# Efficacy of high therapeutic doses of iodine-131 in patients with differentiated thyroid cancer and detectable serum thyroglobulin

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**Abstract.** Serum thyroglobulin (Tg) is usually the best marker of residual or metastatic disease after treatment of differentiated thyroid cancer. We evaluated the effect of so-called blind therapeutic doses of iodine-131 in patients with detectable Tg during suppressive levothyroxine treatment (Tg-on), and in patients with a negative diagnostic scintigram but detectable Tg during the hypothyroid phase (Tg-off). Twenty-two patients with differentiated thyroid carcinoma underwent total thyroidectomy and radioiodine ablation. During the follow-up, six patients with detectable Tg-on and 16 patients with detectable Tg-off were identified. All patients were treated with a blind therapeutic dose of 7,400 MBq iodine-131. Diagnostic scintigrams were compared with post-treatment scintigrams. Tg-off was measured in 16 cases, 1 year after the administration of the blind therapeutic dose, at the time of the follow-up diagnostic scintigram. Six patients were followed up by Tg-on only. Post-therapy scintigrams revealed previously undiagnosed local recurrence or distant metastases in 13/22 cases (59%); the remaining nine post-therapy scintigrams were negative. At the time of the blind therapeutic doses, Tg-off values ranged from 8 to 608 µg/l. After 1 year of follow-up, Tg-off decreased in 14/16 (88%) patients. In all patients who were followed by Tg-on only ($n$=6), a decrease in Tg values was measured. It is concluded that blind therapeutic doses resulted in a decrease in Tg levels in the majority of patients with suspected recurrence or metastases. The post-treatment scintigrams revealed pathological uptake in 59% of patients.

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## Introduction

Iodine-131 has been recommended extensively as a treatment modality for thyroid cancer [1, 2, 3, 4, 5, 6]. After initial treatment (near-total or total thyroidectomy), most patients are treated with $^{131}$I for ablation of residual thyroid tissue. One of the reasons for radioiodine ablation is to destroy any remaining normal thyroid tissue, thereby increasing the sensitivity and the specificity of measurements of serum thyroglobulin (Tg) in the detection of persistent or recurrent disease. Tg is the 660,000-kDa glycoprotein that serves as the prohormone for thyroid hormone production. It is exclusively produced by normal thyroid tissue and differentiated thyroid cancers (DTC) [7, 8, 9].

The serum Tg level is widely used as a tumour marker for detecting recurrence and for monitoring persistence of DTC, since there is usually a good correlation between serum Tg levels and the amount of differentiated thyroid tissue present [8, 9, 10, 11]. In addition to serum Tg measurements, whole-body diagnostic scintigraphy is advocated during the follow-up of patients with DTC [12]. It is not uncommon to find patients with detectable serum Tg levels but negative whole-body diagnostic scintigrams. In these cases, $^{131}$I post-therapy whole-body scintigrams can detect residual or metastatic disease not previously observed in the diagnostic scintigram [13].

The aim of this study was to evaluate the effect of a so-called blind therapeutic dose of $^{131}I$ in patients with detectable serum Tg during levothyroxine ($LT_4$) suppressive therapy, and in patients with detectable Tg during the hypothyroid phase [high thyroid-stimulating hormone (TSH)] and a negative diagnostic $^{131}I$ scintigram.

## Materials and methods

Twenty-two patients, 11 females and 11 males, ranging in age from 22 to 70 years, were included. The histological examination revealed papillary thyroid carcinoma in 18 patients and follicular thyroid carcinoma in four. All patients underwent a (near) total thyroidectomy and a $^{131}I$ ablation (dose 3,700 MBq, Mallinckrodt Medical b.v., Petten, The Netherlands). The total ablation was confirmed by the routine 1-year follow-up diagnostic scintigram. The criterion for a successful ablation was the absence of thyroid bed activity. During the follow-up, six patients with detectable Tg during $LT_4$ suppressive therapy (Tg-on) and 16 patients with detectable Tg during the hypothyroid phase (high TSH) (Tg-off) were identified. To avoid the potential "stunning" effect of diagnostic scintigraphy and to reduce time delay and expense, we omitted the diagnostic scintigram in the six patients with a detectable Tg-on. The other 16 patients underwent this diagnostic procedure prior to radioiodine therapy. In these 16 patients, the results of the diagnostic scintigrams were compared with the post-therapy scintigrams.

In preparation for $^{131}I$ scintigraphy or $^{131}I$ therapy, patients discontinued $LT_4$ 4–6 weeks prior to the administration of the diagnostic dose (370 MBq $^{131}I$) or the therapeutic dose (7,400 MBq $^{131}I$). In patients with a negative diagnostic scintigram (DxWBS) and detectable Tg-off, a therapeutic dose was administered after 1 week. One week later a post-therapy whole-body scintigram was performed (RxWBS).

Patients were hospitalized for 1 day for the diagnostic dose and for 2–4 days following administration of the therapeutic dose, until the radiation exposure was below the limit of 50 µSv/h at 50-cm distance. All patients had a serum TSH concentration of 30 mU/l or more at the time of the administration of $^{131}I$. At the time of administration of $^{131}I$, blood samples were taken for measurement of serum TSH, (free)$T_4$ and Tg and Tg antibody levels (Roche Diagnostics GmbH, Mannheim, Germany). Tg autoantibodies were measured in all samples at the time of Tg determination. Patients were prepared with a low-iodine diet over 1 week (5 days before $^{131}I$ administration and 2 days after $^{131}I$ administration) [6, 14]. During hospitalization, patients were instructed to take lemon drops in order to stimulate the salivary glands for $^{131}I$ excretion.

One week after the administration of $^{131}I$, whole-body scintigraphy was performed using an Elscint large field of view gamma camera with a high-energy parallel-hole collimator.

One year after the "blind" therapeutic dose, a whole-body diagnostic $^{131}I$ (370 MBq) scintigram was performed in 16 patients after discontinuation of $LT_4$ replacement. At this time Tg-off measurements were repeated. Six patients were followed up by Tg-on measurements only.

Prior to diagnostic scintigraphy, only patients with detectable Tg-on had neck ultrasound and/or spiral computed tomography (CT) scanning of the neck and chest. These procedures were negative in all cases. In patients with undetectable Tg-on, there was no reason to perform these investigations prior to the 1-year follow-up diagnostic $^{131}I$ scintigraphy.

Patients showing high uptake at the RxWBS were retreated with $^{131}I$ at 4–6 months. These patients were excluded from this study.

In order to verify the decline in Tg values, the Wilcoxon signed-rank test [SPSS/PC+ v8.0 (SPSS Inc., Chicago, III.)] was used to detect statistical significance at the level $P<0.05$.

## Results

As shown in Table 1, six patients showed detectable Tg-on measurements ranging from 9 to 78 µg/l. They were treated without prior diagnostic scintigraphy. Post-therapy scintigraphy showed radioiodine uptake in two of these patients. In one patient a metastatic lung lesion was confirmed by a chest X-ray. Because there was only slight $^{131}I$ uptake, it was decided to wait for a 1-year diagnostic $^{131}I$ follow-up in combination with Tg measurements, and not to treat this at 4–6 months after the first therapeutic dose, as usually recommended.

Sixteen patients underwent a diagnostic $^{131}I$ scintigram prior to the administration of the blind therapeutic dose. They showed detectable Tg-off(D) values (Tg-off measurement at the time of the diagnostic scintigram) ranging from 4 to 118 µg/l (median 14 µg/l). Prior diagnostic scintigraphy was negative in all cases. Post-therapy scintigrams revealed $^{131}I$ uptake in 11 of 16 (69%) patients (Table 1), indicating a positive scintigram, while prior diagnostic scintigraphy was negative. Tg antibodies were negative in all patients. Overall, 13/22 (59%) post-therapy scintigrams showed pathological $^{131}I$ uptake. At the time of the blind therapeutic doses, Tg-off values [Tg-off(T)] ranged from 8 to 608 µg/l (median 37.5 µg/l). After 1 year, a 370 MBq $^{131}I$ follow-up diagnostic scintigram (in 16 patients) showed no pathological uptake.

The Tg values decreased in 20 of 22 patients ($P=0.001$). In 14/16 patients the Tg-off values decreased and in all six patients who were followed by Tg-on only, the Tg value decreased (Table 1). This is illustrated by Fig. 1.

Two patients showed an increase in Tg-off (patients 3 and 6). The pathological uptake in patient 3 could not be confirmed by other imaging modalities and a "wait and see" policy was decided upon. In patient 6 the pathological uptake was confirmed by repeated ultrasound of the neck, and a guided biopsy revealed a metastasis of the papillary thyroid carcinoma. This patient underwent a lymph node dissection, and after this procedure, the Tg-on declined.

During the follow-up, in four patients (nos. 5, 6, 16 and 22) with a negative post-therapy scintigram, a metastatic lesion was found by other imaging studies [thallium-201, fluorine-18 fluorodeoxyglucose ($^{18}F$-FDG) or ultrasound]. In one patient (no. 6) this was confirmed by pathology. In 4 out of 13 patients with a positive post-therapy scintigram, a metastatic lesion was confirmed by $^{18}F$-FDG (nos. 1 and 3), ultrasound and pathology (no. 9) or magnetic resonance imaging (MRI) (no. 21) (Fig. 2).

**Table 1.** Results of serum Tg (µg/l) measurements, post-therapy scintigrams (RxWBS) and 1-year follow-up diagnostic scintigraphy (DxWBS) and serum Tg measurements

| Patient no. | Tg-on | Tg-off (D) | Tg-off (T) | RxWBS | DxWBS (1 yr) | Tg-off (1 yr) |
|---|---|---|---|---|---|---|
| 1 | <1 | 12 | 15 | Neck | No uptake | 9 |
| 2 | <1 | 22 | 23 | Neck | No uptake | 13 |
| 3 | <1 | 91 | 93 | Neck | No uptake | 103 |
| 4 | <1 | 118 | 144 | Neck | No uptake | 117 |
| 5[a] | 56 | – | 420 | No uptake | No uptake | 342 |
| 6[a] | 32 | – | 39 | No uptake | No uptake | 143 |
| 7[a] | 40 | – | 608 | Neck | No uptake | 540 |
| 8 | <1 | 12 | 13 | No uptake | No uptake | 6 |
| 9 | <1 | 62 | 123 | Neck | No uptake | 58 |
| 10 | <1 | 4 | 14 | Mediastinum | No uptake | 3 |
| 11 | <1 | 28 | 36 | Mediastinum | No uptake | 32 |
| 12 | <1 | 15 | 29 | No uptake | No uptake | 6 |
| 13 | <1 | 13 | 15 | Neck | No uptake | 5 |
| 14 | <1 | 9 | 11 | No uptake | No uptake | 9 |
| 15[a] | 9 | – | 144 | No uptake | – | 1[b] |
| 16 | <1 | 82 | 93 | No uptake | – | 4[b] |
| 17[a] | 78 | – | 162 | Lung | No uptake | 23 |
| 18 | <1 | 8 | 12 | No uptake | – | <1[b] |
| 19 | <1 | 7 | 8 | Lung | – | <1[b] |
| 20 | <1 | 5 | 10 | Neck | – | <1[b] |
| 21 | <1 | 92 | 100 | Mediastinum | No uptake | 29 |
| 22[a] | 12 | – | 306 | No uptake | – | 11[b] |

Tg-off(D), Tg-off measurement at the time of the diagnostic scintigram; Tg-off(T), Tg-off measurement at the time of the blind therapeutic dose)
[a] No prior diagnostic scintigram because of detectable Tg-on
[b] Tg-on

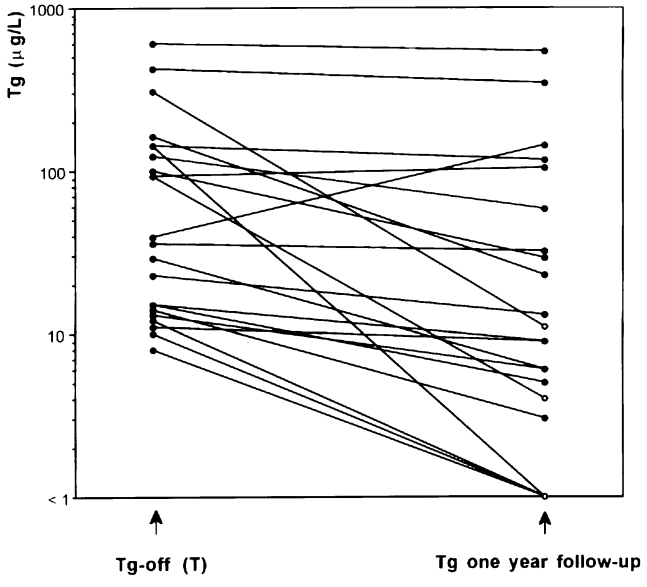


**Fig. 1.** Comparison of 22 paired samples of serum Tg levels at the time of administration of the "blind" therapeutic dose [*Tg-off (T)*] and at 1-year follow-up (*Tg one year follow-up*). *Open circles* are serum Tg measurements during $LT_4$ suppression

## Discussion

One of the most compelling problems encountered during careful follow-up of patients with differentiated thyroid carcinoma is the presence of a detectable serum Tg concentration without pathological uptake on whole-body $^{131}$I-imaging studies. A negative $^{131}$I scintigram in the presence of a detectable serum Tg level may be due to anti-Tg antibodies, which may falsely elevate or decrease the results of serum Tg measurements [7], low serum TSH, iodine contamination, a tumour that does not trap or only weakly traps $^{131}$I, or a tumour that traps it but is too small to visualize with a diagnostic dose of $^{131}$I [15].

Metastatic disease is sometimes first identified on post-therapy scintigrams in patients with detectable serum Tg values and negative diagnostic scintigrams [13].

Our study demonstrated that therapeutic doses of $^{131}$I provide a beneficial response as well as increased scintigraphic sensitivity in the majority of patients who have detectable serum Tg values in conjunction with no evidence of recurrence or metastases at diagnostic scintigraphy or radiographic studies. Most patients showed a decline in Tg values after treatment with a blind therapeutic dose, and previously unknown recurrences or metastatic lesions were detected by post-therapy scintigraphy in 59% of patients. Eight patients showed pathological uptake in the neck, and in five patients $^{131}$I was observed outside the neck (mediastinum or lungs). This implies that in eight patients there was surgically accessible disease (thyroid bed or lymph node metastases). Surgery may lead to a decrease in Tg levels, as shown by patient 6 and described by other authors [16]. These findings extend the observations of previous investigators [13, 16, 17] and may support a generalized recommendation for $^{131}$I therapy of Tg-positive, diagnostic scan-negative pa-

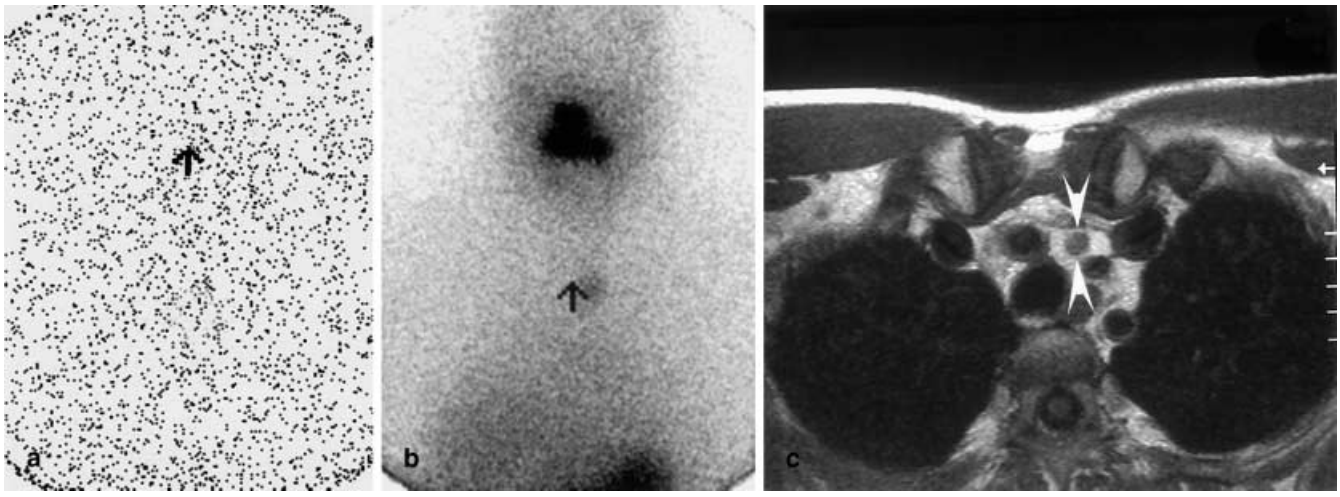


**Fig. 2. a** Diagnostic scintigram (patient 21, anterior view) 1 week after 370 MBq $^{131}$I shows no pathological uptake (*black arrow*, sternal notch). **b** The post-therapeutic scintigram (anterior view), 1 week after 7,400 MBq $^{131}$I, reveals pathological uptake just left of the midline (*black arrow*, sternal notch). **c** MRI (transaxial slice) clearly demonstrates a pathological lymph node at the same localization (*white arrows*)

tients, as suggested in a recent review article by Fatourechi and Hay [18]. Pacini et al. [13] reported the use of therapeutic doses of $^{131}$I (1,850–5,550 MBq) as a diagnostic tool in 17 patients with a negative diagnostic 185 MBq $^{131}$I scintigram. The post-therapy scintigram was positive in 16 cases, while Tg levels were reduced in seven patients, increased in one, and unchanged in the others. Pineda et al. [17] treated 17 patients with differentiated thyroid carcinoma whose serum Tg levels were elevated when hypothyroid, but whose diagnostic whole-body scintigrams (55 and 185 MBq $^{131}$I) were negative with therapeutic doses varying from 5,550 to 11,100 MBq $^{131}$I. Post-therapy scintigraphy revealed undiagnosed local recurrence and/or metastases in 16/17 patients. Follow-up Tg concentrations decreased in 81% of patients after the first treatment, in 90% after the second treatment (13 patients) and in 100% after the third treatment (5 patients). Pachucki and Burmeister [16] treated 11 patients with a high therapeutic dose of $^{131}$I, which resulted in demonstrable uptake on post-therapy scintigrams in seven cases. Despite the uptake on the post-therapy scintigrams, the Tg did not decrease in three patients.

When a pathological lesion is found at the post-therapy scintigram, it can be confirmed by other imaging studies, such as ultrasound, CT or MRI. There is also an important role for $^{18}$F-FDG imaging in patients with negative post-therapy scintigrams [19, 20].

As an inclusion criterion for the study we used detectability of serum Tg levels by a sensitive method. However, questions remain as to what cut-off point should be used to indicate the presence or absence of cancer, and whether measurements on replacement are as valuable as those off replacement. Ozata et al. [11] conclude that Tg and $^{131}$I scintigram are complementary in the follow-up of patients with differentiated thyroid cancer, and that in most patients Tg determination cannot be used to rule out the presence of cancer. However, patients who have undergone a (near) total thyroidectomy and $^{131}$I ablation, and who have a negative post-ablation scintigram and values of serum Tg-on <2 μg/l or Tg-off <3 μg/l, very rarely have recurrent disease. Mazzaferri [15] recommends that patients with a very low serum Tg-on (<5 μg/l) should not be treated with a therapeutic dose of $^{131}$I.

All studies indicate therapeutic efficacy of $^{131}$I, when considered in terms of reduction of serum Tg levels. However, whether occult tumours all represent clinically important disease is open to debate. There are some data showing that early treatment reduces the long-term risk of thyroid cancer death [2]. Maxon and Smith [6] state that if the calculated dose to the tumour is less than 35 Gy, it is unlikely to respond to $^{131}$I therapy. By contrast, our study suggests that $^{131}$I therapy may be useful in treating metastases or recurrence detected only by serum Tg and with negative diagnostic scintigraphy, when the visual $^{131}$I tumour uptake is relatively low.

A diagnostic scintigram was performed in the majority of patients in our study. However, if detectable Tg-off can be determined by the laboratory and the outcome is known prior to the administration of a diagnostic dose, one can decide to omit this diagnostic scintigraphic procedure and to treat the patient with a therapeutic dose at once to prevent a possible “stunning” effect.

As in all circumstances in which $^{131}$I therapy is used to treat thyroid cancer, its potential benefit must be balanced against risks. The individual and cumulative doses of $^{131}$I used in this study are within the dose ranges used in the conventional therapy of this disease. Potential side-effects that have been encountered include nausea, sialoadenitis, transient reduction in testicular and ovarian

function, bone marrow suppression and the induction of second malignancies, such as leukaemia and bladder cancer, although the risk of second malignancies is not significantly increased at cumulative doses equal to or less than 500 mCi [6, 21, 22, 23].

In conclusion, our observations indicate that therapeutic doses of $^{131}I$ are effective in patients with detectable serum Tg levels and negative diagnostic whole-body scintigrams, who have had negative prior radiological studies. However, as in many studies in thyroid cancer, the follow-up period was inadequate to prove enhanced survival. We suggest that patients with detectable Tg-on or Tg-off should be treated at least once with a blind therapeutic dose, especially in cases in which other imaging studies are negative.

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