OUTCOME OF RADIOIODINE TREATMENT IN GRAVES' DISEASE PATIENTS AT SRINAGARIND HOSPITAL

Charoonsak SOMBOONPORN, M.D.
Krisana ROYSRI, M.D.

ABSTRACT

Background: Although being an effective and convenient means in the treatment of Graves' hyperthyroidism, radioiodine-131 (^{131}I) therapy usually provides unpredictable results with a major disadvantage of permanent hypothyroidism.

Objective: The study was conducted with the aim to explore the treatment outcomes of ^{131}I in the patients with Graves' disease. The obtained data would to be used in the evaluation and improvement of current management in this group of patients in our unit.

Design: Retrospective, descriptive study
Setting: Srinagarind Hospital, Faculty of Medicine, Khon Kaen University
Study methods: Reviewing medical records of patients with Graves'disease referred for ^{131}I therapy at our unit between June 1994 to August 2000 was performed. Three treatment outcomes were analyzed including efficacy of ^{131}I in the treatment of hyperthyroidism with the first dose, the number of ^{131}I dose used to cure hyperthyroidism and thyroid status of patients at the specific points of time after the last treatment dose.

Results: Nine hundred and eighty-four Graves' disease patients (793 females, 191 males) were analyzed. In the 693 cases who were followed up and evaluated for the result of treatment with determinable outcome, 247 cases (35.6%) were cured from hyperthyroidism with the first dose of ^{131}I. Of all 449 cases with adequate follow-up, 291 (64.8%) and 116 cases (25.8%) were cured by one and two doses of ^{131}I respectively, leaving nearly 10% of patients having to be retreated with additional dose. In evaluating thyroid status, incidence of persistent hyperthy- roidism decreased from 45.6% after the first year to 13.9% at the end of the fifth year while incidence of permanent hypothyroidism tended to rise from 9.3% after the first year to 28.1% and 22.2% at the end of the forth and the fifth year respectively.

Conclusion: Our study revealed that outcomes of ^{131}I therapy in patients with Graves' disease were rather unpredictable. We think that the aim of treatment should be more stressed on the earlier cure of hyperthyroidism rather than the avoidance of inevitable permanent hypothyroidism. Our dosage regimen therefore should be reconsidered to achieve a higher dose of radioiodine to cure hyperthyroidism within an earlier period and by a lower number of treatment dose.

Key words: Graves' disease, Radioiodine, Treatment outcome, Hypothyroidism

Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.

INTRODUCTION

Radioactive iodine, ^{131}I, has been used in the treatment of hyperthyroidism for more than half of a century. The major advantages over other treatment modalities, antithyroid drug (ATD) and thyroidectomy, lies in its simplicity, convenience, safe, relatively low cost, high effectiveness and absence of significant complication.[1] The ideal outcome of ^{131}I treatment is to make patient be euthyroidism by a single administered dose and to remain this thyroid status as long as possible. However, this goal is usually unlikely and unpredictable in the clinical practice. Reciprocal relationship is usually obtained by the failure of treatment and the incidence of hypothyroidism.[2-4] The outcome varies from institution to institution and from country to country depending on the indications for treatment, criteria in patient selection and regimen of dose selection.[5] Moreover, pretreatment with ATD, methods and experience in the estimation of thyroid gland weight and regimen in the follow-up of patients are also important factors affecting the treatment outcome.[6-7]

Although our thyroid clinic at Nuclear Medicine Division, Srinagarind Hospital has been the largest one of its kind providing ^{131}I therapy for hyperthyroid patients, mostly from the northeast Thailand, the results of treatment has never been reported. The treatment outcomes of ^{131}I therapy in Graves' disease patients during the past 7 years therefore were studied with the ultimate goal to improve medical services of our unit by using the data obtained from the study. Three aspects of outcome were analyzed including efficacy of the first ^{131}I dose, number of doses needed to cure hyperthyroidism and patient's thyroid status after the specific points of the follow-up time.

MATERIALS AND METHODS

Medical records of consecutive hyperthyroid patients referred for ^{131}I treatment at Division of Nuclear Medicine, Department of Radiology, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University from June 1994 to August 2000 were reviewed. After patients with toxic adenoma and toxic multinodular goitre were excluded, 1,032 Graves' disease subjects were enrolled into the study. Clinical diagnosis of Graves' disease was determined by experienced physicians and was supported by the elevation of serum thyroxine or triiodothyronine level with or without serum thyroid stimulating hormone (TSH) measurement. Euthyroidism and permanent hypothyroidism in the follow-up visits were determined clinically, mostly with simultaneous thyroid function test results. Data regarding age at the time of the first ^{131}I treatment, sex, indication for ^{131}I therapy, history of ATD allergy or co-morbidities prior to ^{131}I therapy, weight of thyroid gland estimated by palpation, date of each ^{131}I treatment, date of established euthyroidism and permanent hypothyroidism occurring following ^{131}I treatment and date of the last follow-up were collected by one nuclear medicine physician, the first author. The last evaluation was at the end of July 2001.

^{131}I TREATMENT

Contraindications for ^{131}I treatment, such as women during pregnancy or lactation, were excluded, not giving treatment. Radioiodine thyroid uptake test was performed in all cases to confirm the diagnosis and, more importantly, to help in the calculation of the administered doses. ATD was stopped at least 7 days before ^{131}I therapy. Other drugs and foods known to affect iodine uptake by thyroid gland were also refrained for their appropriate periods of time.[8] At least 4-hour fasting before ^{131}I administration was recommended in all subjects to make sure that

radioiodine was properly absorbed by gastrointestinal tract. In determining ^{131}I dose for individual patient, 24-hour thyroid uptake value and estimated thyroid gland weight were used for the calculation to achieve 100 microCuries of ^{131}I per gram of thyroid tissue. Some patients with history of cardiac failure or concomitant cardiac arrhythmia were treated with a higher dose regimen of 150 microCuries per gram of thyrold. There were two nuclear medicine physicians involving in the treatment during this period. Thyroid scintigraphy with technetium-99m pertechnetate was not routinely performed but was considered only in some cases suspected of nodule on palpation.

ATD and beta-blocker were prescribed as needed after ^{131}I treatment to individual case according to the justification of physicians. Although there was no exact follow-up schedule after ^{131}I treatment, each follow-up time was usually between 3 months and one year mostly according to the severity of hyperthyroidism. Retreatment with ^{131}I was considered in persistent hyperthyroid cases in no shorter than 3 months after the previous dose. Thyroxine replacement therapy was administered in those who developed permanent hypothyroidism.

TREATMENT OUTCOMES

There were 3 outcomes aimed to be explored. Firstly, the percentage of successful treatment after the first dose of ^{131}I. Subjects were classified into one of the three results including success, failure or undetermined. The success was determined at 6 months after treatment with patients having no symptoms and signs of hyperthyroidism even not taking ATD. The failure was defined as the patients still had symptoms and signs of hyperthyroidism at least 6 months after treatment or retreatment with ^{131}I was administered. The undetermined subjects were defined for those whose follow-up time was less than 6 months and the subjects were not retreated during this time.

Secondly, the number of ^{131}I doses needed to cure hyperthyroidism in each subject. In determining this outcome, the subjects to be analyzed were those who had an adequate follow-up that their last follow-up time showed euthyroid or permanent hypothyroid status. The subjects that still were hyperthyroidism, classified as inadequate follow-up, were excluded.

The last outcome was the incidence of thyroid status-hyperthyroidism, euthyroidism and permanent hypothyroidism-documented after the specific points of time,1, 2, 3, 4 and 5 years respecfively following the last treatment dose. The subjects who were evaluated at one point of time had to be followed up at the next point of time, otherwise were excluded.

DATA HANDLING

Data entry and editing were performed before the raw and edited data were prepared for analysis. The data analyses were performed using the Statistical Package for the Social Sciences (SPSS) program for Windows, version 9.0.

For descriptive analysis of patient' s characteristics, continuous variables including age, thyroid gland weight and ^{131}I administered dose were reported as mean $\pm$ standard deviation (SD) or median (minimum, maximum) as proper, whereas ratio or percentage was used to present categorical variables including sex and indication for ^{131}I therapy. All outcomes were shown as the percentage. This study was approved by the Ethics Committee of Faculty of Medicine, Khon Kaen University.

RESULTS

DESCRIPTION OF THE STUDY POPULATION

Of all 1,032 Graves' disease subjects treated by radioiodine during the time of study, 48 cases were excluded due to incomplete data obtained. The rest 984 cases were enrolled for analysis. Almost all subjects lived in the northeast Thailand. Characteristics of subjects including age, sex, estimated thyroid gland weight and indications for ^{131}I treatment-new cases without prior ATD treatment, medical failure within 6-month ATD treatment, failure between 6-month and 2-year ATD treatment, failure after 2-year ATD treatment, relapse of hyperthyroidism within 2 years after ATD cessation, relapse beyond 2 years after ATD cessation and relapse after thyroidectomy-were shown (Table 1). The documented co-morbidities before ^{131}I therapy included 68 cases of congestive heart failure and/or cardiac arrhythmia, 2 cases of thyroid storm and a case of hypokalemic periodic paralysis. There were 31 cases having history of allergy to ATD. A cold thyroid nodule was found in 5 cases, documented by thyroid scintigraphy and a thyroid nodule was clinically palpated in other 5 subjects without the result of thyroid scintigraphy.

TREATMENT OUTCOMES

In determining the outcome after the first dose of ^{131}I treatment, 291 of 984 cases (29.6%) were excluded since the outcome could not be definitely determined due to less than 6-month follow-up time according to the criteria. As a result, the outcome of the rest 693 cases was evaluated and defined as success or failure. Characteristics of subjects who could and could not be evaluated for this outcome were comparable (Table 2). The success rate after the first dose of treatment was found in 247 of 693 cases (35.6%) as shown in Table 3.

Regarding the number of ^{131}I administered dose needed to cure hyperthyroidism, 449 of 984 cases (45.6%) whose follow-up times were long enough to render euthyroidism or permanent hypothyroidism were analyzed. Characteristics of subjects who were and were not adequately followed up were comparable (Table 4). It was noted that the majority of subjects (64.8%) were cured by a single dose. The distribution of the number of administered dose was shown in Table 5.

In determining thyroid status of subjects after the last dose of treatment of all 984 subjects, there were 441, 257, 132, 64 and 36 subjects that could still be followed up at 1, 2, 3, 4 and 5 years respectively. The incidence of hyperthyroidism, euthyroidism and permanent hypothyroidism at these follow-up periods was shown (Fig. 1). It was noted that the incidence of hyperthyroidism decreased from 45.6% at the end of the first year down to 26.8%, 22%, 17.2% and 13.9% at the end of 2, 3, 4 and 5 years respectively. On the contrary, the incidence of permanent hypothyroidism tended to rise progressively from 9.3% at the end of the first year to 19.1%, 22%, 28.1% and 22.2% respectively.

TABLE 1. Characteristics of all subjects.

Characteristics	Number
Female: male ratio	793: 191 (4.2 : 1)
Mean age ± SD (y)	40.9 ± 11.6
(range)	(14 -80)
Median thyroid weight (g)	35
(min, max)	(20, 200)
Indications	
New	19 (1.9%)
ATD < 6 m	145 (14.7%)
ATD 6 m - 2 y	276 (28%)
ATD > 2 y	384 (39%)
Relapse < 2 y	79 (8%)
Relapse > 2 y	35 (3.6%)
Relapse after surgery	46 (4.7%)

TABLE 2. Characteristics of subjects in the determinable and undeterminable treatment outcome groups for the first dose.

Characteristics	Determinable outcome (N = 693)	Indeterminable outcome (N = 291)
Female: male ratio	558: 135 (4.1:1)	235: 56 (4.2:1)
Mean age ± SD (y)	40.3±11.6	41.6±11.6
(range)	(15-75)	(14-80)
Median thyroid weight (g)	40	35
(min, max)	(20, 200)	(20, 120)
Median ^{131}I dose (mCi)	5	5
(min, max)	(3, 27)	(3, 20)
Indications		
New	12 (1.7%)	7 (2.4%)
ATD < 6 m	84 (12.2%)	61 (20.9%)
ATD 6 m - 2 y	200 (28.9%)	76 (26.1%)
ATD > 2 y	287 (41.4%)	97 (33.3%)
Relapse < 2 y	52 (7.5%)	27 (9.3%)
Relapse > 2 y	27 (3.8%)	8 (2.7%)
Relapse after surgery	31 (4.5%)	15 (5.2%)

TABLE 3. Treatment outcome of the first dose of ^{131}I.

Outcome	Number
Success	247 (35.6%)
Failure	446 (64.4%)
Total	693 (100%)

TABLE 4. Characteristics of subjects who were and were not adequately followed up to determine the number of administered doses of ^{131}I to cure hyperthyroidism.

Characteristics (Total = 938)	**Adequate FU** (N = 449)	**Inadequate FU** (N = 535)
Female: male ratio	388: 61 (6.4: 1)	405: 130 (3: 1)
Mean age ± SD (y)	40.6 ± 11.6	41.3 ± 11.5
(range)	(16 – 75)	(14 – 80)
Median thyroid weight (g)	35	40
(min, max)	(20, 200)	(20, 150)
Indications		
New	9 (2%)	10 (1.9%)
ATD < 6 m	64 (14.3%)	81 (15.1%)
ATD 6 m – 2 y	128 (28.5%)	148 (27.7%)
ATD > 2 y	173 (38.5%)	211 (39.4%)
Relapse < 2 y	38 (8.4%)	41 (7.6%)
Relapse > 2 y	21 (4.7%)	14 (2.6%)
Relapse after surgery	16 (3.6%)	30 (5.6%)

TABLE 5. Distribution of the number of administered doses of ^{131}I in the adequately followed-up group.

Number of ^{131}I administered dose	**Number of subjects** (Total = 449)
1	291 (64.8%)
2	116 (25.8%)
3	37 (8.2%)
4	4 (0.9%)
5	1 (0.2%)

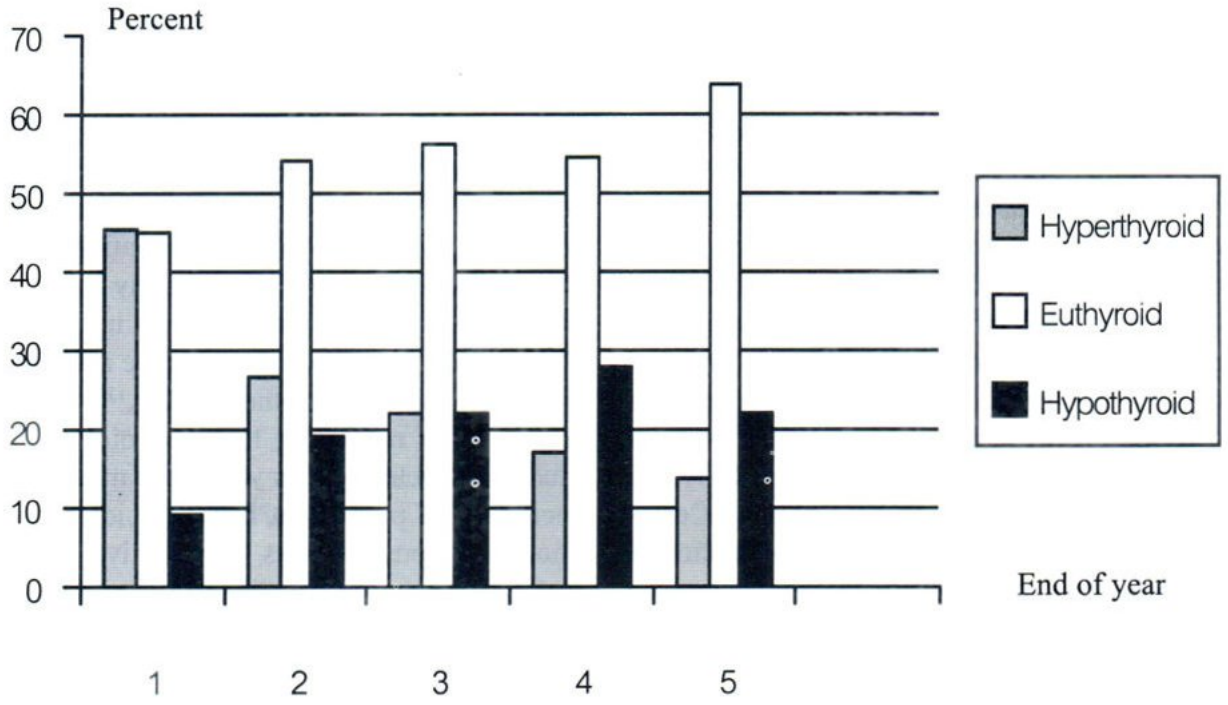

Fig. 1. Incidence of thyroid status at the specific points of time after the last ^{131}I treatment.

DISCUSSION

The aim of radioiodine therapy in hyperthyroidism is to destroy sufficient thyroid tissue to cure hyperthyroidism by rendering the patient either euthyroidism or hypothyroidism. Despite more than half a century of experience, there is little agreement regarding the most appropriate dose regimen.[9-10] Although several studies have attempted to determine the optimal dose of radioiodine for curing hyperthyroidism and avoiding the development of permanent hypothyroidism,[11-12] the results of treatment is still unpredictable.

Our study revealed the outcomes of ^{131}I treatment in Graves' disease patients who mostly resided in the provinces of northeast Thailand. Female sex predilection of the subjects was about 4:1 and was comparable to those in the literatures.[11-13] It was noted that the majority (81.7%) of indications for ^{131}I therapy was the medical failure after being treated by ATD.

About one-third of patients were cured from hyperthyroidism by only one dose of ^{131}I while hyperthyroidism was still existed in almost two-third and was subsequently considered for retreatment. The follow-up time of 6 months after treatment was used to determine the success of ^{131}I therapy since most of the patients who were successfully treated usually rendered euthyroid or hypothyroid state within this period and those who still were hyperthyroidism beyond this period were considered as the candidate for retreatment. Although nearly 30% of subjects were lost to follow-up, resulting in undeterminable outcome of the first ^{131}I dose, the characteristics of these subjects were comparable to those who could be adequately followed up. The success rate of the first treatment dose in our study was rather low compared with those in some studies.[5,14] Apart

from the difference in dose selection regimen used,[5] this was probably because most of our study population (81.7%) had received ATD before radioiodine treatment. Some studies suggested that there was a relative radioresistance in those prescribed ATD before or after radioiodine.[6-7,15-16] Another possible reason was the error in the estimation of thyroid gland weight, which was performed by palpation. This method was somewhat subjective and interpersonal error could be very high in a large gland. Since we calculated the treatment dose according to the 24-hour radioiodine uptake value and estimated thyroid gland weight to achieve about 100 microCuries per gram of thyroid tissue, the underestimation of gland weight could lead to the underdose of radioiodine administered. A more objective and clinically probable method using the ultrasound technique in the calculation of thyroid volume could be used.[17] Moreover, more sophisticated but probably not practical techniques in measuring metabolically active volume of the thyroid were also recommended including ^{123}I single photon emission computed tomographic (SPECT) imaging or ^{124}I positron emission tomographic (PET) imaging.[18-20] Apart from the accuracy in estimation of thyroid gland size, the thyroid gland size itself might relate to the outcome after ^{131}I treatment. It was found that large thyroid, over 26 grams, was one of the main predictors of non-response to radioiodine therapy if the dose range of 60-90 Grays was aimed to thyroid tissue.[5]

Curing patients from hyperthyroidism with a single dose is the goal of ^{131}I therapy, we thus explored the number of subjects who were cured by a single dose. It was revealed that about 65% of our subjects in the adequately followed-up group needed only single dose while about one-third of subjects required more than a single dose to achieve euthyroidism or hypothyroidism. This proportion, again, could varied and was depended significantly on the dosage regimen used.[5,13]

The major drawback of ^{131}I therapy is the significant incidence of hypothyroidism, which is cumulative. One of the large studies exploring the long-term incidence of hypothyroidism after ^{131}I treatment in 4,473 hyperthyroid patients during 26-year period reported 6% hypothy-roidism developed within the first year with increasing to 72% within 26 years, or an average rise of 2.6% per year.[21] Like some other studies,[13,22] while the incidence of remaining hyperthyroidism in our study was declining over years after treatment, the incidence of permanent hypothyroidism, which should be considered as the negative end point rather than the complication of treatment, tended to rise progressively. In our study, a significant number of subjects, about 22%, still remained hyperthyroidism even after the third year of follow-up. The occurrence of permanent hypothyroidism within the first four years after treatment was at the average rate of 7% per year. At the end of the fifth year, the incidence of hypothyroidism was lower than that at the end of the forth year likely because a significant number of subjects who already developed hypothyroidism were lost to follow-up between the end of the forth and the end of the fifth year after the last dose. Besides the dose regimen selected, the use of sensitive assay for TSH, resulting in earlier recognition of hypothyroidism, could determine the incidence of hypothyroidism.[22]

Because of this study was done in the retrospective way, therefore it had some limitations. Details of the data depended highly on the accuracy and consistency in recording patient's data by the physicians during the routine services. The subjects who were lost to follow-up definitely affected the outcome. In addition, there was also a limitation regarding the financial status in some subjects. Hence, thyroid status was sometimes documented clinically without simultaneous confirmation by thyroid

function test. However, our study population was one of the largest ever been reported. In addition, a recent study postulated that genetic and cultural factors might also be associated with the treatment response rate.[5] Our patients were mostly the people in the northeast Thailand. Therefore their outcomes were the beneficial data in auditing the treatment of the patients from this region. Further study should be conducted to clearly explore possible factors affecting favorable outcomes of treatment in this population such as age, sex, initial thyroid weight, radioiodine uptake value or prior treatment modalities.

In conclusion, although being an effective means in the treatment of hyperthyroidism, ^{131}I showed rather unpredictable outcomes in our study population. Some patients may remain hyperthyroidism even more than two doses of ^{131}I administered and in a significant follow-up time, whereas all patients had a chance to develop permanent hypothyroidism increasingly with time. However, since thyroxine is generally available and cheap, replacement therapy in permanent hypothyroidism following ^{131}I therapy is easy and usually acceptable. We think that our dosage regimen should be reconsidered to give a higher dose of radioiodine to get cure of hyperthyroidism within an earlier period and by a lower number of treatment doses without increasing rate of hypothyroidism.

REFERENCES

1. Solomon B, Glinoer D, Lagasse R, Wartofsky L. Current trends in the management of Graves' disease. J Clin Endocrinol Metab 1990; 70: 1518-24.
2. Hamburger JI, Paul S. When and how to use higher ^{131}I doses for hyperthyroidism. N Engl J Med 1968; 279: 1361-5.
3. Holm LE, Lundell G, Dahlqvist I, Israelsson A. Cure rate after ^{131}I therapy for hyperthyroidism. Acta Radiol 1981; 20: 161-6.
4. Sridama V, McCormick M, Kaplan EL, Fauchet R, DeGroot LJ. Long-term follow -up study of compensated low dose ^{131}I therapy for Graves' disease. N Engl J Med 1984; 311: 426-32.
5. Howarth D, Epstein M, Lan Linda, Tan P, Booker J. Determination of the optimal minimum radioiodine dose in patients with Graves' disease: a clinical outcome study. Eur J Nucl Med 2001; 28: 1489-95.
6. Tuttle RM, Patience T, Budd S. Treatment of propylthiouracil before radioactive iodine therapy is associated with a higher treatment failure than therapy with radioactive iodine alone in Graves' disease. Thyroid 1995; 5: 243-7.
7. Sabri O, Zimmy M, Schulz G, et al. Success rate of radioiodine therapy in Graves' disease: the influence of thyrostatic medication. J Clin Endocrinol Metab 1999; 84: 1229-33.
8. Mettler FA Jr, Guiberteau MJ. Essentials of nuclear medicine imaging 4th ed. Philadelphia: W.B. Saunders, 1998: 109.
9. Franklyn JA. The management of hyperthyroidism. N Engl J Med 1994; 330:1731-8.
10. Shapiro B. Optimization of radioiodine therapy of thyrotoxicosis: what have we learned after 50 years? J Nucl Med; 34: 1638-41.
11. Allahabadia A, Daykin J, Sheppard MC, Gough SC, Franklyn JA. Radioiodine treatment of hyperthyroidism-prognostic factors for outcome. J Clin Endocrinol Metab 2001; 86: 3611-7.
12. Nordyke RA, Gilbert FI Jr. Optimal iodine -131 dose for eliminating hyperthyroidism in Graves' disease. J Nucl Med 1991; 32: 411-6.

13. Tavintharan S, Sundrum FX, Chew LS. Radioiodine ^{131}I therapy and the incidence of hypothyroidism. Ann Acad Med Singapore 1997; 26: 128-31.
14. Sabri O, Zimmy M, Schreckenberger M, et al. Characterization of therapy failures in radioiodine therapy of Graves' disease without simultaneous antithyroid agents. Nuklearmedizin 2001; 40: 1-6.
15. Sabri O, Zimmy M, Schreckenberger M, Reinartz P, Ostwald E, Bull U. Radioiodine therapy in Graves' disease with large diffuse goiter with or without carbimazole at the time of radioiodine therapy. Thyroid 1999; 9: 1181-8.
16. Koroscil TM. Thioamides alter the efficacy of radioiodine treatment in patients with Gravs' disease. South Med J 1995; 88: 831-6.
17. Bockisch A, Jamitzky T, Derwanz R, Biersack HJ. Optimized dose planning of radioiodine therapy of benign thyroidal diseases. J Nucl Med 1993; 34: 1632-8.
18. Frey P, Townsend D, Flattet A, et al. Tomographic imaging of human thyroid using ^{124}I. J Clin Endocrinol Metab 1986; 63: 918-27.
19. Ott RJ, Batty V, Webb S, et al. Measurement of radiation dose to the thyroid using positron emission tomography. Br J Radiol 1987; 60: 245-51.
20. Crawford DC, Flower MA, Pratt BE, et al. Thyroid volume measurement in thyrotoxic patients: comparison between ultrasonography and iodine-124 positron emission tomography. Eur J Nucl Med 1997; 24: 1470-8.
21. Holm LE, Lundell G, Dahlqvist I, Israelsson A. Incidence of hypothyroidism occurring long after iodine-131 therapy for hyperthyroidism. J Nucl Med 1982; 23: 103-7.
22. Holm LE. Changing annual incidence of hypothyroidism after iodine-131 therapy for hyperthyroidism, 1951-1975. J Nucl Med 1982; 23: 108-12.