of ^{131}I therapy outcome (15). Other authors have

suggested a role of ^{201}Tl imaging in Tg-positive patients, especially when diagnostic ^{131}I imaging is negative (16,17). For this group of patients, the newer $^{99\text{m}}\text{Tc}$ -labeled agents, such as $^{99\text{m}}\text{Tc}$ -sestamibi and $^{99\text{m}}\text{Tc}$ -tetrofosmin, or PET with FDG may become attractive alternatives for ^{201}Tl (18–20).

CONCLUSION

Although the mean follow-up of the patients is still relatively short (2.7 y), Tg plays a key role in the follow-up and in making decisions to treat patients with differentiated thyroid carcinoma. When Tg levels are elevated after thyroid remnant ablation, ^{131}I therapy with or without prior low-dose ^{131}I screening is indicated. Given the low diagnostic yield of ^{201}Tl compared with post-therapy scintigrams, we consider ^{201}Tl imaging of limited benefit; however, it may be an option when autoantibodies against Tg are present or when visualization of lesions is desired in patients with elevated Tg and a negative low-dose ^{131}I study and in whom additional data are needed to decide in favor of additional high-dose ^{131}I treatment.

REFERENCES

1. North American Association of Central Cancer Registries. *Cancer in North America 1990–1994*. Sacramento, CA: North American Association of Central Cancer Registries; 1998.
2. van den Bergh JP, Pieters GF, Beex LV, Ross HA, Corstens FH, Smals AG. Compared to whole body scanning thyroglobulin assay is reliable in the follow-up of thyroidectomized patients with thyroid carcinoma [in Dutch]. *Ned Tijdschr Geneesk*. 1993;137:1344–1348.
3. Schlumberger MJ. Papillary and follicular thyroid carcinoma. *N Engl J Med*. 1998;338:297–306.
4. Van Sorge-van Bortel RA, van Eck-Smit BL, Goslings BM. Comparison of serum thyroglobulin, ^{131}I and ^{201}Tl scintigraphy in the postoperative follow-up of differentiated thyroid cancer. *Nucl Med Commun*. 1993;14:365–372.
5. Pineda JD, Lee T, Ain K, Reynolds JC, Robbins J. Iodine-131 therapy for thyroid cancer patients with elevated thyroglobulin and negative diagnostic scan. *J Clin Endocrinol Metab*. 1995;80:1488–1492.
6. Clark OH, Hoelting T. Management of patients with differentiated thyroid cancer who have positive serum thyroglobulin levels and negative radioiodine scans. *Thyroid*. 1994;4:501–505.
7. Reynolds JC, Robbins J. The changing role of radioiodine in the management of differentiated thyroid cancer. *Semin Nucl Med*. 1997;27:152–164.
8. Spencer CA, Takeuchi M, Kazarosyan M, et al. Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab*. 1998;83:1121–1127.
9. Kumar A, Shah DH, Shrihari U, Dandekar SR, Vijayan U, Sharma SM. Significance of antithyroglobulin autoantibodies in differentiated thyroid carcinoma. *Thyroid*. 1994;4:199–202.
10. Brendel AJ, Guyot M, Jeandot R, Lefort G, Manciet G. Thallium-201 imaging in the follow-up of differentiated thyroid carcinoma. *J Nucl Med*. 1988;29:1515–1520.
11. Lorberboym M, Murthy S, Mechanick JI, Bergman D, Morris JC, Kim CK. Thallium-201 and iodine-131 scintigraphy in differentiated thyroid carcinoma. *J Nucl Med*. 1996;37:1487–1491.
12. Hoefnagel CA, Delprat CC, Marcuse HR, de Vijlder JJ. Role of thallium-201 total-body scintigraphy in follow-up of thyroid carcinoma. *J Nucl Med*. 1986;27:1854–1857.
13. Ramanna L, Waxman A, Braunstein G. Thallium-201 scintigraphy in differentiated thyroid cancer: comparison with radioiodine scintigraphy and serum thyroglobulin determinations. *J Nucl Med*. 1991;32:441–446.
14. Iida Y, Hidaka A, Hatabu H, Kasagi K, Konishi J. Follow-up study of postoperative patients with thyroid cancer by thallium-201 scintigraphy and serum thyroglobulin measurement. *J Nucl Med*. 1991;32:2098–2100.
15. Nakada K, Katoh C, Kanegae K, et al. Thallium-201 scintigraphy to predict therapeutic outcome of iodine-131 therapy of metastatic thyroid carcinoma. *J Nucl Med*. 1998;39:807–810.
16. Carril JM, Quirce R, Serrano J, et al. Total-body scintigraphy with thallium-201 and iodine-131 in the follow-up of differentiated thyroid cancer. *J Nucl Med*. 1997;38:686–692.
17. Lin JD, Kao PF, Weng HF, Lu WT, Huang MJ. Relative value of thallium-201 and iodine-131 scans in the detection of recurrence or distant metastasis of well differentiated thyroid carcinoma. *Eur J Nucl Med*. 1998;25:695–700.
18. Gallowitsch HJ, Mikosch P, Kresnik E, Unterweger O, Gomez I, Lind P. Thyroglobulin and low-dose iodine-131 and technetium-99m-tetrofosmin whole-body scintigraphy in differentiated thyroid carcinoma. *J Nucl Med*. 1998;39:870–875.
19. Miyamoto S, Kasagi K, Misaki T, Alam MD, Konishi J. Evaluation of technetium-99m-MIBI scintigraphy in metastatic differentiated thyroid carcinoma. *J Nucl Med*. 1997;38:352–356.
20. Feine U, Lietzenmayer R, Hanke JP, Held J, Wöhrle H, Müller-Schauenburg W. Fluorine-18-FDG and iodine-131-iodide uptake in thyroid cancer. *J Nucl Med*. 1996;37:1468–1472.