CLINICAL STUDY

Glucocorticoids do not influence the effect of radioiodine therapy in Graves' disease

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Abstract

Objective: We evaluated, in a retrospective study, whether glucocorticoids given in order to avoid initiation or aggravation of ophthalmopathy during radioiodine (^{131}I) therapy have an inadvertent effect on the final thyroid function.

Methods: Consecutive patients with Graves' disease (median age 50 years, range 21–82 years) treated with ^{131}I therapy for the first time were included. Ninety-six patients (group 1) were given prednisolone (25 mg daily for 30 days beginning 2 days before ^{131}I therapy) because of present or previous mild ophthalmopathy or the presence of risk factors (tobacco smoking and high concentrations of TSH-receptor antibodies) for developing this complication. One hundred and eleven patients received ^{131}I therapy without prednisolone prophylaxis (group 2).

Results: The patients in group 1 were younger than those in group 2 (44.6 ± 12.0 years versus 51.3 ± 15.1 years; $P = 0.001$). At 1 year post therapy the patients were classified as hypothyroid, euthyroid or hyperthyroid. In group 1, the numbers of patients were 23, 35 and 38, respectively, while the corresponding numbers in group 2 were 26, 40 and 45, respectively ($P = 0.99$ between groups). The cure rate (attainment of euthyroidism or hypothyroidism) was 60% in group 1 and 59% in group 2 ($P = 0.97$). No significant between-group difference was found, neither in the median time-interval until development of hypothyroidism nor until recurrence of the hyperthyroidism. Using logistic regression the cure rate correlated negatively with age ($P = 0.041$) and the size of the thyroid gland ($P = 0.010$) and positively with serum TSH at treatment ($P = 0.034$), whereas no significant impact was found for the use of prednisolone, gender, smoking, presence of anti-thyroid peroxidase antibodies, use of anti-thyroid drugs or the presence of eye symptoms.

Conclusions: Although glucocorticoids in some contexts seem to attenuate the radiation-induced oxidative stress this had no impact on the final outcome following ^{131}I therapy of patients with Graves' disease.

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Introduction

Radioiodine (^{131}I) has for many years been used worldwide in the treatment of Graves' disease, either initially or in cases of recurrent disease after a treatment course with anti-thyroid drugs (ATD). There are data indicating that ^{131}I therapy may have an adverse effect on the development and/or the worsening of Graves' ophthalmopathy. Thus, following therapy, 15–33% of patients with Graves' disease may develop eye disease, or pre-existing ophthalmopathy may worsen (1, 2). The pathogenesis of the orbital inflammation encountered with ^{131}I therapy is not well understood but is probably explained by the release of thyroid antigens, eliciting an autoimmune response (3, 4). Since some thyroid antigens are shared by the orbital tissues an

inflammatory reaction in this region may result. In randomized trials, glucocorticoids have been shown to significantly reduce the risk of ophthalmopathy following ^{131}I therapy (1). It is therefore recommended by many experts that patients with Graves' ophthalmopathy or with risk factors for developing this complication should be treated with glucocorticoids during the ^{131}I therapy (4, 5).

However, recent studies (6–8) suggest that glucocorticoids in some contexts may protect against DNA damage, the mechanism by which ^{131}I therapy exerts its destructive effect on the thyroid. Thus, although being of benefit for eye protection, it may be speculated as to whether glucocorticoids have an inadvertent effect as regards the efficacy of ^{131}I therapy. The aim of this study was to investigate whether the cure rate

following ^{131}I therapy of Graves' disease was diminished in patients given glucocorticoids – an issue not hitherto evaluated in a large scale set-up.

Materials and methods

Patients and study design

We reviewed, retrospectively, patients suffering from Graves' disease admitted consecutively to our department from 1994 through 2001, and who were treated with ^{131}I therapy for the first time. The diagnosis was based on clinical symptoms, biochemical evidence of hyperthyroidism, a non-nodular structure of the thyroid gland demonstrated by thyroid ultrasonography as well as $^{99\text{m}}\text{Tc}$ -scintigraphy and/or the presence of thyrotropin (TSH) receptor antibodies in the serum. Indication for ^{131}I therapy was recurrence of Graves' disease after treatment with an ATD for at least 12 months. Conditions excluding patients from ^{131}I therapy were pregnancy or anticipation of pregnancy, lactation, suspicion of thyroid malignancy and large or partly intrathoracic goitre. Patients with severe active Graves' ophthalmopathy – defined as severe periorbital swelling, symptoms or signs of severe conjunctival inflammation, retrobulbar pain or any indication of optic nerve involvement – were not considered for ^{131}I therapy.

During the study period, the routine in our department was to give prednisolone (Nycomed A/S, DK-4000 Roskilde, Denmark) in selected cases to prevent development or worsening of Graves' ophthalmopathy caused by the ^{131}I therapy. Patients given this prophylaxis were those with present or previous non-severe ophthalmopathy or patients having risk factors for developing post ^{131}I ophthalmopathy (tobacco smoking (9) in addition to high titres of thyroid-stimulating immunoglobulins (TSI) or TSH-receptor antibodies (TRAB)). A regimen of 25 mg prednisolone once daily for 30 consecutive days (no tapering) beginning 2 days before ^{131}I therapy was used throughout the study period.

In order to assess a possible influence on the final outcome following ^{131}I therapy, we stratified the patients into those given prednisolone concomitant with ^{131}I and those treated without prednisolone.

Assays and thyroid imaging

Total serum thyroxine (T4) (normal range 65–135 nmol/l) and tri-iodothyronine (T3) (normal range 1.00–2.10 nmol/l) were measured by RIA (Diagnostic Products Corp., Los Angeles, CA, USA and Johnson & Johnson, Amersham, UK respectively). Serum TSH (normal range 0.30–4.0 mU/l) was determined by DELFIA (Wallac OY, Turku, Finland). Free T4 (FT4) and free T3 (FT3) indices were calculated by multiplying the total T4 and T3 values respectively by

the T3 resin uptake in per cent. Serum anti-thyroid peroxidase antibodies (anti-TPOab) were determined by the RIA DYNO test (Brahms Diagnostica, Berlin, Germany; normal range <200 U/l). TSI and TRAB were determined by Medi-Lab, Copenhagen, Denmark (normal range for TSI <14 U/l, normal range for TRAB <1.0 U/l). Thyroid $^{99\text{m}}\text{Tc}$ -scintigraphy was performed at baseline on high resolution gamma camera equipment. Thyroid ultrasound including planimetric volume estimation (type 1846; Brüel & Kjær, Copenhagen, Denmark) was performed at baseline and 1 year after ^{131}I by trained endocrinologists (S J B or L H). This method for thyroid volume determination has an intra- and inter-observer coefficient of variation of 5% and 7% respectively (10).

Evaluation of eye symptoms

At each visit, a thorough evaluation of eye symptoms was performed by a trained thyroidologist (S J B or L H). The severity of the ophthalmopathy was assessed according to 'NOSPECS' and 'activity score' (11). A regular examination by an ophthalmologist was not part of the routine in our department, but in cases with eye symptoms of uncertain etiology or if eye symptoms emerged in the study period the patient was examined by an ophthalmologist. Uni- or bilateral proptosis, conjunctival inflammation, periorbital oedema, complaints of retro-orbital pain or extraocular muscle impairment were attributed to Graves' ophthalmopathy. If one or more of these signs or symptoms had been present at any time during the course of the disease ^{131}I therapy under cover of prednisolone was recommended (active, severe cases were not treated with ^{131}I).

^{131}I therapy and ATD regimens

Various regimens were used during the 9-year study period. ^{131}I therapy was given as a single oral dose in an out-patient setting. The dose was calculated based on one of two algorithms. (a) According only to the thyroid volume assessed by ultrasound (volume <30 ml, 200 MBq; volume 30–60 ml, 400 MBq; volume >60 ml, 600 MBq) and (b) according to the formula: $3.7 \text{ MBq/ml} \times \text{volume (ml)} \times 100\%/24\text{-h thyroid } ^{131}\text{I uptake (\%)}$.

The hyperthyroidism before and after the ^{131}I therapy was managed according to one of four different regimens. As ATD either methimazole (GEA A/S, DK-2000 Frederiksberg, Denmark) or propylthiouracil (PTU) (Medic Team A/S, DK-3450 Allerød, Denmark) was used. (1) No ATD was used and the patient was thus treated with ^{131}I in a hyperthyroid state. (2) Euthyroidism was obtained by ATD which was discontinued 4 days before ^{131}I without resumption of ATD post therapy. (3) Euthyroidism was obtained by ATD which was discontinued 4 days before ^{131}I with

resumption 7 days post therapy. Final discontinuation of ATD was done, at the earliest, 3 weeks after ^{131}I therapy, if euthyroidism was present at this time. (4) Euthyroidism was obtained by ATD which was continued throughout the ^{131}I therapy and it was withdrawn, at the earliest, 3 weeks after ^{131}I therapy, if euthyroidism was present at this time.

Follow-up and evaluation of outcome

In the post- ^{131}I period, the thyroid function was monitored after 3, 6 and 12 weeks, and thereafter every 3 months for a period of 1 year. If the patient had hyperthyroid symptoms before ^{131}I (regimen 1) or in the early post- ^{131}I period (all regimens) these were managed by β -blockers. In cases where hyperthyroidism was present beyond 6 weeks after ^{131}I therapy, ATD was instituted (regimen 1) or resumed (regimens 2–4). This medication was subsequently tapered during the follow-up period and, if this was not successful, a second ^{131}I dose was eventually administered, at the earliest, 9 months after the initial therapy. Hypothyroidism was treated with levothyroxine (GSK Pharma A/S, DK-2605 Brøndby, Denmark). If a low dose of levothyroxine was required, a trial of discontinuation was made within the follow-up period to ensure that the hypothyroidism was not transient.

At the end of follow-up, the patients were classified as hypothyroid, euthyroid or hyperthyroid according to their thyroid function resulting from the initial ^{131}I therapy (e.g. a patient developing myxedema following a second ^{131}I administration due to failure of the initial ^{131}I dose was classified as having recurrence). Euthyroidism was defined as the serum FT4 index and the serum FT3 index within the normal range; hypothyroidism was defined as serum TSH above the normal range, with or without a serum FT4 index below the normal range; hyperthyroidism was defined as serum TSH below the normal range and a serum FT4 index or a serum FT3 index above the normal range.

Since an ophthalmologist was not regularly involved for assessment of the orbital inflammation, a detailed description of the changes in eye symptoms and signs is beyond the scope of this study. Instead, the orbital status was categorized as improvement, aggravation or no change when compared with the pre- ^{131}I status.

Statistical analyses

The results were analyzed with the SPSS software package. Baseline data are presented as frequencies, means $\pm$ s.d. or median and range if not normally distributed. χ^2 -test, one-way ANOVA and Mann–Whitney test (if appropriate) were used to compare baseline characteristics and for analyzing differences in outcome. A backward stepwise logistic regression analysis

was employed for testing correlations. A P value < 0.05 was considered statistically significant.

Results

Baseline data

In the study period, 235 patients with Graves' disease were referred to ^{131}I therapy for the first time. Twenty-eight patients were lost to follow-up, leaving 207 patients for evaluation. Ninety-six patients received prednisolone during ^{131}I therapy (group 1) and 111 patients were treated without prednisolone prophylaxis (group 2). In the period 1994–1998 the ratio between group 1 and group 2 was 30/60 while it was 66/51 from 1999 until 2001 ($P < 0.001$), indicating a higher propensity in the latter period for using prednisolone prophylaxis. Baseline characteristics are listed in Table 1. There was no significant difference in any variable between the two groups, with the exception of age. The patients in group 1 were younger (44.6 ± 12.0 years) than those in group 2 (51.3 ± 15.1 years) ($P = 0.001$). The smoking habits, not registered in 38 patients, was not significantly different between group 1 and group 2 (40/96 versus 46/111; $P = 0.76$). In group 1, 64 of 96 patients had present or previous signs or symptoms of Graves' ophthalmopathy (listed in Table 2) while in the remaining 32 patients prednisolone was given because of smoking in addition to high concentrations of TSI or TRAB. These latter patients had a similar mean age to those with eye symptoms, indicating that patients without eye symptoms ($n = 32$) were more prone to receive prednisolone during ^{131}I therapy if they were young. No clinically relevant side-effects to prednisolone were observed, and no patient experienced steroid withdrawal symptoms. Because of the selection of patients receiving prednisolone prophylaxis, any indication of present or previous Graves' ophthalmopathy was almost absent among patients in group 2. A single patient in this group had proptosis without current signs of inflammation but this subject declined prednisolone.

Outcome: thyroid function

After 1 year of follow-up, the frequency of euthyroidism, permanent hypothyroidism and recurrence of hyperthyroidism was almost similar among patients receiving prednisolone (group 1) compared with those treated with ^{131}I therapy alone (group 2). In group 1, the numbers of patients were 23, 35 and 38 respectively, while the corresponding numbers in group 2 were 26, 40 and 45 respectively (Fig. 1; $P = 0.99$ between groups). The cure rate (euthyroidism or hypothyroidism) was 60% in group 1 and 59% in group 2 ($P = 0.97$). Excluding patients on ATD regimen 4 ($n = 15$) did not change the result (cure rate

Table 1 Baseline characteristics of patients in group 1 (receiving prednisolone during ^{131}I therapy) and group 2 (given ^{131}I therapy alone). Data are given as number, frequency, means $\pm$ s.d. or median and range whenever appropriate.

Characteristics	Group 1 (<i>n</i> = 96)	Group 2 (<i>n</i> = 111)	<i>P</i>
Age (years)	44.6 $\pm$ 12.0	51.3 $\pm$ 15.1	0.001
Gender (male/female)	14/82	25/86	0.158
Cases of recurrence (%)	57 (59)	51 (46)	0.070
Disease duration (years)	3.0 (0.25–30.0)	2.0 (0.25–26.0)	0.119
Smokers (%) (<i>n</i> = 169)	40 (42)	46 (41)	0.759
Thyroid volume (ml)	36 (4–134)	35 (11–144)	0.939
Serum FT4 index (nmol/l)	116 (9–600)	100 (17–694)	0.270
Serum FT3 index (nmol/l)	2.01 (0.70–25.58)	1.98 (0.81–68.60)	0.546
Serum TSH (mU/l)	0.03 (0.00–25.40)	0.02 (0.00–16.30)	0.583
Serum anti-TPOab (IU/ml)	356 (0–10 000)	443 (0–10 000)	0.947
Serum TSI (U/l, <i>n</i> = 56)	14.7 (2.0–311.0)	19.0 (2.0–287.0)	0.268
Serum TRAB (U/l, <i>n</i> = 61)	6.0 (0.3–211.0)	6.5 (0.0–92.0)	0.625
^{131}I dose algorithm (<i>n</i>)			0.249
Algorithm a	70	89	
Algorithm b	26	22	
24-h ^{131}I uptake (%; <i>n</i> = 62)	58.7 $\pm$ 14.7	60.2 $\pm$ 14.7	0.700
^{131}I activity (MBq)	373 $\pm$ 180	362 $\pm$ 176	0.657
Regimens of ATD (<i>n</i>)			0.192
Regimen 1	17	28	
Regimen 2	51	52	
Regimen 3	18	26	
Regimen 4	10	5	
Dose of methimazole (mg, <i>n</i> = 138)	10.5 $\pm$ 7.2	9.5 $\pm$ 6.5	0.419
Dose of PTU (mg, <i>n</i> = 24)	225 $\pm$ 148	196 $\pm$ 86	0.564

of 62% in group 1 and 60% in group 2; $P = 0.88$). As with the final outcome, no significant difference between group 1 and group 2 was found in the median time-interval until the occurrence of hypothyroidism, which was 3 months in both groups (range: 1–12 versus 1–14 respectively; $P = 0.44$), or recurrence of the hyperthyroidism, which was 4 months in both groups (range 1–14 versus 1–19 respectively; $P = 0.63$).

Factors influencing outcome

Compared with patients having treatment failure, those who were cured were slightly younger (46.6 ± 13.9 years versus 50.5 ± 14.2 years; $P = 0.049$) and had significantly smaller glands (32 ml (4–134) versus 42 ml (14–144); $P = 0.003$). To disclose factors with an independent impact on the cure rate following the ^{131}I therapy, a logistic regression analysis was performed taking into account the following variables:

use of prednisolone, age, gender, smoking, thyroid volume, serum FT4 index, serum FT3 index and serum TSH at the time of treatment, presence of anti-TPO antibodies, use of methimazole or PTU and the presence of eye symptoms. A backward stepwise regression showed that the cure rate correlated negatively with age ($P = 0.041$) and the size of the thyroid gland ($P = 0.010$) and positively with serum TSH at the time of treatment ($P = 0.034$). A possible interaction between age and prednisolone played no significant role in the regression analysis ($P = 0.945$). Since the ^{131}I dose was given according to algorithm a in the majority of patients, the applied thyroid dose was higher in the smallest goitres within each dose-interval, and this may explain why the cure rate was associated with the thyroid size. If the regression analysis was performed including only patients given ^{131}I based on the more elaborated algorithm b ($n = 48$), a relationship between cure rate and the initial thyroid size was no longer present.

Table 2 Specification of the symptoms and signs of Graves' ophthalmopathy among 64 patients treated with prednisolone during ^{131}I therapy. Thirty-two patients treated with prednisolone had no clinical evidence of ophthalmopathy.

Symptoms	<i>n</i> (%)
Retro-orbital pain	4 (6)
Proptosis	44 (69)
Conjunctival inflammation	20 (31)
Periorbital oedema	22 (34)
Extraocular muscle impairment	9 (14)

Outcome: eye symptoms

Within the 1-year follow-up period, 11 patients (one man/ten women; nine positive for anti-TPOab; six patients treated with ^{131}I in a hyperthyroid state) experienced an aggravation or development of eye symptoms or signs. Seven of these individuals (7%) belonged to group 1 (four with pre-existing ophthalmopathy) and four patients (3.6%) to group 2 ($P = 0.39$ between groups). Thyroid volume, age and smoking status were not different compared with patients showing no

Figure 1 The influence of prednisolone on thyroid function 1 year after ^{131}I therapy of patients with Graves' disease. ns, not significant.

change or an improvement in eye status (data not shown). In all cases, the ophthalmopathy was mild and of a transient nature. In group 1, 55 patients (57%) showed no change of the orbital status, while a pre-existing ophthalmopathy improved in 34 patients (35%).

Discussion

^{131}I therapy of Graves' disease elicits an immunologic response. This is reflected by increasing serum concentrations of immunoglobulins following ^{131}I therapy (12) and was supported by the observation that ^{131}I therapy may induce Graves' ophthalmopathy (1, 2). The immune response, in concert with other factors, is probably partly responsible for the thyroid destruction that follows ^{131}I therapy. Since glucocorticoids hinder the ^{131}I -induced rise in immunoglobulins (12) this may suggest that a weaker effect is obtained when ^{131}I therapy is combined with glucocorticoids.

Ionizing radiation results in the intracellular formation of reactive oxygen species (ROS), which are mediators of DNA damage and cellular death. Glucocorticoids may interfere with this process (6–8) but the results are conflicting, maybe due to differences in the set-up and the steroid doses used. Prednisolone as well as dexamethasone significantly inhibits the production of ROS in human platelets (6). In contrast, an increased production of ROS has been observed in umbilical endothelial cells exposed to dexamethasone (7). The results may be difficult to interpret, since these effects may be balanced by a parallel increase in ROS scavengers (e.g. glutathione, superoxide dismutase), ending up with a neutral outcome. In a randomized trial (8), 36 patients received either methylprednisolone (15 mg/kg), tirilazad mesylate (an aminogluocorticoid) or placebo before undergoing cardiopulmonary bypass surgery; none of

the steroid drugs reduced the formation of ROS associated with early reperfusion. However, lipid peroxidation, reflecting oxidative stress, was significantly reduced by both glucocorticoids.

Finally, earlier studies have suggested that glucocorticoids may impair thyroid ^{131}I uptake (13–15). Gamstedt *et al.* (13) found that a high dose of beta-methasone for 3 weeks resulted in a nearly halving of the 24-h ^{131}I thyroid uptake in patients with Graves' disease, but this may have been due to a lower activity of the disease, since a significant decrease of the thyroid hormones was seen as well.

The present work is the first large scale study dealing specifically with the possibility that glucocorticoids may adversely influence the outcome of ^{131}I therapy in patients with Graves' disease. More than 200 well-characterized patients were consecutively included, of whom nearly half were treated with a daily dose of 25 mg prednisolone for 30 days starting 2 days prior to the ^{131}I therapy. A precise (10) thyroid volume estimation was performed in all patients – a variable known to have a significant impact on the effect of ^{131}I therapy (16–18). Patients were assigned to receive prednisolone mainly because of their orbital status, but other risk factors like smoking were taken into account as well. The outcome, in terms of the thyroid function after 1 year, was not influenced by the use of prednisolone during the ^{131}I therapy. The overall cure rate was 60% and implies that the ^{131}I dose should generally be increased. However, this suboptimal cure rate makes it possible to disclose other factors being of importance for the outcome. In order to adjust for a possible selection bias, a regression analysis was performed, and this confirmed the neutral effect of prednisolone whereas high age predicted treatment failure. This latter relationship is in contrast to the findings in other retrospective studies (16, 17), while the inverse correlation between

cure rate and thyroid size supports previous observations (16–18). We did not find an adverse influence of either PTU or methimazole use. Although some retrospective studies (19–21) have indicated that ATDs reduce the cure rate following ^{131}I therapy, our present results are in line with the findings in randomized studies by us and others on the use of methimazole (22–24). The fact that we were unable to demonstrate any radioprotective property of PTU is in contrast to that which has been shown by two recent prospective trials (25, 26), and may be due to the relatively few patients receiving this drug.

It cannot be excluded that the presence of ophthalmopathy *per se* is associated with a better effect of ^{131}I therapy on cure rate, and that prednisolone may have counterbalanced this. It is, however, impossible to take such an interaction into account by a regression analysis, since the use of prednisolone and the presence of ophthalmopathy were strictly linked. However, since the presence of ophthalmopathy usually indicates a more severe form of Graves' disease, which *per se* often predicts a poorer outcome of ^{131}I therapy (17), we consider this concern to be theoretical. Ideally, a randomized trial should be performed to clarify whether glucocorticoids have radioprotective properties but it may be considered unethical – at least by some experts – to conduct such a study because prednisolone is now given routinely at many centres in an attempt to protect against ophthalmopathy in susceptible individuals. This approach is based mainly on the large study by Bartalena *et al.* (1), published in 1998, showing that the risk of ^{131}I -induced ophthalmopathy can virtually be extinguished by the administration of prednisolone, starting 2 days after the ^{131}I therapy. A larger fraction of our patients treated after 1998 received prednisolone, reflecting the impact of the above study on clinical practice. To avoid adverse effects of prednisolone we chose to use a slightly lower dose and for a shorter period of time compared with the regimen used by Bartalena *et al.* (1). In addition, prednisolone was initiated 2 days before ^{131}I therapy. Strictly, it remains to be confirmed whether a regimen such as that used by Bartalena *et al.* (1) has a similar neutral influence on the outcome of ^{131}I therapy. Nevertheless, if glucocorticoids could have any inadvertent effect on the ^{131}I -mediated thyroid destruction this is probably exerted within the first few weeks following ^{131}I administration. Gamstedt & Karlsson (12), in a randomized study including 40 patients with Graves' disease, showed that 6 mg betamethasone given each day for a period of 7 weeks attenuated the effect of ^{131}I therapy reflected by a lower rate of hypothyroidism at 1 year. In the study by Bartalena *et al.* (1), which mainly dealt with the issue of ophthalmopathy, no significant difference in the final thyroid function at 1 year was reported between patients treated with or without prednisolone concomitant with ^{131}I therapy. These results (1, 12), conflicting to some extent, may be due to differences

in the dose of glucocorticoids, the timing and/or the length of the regimens.

Our patients did not undergo a regular systematic ophthalmological examination, and an exact evaluation of the orbital status following the ^{131}I therapy is beyond the scope of this study. It is unlikely that a minor uncertainty about the staging of the ophthalmopathy could have invalidated the data on the thyroid function. With our prednisolone regimen, only a few patients (7%) experienced worsening in the ophthalmopathy, not being significantly different from the outcome observed in the non-steroid group. However, the *a priori* risk in the former group for developing ophthalmopathy after ^{131}I therapy, if not given prednisolone, is considerably higher, approximately 15–33%, according to previous studies (1, 2).

In conclusion, our results support the idea that glucocorticoids, being of benefit in the prevention and treatment of Graves' ophthalmopathy, do not affect the final outcome of ^{131}I therapy as regards thyroid function. According to our study, more important factors in the prediction of treatment failure seem to be high age, a large thyroid gland and a low serum TSH at the time of ^{131}I therapy.

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