Treatment of Graves' hyperthyroidism - prognostic factors for outcome

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ABSTRACT

Objective: To determine whether clinical and biochemical features of Graves' disease at presentation predict response to medical and radioiodine treatment.

Methods: We carried out a retrospective 10-year study of 194 consecutive Saudi subjects with Graves' disease who were treated with antithyroid drugs, radioiodine therapy, or both, between January 1995 and December 2004 at King Khalid University Hospital, Riyadh, Saudi Arabia.

Results: At diagnosis, the mean age was 32 ± 0.9 years. Only 26% of patients had successful outcome after a course of antithyroid medication. None of the clinical or biochemical factors were associated with a favorable outcome of antithyroid treatment. One dose of radioiodine [13-15 mCi (481-555 MBq)] cured hyperthyroidism in 83% of patients. Presence of ophthalmopathy at presentation was shown to be a significant contributing factor to failure to respond to a single dose of radioiodine (odds ratio, 6.4; 95% CI, 1.51-24.4; $p<0.01$). Failure of radioiodine treatment was also associated with higher serum free T_3 concentration at presentation ($p=0.003$).

Conclusion: In patients with Graves' hyperthyroidism, radioiodine treatment is associated with higher success rate than antithyroid drugs. A dose of 13-15 mCi (481-555 MBq) seems to be practical and effective, and should be considered as first line therapy. Patients with high free T_3 concentration and, those with ophthalmopathy at presentation were more likely to fail radioiodine treatment. A higher dose of radioiodine may be advisable in such patients.

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Graves' disease is the most common cause of hyperthyroidism. It can be treated with antithyroid drugs, radioiodine, and surgery.[1] Two main opinions exist regarding the first line of therapy. While in Europe and Japan antithyroid drugs are considered the first therapeutic option, more than two thirds of clinical thyroidologists in the USA consider radioiodine as the therapy of choice for Graves' disease.[2] Antithyroid drugs are highly effective in controlling hyperthyroidism, but long term remission is obtained in only 30-50% of patients.[3,4] Radioactive iodine (^{131}I) is the treatment of choice for relapsed Graves' disease, and its use as a first-line therapy for hyperthyroidism is increasing.[1,5,6] Treatment with ^{131}I is safe and effective. Although most patients achieve an euthyroid or hypothyroid state after a single dose of ^{131}I, approximately 10-30% will require more than one dose.[7,8] Furthermore, despite the introduction of ^{131}I into the clinical field in 1941,[9] controversies still exist concerning the most appropriate dose regimen. Several studies have attempted to ascertain factors that could predict the outcome before starting treatment for Graves' disease. These included performing diagnostic tests not routinely practiced. For example, assaying human leukocyte antigen, quantification of thyroid blood flow by Doppler sonography, thyrotropin releasing hormone test and thyroid stimulating hormone (TSH) receptor antibody status as predictors of the response to medical treatment.[3,10-12] Similarly, other factors have been suggested to indicate treatment outcome after ^{131}I therapy; these include: assessment of thyroid size, severity of biochemical hyperthyroidism, radioiodine uptake and turnover.[13,14] To date, none of these tests have been adopted broadly or proved clinically useful. Clinical features at presentation have also been suggested to predict response to treatment in patients with Graves' hyperthyroidism.[7,8,15] However, data from these studies may not be applicable elsewhere, especially in areas with differing iodine intake. In an attempt to determine the clinical and

biochemical factors that may predict response to treatment in patients with Graves' hyperthyroidism, we retrospectively reviewed treatment outcome in 194 patients treated between 1995 and 2004.

Methods. We performed a retrospective chart review of 194 consecutive patients who presented or were referred with Graves' disease to the Endocrine Clinic at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia between January 1995 and December 2004. Graves' disease was defined as the presence of biochemical hyperthyroidism (elevated serum free T_4 concentration and undetectable TSH) with an elevated diffuse thyroid uptake seen in ^{99m}Tc-pertechnetate scan. If an uptake scan were not available, the presence of biochemical hyperthyroidism with 2 of the following was required: diffuse goiter, significant titer of thyroid peroxidase or thyroglobulin autoantibodies (a titer of 1:100 was considered significant), or both, and presence of thyroid ophthalmopathy. Data were also collected from archived laboratory data, and, when needed, from discussion with the patients endocrinologist. Free T_4, Free T_3 and TSH were measured by ELISA (Enzymun-Test, Boehringer Mannheim Immunodiagnostics, Mannheim, Germany) until year 2000, and then by electro chemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN, USA). Thyroid autoantibodies were measured by an antibody agglutination test (SERODIA-AMC and SERODIA-ATG, FUJIREBIO INC., Tokyo, Japan). The presence or absence of goiter was assessed clinically by a staff endocrinologist during the patients' first visit to the endocrine clinic. The size of goiter could not be retrieved due to lack of documentation. Eye disease was defined according to the presence of eye signs in categories 2-6 of the NO SPECS classification.[16] The following factors were assessed and recorded in the database: gender, age at diagnosis, symptoms at presentation, presence of diffuse goiter, presence of eye disease, autoantibody status and titer, and serum concentration of TSH, free T_4 and free T_3. Information regarding duration of antithyroid drugs, timing of radioiodine treatment, and outcome were also recorded. Approval for laboratory and clinical review was obtained from the ethics committee of KKUH.

Patients were divided into those treated primarily by a staff endocrinologist at our institute and those treated initially by other physicians and referred to our clinic for further treatment. In the former group, the decision to treat with antithyroid drugs for 18 months or more versus radioactive treatment or surgery, as a primary treatment, had been taken by the treating endocrinologist. We used a fixed empirical dose of approximately 13-15 mCi [481-555 megabecquerels (MBq)] ^{131}I as described previously.[17] All patients had to stop antithyroid drugs 5 days before radioiodine treatment, and to restart them at least 5 days following treatment. Outcome after a full course 18 months of antithyroid drugs was defined as: 1) successful (euthyroid for at least 6 months after withdrawal of antithyroid drugs), and 2) failed (persistent or relapsed disease after a full course of antithyroid drug treatment and progression to radioiodine or surgery). Successful radioiodine therapy was defined as euthyroidism or permanent hypothyroidism following single dose of ^{131}I. Therapy failure was defined as the need for repeat radioiodine treatment or as persistently elevated thyroid hormone levels after one year of radioiodine treatment.

Statistical analysis. The chi-square test was performed to test for association between 2 categorical factors, and the unpaired t-test was used to assess the relationship between continuous and dichotomous categorical factors. For continuous data that was not normally distributed, the results of t-test were confirmed using the Mann-Whitney test. Results were considered statistically significant at a *P*-value less than 0.05. These analyses were performed using SPSS version 11.0 (Chicago, IL, USA).

Results. The demographic, clinical, and laboratory characteristics at presentation of the 194 patients with Graves' hyperthyroidism are summarized in **Table 1**. The number of patients who were treated primarily by a staff endocrinologist at our institute was 170, and other physicians referred the additional 24 patients to our clinic after failed medical therapy. This later group was included in the analysis of radioiodine treatment outcome only. Duration of follow-up was 49.3 ± 32.9 months (mean ± SD). Of those treated primarily in our institute, the number of patients who received elective medical therapy was 149, of whom 39 had successful medical treatment, 106 failed medical treatment and proceeded to radioiodine treatment or surgery, and 4 remained under follow-up at the time of data collection. Radioiodine treatment outcome was determined in 95 patients, of whom 21 were electively treated with radioiodine, and an additional 74 were treated with radioiodine after failed medical therapy. The number of patients with successful radioiodine treatment was 79, with 16 requiring more than one dose of radioiodine. Two-thirds of patients who were successfully treated with radioiodine developed hypothyroidism within the first 6 months of receiving radioiodine treatment. No difference in outcome was seen between patients treated electively with radioiodine, and those treated with radioiodine after failure of medical therapy.

Characteristics of males and females at presentation with Graves' disease were similar (data not shown), apart from females being younger than males and less

Table 1 - Baseline characteristics of patients with Graves' hyperthyroidism.

Parameters	N (%)
Total no. of patients	**194 (100)**
Age of onset (year)	
Mean ± SEM	32 ± 0.9
Range	8 – 69
Patients < 40 years	147 (75.8)
Patients ≥ 40 years	47 (24.2)
Gender	
Males	54 (27.8)
Females	140 (72.2)
Diffuse goiter	
Yes	170 (87.6)
No	24 (12.4)
Ophthalmopathy	
Yes	104 (53.6)
No	90 (46.4)
Antibody status	
Positive	75 (38.7)
Negative	33 (17)
Unknown	86 (44.3)
Free T_4 at diagnosis (pmol/L)	
Mean ± SEM	54.7 ± 1.8
Range	22.4 – 100
Free T_3 at diagnosis (pmol/L)	
Mean ± SEM	29.1 ± 1.83
Range	4.97 – 76

likely to have ophthalmopathy at presentation. There was no association between gender and outcome of medical and radioiodine treatment. For analysis, patients were divided into 2 groups, those who are less than 40 years at presentation and those who are >40 years. Younger patients were more likely to have diffuse goiter, positive antibody status, and higher free T_4 at presentation. However, both age groups responded similarly to medical and radioiodine treatment. Clinical Graves' ophthalmopathy was noted in 54% of patients; the majority were noted to be mild, consisting of exophthalmus or conjunctival irritation, or both, namely, categories 2 and 3 of the NO SPECS classification. The presence of ophthalmopathy at presentation was shown to be a significant contributing factor to failure to respond to a single dose of radioiodine (estimated odds ratio, 6.4; 95% CI, 1.51-24.4; $p<0.01$). Patients with ophthalmopathy had similar free T_4 (53.1 ± 3.7 versus 51 ± 3.5 pmol/L, $p=0.68$) and free T_3 at presentation (30.6 ± 4.8 versus 27.7 ± 3.5 pmol/L, $p=0.63$) to those without ophthalmopathy. Failure of radioiodine treatment was also associated with higher free T_3 concentration at presentation ($p=0.003$) (**Table 2**). There was no association between age, gender, presence of goiter, thyroid antibody status, and free T_4 concentration at presentation and the response to medical and radioiodine treatment.

Discussion. The outcome of Graves' disease treatment is variable, and hence, identifying factors that could predict treatment outcome before starting treatment will be of help to individual patients. In our experience, the outlook for remission of Graves' disease in adults is poor, with fewer than 30% of patients experiencing successful sustained remission after cessation of medical therapy. This continues the general trend for the decreasing likelihood of remission reported in recent years.[18,19] The finding that a high percentage of patients eventually required radioiodine, has led us to offer radioiodine as an option for first-line therapy.

Physicians who hesitate to use radioiodine as a first-line therapy would like to be able to identify reliable predictors of relapse following antithyroid medication. Winsa et al[12] demonstrated that young age, goiter size, and high thyroid hormone levels correlated significantly with relapse following 24 months of antithyroid medication. In another prospective study, Schleusener et al[3] reported that patients with positive TSH receptor antibodies (TRAb) at the end of therapy have significantly higher relapse rate than those with negative titers. In our study, although the size of goiter could not be retrieved due to lack of documentation, the presences or absence of goiter did not affect treatment outcome. Likewise, TRAb were not routinely assayed at our center, making comparison difficult. Nevertheless, none of the other tested parameters proved to be reliable predictors of antithyroid outcome in our study, similar to others observation.

Radioiodine therapy has assumed a prominent role as first, or second line therapy for Graves' disease in adults, and its use in children with this disease is increasing.[2,20-22] Over the last 3 decades, investigators have been trying to determine suitable regimens of radioiodine doses to achieve euthyroidism. These included fixed low and high doses of radioiodine and doses calculated on the basis of thyroid gland size, uptake, or the turnover of radioiodine. Since several studies have shown comparable results of both fixed and calculated doses, we prefer to use a fixed-dose regimen as it has the advantage of being more convenient with lower cost.[1] Given the importance of preventing persistent hyperthyroidism and the high probability of eventual hypothyroidism after any regimen of radioiodine treatment,[23,24] we decided that our goal of therapy was to induce hypothyroidism within one year of treatment with a single dose of ^{131}I. Our results confirmed the effectiveness of this regimen, with 83% of the patients became euthyroid or hypothyroid one year after treatment.

A number of studies have been conducted to identify pre-treatment factors leading to failure to respond to a single dose of radioiodine. Most of these

Table 2 - The relationship of clinical and biochemical parameters with outcome of radioiodine treatment.

Parameters	Successful radioiodine treatment	Failed radioiodine treatment	Statistical significance *(P)* of difference between radioiodine outcome groups (by $\chi 2$ /test)
Age of onset (years)			
< 40 years (%)	84.1	15.9	0.70
≥ 40 years (%)	80.8	19.2	
Gender			
Males (%)	83.3	16.7	0.98
Females (%)	83.1	16.9	
Diffuse goiter			
Yes (%)	82.7	17.3	0.78
No (%)	85.7	14.3	
Ophthalmopathy			
Yes (%)	71.1	28.9	0.007
No (%)	94	6	
Antibody status			
Positive (%)	89.3	10.7	0.22
Negative (%)	100	0	
Free T_4 at diagnosis (pmol/L; mean ± SEM)	50.36 ± 2.74	62.22 ± 7.15	0.10
Free T_3 at diagnosis (pmol/L; mean ± SEM)	24.02 ± 2.77	43.85 ± 6.71	0.003

studies have suggested that patients with larger thyroid gland volume and severe hyperthyroidism are more likely to fail to respond to treatment.[8,25-30] Alexander et al[7] examined 261 patients with Graves' disease treated with an average ^{131}I dose of 14.6 mCi (540 MBq) and found 86% of the patients euthyroid or hypothyroid one year after treatment. Patients with persistent hyperthyroidism were younger; had a larger thyroid gland, a higher serum T_4 concentration, more evidence of ophthalmopathy, and were more likely to have taken antithyroid medications before ^{131}I treatment compared with those with successful outcome.

Interestingly, we found that patients who failed to respond to a single dose of ^{131}I had higher prevalence of ophthalmopathy. On the other hand, absence of ophthalmopathy was found to be a significant independent predictor of favorable treatment outcome to single radioiodine dose. The association between the presence of ophthalmopathy and failure of radioiodine was not explained by the presence of higher free T_4 or free T_3 concentrations, since both were similar in patients with and without ophthalmopathy. Although the association between ophthalmopathy and failure to respond to single dose of ^{131}I had been noticed by Alexander et al,[7] other studies did not report this association.[8,15] The reason(s) behind this inconsistency is not clear. However, it is important to note that there is a limitation to retrospective studies in general. Statistics derived from such studies may contain some missing information and thus may serve as a stimulus to further prospective work to clarify findings. The present data must be interpreted in the knowledge of the defects inherent in such studies. Nevertheless, our results are in agreement with earlier reports.[7,17,25]

Previous reports had confirmed that patients with ophthalmopathy have high levels of TRAb, which had been suggested to correlate with the severity and activity of eye disease, and to be associated with failure of radioiodine therapy.[31,32] This might explain our findings. However, since TRAb was not measured in our cohort and is not routinely carried out in patients with Graves' disease, further studies are needed to test this assumption. As patients with Graves' disease and ophthalmopathy responded less well to a single dose of radioiodine, we suggest the need for a higher initial dose of radioiodine be evaluated in these patients. However, in view of reports of worsening ophthalmopathy following radioiodine treatment,[33-35] imploring alternative or modified mode of therapy in patients with significant eye disease needs to be considered. Such therapy would include surgery or radioiodine with corticosteroids.[36,37] In addition, our results for the influence of age and gender on the response to radioiodine treatment are consistent with others who found these factors not to be predictors of radioiodine treatment outcome in Graves' disease.[38,39] These findings contrast with other studies in which males and patients aged below 40 years were shown to have poor response to radioiodine therapy.[7,8,15] This disparity from others findings are not clear. It may however, be due to the different population studied. For instance, our findings correlated with Ghadban et al[38] who studied the same ethno-cultural society as our cohort.

In summary, medical therapy for Graves' disease carries an unfavorable success rate and lacks identifiable predictors for its outcome. On the other hand, single fixed dose of 13-15 mCi (481-555 MBq) radioiodine is effective in curing Graves' hyperthyroidism. The striking findings of influence of ophthalmopathy at presentation, determine that this easily defined clinical feature should be taken into consideration when planning disease management. The association between ophthalmopathy and failure to respond to single dose of radioiodine was significant and was shown to be independent of other clinical and biochemical factors. A higher dose of radioiodine may be advisable in such patients, however, further prospective studies are needed to clarify our findings.

References

1. Franklyn JA. The management of hyperthyroidism. ***N Engl J Med*** 1994; 330: 1731-1738.
2. Wartofsky L, Glinoer D, Solomon B, Nagataki S, Lagasse R, Nagayama Y, et al. Differences and similarities in the diagnosis and treatment of Graves' disease in Europe, Japan, and the United States. ***Thyroid*** 1991; 1: 129-135.
3. Schleusener H, Schwander J, Fischer C, Holle R, Holl G, Badenhoop K, et al. Prospective multicentre study on the prediction of relapse after antithyroid drug treatment in patients with Graves' disease. ***Acta Endocrinol (Copenh)*** 1989; 120: 689-701.
4. Vitti P, Rago T, Chiovato L, Pallini S, Santini F, Fiore E, et al. Clinical features of patients with Graves' disease undergoing remission after antithyroid drug treatment. ***Thyroid*** 1997; 7: 369-375.
5. Gittoes NJ, Franklyn JA. Hyperthyroidism. Current treatment guidelines. ***Drugs*** 1998; 55: 543-553.
6. Solomon B, Glinoer D, Lagasse R, Wartofsky L. Current trends in the management of Graves' disease. ***J Clin Endocrinol Metab*** 1990; 70: 1518-1524.
7. Alexander EK, Larsen PR. High dose of (131)I therapy for the treatment of hyperthyroidism caused by Graves' disease. ***J Clin Endocrinol Metab*** 2002; 87: 1073-1077.
8. Allahabadia A, Daykin J, Sheppard MC, Gough SC, Franklyn JA. Radioiodine treatment of hyperthyroidism-prognostic factors for outcome. ***J Clin Endocrinol Metab*** 2001; 86: 3611-3617.
9. Becker DV, Sawin CT. Radioiodine and thyroid disease: the beginning. ***Semin Nucl Med*** 1996; 26: 155-164.
10. Saleh A, Cohnen M, Furst G, Modder U, Feldkamp J. Prediction of relapse after antithyroid drug therapy of Graves' disease: value of color Doppler sonography. ***Exp Clin Endocrinol Diabetes*** 2004; 112: 510-513.
11. Weetman AP, Ratanachaiyavong S, Middleton GW, Love W, John R, Owen GM, et al. Prediction of outcome in Graves' disease after carbimazole treatment. ***Q J Med*** 1986; 59: 409-419.
12. Winsa B, Dahlberg A, Jansson R, Agren H, Karlsson FA. Factors influencing the outcome of thyrostatic drug therapy in Graves' disease. ***Acta Endocrinol (Copenh)*** 1990; 122: 722-728.
13. Laurberg P, Buchholtz Hansen PE, Iversen E, Eskjaer Jensen S, Weeke J. Goitre size and outcome of medical treatment of Graves' disease. ***Acta Endocrinol (Copenh)*** 1986; 111: 39-43.
14. McGregor AM, Smith BR, Hall R, Petersen MM, Miller M, Dewar PJ. Prediction of relapse in hyperthyroid Graves' disease. ***Lancet*** 1980; 1: 1101-1103.
15. Allahabadia A, Daykin J, Holder RL, Sheppard MC, Gough SC, Franklyn JA. Age and gender predict the outcome of treatment for Graves' hyperthyroidism. ***J Clin Endocrinol Metab*** 2000; 85: 1038-1042.
16. Werner S. Modification of the classification of the eye changes of Graves' disease: recommendations of the Ad Hoc Committee of the American Thyroid Association. ***J Clin Endocrinol Metab*** 1977; 44: 203-204.
17. Kendall-Taylor P, Keir MJ, Ross WM. Ablative radioiodine therapy for hyperthyroidism: long term follow up study. ***Br Med J (Clin Res Ed)*** 1984; 289: 361-363.
18. Nedrebo BG, Holm PI, Uhlving S, Sorheim JI, Skeie S, Eide GE, et al. Predictors of outcome and comparison of different drug regimens for the prevention of relapse in patients with Graves' disease. ***Eur J Endocrinol*** 2002; 147: 583-589.
19. Crivellaro C, Oberhofer R, Leimgruber K, Amor H. Graves' disease. Clinical features and treatment results. ***Acta Med Austriaca*** 2001; 28: 47-51.
20. Mithal A, Shah A, Kumar S. The management of Graves' disease by Indian thyroidologists. ***Natl Med J India*** 1993; 6: 163-166.
21. Ward L, Huot C, Lambert R, Deal C, Collu R, Van Vliet G. Outcome of pediatric Graves' disease after treatment with antithyroid medication and radioiodine. ***Clin Invest Med*** 1999; 22: 132-139.
22. Gruneiro-Papendieck L, Chiesa A, Finkielstain G, Heinrich JJ. Pediatric Graves' disease: outcome and treatment. ***J Pediatr Endocrinol Metab*** 2003; 16: 1249-1255.
23. Cunnien AJ, Hay ID, Gorman CA, Offord KP, Scanlon PW. Radioiodine-induced hypothyroidism in Graves' disease: factors associated. ***J Nucl Med*** 1982; 23: 978-983.
24. Graham GD, Burman KD. Radioiodine treatment of Graves' disease. An assessment of its potential risks. ***Ann Intern Med*** 1986; 105: 900-905.
25. Nordyke RA, Gilbert FI, Jr. Optimal iodine-131 dose for eliminating hyperthyroidism in Graves' disease. ***J Nucl Med*** 1991; 32: 411-416.
26. Watson AB, Brownlie BE, Frampton CM, Turner JG, Rogers TG. Outcome following standardized 185 MBq dose 131I therapy for Graves' disease. ***Clin Endocrinol (Oxf)*** 1988; 28: 487-496.
27. Sridama V, McCormick M, Kaplan EL, Fauchet R, DeGroot LJ. Long-term follow-up study of compensated low-dose 131I therapy for Graves' disease. ***N Engl J Med*** 1984; 311: 426-432.
28. Franklyn JA, Daykin J, Holder R, Sheppard MC. Radioiodine therapy compared in patients with toxic nodular or Graves' hyperthyroidism. ***QJM*** 1995; 88: 175-180.
29. Blahd WH, Hays MT. Graves' disease in the male. A review of 241 cases treated with an individually calculated dose of sodium iodide I 131. ***Arch Intern Med*** 1972; 129: 33-40.
30. Roudebush CP, Hoye KE, DeGroot LJ. Compensated low-dose ^{131}I therapy of Graves' disease. ***Ann Intern Med*** 1977; 87: 441-443.

31. Eckstein AK, Plicht M, Lax H, Hirche H, Quadbeck B, Mann K, et al. Clinical results of anti-inflammatory therapy in Graves' ophthalmopathy and association with thyroidal autoantibodies. ***Clin Endocrinol (Oxf)*** 2004; 61: 612-618.
32. Bojarska-Szmygin A, Janicki K, Pietura R, Janicka L. Changes in TSH receptor antibody levels (TRAb) as markers of effectiveness of various therapies in Graves-Basedow's disease. ***Ann Univ Mariae Curie Sklodowska Med*** 2003; 58: 248-253.
33. DeGroot LJ, Gorman CA, Pinchera A, Bartalena L, Marcocci C, Wiersinga WM, et al. Therapeutic controversies. Retro-orbital radiation and radioactive iodide ablation of the thyroid may be good for Graves' ophthalmopathy. ***J Clin Endocrinol Metab*** 1995; 80: 339-340.
34. Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. ***N Engl J Med*** 1998; 338: 73-78.
35. Tallstedt L, Lundell G, Torring O, Wallin G, Ljunggren JG, Blomgren H, et al. Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. The Thyroid Study Group. ***N Engl J Med*** 1992; 326: 1733-1738.
36. Bartalena L, Marcocci C, Bogazzi F, Panicucci M, Lepri A, Pinchera A. Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. ***N Engl J Med*** 1989; 321: 1349-1352.
37. Dasgupta S, Savage MW. Evaluation of management of Graves' disease in District General Hospital: achievement of consensus guidelines. ***Int J Clin Pract*** 2005; 59: 1097-1100.
38. Ghadban WK, Zirie MA, Al-Khateeb DA, Jayyousi AA, Mobayedh HM, El-Aloosy AS. Radioiodine treatment of hyperthyroidism. Success rate and influence of thyrostatic medication. ***Saudi Med J*** 2003; 24: 347-351.
39. Erem C, Kandemir N, Hacihasanoglu A, Ersoz HO, Ukinc K, Kocak M. Radioiodine treatment of hyperthyroidism: prognostic factors affecting outcome. ***Endocrine*** 2004; 25: 55-60.

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Al-Kaabi JM, Hussein SS, Bukheit CS, Woodhouse NJ, Elshafie OT, Bererhi H. Radioactive iodine in the treatment of Graves' disease. ***Saudi Med J*** 2002; 23: 1049-1053.