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ORIGINAL

Correlation of radioiodine doses for 6-hr and 24-hour iodine-131 thyroid uptake values for Graves' hyperthyroidism

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Abstract. The destruction of thyroid follicular cells by iodine-131 treatment for Graves' hyperthyroidism to a large extent depends on the amount of intrathyroidal activity absorbed (IAA). A thyroid weighing 50 g should receive an iodine-131 therapeutic dosage of between 110 MBq and 350 MBq for the effective treatment of Graves' hyperthyroidism. An IAA received of more than 350 MBq to the thyroid will bestow an unnecessary high iodine-131 therapeutic dosage. The objective of the study was to determine if the IAA would remain between 110 MBq and 350 MBq if the calculated administered activity (CAA) has been used with the highest radioactive iodine uptake (RAIU) value. A retrospective analysis was made of the 6- and 24-hr iodine-131 RAIU results of Graves' hyperthyroid patients (n = 124). Male (n = 18) and female (n = 106) patients from different racial groups and ranging from 15 to 75 years of age were included in the study. Overall, the CAA using the 6-hr RAIU value was higher. The CAA by the 6-hr RAIU values was used with the 24-hr RAIU values to calculate the IAA. 53.3% (n = 66) of the study group would have received IAA higher than 350 MBq when the CAA by the 6-hr RAIU values was used with the 24-hr RAIU values to calculate the IAA. These results suggested that the 24-hr RAIU value was most valuable for the calculation of an administered activity so that IAA of between 110 and 350 MBq can be achieved.

Key words: Graves' disease, Hyperthyroidism, Radioiodine therapy, Iodine-131 radioactive iodine uptake

THE MEASUREMENT OF RAIU by the thyroid gland for diagnostic purposes has been used as early as the 1940s [1-3]. Iodine-131 has a radionuclide nature to be both organified and taken up by the thyroid gland. These characteristics make it ideal for RAIU test use and therapy for Graves' disease in both adult and paediatric patients [4, 5]. Therefore, the RAIU of the thyroid not only reflects the early phase of thyroid hormonegenesis, but also reveals information about the overall function of the thyroid gland [6]. The iodine-131 thyroid uptake technique described by the International Atomic Energy Association (IAEA) was developed to standardise RAIU worldwide [7]. This technique has been used globally in the assessment of thyroid function and diagnostic testing [8]. The administered activity recommended by the IAEA for iodine-131 RAIU measurement should not exceed 0.37 megabequerel (MBq) iodine-131 [6]. The radiation exposure for iodine-131 to the thyroid is very high, namely 0.27–0.54 gray per megabequerel (Gy/MBq). Iodine-131 RAIU should thus be performed to (i) confirm the diagnosis of Graves' hyperthyroidism; and (ii) to calculate the administration activity for therapeutic dosage.

Treatment with iodine-131 is a beneficial option for Graves' hyperthyroidism, since it is safe, easy to use and yields good treatment results [9]. The calculation of the correct therapeutic administration activity for Graves' hyperthyroidism is important, because the destruction of thyroid follicular cells by iodine-131 to a large extent depends on the amount of intrathyroid activity absorbed (IAA). The maximum RAIU value is important for the calculation of the optimal iodine-131 therapeutic dosage to treat Graves' hyperthyroidism. In the case of euthyroid patients, the maximum RAIU in the thyroid occurs between 24 and 48 hours after administration [10]. With Graves' hyperthyroidism, the maximum RAIU in the thyroid may reach a peak earlier than 24 hours. Therefore, it has been suggested that an RAIU is taken at a relatively early stage after 4–6 hours, and also at 24 hours. The "rapid turnover" process of iodine was defined as a short effective half-life (T_{eff}) of iodine-131 in the thyroid

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[10]. In cases where "rapid turnover" occurs, it is necessary to increase the iodine-131 therapeutic dosage, as the 24-hr RAIU value would give a low uptake value compared to the 6-hr RAIU value. Therefore, if the 24-hr RAIU value is low, it would not indicate the peak of the turnover and lead to an undertreatment of the patient when the treatment dose is calculated. Undertreatment of Graves' hyperthyroidism with iodine-131 has the risk of recurrence of disease. The 6-hr RAIU value should be used to calculate the iodine-131 treatment dosage circumstances of "rapid turnover" of iodine-131 in the thyroid.

It has been proposed that the 24-hr iodine-131 RAIU value could be discarded and that the 6-hr RAIU value alone could be used to calculate the therapeutic dosage [1]. The scope of iodine-131 absorbed activity per gram (g) of thyroid tissue for the effective treatment of Graves' hyperthyroidism, according to the European Association of Nuclear Medicine (EANM), is from 2.2–3.0 MBq/g up to 6.0–7.0 MBq/g [11]. The conclusion that could be drawn, is that a thyroid weighing 50 g should receive an iodine-131 therapeutic dosage of between 110 MBq and 350 MBq for the effective treatment of Graves' hyperthyroidism. A patient with Graves' disease who receives an IAA of more than 350 MBq has been administered unnecessary iodine-131 therapeutic activity to the thyroid gland. It has not yet been determined whether only the 6-hr RAIU value alone is used if it falls within the most effective IAA required to treat Graves' hyperthyroidism, which must be between 110 MBq and 350 MBq [11].

Subjects and Methods

Subjects

The medical records of 178 patients with confirmed Graves' hyperthyroidism referred to the Nuclear Medicine Department at Universitas Academic Hospital in Bloemfontein, South Africa, over a two-year period were reviewed. Included in the study was the information of patients diagnosed with Graves' hyperthyroidism for the first time and treated with radioiodine therapy. Graves' hyperthyroidism was confirmed by the following factors: (i) suppressed thyroid stimulating hormone; (ii) elevated serum thyroid hormones (total T_4 and/or total T_3); (iii) a diffuse increased uptake of technetium-99-metastable-pertechnetate indicated of thyroid scintigraphy; and (iv) an increased 6-hr and 24-hr iodine-131 RAIU value.

Both male (n = 18) and female (n = 106) patients from different racial groups and ranging from 15 to 75 years of age were included in the study. Fifty-four patients were excluded. Patients were excluded when they were taking medication, which included atenolol (n = 1), carbimazole (n = 1), propranolol (n = 13) and thyroxine (n = 2), as these agents could have influenced the RAIU values. Patients with serious systemic disease, iodine contamination, thyroid nodules or other causes of hyperthyroidism were also excluded from the study. Only one patient had undergone magnetic resonance imaging (MRI) of the orbits with iodine contrast administration and was also excluded. From the 178 patients thirty-three patients were diagnosed with multi-nodular thyroid disease, one had Plummer's disease and one had Marine-Lenhardt syndrome and were therefore excluded upon evaluation of scintigraphy images. Two patients had lobes removed and one had toxic autonomic adenoma and were a to determine if the IAA would remain between 110 MBq and 350 MBq if the CAA has been used with the highest RAIU value (24-hr iodine-131 RAIU) also excluded.

The protocol was approved by the institutional review board of the Universitas Academic Hospital and the Ethics Committee of the Faculty of Health Sciences, University of the Free State. All research was conducted in accordance with the guidelines proposed in the Declaration of Helsinki.

The patients' 6- and 24-hr RAIU values were evaluated to determine how many patients had "rapid turnover" in their iodine-131 transit pattern. The highest RAIU value at either 6- or 24 hours would be the most effective to determine the correct iodine-131 therapy dosage for Graves' hyperthyroidism [12]. The transit patterns of the two RAIU values were also evaluated to determine which of the 6- or 24-hr RAIU values had the highest uptake. The most effective IAA required to treat Graves' hyperthyroidism should be between 110 MBq and 350 MBq [11].

The calculated administered activity (CAA) for the 6-hr RAIU values was compared to the CAA of the 24-hr RAIU values. The 24-hr RAIU value was indicated in the literature as in the majority of cases as the highest and also the preferred RAIU value to calculate the iodine-131 therapeutic dosage. The 24-hr RAIU values was therefore also used with the CAA of the 6-hr RAIU values, to determine if the IAA would still fall within the limits of 110–350 MBq [10]. The following equation was used and adjusted from the literature [13] to determine if the IAA would remain between 110 MBq and 350 MBq if the CAA has been used with the highest RAIU value (24-hr iodine-131 RAIU) [13]:

$$\text{CAA from iodine-131 RAIU value for 6-hr RAIU} = \frac{\text{Aimed IAA X 100}}{\text{\% (value) 24-h iodine-131 RAIU}}$$

Statistics

Results were summarised by means and standard devi-

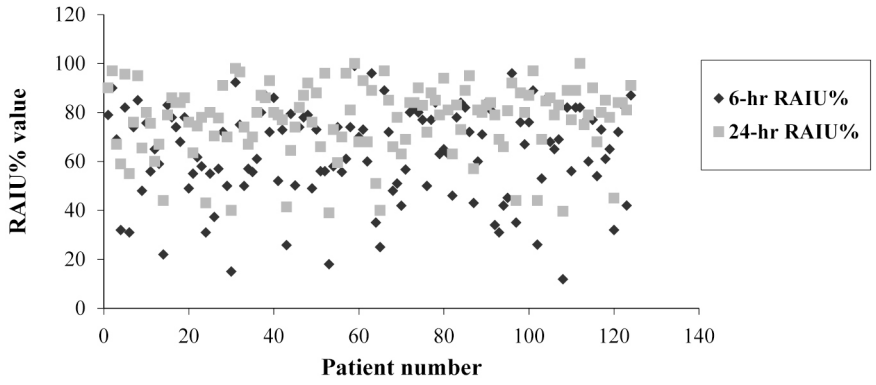

Fig. 1 6-hr and 24-hr iodine-131 RAIU values.

Distribution of the 6-hr (black diamonds) and 24-hr (grey squares) iodine-131 RAIU values for the subjects with Graves' disease. The 6-hr RAIU values apt to fall in the lower and higher percentage values, whereas the 24-hr RAIU values apt to fall only in the higher percentage range.

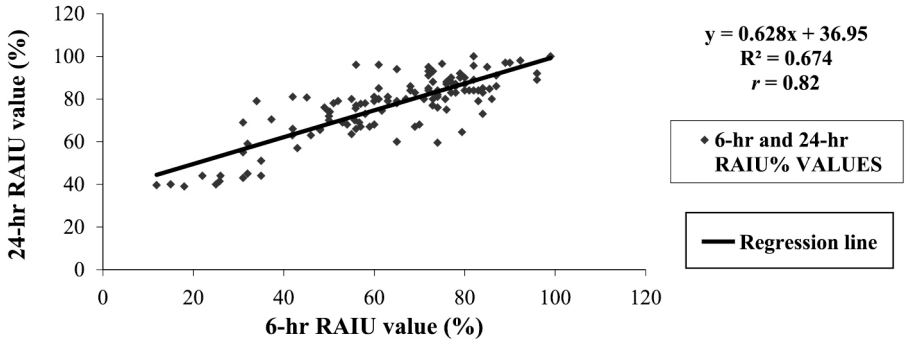

Fig. 2 Pearson's correlation between the 6-hr and 24-hr RAIU values.

The relationship between the 6-hr and the 24-hr iodine-131 RAIU was analysed by a Pearson's product-moment correlation (straight line). There was a strong positive correlation between the 6-hr and the 24-hr RAIU values (r = 0.82). No significant outliers were present.

ations or medians and percentiles for continuous data, and frequencies and percentages for categorical data. The 95% confidence intervals (95% CI) were calculated for the difference in mean and median values. The Pearson correlation coefficient was used to determine the correlation between different variables. A regression analysis between the 6-hr and 24-hr iodine-131 RAIU values was performed. The different transit patterns of patients with Graves' disease included in the study were also analysed. This analysis of the transit patterns was done to determine how many of these patients had rapid turnover of iodine in their thyroid glands.

Results

Comparison of 6- and 24-hr RAIU uptake values

Fig. 1 demonstrates the values for the 6- and 24-hr RAIU of the study group (n = 124). The 24-hr RAIU values tended to fall more in the higher percentage range, whereas the 6-hr RAIU values were between the lower and higher percentage values. The median of the 6-hr and 24-hr RAIU values was 67.5% (51.5–78%) and 80.0% (69–87%), respectively.

Results of the regression analysis that was done to determine whether there was any relation between the 6-hr and 24-hr RAIU values are shown in Fig. 2. A strong positive linear relationship was found between the 6-hr and 24-hr RAIU values, with a Pearson correlation coefficient of r = 0.82. A 5% or smaller difference between the 6-hr and 24-hr RAIU values was observed in only 11 (8.9%) of the 124 patients with Graves' hyperthyroidism.

Transit patterns

The 24-hr RAIU value was higher in 88.7% (n = 110) of the patients, compared to 14 (11.3%) patients with higher 6-hr RAIU values. A less than 5% value difference between the 6-hr and 24-hr RAIU values was observed in only 11 (8.9%) of the 124 Graves' disease patients.

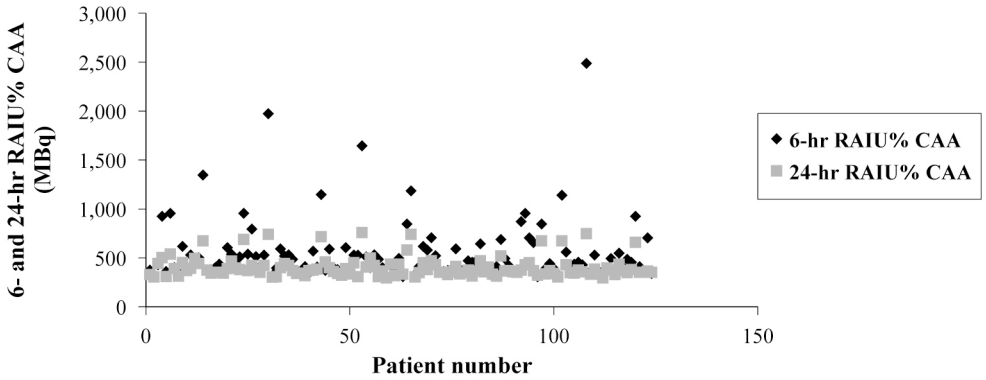

Fig. 3 CAA for 6-hr and 24-hr iodine-131 RAIU values.

Distribution of the CAA for the 6-hr (black diamonds) and 24-hr (grey squares) RAIU values. The CAA for the 6-hr RAIU values were dispersed in the higher ranges, whereas the CAA for the 24-hr RAIU values were in the lower ranges and distributed closer together.

Table 1 Summary of calculated administered activity (CAA) by the 6-hr and 24-hr radioactive iodine uptake (RAIU) values for the study group (n = 124)

Variable	6-hour RAIU (MBq)	24-hour RAIU (MBq)
Lower quartile	380.0	344.0
Median	438.5	370.0
Upper quartile	564.0	429.0
Minimum	299.0	296.0
Maximum	2,487.0	759.0

Table 2 Difference between the 6-hr and 24-hr radioactive iodine uptake (RAIU) calculated administered activity (CAA) values for the study group (n = 124)

Variable	Difference between 6-hr and 24-hr CAA (MBq)
Lower quartile	28.0
Median	76.0
Upper quartile	168.5
Minimum	–98.0
Maximum	1,739.0

Correlating the values of the 6-hr and the 24-hr CAA values

Fig. 3 represents the different values for the 6-hr and 24-hr RAIU CAA for the 124 patients with Graves' disease, showing that the 6-hr RAIU CAA values were much higher than the 24 hr RAIU CAA values. The 24-hr RAIU CAA values were distributed closer together, whereas the 6-hr RAIU CAA values were more widely dispersed. The 6-hr RAIU CAA had higher values compared to the 24-hr RAIU CAA.

Table 1 summarises the 6-hr and 24-hr RAIU CAA values of the patients in the study. The median 6-hr RAIU CAA value was 438.5 MBq (380.0–2487.0 MBq) while the median 24-hr value 370.0 MBq (344.0–759.0 MBq).

The results of the difference between the 6-hr and 24-hr CAA values are summarised in Table 2.

Intrathyroid absorbed activity

The calculated IAA results utilising the revised equation, where the 24-hr RAIU values were utilised with the CAA from the 6-hr RAIU values are graphically displayed (Fig. 4). Visual assessment of the IAA in Fig. 4 shows IAA above the recommended maximum of 350 MBq. Table 3 shows the statistical findings when the 24-hr RAIU value was used with the CAA from the 6-hr RAIU value. The minimum value for the IAA calculated when the 24-hr RAIU value was used with the CAA calculated from the 6-hr RAIU value, was 238 MBq, which was within the recommended range of 110–350 MBq. The maximum IAA on the other hand, was notably higher than the most effective IAA (985 MBq). The median for this specific calculated IAA was 357.5 MBq (321.5–985.0 MBq). Therefore, the median of the 24-hr value used with the CAA by the 6-hr RAIU value did not fall within the recommended range.

Fifty-eight (46.8%) of the patients with Graves' hyperthyroidism received IAA within the recommended range, while in the remaining 53.3% (n = 66) of patients, a higher IAA than the recommended range was administered when the 24-hr RAIU was used with the CAA calculated by the 6-hr RAIU.

Discussion

The thyroid gland takes up radioactive iodine up similar as natural iodine and has a high avidity for iodine [14]. Iodine-131 in not only "trapped" in the thyroid

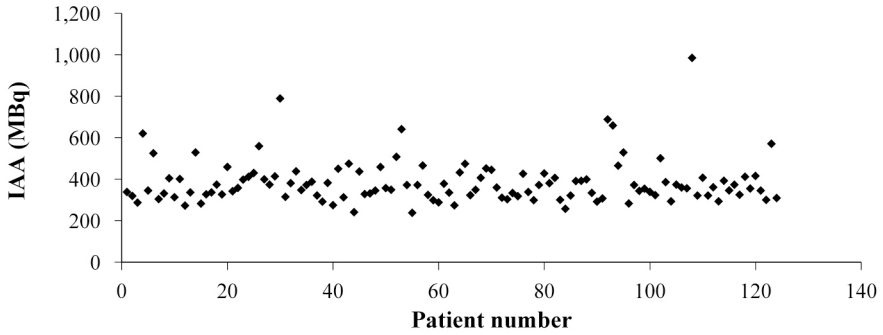

Fig. 4 IAA calculated with 24-hr RAIU and CAA for the 6-hr RAIU values.
The distribution of the 124 Graves' patients IAA calculated using the adjusted equation with the 24-hr RAIU and the CAA for the 6-hr RAIU values. Values above the maximum recommended IAA of 350 MBq is shown.

gland, but also gets organified and with the characteristic of being a long half-live radionuclide it is ideal for treatment also. Thus, iodine-131 has a dual purpose in the case of Graves' disease, firstly as part of diagnosis where it is administered as a low dosage as part of RAIU thyroid functional testing. Secondly, providing effective treatment of Graves' disease through its abilities not only to be "trapped in the thyroid gland, but also because it is organified in the thyroid cells. The amount of radioactivity taken up in the thyroid is proportional to the dose that will be received by the thyroid. Worldwide, different approaches to determine radioiodine administration doses for the treatment of Graves's hyperthyroidism are available. Clinical estimation, scintigraphic imaging techniques and ultrasound have been included in complex calculations to determine the thyroid size as part of different dose treatment techniques [15]. These various techniques can provide adequate dose, but the question may be, is the administered dosage patient-centered to ensure non-recurrence of disease in a specific patient and to ensure that unnecessary radiation dose is not delivered to the patient [16]. The optimal treatment for determining iodine-131 treatment doses remains a debatable topic. Even though it might be cost-effective to follow a one-day 131-iodine RAIU procedure, a patient can receive a higher administered dose than necessary. Each patient results of the 6- and 24-hr RAIU values obtained for this study, utilsed the "trapping" and organification functional properties of iodine-131 by the thyroid gland. Increasing the validity, reliability and accuracy of the results obtained. Our study reported that in 88.7% (n = 110) of the study group, the 24-hr RAIU value was higher than the 6-hr RAIU. Therefore, according to RAIU procedure values, only 11% of patients demonstrated "rapid turnover" of iodine in their thyroids. The transit patterns consequently demonstrated that the 24-hr RAIU value will be the most effective to determine the iodine-131 therapy dosage for Graves' disease in the majority of patients.

Table 3 Statistics of the intrathyroid absorbed activity (IAA) calculated for the study group (n = 124) when the 24-hr radioactive iodine uptake (RAIU) value was used with the calculated administered activity (CAA) of the 6-hr RAIU value

Variable	Intrathyroid absorbed activity (IAA) in MBq
Lower quartile	321.5
Median	357.5
Upper quartile	411.5
Minimum	238.0
Maximum	985.0

The CAA calculated from the 6-hr RAIU values were compared with the CAA calculated from the 24-hr RAIU values. The median of the CAA by the 6 hr RAIU values was higher than the median of the CAA by the 24-hr RAIU values (438.5 MBq and 370 MBq, respectively), with the most effective IAA being between 110 MBq and 350 MBq [11]. Van Isselt *et al.* [10] stated that the 24-hr iodine-131 RAIU is most effective to determine the CAA. Therefore, the 24-hr RAIU values were used with the CAA calculated by utilising the 6-hr RAIU values to determine if the IAA would still fall within the limits of 110–350 MBq, which yielded a minimum IAA value of 238 MBq. The maximum IAA of 985 MBq, on the other hand, was much higher than the most effective IAA. For these patients with Graves' hyperthyroidism, the median of the IAA calculated by the 24-hr RAIU values used with the CAA by the 6-hr RAIU (357.5 MBq), suggested that if the 6-hr RAIU was used for calculating the administration activity for the study group, the median of the IAA was higher than the recommended maximum value of 350 MBq [11].

Hayes *et al.* [1] hypothesised that the 24-hr iodine-131 uptake value could be predicted with a specific equation

in all patients to calculate the therapeutic radioiodine doses. Firstly, this equation did not take into account the "rapid turnover" of iodine in a small percentage of patients. Another important factor to consider is the IAA and to ascertain that it is within the recommended range proposed by the EANM [11], an international representative of nuclear medicine. This research concluded that the transit pattern was indicative of the 24-hr iodine-131 RAIU value being more accurate to determine the CAA for an IAA between 110 MBq and 350 MBq.

At a time when research-based practice is taking on an increasingly important role, it is essential for nuclear medicine departments with endocrinologists to make evidence-based recommendations for personalised treatment [17]. The investigation into the correlation between the 6-hr and 24-hr RAIU values to determine the administered dose for treatment of Graves' hyperthyroidism, clearly justified the cost spent for the patients' overnight stay required to calculate the 24-hr iodine-131 RAIU value. It should also be kept in mind that the higher the measurement of the iodine-131 RAIU value, the lower the therapeutic dosage needed to improve accuracy of treatment dose and decrease the radiation dose to the patient and cost of radioiodine treatment. The quality of the therapeutic dose administration procedure is therefore improved, as no estimation of iodine-131 therapeutic dose is made, and the treatment procedure is then disease-centred for a specific patient.

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Conflict of Interest

The author has no conflict of interest associated with this research.

References

1. Hayes AA, Akre CM, Gorman CA (1990) Iodine-131 treatment of Graves' disease using modified early iodine-131 uptake measurements in therapy dosage calculations. *J Nucl Med* 31: 519–522.
2. Meier DA, Kaplan MM (2001) Radioiodine uptake and thyroid scintiscanning. *Endocrinol Metab Clin North Am* 30: 291–313.
3. Bonnema SJ, Hegedüs L (2012) Radioiodine therapy in benign thyroid diseases: effects, eide effects, and factors affecting therapeutic outcome. *Endocr Rev* 33: 920–980.
4. Meier DA, Brill DR, Becker DV, Clarke SEM, Silberstein EB, *et al.* (2002) Procedure guideline for therapy of thyroid disease with ^{131}Iodine. *J Nucl Med* 43: 856–861.
5. Rivkees SA, Dinauer C (2007) An optimal treatment for pediatric Graves' disease is radioiodine. *J Clin Endocrinol Metab* 92: 797–800.
6. Early PJ, Sodee DB (1994) Principles and practice of nuclear medicine (2nd). Mosby, St. Louis, USA: 627–630.
7. Group of Consultants of the International Atomic Energy Agency (IAEA) (1962) The calibration and standardization of thyroid uptake measurements. *Phys Med Biol* 6: 533–540.
8. Braunwald E, Isselbacher KJ, Petersdorf RG, Wilson JD, Martin JB, *et al.* (1987) Harrison's principles of internal medicine (11th). Mc Graw-Hill, New York, USA: 1736–1745.
9. De Bruin TW, Croon CD, De Klerk JM, Van Isselt JW (1994) Standardized radioiodine therapy in Graves' disease: the persistent effect of thyroid weight and radioiodine uptake on outcome. *J Intern Med* 263: 507–513.
10. Van Isselt JW, De Klerk JM, Koppeschaar HP, Van Rijk PP (2000) Iodine-131 uptake and turnover rate vary over short intervals in Graves' disease. *Nucl Med Commun* 21: 609–616.
11. European Association of Nuclear Medicine (EANM) (2003) EANM Procedure guidelines for therapy with iodine-131. *Eur J Nucl Med Mol Imaging* 30: BP27–BP31.
12. Harbert J, Da Rocha AFG (1984) Textbook of nuclear medicine (2nd). Lea & Febiger, Philadelphia, USA: 9–35.
13. Alexander EK, Larsen PR (2002) High dosage ^{131}I therapy for the treatment of hyperthyroidism caused by Graves' disease. *J Clin Endocrinol Metab* 87: 1073–1077.
14. Wagner HN, Szabo Z, Buchanan, JW (1995) Principles of nuclear medicine (2nd). W.B. Saunders Company, Philadelphia, USA: 598–628.
15. Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, *et al.* (2003) A randomized comparison of radioiodine doses in Graves' hyperthyroidism. *J Clin Endocrinol Metab* 88: 978–983.
16. Mumtaz M, Lin LS, Hui KC, Mohd Khir AS (2009) Radioiodine I-131 for the therapy of Graves' disease. *Malays J Med Sci* 16: 25–33.
17. Day AJ, Yeh MW, Livhits MJ (2018) Surgery for hyperthyroidism lowers cardiovascular mortality compared with radioactive iodine. *Clin Thyroidol* 30: 15–17.