Abstract. Previous studies demonstrated that preparation with recombinant human thyroid-stimulating hormone (rhTSH) for thyroid remnant ablation results in lower extrathyroidal radiation compared to hypothyroidism. The results of 50 radioiodine therapies (RITs) under rhTSH, regarding iodine half-life, were evaluated and compared with 50 RITs performed on patients with hypothyroidism following thyroxine withdrawal. The patients were treated with 3700 MBq (100 mCi) of $^{131}$I. Forty-eight hours after RIT, patients were measured with a radiation detector at a 1-meter (m) distance for evaluation of the effective dose ($\mu$Sv/h). TSH and thyroglobulin (Tg) maximal values were also compared. rhTSH-stimulated patients had a significantly lower whole-body retention of $^{131}$I (8.5±7.3 $\mu$Sv/h), extrapolated from the measurements of the effective dose at a 1-m distance, compared to endogenously stimulated patients (13.6±8.1 $\mu$Sv/h; $p=0.001$). Furthermore, TSH mean and Tg median levels were significantly higher in the rhTSH-stimulated patients (89.9±15.3 mU/l and 7.7 ng/ml, respectively) compared to the hypothyroid group (59.2±25.1 mU/l and 3.3 ng/ml; $p<0.001$ and $p=0.003$, respectively). Compared to thyroid hormone withdrawal, the use of rhTSH prior to RIT was associated with significantly lower whole-body retention of $^{131}$I and with greater efficacy in reaching TSH levels greater than 30 mU/l, confirming data previously described.

Introduction

Differentiated thyroid cancer comprises the majority of thyroid malignancies (approximately 95%). Papillary thyroid cancer (PTC) accounts for 85% of differentiated thyroid cancers, and follicular thyroid cancer (FTC) for 10%. Total thyroidectomy is the initial treatment for the majority of patients with differentiated thyroid cancer. Postoperative remnant ablation with $^{131}$I is indicated for all patients with stage 3 and 4 disease and for some patients with stage 1 and 2 disease (1). It supplements surgery by destroying normal thyroid remnants, thus increasing the sensitivity of subsequent $^{131}$I whole-body scanning, and of serum thyroglobulin (Tg) measurements in detecting persistent or recurrent disease. It also destroys microscopic neoplastic tissue, decreasing the long-term recurrence rate (1-3).

Remnant ablation requires TSH stimulation. This may be accomplished by withdrawing thyroid hormone treatment or by using recombinant human thyroid-stimulating hormone (rhTSH). These approaches have been approved for ablative therapy and diagnostic purposes (1).

Certain studies have found that the two methods are equally effective in preparing patients for $^{131}$I remnant ablation, with a greater quality of life achieved when rhTSH is used (4-6). Other authors demonstrated that the use of rhTSH is associated with a significant decrease in whole-body irradiation (7-12), which may be relevant with regards to the radiation exposure of the general population. The amount of $^{131}$I retained depends on factors such as the presence of metastatic disease, hydration level, bowel functioning, pre-therapeutic diet and renal clearance (9). The preserved renal clearance in patients prepared with rhTSH should explain the lower whole-body retention in these individuals, since it is known that renal clearance of $^{131}$I is reduced to approximately 50% in hypothyroid patients (13).

We retrospectively evaluated 100 patients submitted to postoperative remnant ablation with $^{131}$I. Of those, 50 patients were prepared with thyroid hormone withdrawal and 50 patients were prepared with rhTSH, with particular emphasis on the whole-body retention of $^{131}$I, extrapolated from the measurements of the effective dose at a 1-meter (m) distance.

Materials and methods

The study was approved by the ethics committee of the hospital. A total of 100 randomly selected patients, submitted to post-
operative remnant ablation with \(^{131}\)I at the Portuguese Oncology Institute of Lisbon (Portugal) in 2008, were evaluated retrospectively. The patients had undergone a low-iodine diet, and those with positive anti-Tg antibodies, <18 years of age or with impaired renal function (estimated by the creatinine blood level) were excluded.

Of the 100 patients, 50 were prepared with thyroid hormone withdrawal (hypothyroidism group): levothyroxine (LT\(_4\)) was discontinued and switched to triiodothyronine (LT\(_3\)) for 6 weeks, followed by LT\(_3\) withdrawal for 2 weeks prior to ablation. The remaining 50 patients were prepared with rhTSH (rhTSH group): rhTSH 0.9 mg was administered intramuscularly in the 2 days prior to ablative therapy.

Data on the maximal TSH and Tg levels were collected. Radioiodine therapy (RIT) regimen comprised 3700 MBq (100 mCi) of \(^{131}\)I and administered \textit{per os} to all patients. None of the patients were submitted to diagnostic radioiodine scanning prior to ablative therapy.

The whole-body retention of \(^{131}\)I was extrapolated from the measurements of the effective dose at 1 m between the probe and the patient, as recommended in the ATA guidelines (14). The probe was a whole-body counter, model TAM/S Single Area Monitor, from Tema Sinergie (Faenza, Italy).

\textbf{Statistical analysis.} Data are reported as the means ± SD. The differences between groups were tested for significance using the Student's t-test, Mann-Whitney test and \(\chi^2\) test, where appropriate. \(P<0.05\) was considered to indicate a statistically significant difference.

\section*{Results}

Demographic characteristics did not vary significantly between the two groups (Table I).

The whole-body retention of \(^{131}\)I, extrapolated from the measurements of the effective dose at 1 m, was significantly lower in the rhTSH group at 8.5±7.3 \(\mu\)S/h versus 13.6±8.1 \(\mu\)S/h in the hypothyroid group (\(P<0.001\;\text{Fig. 1}\)).

All rhTSH-stimulated patients reached TSH >30 mU/l (Fig. 2). Mean maximal TSH values were significantly higher in the rhTSH group at 89.9±15.3 mU/l versus 59.2±25.1 mU/l in the hypothyroid group (\(P<0.001\)).

Maximal Tg values were also significantly different between the two groups (\(P=0.003\)) with a median of 7.7 ng/ml in the rhTSH group versus 3.3 ng/ml in the hypothyroid group (Fig. 3). Undetectable Tg levels were present in 20 cases (40%) in the hypothyroid group and in 11 cases (22%) in the rhTSH group (\(P=0.05\)).

\section*{Discussion}

Preparation for RIT following hormone withdrawal is usually well tolerated but may be harmful in a subset of patients (6,7,15), such as the elderly, patients with cardiac dysfunction or patients with psychiatric conditions. Other individuals, including those with hypopituitarism, may be unable to endogenously raise TSH. In these circumstances the use of rhTSH is advisable.

There is general agreement that rhTSH administration provides a better quality of life. One of the major drawbacks for
its more generalized use is its cost (16). Although it is believed that it can be counterbalanced by improved productivity and reduced work absenteeism when hypothyroidism is avoided (17,18), its exact economic impact is difficult to ascertain (19).

Our primary goal was to evaluate the whole-body retention time of $^{131}$I, extrapolated from the measurements of the effective dose at a 1-m distance, associated with each strategy of preparing patients for postoperative remnant ablation with $^{131}$I. We found lower whole-body retention of $^{131}$I in the rhTSH group. Our results, regarding whole-body retention of $^{131}$I and maximal TSH values reached, support previously reported data (5,10-13,20).

Although it was not our primary objective, the comparison of peak Tg levels between groups demonstrated that the levels were significantly higher in the rhTSH group. There are several possible explanations for this finding. One is that TSH levels in the rhTSH group are higher than in the hypothyroid group, which clearly stimulates the release of Tg by the remaining thyroid tissue. Another reason is that the acute stimulation obtained with rhTSH releases Tg stored in thyroid cells, whereas a more chronic TSH stimulation, as obtained with thyroid hormone withdrawal, gradually depletes the pool of stored Tg. A previous study has also documented higher Tg levels with rhTSH preparation compared to those of hypothyroidism (12), although it was interpreted as a consequence of the more aggressive tumor subtypes in the group of patients prepared with rhTSH. This is not the case in our study, since no differences were observed in TNM staging between the two groups (data not shown).

The safety of rhTSH use for diagnostic and ablative purposes has been well documented (16,21). The question of whether the sudden increase in TSH resulting from rhTSH administration may lead to tumor expansion (10) in patients with occult metastatic disease, or whether the more prolonged TSH stimulation related to hypothyroidism is more life-threatening, remains to be resolved. Although studies have been carried out to address the efficacy and safety of rhTSH in metastatic disease (22,23), its use has not yet been approved for this purpose.

In conclusion, in our series, the use of rhTSH in the preparation of patients for postoperative remnant ablation with $^{131}$I was associated with lower radioiodine toxicity and with greater efficacy in achieving the desirable TSH level (>30 mU/l). However, the use of rhTSH was also associated with greater Tg levels and an undetectable Tg level was more frequently found in the hypothyroid group (40%) as compared to the rhTSH group (22%; p=0.05). Since an undetectable Tg level at the time of postoperative $^{131}$I remnant ablation generally reflects complete remission (24-26), patients treated with rhTSH who do not have undetectable Tg levels when treated with $^{131}$I may not be regarded as disease-free. Therefore, we believe that clinicians should not disregard the possibility of complete tumor eradication in patients presenting with low, but not undetectable, Tg levels at the time of ablation with rhTSH.

References


