TÜBİTAK

Original Article

Turk J Med Sci
2011; 41 (6): 981-988
© TÜBİTAK
E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-1010-1232

Prognostic role of Tc-99m pertechnetate thyroid scintigraphy prior to fixed-dose radioiodine therapy of toxic multinodular goiters*

Doğangün YÜKSEL, Fatma Suna KIRAÇ, Olga YAYLALI, Işıl DEMİRAY UĞUZ

Aim: To investigate the prognostic role of Tc-99m pertechnetate thyroid scintigraphy pretreatment in patients with toxic multinodular goiters (TMNG) who were then treated with fixed I-131 doses.

Materials and methods: We retrospectively evaluated 28 patients (18 females and 10 males; mean ± SD = 63 ± 11 years) that were treated with 740 megabecquerels (MBq) of I-131 for TMNG. Information, including age, Tc-99m pertechnetate thyroid scintigraphy and ultrasonography findings, antithyroid medication, thyroid hormone profile, and clinical status before treatment, was recorded. The regions of interest were drawn over the hot nodules, salivary glands, and the background on the anterior thyroid images. The net nodule counts, net salivary counts, nodule-to-salivary ratios, and nodule-to-background ratios were then calculated. The data were statistically compared for the hypothyroid and euthyroid patient groups after radioiodine treatment.

Results: In the study group, the mean follow-up period was 7 ± 2 months (range: 6-12 months). We detected hyperthyroidism in 1 patient, euthyroidism in 19 patients, and hypothyroidism in 8 patients. The pretreatment mean net nodule counts (34.79 ± 14.06 counts) in the patients that developed hypothyroidism were significantly higher than in those patients that developed euthyroidism (26.80 ± 11.04 counts) (P = 0.014). The other 3 parameters did not show significant differences between the 2 groups.

Conclusion: The Tc-99m pertechnetate uptake level of hot nodules calculated from the pretreatment of thyroid scintigraphy in patients with TMNG treated with a fixed 740-MBq I-131 dose may predict early hypothyroidism in patients.

Key words: Radioiodine, I-131, toxic multinodular goiter, Tc-99m pertechnetate

Toksik multinodüler guatrın sabit doz radyoiyot ile tedavisi öncesi Tc-99m perteknetat tiroit sintigrafisinin prognostik rolü

Amaç: Bu çalışmanın amacı sabit I-131 dozu ile tedavi edilen toksik multinodüler guatrlı (TMNG) hastalarda tedavi öncesi çekilen Tc-99m perteknetat tiroit sintigrafisinin prognostik rolünü araştırmaktı.

Yöntem ve gereç: TMNG nedeniyle 740 MBq I-131 ile tedavi edilen 28 hasta (18 K / 10 E; ortalama ± SD = 63 ± 11 yıl) geriye dönük değerlendirildi. Kayıt edilen veriler tedavi öncesi yaş, Tc-99m perteknetat tiroit sintigrafisi ve ultrason bulguları, antitiroit medikasyon, tiroit hormon profili ve klinik durumu içermekteydi. Anterior tiroit görüntüleri üzerinde sıcak nodüllerinin, tükürük bezlerinin ve geri-planın üzerine ilgi alanları çizildi. Net nodül sayımları, net tükürük bezi sayımları, nodül/tükürük bezi oranları ve nodül/geri-plan oranları hesaplandı. Bu değerler radyoiyot tedavisi sonrası hipotiroidili ve ötiroidili hastalar için istatistiksel olarak karşılaştırıldı.

Received: 19.10.2010 – Accepted: 10.01.2011

Department of Nuclear Medicine, Faculty of Medicine, Pamukkale University, Denizli - TURKEY

Correspondence: *Doğangün YÜKSEL, Department of Nuclear Medicine, Faculty of Medicine, Pamukkale University, PAÜ-SARUM Bayramyeri Hastanesi, Doktorlar Cad. No: 42, 20100 Denizli - TURKEY*
E-mail: dyuksel@pau.edu.tr

* This study is part of a project supported by the Scientific Research Projects Unit of Pamukkale University (No: 2007KRM004).

Bulgular: Çalışma grubunda ortalama izlem süresi 7 ± 2 aydı (aralık, 6-12 ay). Bir hastada hipertiroidi, 19 hastada ötiroidi ve 8 hastada hipotiroidi saptadık. Hipotiroidi gelişen hastalarda tedavi öncesi ortalama net nodül sayımları (34,79 ± 14,06 sayım), ötiroidi gelişen hastalarınkinden (26,80 ± 11,04 sayım) anlamlı şekilde daha yüksekti (P = 0,014). Diğer üç parametre iki grup arasında anlamlı farklılık göstermedi.

Sonuç: Sabit 740 MBq I-131 dozu ile tedavi edilen TMNG'lı hastalarda tedavi öncesi çekilen tiroit sintigrafisinde hesaplanan sıcak nodülün Tc-99m perteknetat tutulum düzeyi erken hipotiroidizm gelişecek hastaları önceden saptayabilir.

Anahtar sözcükler: Radyoiyot, I-131, toksik multinodüler guatr, Tc-99m perteknetat

Introduction

Although radioactive iodine (RAI) has been used for 60 years in the treatment of hyperthyroidism, no consensus regarding the best method for dose choice exists. One reason for this lack of consensus is the diversity of the disease's natural course, which causes hyperthyroidism. The expected responses during the administration of RAI in Graves' disease and toxic multinodular goiter (TMNG) are not identical. In other words, euthyroidism and hypothyroidism should be expected following the treatment of Graves' disease with RAI. Contrastingly, in cases with toxic nodular disease (i.e. autonomous toxic multinodular goiter and autonomous solitary toxic adenoma), the nodules function differently from normal thyroid cells and do not respond to thyroid-stimulating hormone (TSH) treatment. The autonomously functioning nodules concentrate iodine-131 (I-131). The suppressed extranodular tissue does not concentrate I-131 and is exposed to less radiation. Suppressed thyroid tissue returns to its normal function when TSH reaches a normal level following radioiodine treatment (RIT). Thus, the expected response in patients following RIT is euthyroidism, whereas hypothyroidism is the undesired result of the treatment (1).

Several approaches in determining the most appropriate dose of I-131 for the treatment of toxic nodular disease with RAI exist. These approaches include the calculated-dose, fixed-dose, and graded-dose methods. One of the calculated-dose methods is the calculation of the autonomous tissue mass that functions in the thyroid based on the technetium-99m (Tc-99m) pertechnetate thyroid uptake under TSH suppression (TcTUs) and, accordingly, the determination of the I-131 dose (2-10). In contrast, no study has used the fixed-dose or graded-dose method to evaluate the use of the level of Tc-99m uptake efficiency in the thyroid. Tc-99m pertechnetate scintigraphy is frequently used as a diagnostic tool in patients with toxic nodular goiter; however, it has not been used for evaluating the dose selection for RAI treatment or posttreatment prognoses.

In the present study, the prognostic role of Tc-99m pertechnetate thyroid scintigraphy prior to the fixed-dose I-131 treatment of patients with TMNG was investigated.

Materials and methods

A total of 28 patients with TMNG were treated with 740-megabecquerel (MBq) fixed I-131 doses between 2002 and 2008 and were retrospectively evaluated. Ages, genders, thyroid ultrasound (US) and Tc-99m pertechnetate thyroid scintigraphy findings (i.e. the number of nodules and level of extranodular thyroid tissue suppression), antithyroid drug use, and thyroid hormone profiles (i.e. free triiodothyronine (FT3) and free thyroxine (FT4), TSH) were recorded.

The patients were classified as hypothyroidic, euthyroidic, and hyperthyroidic according to the outcome of RIT. Euthyroidism was diagnosed if the patients remained in euthyroid status without antithyroid drug treatment ≤3 months after achieving normal TSH, FT3, and FT4 ranges of 0.4-4.0 μIU/mL, 1.5-4.1 pg/mL, and 0.8-1.9 ng/mL, respectively. Hypothyroidism was diagnosed if TSH exceeded its normal range (>4.0 μIU/mL) and FT4 fell below its normal reference range (<0.8 ng/mL). If this situation continued for 3 months, the patient was diagnosed with permanent hypothyroidism. Thyroid hormone replacement was commenced following confirmation of hypothyroidism with laboratory and clinical findings. If free T4 or T3 remained elevated for 6 months after RIT, the patients were diagnosed

with persistent hyperthyroidism, indicating that the single dose RAI treatment had failed. After this decision, a second dose of RAI, increased by 25%, was administered to those patients (11).

In our department, Tc-99m pertechnetate thyroid scintigraphy is performed using a gamma camera equipped with a pinhole collimator (insert diameter of 5 mm). Anterior thyroid images are obtained 20 min after intravenous injection of 185 MBq of Tc-99m pertechnetate. The distance from the insert of the pinhole collimator to the neck of the patient, who lies in a supine position, is adjusted to 10 cm, and 150,000 counts are accumulated on the thyroid. Energy discrimination is provided with a 20% window that is centered on the 140-keV Tc-99m photopeak.

In the present study, pre- and post-RAI treatment anterior neck scintigraphic images of 28 TMNG patients were evaluated and accompanied with US. The level of extranodular thyroid parenchymal tissue suppression was visually determined from the anterior Tc-99m pertechnetate thyroid scintigraphy. If extranodular thyroid parenchymal tissue was slightly observed in the scan, it was deemed as partial suppression, or, if not, the tissue was accepted as totally suppressed.

The images were evaluated in the linear gray scale. The default upper and lower limits of the gray scale were unchanged. Regions of interest (ROI) were drawn on the thyroid hot nodules, salivary glands, and neck tissue adjacent to the thyroid for background activity on the images recorded prior to RIT. The locations of ROIs were determined by consensus from 2 nuclear medicine physicians (Figure). For standardization, the mean counts per pixel in the ROIs were used in the calculations. Nevertheless, in our retrospective study, the nodule sizes measured by US could not be used to calculate the thyroid volume because the US results were acquired in different centers and by different operators without standardization.

The net nodule and net salivary gland counts were calculated by subtracting the mean counts per pixel in the background ROI (C_B) from the mean counts per pixel of ROIs within the nodules (C_N) and the salivary glands (C_S) (Figure), as follows:

$$\text{Net } C_N = C_N - C_B,$$

$$\text{Net } C_S = C_S - C_B.$$

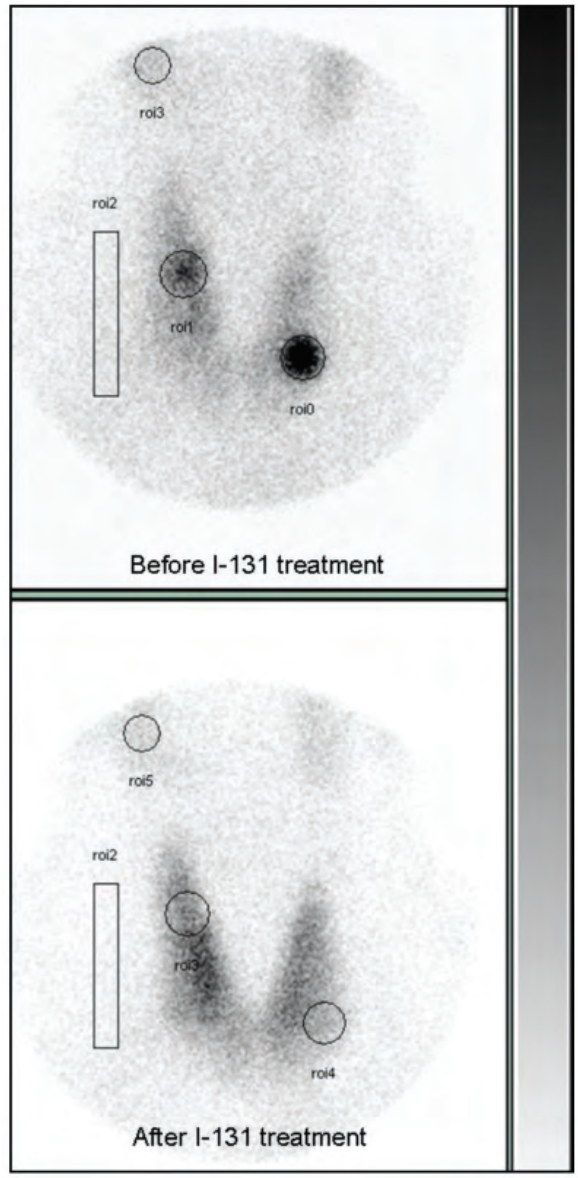

Figure. Regions of interest were drawn on the thyroid hot nodules, salivary glands, and neck tissue adjacent to the thyroid for background activity of the recorded Tc-99m pertechnetate images before and after RIT.

The net nodule (net C_N) or salivary gland (net C_S) counts were used to calculate the nodular-to-salivary gland ratio and the nodular-to-background activity ratio. These data were statistically compared to results from the hyperthyroid and euthyroid patient groups after RAI treatment using the nonparametric Mann-Whitney U test. Because there was only one patient in the hyperthyroid group, this patient was not included in the statistical analyses.

Results

The retrospective patient data are shown in Table 1. Out of the 28 patients (mean age: 63 ± 11 years) that enrolled in the present study, 18 were female and 10 were male. During the follow-up period, euthyroidism, hypothyroidism, and hyperthyroidism developed in 19 patients, 8 patients, and 1 patient, respectively. In the study group, the mean follow-up period was 7 ± 2 months (range: 6-12 months). In the euthyroid group, the mean time for euthyroidism was 3 ± 1 months (range: 1-6 months). In the hypothyroid group, the mean time was 4 ± 2 months (range: 2-6 months) to develop hypothyroidism. Only 1 patient remained in hyperthyroid status 6 months after RIT, and that patient received a second dose of I-131.

No significant differences between the patients developing hypothyroidism and euthyroidism in terms of age, gender, thyroid hormone and TSH levels, number of nodules, or the duration of antithyroid drug use were observed ($P > 0.05$). All patients received antithyroid (propylthiouracil) treatment (9 ± 11 months; range: 1-45 months), and their antithyroid medication was discontinued 1 week before radionuclide imaging.

The pretreatment mean net nodule count (34.79 ± 14.06 counts; range: 17.60-78.35 counts) in the patients who developed hypothyroidism after RIT was found to be significantly higher than that of those patients who developed euthyroidism (26.80 ± 11.04 counts; range: 8.01-58.50 counts) ($P = 0.014$). No difference was found between the patients with hypothyroidism and euthyroidism in terms of the other parameters (i.e. net salivary gland count, nodular-to-salivary gland ratio, and nodular-to-background ratio) (Table 2).

Discussion

The appropriate treatment dose for patients with TMNG remains difficult to determine due to the generally irregular structure of the thyroid gland. Therefore, many authors recommend the use of TcTUs to determine the size of the thyroid tissue, which demonstrates autonomous function (5,9,10). Dose calculations through the use of TcTUs have been

Table 1. Data recorded from patients with TMNG.

	Euthyroidism	Hypothyroidism	Hyperthyroidism
Patients (n)	19	8	1
Age (year)	64 ± 11	61 ± 13	65
Sex	11 F / 8 M	6 F / 2 M	F
Mean time of antithyroid drug use (months)	9 ± 8	5 ± 4	36
FT3 (before RIT)	4.96 ± 2.35	4.31 ± 1.15	4.87
ST4 (before RIT)	1.93 ± 0.90	1.89 ± 0.73	0.96
TSH (before RIT)	0.08 ± 0.21	0.04 ± 0.02	0.001
Suppression level of extranodular thyroid tissues in the anterior Tc-99m pertechnetate thyroid scintigraphy before RIT			
Complete suppression (n)	8	4	1
Partial suppression (n)	11	4	

Abbreviations: FT3, free triiodothyronine (normal range = 2-4.4 pg/mL); FT4, free thyroxine (normal range = 0.93-1.7 ng/mL); TSH, thyroid-stimulating hormone (normal range = 0.27-4.2 μIU/mL); F, female; M, male; RIT, radioactive iodine treatment.

Table 2. Quantitative data analyses obtained from Tc-99m pertechnetate scintigraphy according to responses following treatment with I-131.

	Euthyroidism	Hypothyroidism	Hyperthyroidism
Patients (n (%))	19 (68)	8 (29)	1 (3)
Total nodules (n)	52	18	2
Number of nodules per patient	3 ± 1	2 ± 1	2
Mean net nodule count before RIT*	**26.80 ± 11.04**	**34.79 ± 14.06**	40.30
Mean net salivary gland count before RIT	5.00 ± 2.69	4.93 ± 1.70	2.50
Mean nodular-to-salivary gland ratio before RIT	8.68 ± 6.99	5.17 ± 8.06	16.12
Mean nodular-to-background ratio before RIT	19.39 ± 13.00	12.52 ± 16.20	43.81

*The pretreatment mean net nodule count in patients who developed hypothyroidism after RAI treatment is significantly higher than that of those who developed euthyroidism (P = 0.014).

shown to increase treatment success rates by 92% and to decrease the incidences of hypothyroidism by 0.9% (5). When I-131 doses were previously calculated using the calculated-dose methods by increasing the absorbed tissue dose according to the TcTUs values, the patients with high TcTUs values (above the range of 3.5%-4%) displayed significant decreases in treatment success rates (9). This correlation has been suggested to be due to the significant photon attenuation in patients with a large goiter, leading to low TcTUs values, and, consequently, the calculated target volume is smaller than the real tissue volume (**8**). In these studies, the aim of using TcTUs is the requirement to perform accurate measurements of autonomous tissue volume. No evaluation was made to predict the treatment outcome in any of these studies. The posttreatment results were used to make adjustments to the calculated-dose method.

Some studies have suggested that the fixed-dose method is an easier and more effective treatment modality because complex formulas are not used to calculate the I-131 dosage (12). In contrast, there is a need for a simple and inexpensive method that can predict the response to treatment in patients with TMNG. Tc-99m pertechnetate is an appropriate radiopharmaceutical because it is easily available, inexpensive, and has an appropriate energy for imaging. Thyroid scintigraphy with Tc-99m pertechnetate is a strongly recommended imaging modality for patients with TSH levels that are below normal. This method is also routinely used in patients with TMNG for diagnostic purposes (13,14). As is known, administration of a fixed dose for RAI treatment in patients with TMNG is an easy method, and its efficacy has been proven (1).

The aim of RIT in patients with autonomous TMNG is to reach euthyroidism by eliminating the autonomous tissue (14). In our patient group, this objective was attained in 19 of the 28 patients using 740-MBq doses of I-131. Hypothyroidism developed in 8 of the 28 patients, whereas hyperthyroidism could not be treated in only 1 patient and required a second dose of I-131. Many studies have investigated factors that increase the risk of hypothyroidism following RIT, including age, gender, high radioiodine uptake, administered I-131 dose, level of extranodular thyroid tissue suppression, and the use of antithyroid drugs prior to RAI treatment (15,16). When these factors were considered, the mean age of our patients was >45 years, and no significant differences were found between the groups. All patients were treated with antithyroid medication prior to RAI treatment. The I-131 dose could not be considered as a prognostic factor because a fixed dose was

administered to all patients. The I-131 uptake test is important to ensure adequate uptake at the time of therapy and to help determine the dose of RAI in the calculated-dose methods (11). Nevertheless, the fact that no radioiodine uptake test was performed in any of the patients before RAI treatment is an important limitation of our retrospective study. We did not conduct the radioiodine uptake test in our study because of technical reasons; however, hyperthyroidism was successfully treated in 27 of 28 patients. Therefore, adequate I-131 uptake in the nodules was achieved. Depending on our results, the radioiodine uptake test may not be necessary for calculating I-131 doses, especially in the fixed-dose treatment protocol that was used in our study. Perhaps the I-131 uptake test could have been useful in defining the appropriate iodine dose to cure the patient with ongoing hyperthyroidism after RIT. However, the lack of the I-131 uptake test does not affect the major results of this study.

In our clinic, patients subject to RIT are followed up with in accordance with the instructions of the AACE (11). Euthyroidism occurred in most patients, except 1, in the range of 1-6 months (mean time: 3 ± 1 months). Hypothyroidism occurred within a range of 2-6 months (mean time: 4 ± 2 months) in our group. Similar to our results, Nygaard et al. (17) reported that the median time to become euthyroidic after RIT was 5 weeks (range: from 3 weeks to 24 months) after the final RIT. The AACE guidelines report that patients usually develop hypothyroidism within 3 months and that the median time is 12 months (range: 3-30 months) (11). Our results are in accord with these reports.

A few published studies have addressed the development of hypothyroidism in patients treated with I-131 for TMNG. These studies reported hypothyroidism rates that ranged from 8.4% to 47% (16-23). In the patients with a 1-year follow-up in the literature, the incidence of hypothyroidism ranged from 8.4% to 31.7% (16,18,19,22). Our hypothyroidism rate was 29% within 1 year. Although our rate is higher than the 6-month management period (8.9%-16%) given in the literature (18,19,21,22), our hypothyroidism rate is in a similar range as that given for 1 year. The possible reason for this discrepancy is that we used higher fixed doses in patients with TMNG when compared to the previously published studies (16-23).

The patients in our study group who developed euthyroidism and hypothyroidism had similar characteristics. This similarity facilitates our evaluation on the findings of Tc-99m pertechnetate scintigraphy prior to RAI treatment as a prognostic factor.

The level of extranodular thyroid tissue suppression has been investigated as a prognostic factor for the risk of hypothyroidism after I-131 treatment (15,16). No differences were demonstrated between the patients with euthyroidism and hypothyroidism with regard to the distribution of patients with partial suppression in our study. Complete or partial extranodular tissue suppression in patients with TMNG is not considered as an effective factor in the development of euthyroidism and hypothyroidism. The incidence of hypothyroidism following RAI treatment in patients with TMNG varies between 8.4% and 47% (16-23). However, the level of extranodular tissue suppression in the Tc-99m pertechnetate thyroid scintigraphy was not evaluated in these studies (16-23).

The main result of the present study is that Tc-99m pertechnetate mean net nodule counts of hot nodules in thyroid scintigraphy prior to radioiodine therapy in hypothyroid patients were significantly higher than in euthyroid patients. Reinhardt et al. (8) investigated patients with both diffuse toxic goiters and toxic nodular goiters using the calculated-dose method based on a tissue absorption dose increase, by the increasing values of TcTUs for I-131 dose calculations. The authors reported that the I-131 treatment success rates decreased in patients with high TcTUs values, suggesting that these results were due to the calculation of doses that were lower than the normally required doses, as related to the attenuation in patients with large goiters. The patients that reached the lower treatment success rates had hyperthyroidism that could not be treated by RAI. However, in our study, euthyroidism was accepted as a criterion for RAI treatment success, whereas the development of hypothyroidism was considered as an undesired result. According to our findings, we believe that patients with pretreatment high net nodule

counts may be predicted to develop hypothyroidism in an early period after RIT. Therefore, an I-131 dose of <740 MBq is suitable to reach euthyroidism status, rather than hypothyroidism, in the patients with high net counts of thyroid hot nodule(s). Further studies with a larger sample size are required to determine whether such an approach would increase treatment success rates.

In conclusion, the probability of developing early hypothyroidism following fixed-dose radioactive iodine treatment of TMNG may be predicted by the Tc-99m pertechnetate uptake level of hot nodules, determined by thyroid scintigraphy obtained prior to radioiodine therapy. However, evaluation in large series and calculation of the threshold value for routine clinical usage are necessary.

References

1. Kaplan MM, Meier DA, Dworkin HJ. Treatment of hyperthyroidism with radioactive iodine. Endocrinol Metab Clin 1998; 1: 205-23.
2. Bähre M, Hilgers R, Lindemann C, Emrich D. Physiological aspects of the thyroid trapping function and its suppression in iodine deficiency using ^{99m}Tc-pertechnetate. Acta Endocrinol (Copenh) 1987; 115: 175-82.
3. Emrich D, Erlenmaier U, Pohl M, Luig H. Determination of the autonomously functioning volume of the thyroid. Eur J Nucl Med 1993; 20: 410-4.
4. Reinhardt M, Emrich D, Krause T, Bräutigam P, Nitzsche E, Blattmann H et al. Improved dose concept for radioiodine therapy of multifocal and disseminated thyroid autonomy. Eur J Endocrinol 1995; 132: 550-6.
5. Oexle C, Reinhardt M, Moser E. First results of radioiodine therapy of multifocal and disseminated thyroid gland autonomy and use of a TcTUs-adapted dose concept. Nuklearmedizin 1998; 37: 192-6.
6. Reinhardt MJ, Högerle S, Trupkovic T, Krause TM, Moser E. Influence of urinary iodine excretion on thyroid technetium-99m pertechnetate uptake with and without TSH suppression: what happens when iodine supply increases? Eur J Nucl Med 1998; 25: 1475-81.
7. Meller J, Wisheu S, Munzel U, Behe M, Gratz S, Becker W. Radioiodine therapy for Plummer's disease based on the thyroid uptake of technetium-99m pertechnetate. Eur J Nucl Med 2000; 27: 1286-91.
8. Reinhardt MJ, Joe A, Mallek DV, Zimmerlin M, Manka-Waluch A, Palmedo H et al. Dose selection for radioiodine therapy of borderline hyperthyroid patients with multifocal and disseminated autonomy on the basis of 99mTc-pertechnetate thyroid uptake. Eur J Nucl Med 2002; 29: 480-5.
9. Reiners C, Schneider P. Radioiodine therapy of thyroid autonomy. Eur J Nucl Med 2002; 29: 471-8.
10. Gotthardt M, Nowack M, Behe MP, Schipper ML, Schlieck A, Hoffken H et al. Negative correlation between therapeutic success in radioiodine therapy and TcTUs: are TcTUs-adapted dose concepts the only possible answer? Eur J Nucl Med Mol Imaging 2003; 30: 1165-8.
11. Baskin HJ, Cobin RH, Duick DS, Gharib H, Guttler RB, Kaplan MM et al. AACE Thyroid Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocrine Practice 2002; 8: 457-69.
12. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009; 19: 1167-214.
13. Gharib H, Papini E, Valcavi R, Baskin HJ, Crescenzi A, Dottorini ME et al. AACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract 2006; 12: 63-102.
14. Sisson JC, Avram AM, Rubello D, Gross MD. Radioiodine treatment of hyperthyroidism: fixed or calculated doses; intelligent design or science? Eur J Nucl Med Mol Imaging 2007; 34: 1129-30.
15. Körber C, Schneider P, Körber-Hafner N, Hanscheid H, Reiners C. Antithyroid drugs as a factor influencing the outcome of radioiodine therapy in Graves' disease and toxic nodular goitre? Eur J Nucl Med 2001; 28: 1360-4.
16. Allahabadia A, Daykin J, Sheppard MC, Gough SCL, Franklyn JA. Radioiodine treatment of hyperthyroidism - prognostic factor for outcome. J Clin Endocrinol Metab 2001; 86: 3611-7.
17. Nygaard B, Hegedus L, Ulrihsen P, Nielsen KG, Hansen JM. Radioiodine therapy for multinodular toxic goiter. Arch Intern Med 1999; 159: 1364-8.
18. Franklyn JA, Daykin J, Holder R, Sheppard MC. Radioiodine therapy compared in patients with toxic nodular or Graves' hyperthyroidism. Q J Med 1995; 88: 175-80.
19. Danaci M, Feek CM, Notghi A, Merrick MV. 131-I radioiodine therapy for hyperthyroidism in patients with Graves' disease, uninodular goiter and multinodular goiter. N Z Med J 1988; 101: 784-6.
20. Berg G, Michanek A, Holmberg E, Nystrom E. Clinical outcome of radioiodine treatment of hyperthyroidism: a follow-up study. J Int Med 1996; 239: 165-71.

21. 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.

22. Ahmad AM, Ahmad M, Young ET. Objective estimates of the probability of developing hypothyroidism following radioactive iodine treatment of thyrotoxicosis. Eur J Endocrinol 2002; 146: 767-75.

23. Abós MD, Banzo J, Razola P, Garcia F, Prats E. Treatment with I-131 of toxic multinodular goiter. Assessment of a fixed dose protocol. Rev Esp Med Nucl 2000; 19: 182-6.