The Gulf Journal of Oncology

Indexed By PubMed and Medline Database

Issue 45, May 2024
ISSN No. 2078-2101





Tafaul-Al-Ahsa Cancer Foundation Wins EXCELLENCE AWARD for Cancer Awareness Initiatives at Gulf Cancer Awareness Week 2024





The Gulf Oncology Society meeting resulted in fruitful outcomes, with young doctors showing keen enthusiasm for assuming leadership roles and implementing impactful initiatives.

The Official Journal of the Gulf Federation For Cancer Control

Table of Contents

Original Articles

Comparison of Acute Toxicities, Overall Treatment Time and Quality of Life in Head and Neck Cancer Patients Treated with IMRT and Helical Tomotherapy **07**
Yashaswini B R, Kumara Swamy, Chundru Swaroopa, Vikram Maiya

Assessment of Radiation Induced Pneumonitis and Pericarditis in Patients Undergoing Breast Conservative Treatment Using Hypofractionated Simultaneous Integrated Boost Technique **15**
Senthamizhan Sundaramoorthy, Gunaseelan Karunanidhi, Pravati Pal, Sunitha.V.C, Hanumitha Radhakrishnan

Histopathological Study of Breast Cancer at the Oran University Hospital Center on a Population from Western Algeria **30**
F.Z.Boussouf, A.Medjdoub, Z.Tahari, F.Z.Tahari, H.Ouldcadi, S. Seddiki, T.Sahraoui.

Assessing Mismatch Repair Expression by Immunohistochemistry in Colorectal Adenocarcinoma –Insight from a Tertiary Care Centre **35**
Rachana Lakhe, Rajeev Doshi, Preeti Doshi, Amrutraj Patil, Ravindra Nimbargi

Cost of Healthcare Services in Geriatric Neuro–oncology: A descriptive Analysis **42**
Zainab Saif Al–Siyabi, Omar Al–Mahrouqi, Osama Al–Senani, Suha Al–Amri, Zainab Al–Ajmi, Anfal Al–Nazwani, Fatema Taheri, Hashim Al–Hashimi, Mallak Al–Sheriyani, Mustafa Talib Al–Ani, Shima Al–Shamli, Salim Al–Abri, Tariq Al–Saadi

Establishing and Monitoring an Effective Management of Benign Nontoxic Multinodular Goitre in Kuwait "Utilizing Two Different Dose Levels of Recombinant Human TSH in Combination with Radioactive Iodine" **49**
Iman Al–Shammeri, Michael Masoomi, Nael Al–Shammeri, Fawaz Al–Abdali, Amna Al–Shagooli

Laparoscopic Versus Open Surgery for Colorectal Cancers: Clinical and Pathological Outcomes from a Single Institution in Bahrain **64**
Khaled Nazzal, Layla Hasan, Asma Alqaseer, Hussain A. Abdulla, Aalaa S. Majed, Mohamed A. Abushwemeh, Esra S. Salman, Mohamed Arafa, Ahmed Jawad

Clinical Outcomes and Dosimetric Evaluationof Interstitial Brachytherapyin Gynecological Malignancies **69**
NV Vinin, Adarsh Dharmarajan, Joneetha Jones, EK Nabeel Yahiya, Geetha Muttath, Nayan Sneha

Review Article

Epidemiological, Diagnostic and Therapeutic Aspects of Hepatocellular Carcinoma in Morocco: A Case Series and Review of Literature **75**
Imane Zouaki, Adil Aiterrami, Zouhour Samlani, Sofia Oubaha, Khadija Krati.

Case Report

Polycythemia Vera Masked by Megaloblastic Anemia **91**
M. Loukhnati, K.Khalil, FE. Lahlimi, I.Tazi

Managing Inconsistent Bladder Volumes in the Prostate Cancer Patient Using Daily Online Adaptive RT: A Case Report **94**
Venkada Manickam Gurusamy, Yoganathan Sullimullur Arunachalam, Mohamed Riyaz Poolakundan, Sarah Fiona Mc Cabe, Rabih Wafiq Hammoud, Noora Al–Hammadi

Special Review

Evaluating Primary and Secondary Prevention Interventions for Oral Cancer: Insights from the IARC Handbooks on Cancer Prevention Volume 19 Volume 19, Oral Cancer Prevention **100**
Samar Alhomoud

Conference Highlights/Scientific Contributions

• **News Notes** **102**

• **Advertisements** **107**

• **Scientific Activities** **108**

Original Article

Establishing and Monitoring an Effective Management of Benign Nontoxic Multinodular Goitre in Kuwait "Utilizing Two Different Dose Levels of Recombinant Human TSH in Combination with Radioactive Iodine"

Iman Al–Shammeri[1], Michael Masoomi[1,5], Nael Al–Shammeri[2], Fawaz Al–Abdali[3], Amna Al–Shagooli[4]

[1]Nuclear Medicine Department, Adan Hospital, Ministry of Health, Kuwait
[2]Department of Surgery, Adan Hospital, Ministry of Health, Kuwait
[3] Department of Endocrinology, KOC, Kuwait
[4] Department of Endocrinology, Adan Hospital, Ministry of Health, Kuwait
[5]Deprtment of Research and Innovation, Portsmouth University Hospital, UK

Abstract

Introduction: rhTSH–assisted radioiodine therapy of multinodular goiter is not fully known and only a few studies, with a limited number of patients have evaluated the effect of rhTSH assisted radioiodine therapy beyond 1 year. Though there is an effective and safe management of benign non–toxic MNG available, it is not applicable to all patient categories in Kuwait covering the impact of the past environmental events (Gulf War) and the genetic relation. The proposed project aims to address those points raised, that is exclusive to the Kuwait population.

Materials and Methods: In this cohort study, 2 groups of patients, group one (G1) and group two (G2) patients (N=50, ≥18 years old) went undergo evaluated according to a proposed criteria followed by FNA to exclude cancer, toxicity and those who have refused surgery. All patients had a CT scan, TSH, T3, T4 and CBC and complete biomedical tests at a 6–months interval during the treatment period and the follow up. The Volumetric application of GE 670 SPECT/CT (i.e. Xeleris) and in–house developed MATLAB used for quantitative measurement. All patients had a 131–I uptake at baseline and 24 intervals post intramuscular a single dose of 0.3mg or 0.1mg (group 1, group 2) of rhTSH.

Results: There was no significant difference in TSH levels at 24–month follow–up between the two groups (p=0.327), whereas there was a statistically significant difference at the baseline and at the 6–months interval between the 2 groups for T4. Post treatment follow up at the 24–hour time point, Group 1 displayed significantly higher uptake than Group 2 (G1:41.74 ± 6.27 vs. G2:34.80 ± 3.84, $p < 0.001$). The change in I131 uptake from baseline to 24 hours was significantly greater in Group 1compared to Group 2 ($p < 0.001$). The ROC analysis (AUC) post treatment indicated an excellent discriminatory power for AUC (0.960) and ($p < 0.001$). There was a much better correlation post–treatment between BMI and thyroid volume for group 1 ($R^2=0.661$) than for group 2 ($R^2=0.008$). Our results suggest 42.1% thyroid volume reduction for group 1 and 20% for group 2.

Conclusion: The study underscores the potential benefits of the higher rhTSH dose (0.3mg) in managing multinodular non–toxic goiter for the Kuwaiti population and the region considering the impact of dietary, and experience to the drastic environmental exposure.

Keywords: Radioiodine treatment, Multinodular goitre, recombinant human TSH, effective management of NTMNG

Introduction

Benign nodular thyroid disease constitutes a heterogeneous thyroid disorder, which is highly prevalent in iodine–deficient areas. On a very general basis, it can be divided into solitary nodular and multinodular thyroid disease. Histologically, benign thyroid nodules are distinguished as 1): encapsulated lesions (true adenomas) or adenomatous nodules, which lack a capsule; and

Corresponding author: Iman Al–Shammeri, MD KBNM, Nuclear Medicine Department, ADAN Hospital, Kuwait. Email: imss6464@gmail.com

2): by morphological criteria according to the World Health Organization (WHO) classification [1]. On functional grounds, nodules are classified as either "cold," "normal," or "hot" depending on whether they show decreased, normal, or increased uptake on a nuclear medicine scan. Approximately 85% of all nodules are cold, 10% are normal, and 5% are hot [2– 3], although the prevalence may vary geographically with the ambient iodine supply.

MNG refers to an enlargement of the thyroid with deformation of the normal parenchymal structure by the presence of nodules. These nodules vary considerably in size, morphology, and in areas without endemic goiter, MNG is often referred to as a sporadic nontoxic goiter. MNG usually develops in an already enlarged thyroid, independent of the cause of hyperplasia**.** Over time (sometimes decades), many MNGs enlarge further, and some develop subclinical hyperthyroidism and subsequently present as TMNG [4–6]. The main epidemiological determinants for the development of MNG and TMNG are iodine deficiency, age, sex, and duration of goiter in iodine–deficient [7–8] as well as in iodine–sufficient areas. It is widely accepted that the basis for the development of nodular structures is an early stimulus that causes enlargement of the thyroid. However, clinical manifestations of MNG might only appear over a long period of time (sometimes up to 30+ years). In general, the development of MNG proceeds in two phases: global activation of thyroid epithelial cell proliferation (e.g. as the result of iodine deficiency or other goitrogenic stimuli) leading to goiter, and a focal increase of thyroid epithelial cell proliferation causing thyroid nodules. So far, the most common stimulus for local proliferation is somatic mutations.

The expression of the progressive and the nodular increase of the thyroid in non–toxic benign goiters are the results of a combination of genetic and environmental factors, of which iodine deficiency is the most important [9]. Iodine deficiency is by far the best studied epidemiological risk factor for nodular thyroid disease. The prevalence of nodular thyroid disease (as well as goiter) is inversely correlated with the population's iodine intake. This has formerly been assessed clinically by palpation, nowadays considered highly inaccurate [10–11], but is also clearly documented by thyroid ultrasonography. Screening has been performed for other "environmental factors" [12] and smoking has been proposed as a risk factor for goiters, and nodules were found with higher prevalence in goiters of smokers compared with nonsmokers.

Several studies suggest that thyroid volume is also significantly correlated with body weight and body mass index. In agreement with this, a recent study has shown that in obese women, weight loss of more than 10% may result in a significant decrease in thyroid volume. Nodular disease is more frequent (5– to 15–fold) [13] in women, but the reasons for this are poorly understood. At present, one can only speculate as to a genetic susceptibility for thyroid disease and/or a direct impact of steroid hormones. In fact, a growth promoting effect of estrogen has been described in vitro in rat FRTL–5 cells and thyroid cancer cell lines and has been proposed as a possible contributing, constitutional effect of gender [14]. Radiation is another environmental risk factor not only for thyroid malignancy but also for benign nodular thyroid disease. An increased prevalence of nodular disease has been associated with exposure to radio nuclear fallouts and therapeutic external radiation, and this theory is being discussed by some authors to explain occupational exposure to low–level radiation [15]**.**

The treatment of benign NTG is a challenge for clinicians and endocrinologists. Similarly, to how patients with single thyroid nodules are assessed. All individuals with benign non–toxic goiter must undergo careful evaluation with serum TSH measurement and thyroid ultrasonography to guide the selection of the nodule (or nodules) to be biopsied. After exclusion of malignancy, treatment should be considered for individuals with compression of local structures, cosmetic concerns, and/or thyroid hyperfunction. The choice of treatment in patients with benign non–toxic goiter can be challenging, considering that the size of the goiter and the occurrence of symptoms often follow a nonlinear association. The ideal treatment for MNG is controversial, in part due to the variation in the natural history of these goiters. Some patients present an enlargement in goiter size with time along with the development of nodules, symptoms of compression, and cosmetic reasons**.** In contrast, the enlargement of the goiter may become stable or reduce spontaneously with time in around 20% of the women and 5% of the men [16]. There is still no consensus regarding the treatment of nontoxic MNGs. Hence, its optimal management remains controversial; possible therapies include levothyroxine (LT4), the medical treatment, decompression surgery, and radioactive iodine (131–I).

The efficacy of 131–I therapy on the multinodular goiter is hampered by the irregular 131–I uptake in the gland, the low iodine uptake, and the relative goiter reduction is inversely correlated with the initial goiter size**.** The number of suppressed nodules and the extent of degenerated tissue probably set an upper limit for the obtainable reduction with this treatment. Low isotope accumulation in inactive and partially suppressed areas around the nodule is a limitation of radioiodine treatment in patients with MNGs. This problem may be solved by increasing the radioactive iodine uptake (RAIU) in such

nodular goiters. For this purpose, recent studies using rhTSH (Thyrogen) in preparation for radioiodine therapy have shown good results [17]. Several studies have assessed the adjuvant role of rhTSH in the radioiodine treatment of NNG. Administration of rhTSH is associated with a twofold to fourfold increase in RAIU by the thyroid. In fact, rhTSH has been shown to distribute the radioiodine more homogeneously in the goiter, allowing a decrease in the dose of radioiodine to be administered. Most studies analyzing rhTSH in this setting have used fixed doses of radioiodine ranging from ~14 to ~42 mCi [18] and treatment with one or two rhTSH doses ranging from 0.1 to 0.3 mg administered 24 h prior to the radioiodine. It has been reported that the optimal dose of rhTSH in the context of 131–I therapy for nontoxic MNG remains to be established and the dose with ideal efficacy and safety is yet to be defined [19]. A few studies, including a limited number of patients have evaluated the effect of rhTSH–stimulated 131–I therapy beyond 1 year with conflicting results. During the Gulf war, Kuwaiti populations experienced a fall out of depleted uranium, smoke and chemical pollution released by the continuous oil–well fires, pesticides and insecticides and widespread distribution of toxins in the environment [20]. Radioiodine (131–I) therapy of nontoxic goiter, in most but not all studies, has demonstrated an inverse relationship between goiter reduction and the pretreatment thyroid volume, despite the application of similar thyroid doses [21]. Such a correlation seems logical because the relative amount of degenerated fibrous tissue and hibernating thyrocytes –not being affected by radiation to any greater extent—probably increases with goiter size. A quantitative analysis of how the amount of degenerated thyroid tissue affects the goiter reduction after 131–I therapy remains to be performed. Ahmadi area in Kuwait which accommodates over 1,000,000 inhabitants, has many patients with nontoxic MNG who are visiting ADAN hospital (i.e. most patients are women).

Materials and Methods

In this cohort study, patients were referred mainly from the endocrinology and surgery departments at the Adan Hospital. Patients were Kuwaiti individuals with benign non–toxic goiter who underwent careful evaluation (serum TSH measurement, thyroid ultrasonography followed by FNA as it may require) to exclude cancer, toxicity and those who had refused surgery. We proposed to study 50 patients (male and female of 18 years old and over) based on a power calculation having a confidence interval of 10% (margin of error) and confidence level of 90%. All patients provided written informed consent prior to participating in the study. The patient information sheet detailed the procedures involved and were explained to each patient by the investigator. The chart, (Table 1), describes the patient selection and management of the non–toxic MNG. This study is focusing on the application of multi–dose THYROGEN™ plus radioactive iodine in non–toxic MNG to assess its effectiveness and the optimal management proposal. Thyrogen (thyrotropin Alfa for injection) is a heterodimeric glycoprotein produced by recombinant DNA technology. It has comparable biochemical properties to human pituitary thyroid stimulating hormone (TSH). Binding of thyrotropin Alfa to TSH receptors in normal thyroid epithelial cells or on well–differentiated thyroid cancer tissue stimulates iodine uptake and organification, and synthesis and secretion of thyroglobulin (Tg), triiodothyronine (T_3) and thyroxine (T_4). Patients were divided into 2 groups, G1 and G2, and enrolled in the groups randomly, receiving 2 different single doses (0.3 and 0.1 mg) of rhTSH via intramuscular injections 24 hours prior to administration of therapeutic radioactive iodine (131–I).

All patients had CT scan prior to their treatment to assess the size and extension of the thyroid gland, to exclude retrosternal thyroid and compression of goiter. US scan also performed to exclude cancerous nodules (in conjunction with FNA), at the early stage and throughout the treatment and follow–up. The laboratory tests, including TSH, T4, routine tests (CBC and complete biomedical), as well as thyroid scan and uptake at 6–month intervals, were performed for the patients during the treatment period and the follow up to 2 – year period. A neck and a body phantom were acquired as complementary to ascertain the viability and accuracy of the adopted procedure for the quantification. The Atomlab 960 Medical Spectrometer Gamma Probe using a 1024 multi–channel analyzer and a single 5 cm thick NaI scintillation crystal were used to perform thyroid uptake measurement. The sensitivity of the system was measured to be 2106 C*min–1*µCi–1.

For 99m–Tc quantitative measurement, we used the available "Volumetric Application" that was available in our GE 670 SPECT/CT processing station, i.e. Xeleris. We utilized an International Electrotechnical Commission (IEC) body phantom with spherical inserts to obtain the calibration factor for quantification. All acquired SPECT data were reconstructed using an OSEM algorithm with attenuation and scatter correction based on the CT data. The system calibrations were calculated to be 168C*min–1*µCi–1and 300 C*min–1*µCi–1 for the imaging system (GE Discovery 670) in a static and SPECT mode using a LEHR collimator and 128x128 matrix. In addition, we used voxel–based quantitative and qualitative methods the Sante 64 bits DICOM file information and Matrix Laboratory (MATLAB) software in parallel to the above. MATLAB is a multi –paradigm numerical computing environment and proprietary programming language which offers simple

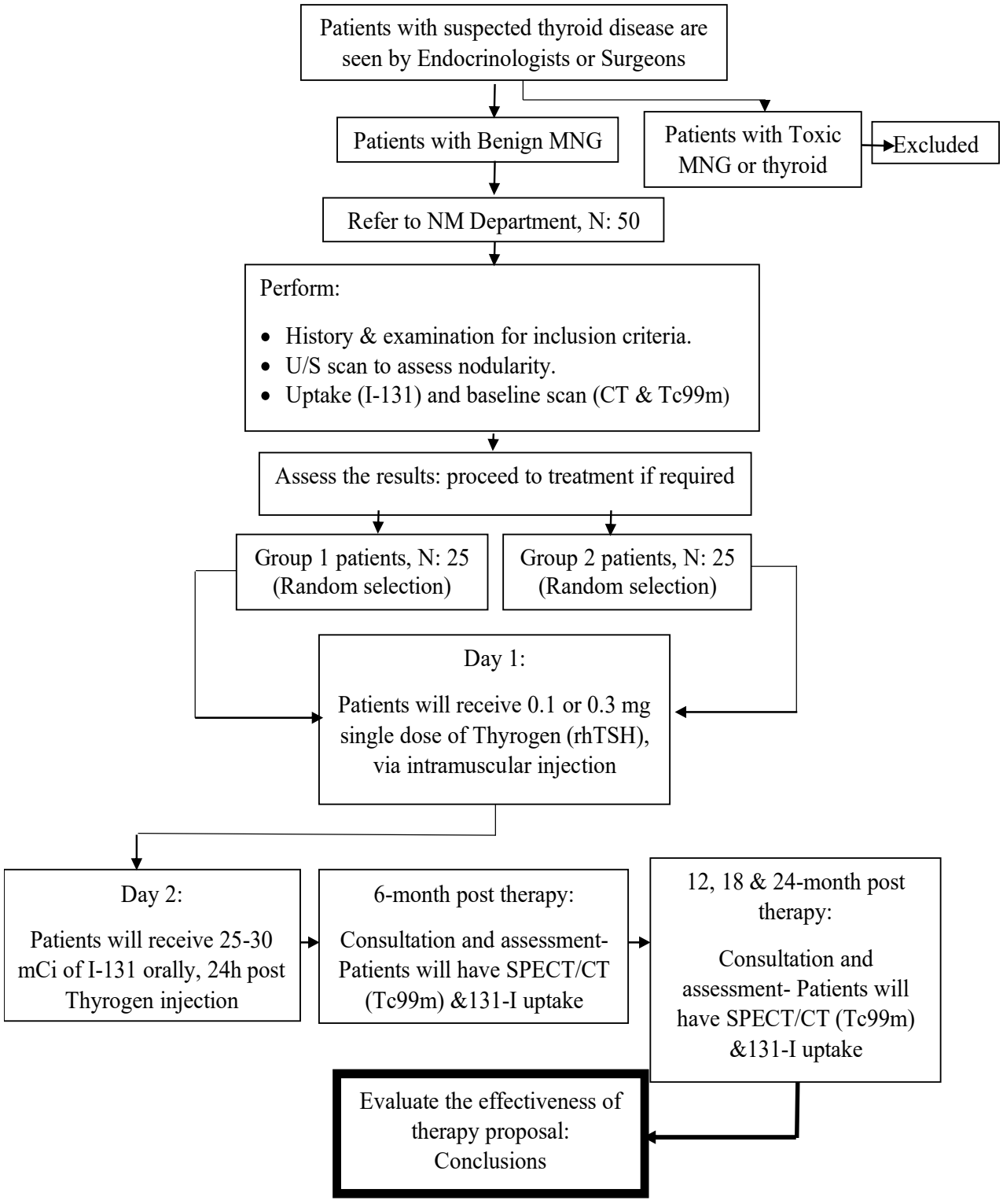


Table 1. Methodology Chart (Patient Selection and management)

functions that can read images of many file formats and supports several color maps. Thyroid ^{99m}Tc scan uptake ranges (0–4%) and 131–I uptake (15–35%) was considered normal. The radiation exposure mainly affects the thyroid. The radiation exposure of the other organs is in the range of thousandths lower than that of the thyroid. However, the dose–response relationship is very complex and involves adaptive processes that differ between *in vivo* and *in vitro* conditions [22]. We used Organ Level Internal Dose Assessment/Exponential Modeling (OLINDA/EXM), to calculate thyroid radiation doses from administered radioactive 131–I [23].

Patient preparation:

After exclusion of malignancy and toxicity, treatment was considered for individuals with compression of local structures and cosmetic concerns. All relevant clinical history was obtained on attendance, including thyroid medication, investigations with contrast media, other relevant medication, including Amiodarone, Lithium, kelp, previous surgery, and diet (patient must not eat shellfish on the day of, or the day prior to the appointment). We made sure that all other relevant investigations are available, including results of thyroid function tests (TFT), CBC and ultrasound examinations. Patient weight and blood pressure was noted down. The following medication will have an impact on 131–I uptake and were noted as part of obtaining a clinical history of an individual: a): Adrenocorticosteroids, Bromides, Butazolidin, methimazole (Tapazole), Nitrates, Perchlorate, Propylthiouracil, Salicylates (large doses), Sulfonamides, Thiocyanate stopped for a period of 1 week, b): Triiodothyronine (Cytomel) and Thyroid extract (Synthroid & Proloid) were stopped for a period of 2–3 & 4 weeks, respectively, c): Intravenous contrast agents, Oil–based iodinated contrasts and Amiodarone were stopped for the period 1–2 and 3 to 6 months, respectively. All patients who met the following categories were included in the study: a): Those over 18 years old who had contraindication for surgery or were reluctant to have surgery, b): Those whose medical condition(s) were not affected by the intended practice, c): Those who have had fast–growing goiter with obstructive symptoms, d): Those women who were not pregnant or lactating and children, e): Those with no malignancy and no toxic MNG.

Data acquisition:

All patients had SPECT/CT imaging on a GE 670, 16–slice SPET/CT scanner (GE Medical Systems, Milwaukee, Wisconsin, USA). Standard daily and weekly quality control procedures were performed before imaging. A dose of 120 MBq ^{99m}TC (planar) and 185 MBq ^{99m}TC (SPECT) were measured and administered via intravenous injection. Static or SPECT/CT images of patients were taken 20 min post injection. Patients were positioned in a supine position on the scanner and immobilized to ensure minimal movement. A 5 min static image (AP, PA and lateral), 128x128 acquisition matrix, and LEHR, of the thyroid, were acquired 20 min after injection. SPECT/CT images were acquired under a proposed clinical imaging condition (60 projections, 20s per projection, total angular rotation 360°, 6° per view, without the body contour option and 128×128 acquisition matrix, LEHR). The SPECT data were reconstructed using an OSEM algorithm, 2 iterations and 10 subsets, with attenuation and scatter correction based on the CT data (120Kvp and 170 mAs, with spiral pitch of 1.37 and 2.5mm pixel thickness). Quantification was carried out as per earlier description. All patients had a radioiodine uptake at baseline and 24 intervals post intramuscular (buttock) administration of a single dose of 0.1mg or 0.3 mg (as per group 1 or group 2) of rhTSH. A dose of 0.37 MBq of 131–I was administered to patients followed by 60s uptake at a 4–hour delay (i.e. Baseline) and then a 24–hour delay using a single 5 cm thick Sodium Iodide (NaI) scintillation detector. The Acquired quantitative data and images for each individual patient were reviewed and assessed by the lead investigator prior to proceeding with rhTSH combined 131–I therapy treatment. Prior to administering a therapeutic dose of 20–30 mCi of 131–I, the procedure and the follow–up safety precautions were explained to patients.

Results

We were able to treat fifty patients who met the inclusion categories. All patients had a careful evaluation of serum TSH, T4 and had ultrasonography followed by FNA to exclude cancer and toxicity. All patients were of Kuwait origin. Table 2 presents the characteristics of patients in both groups. Group 1 (No=25) received 0.3 mg of rhTSH, while Group 2 (No=25) received 0.1 mg of rhTSH via intramuscular injection. The mean age in Group 1 was 69.0 $\pm$6.14 years (40% male and 60% female), and in Group 2 was 73.6 $\pm$ 3.33 years (60% male and 40% female). The mean body mass index (BMI) was 32.62 $\pm$ 5.63 kg/m^2 and 33.03 $\pm$ 5.37kg/m^2 for groups 1 and 2 respectively. All patients in both groups were in a euthyroid state. 21 patients (84.0%) had no surgery, while 4 patients (16.0%) had subtotal thyroidectomy in group one, whereas in Group two, 22 patients (88.0%) had no surgery, 1 patient (4.0%) had lobectomy, and 2 patients (8.0%) had subtotal thyroidectomy. There was no significant difference in age, gender, BMI, and surgical history distribution between the two groups (p=0.425). Patients in both groups received orally, a single therapeutic dose of I–131 in the range of 20–30 mCi (mean value = 24.86 +/–3.5 mCi). Table 3 presents TSH and T4 measurements at baseline (0 hours) and at the 6–months interval follow–up. The mean TSH levels at the baseline for G1 were 0.49 $\pm$0.13 uIU/mL and G2 was 0.63 $\pm$0.16 uIU/mL, whereas at 24 months post treatment was 1.76 $\pm$ 0.89 uIU/mL and 1.71 $\pm$ 0.49 uIU/mL for G1 and G2. There was no significant difference in TSH levels at 24–month follow–up between the two groups (p=0.327). As for T4, there was a statistically significant difference at the baseline and at the 6–monthS interval between 2 groups (p= 0.028, <0.001, 0.049, 0.001 and <0.001, respectively). The baseline mean value for G1 was 16.78 $\pm$ 3.23 pmol/L and G2 was 18.54 $\pm$ 2.44 pmol/L. Figures (1–2) present TSH and T4 levels at baseline and at 6–, 12–, 18– & 24–months follow–up for G1 and G2

		Group (1) 0.3 mg rhTSH (n=25)		Group (2) 0.1 mg rhTSH (n=25)		p– value‡
		N	%	N	%	
Age (years)	Mean± SD	69.0± 6.14		73.6± 3.33		0.081
	Range	55– 73		69– 79		
Gender	Male	10	40.0%	15	60.0%	0.425
	Female	15	60.0%	10	40.0%	
BMI (Kg/ m^2)	Mean± SD Range	32.62± 5.63 25– 39.2		33.03± 5.37 25.16– 40.23		0.465
State of thyroid	Euthyroid	25	100.0%	25	100.0%	–
Surgery	No surgery	21	84.0%	22	88.0%	0.686
	Lobectomy	0	0.0%	1	4.0%	
	S.T thyroidectomy	4	16.0%	2	8.0%	

p>0.05 is non–significant; p≤0.05 is significant. ‡ Mann– Whitney U test. G1: Group 1 and G2: group 2.

Table 2. Patients' characteristics for G1 and G2

		Group (1) 0.3 mg rhTSH (n=25)				Group (2) 0.1 mg rhTSH (n=25)				p– value‡
		Mean	± SD		Range	Mean	± SD		Range	
TSH (uIU/ mL)	Baseline	0.49	0.13	0.32	0.7	0.63	0.16	0.4	0.80	0.003
	At 6th months	0.78	0.65	0.02	1.9	1.05	0.15	0.87	1.2	0.007
	At 12th months	1.30	0.72	0.5	2.6	1.53	0.43	0.76	1.9	0.028
	At 18th months	2.26	0.68	1.4	3.2	1.66	0.42	1.2	2.2	0.001
	At 24th months	1.76	0.89	0.1	2.7	1.71	0.49	1.2	2.4	0.327
p– value‡		<0.001				<0.001				
T4 (pmol/L)	Baseline	16.78	3.23	13.3	22.2	18.54	2.44	14.0	21.0	0.028
	At 6th months	14.60	2.00	12.9	18.4	18.24	2.20	16.0	22.0	<0.001
	At 12th months	16.66	1.87	14.0	19.3	17.54	0.97	16.7	19.2	0.049
	At 18th months	16.14	1.78	14.4	18.8	17.84	0.87	16.4	19.0	0.001
	At 24th months	15.24	2.21	12.0	18.4	18.02	0.99	16.9	19.2	<0.001
p– value‡		<0.001				<0.001				

p>0.05 is non–significant; p≤0.05 is significant. ‡ Mann– Whitney U test. G1: Group 1 and G2: group 2.

Table 3. Thyroid functions tests: TSH and T4 at baseline (0–h) and at 6 months interval follow–up for G1 and G2.

following intramuscular injection of 0.3 mg and 0.1 mg of rhTSH and radioactive iodine.

After treatment, 20 patients in Group 1 (80.0%) still had multinodular goiter and 5 (20%) patients showed regression in the size, while all 25 patients in Group 2 (100.0%) still had multinodular goiter. The difference in the persistence of multinodular goiter between the two groups was statistically significant (p=0.018). Fine Needle Aspiration showed that all patients in G1 and G2 had benign MNG. The mean total thyroid volume, before treatment with rhTSH and 131–I, was 126.7 +/– 86.15 ml, and 239.9 +/– 31.3 ml for G1 and G2. After treatment, the mean total thyroid volume in Group 1 was 64.7 +/– 28.95 ml, and in Group 2 was 195.8 +/– 54.13 ml and the difference in total thyroid volume was statistically significant between the 2 groups (p<0.001), (Table 4). No significant difference in 99m–Tc thyroid uptake at baseline (0 hours) and at 6–months interval between G1 and G2 (p>0.05) was noted. At 24–month follow–up, the mean thyroid uptake in Group 1 was 1.56+/– 0.33 while in Group 2 was 1.4+/– 0.29, (Table 5). The 131–I uptake comparison between Group 1 and Group 2 before, after treatment and the percentage of change are presented in Table 6**.** Before treatment at the 0–hour time point, Group 1 and Group 2 had comparable mean I131 uptake (8.90 ± 2.45 and 8.24 ± 1.74, respectively), with no statistically significant difference (p = 0.142). However, at the 24–

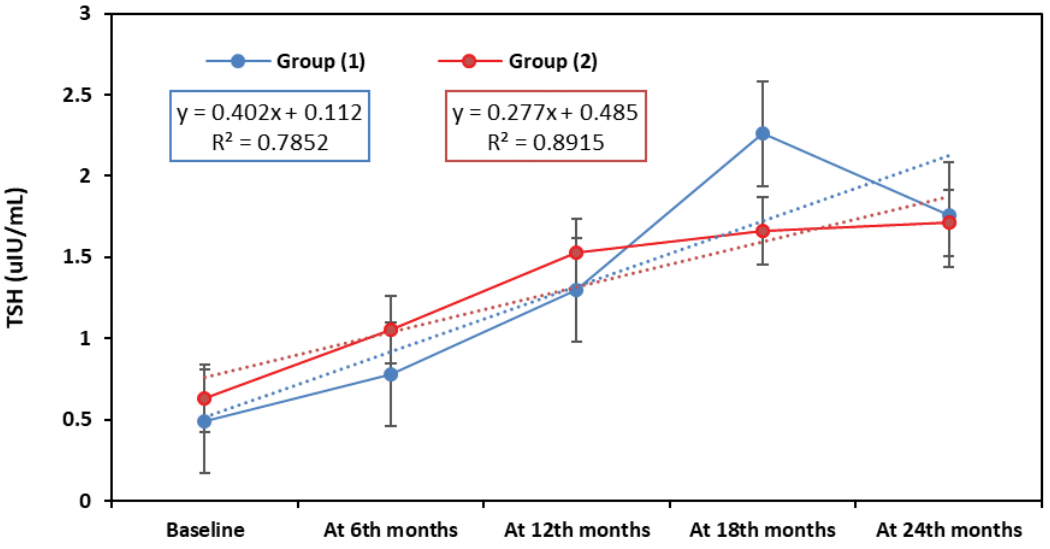


Figure 1. TSH levels at baseline and at 6–, 12–, 18– & 24–months follow–up for G1 and G2

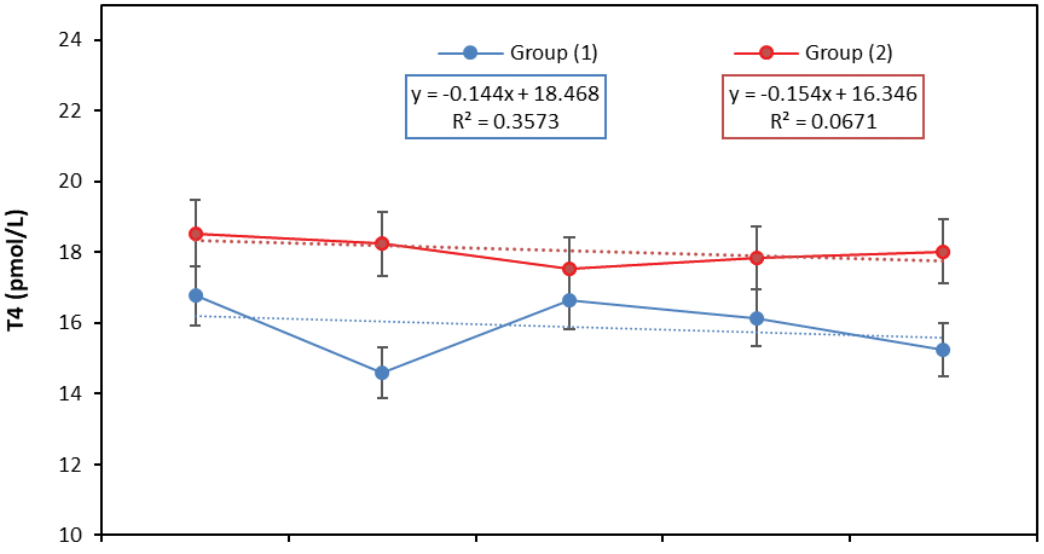


Figure 2. T4 levels at baseline and at 6–, 12–, 18– & 24–months follow–up for G1 and G2

hour time point, Group 1 exhibited significantly higher uptake compared to Group 2 (23.38 ± 4.20 vs. 16.34 ± 3.0, $p < 0.001$). The change in I131 uptake from baseline to 24 hours was also significantly greater in Group 1 compared to Group 2 ($p < 0.001$). The follow up post treatment the 0–hour time point showed no significant difference in mean 131–I uptake between the two groups ($p = 0.222$). However, at the 24–hour time point, Group 1 once more displayed significantly higher uptake than Group 1 (41.74 ± 6.27 vs. 34.8 ± 3.84, $p < 0.001$). The change in 131–I uptake from baseline to 24 hours was significantly greater in Group 1 compared to Group 2 ($p < 0.001$). Receiver operating characteristic (ROC) analysis of 131–I percentage uptake having 2 different dose levels (0.3 and 0.1) of rhTSH treatment and thyroid volume after treatment presented in Table 7 together with Figures 3–4. The AUC (area under the curve) is 0.680 ($p = 0.037$) indicating a fair discriminatory power prior to treatment. Post treatment the AUC was 0.960 ($p < 0.001$) indicating an excellent discriminatory power. There was a much higher correlation post–treatment between BMI and thyroid volume for group 1 than for group 2 (Figures 5–6). Absorbed dose was calculated for patient's thyroid organ to be in the range of 202.85–87.13 Gy (mean value=127.55+/– 40.73) for the both groups, whereas the group 1 (0.3 mg rhTSH) received the higher dose to the thyroid (153.54+/–43.2 Gy) in comparison to the group 2 (0.1 mg rhTSH) who had 101.57+/–13.3 Gy.

		Group (1) 0.3 mg rhTSH (n=25)	Group (2) 0.1 mg rhTSH (n=25)	p– value‡
		Mean ± SD	Mean ± SD	
Total thyroid volume (ml)	**Before treatment**	126.7± 86.15	239.9± 31.3	<0.001
	After treatment	64.7± 28.95	195.8± 54.13	<0.001
p–value		**<0.001**	**<0.001**	
Rt. thyroid volume (ml)	**Before treatment**	87.6± 65.19	108.4± 54.7	0.223
	After treatment	33.76± 31.91	111.14± 33.14	<0.001
Lt. thyroid volume (ml)	**Before treatment**	39.1± 27.5	96.5± 40.4	<0.001
	After treatment	30.3± 29.54	81.42± 46.82	<0.001

p>0.05 is non–significant; p≤0.05 is significant. ‡ Mann– Whitney U test. G1: Group 1 and G2: group 2.

Table 4. Thyroid volume comparison before and after treatment with [131–I + rhTSH]: G1 and G2

Thyroid Uptake with Tc99m	Group (1) 0.3 mg rhTSH (n=25)				Group (2) 0.1 mg rhTSH (n=25)				p– value‡
	Mean	± SD	Range		Mean	± SD	Range		
Baseline	1.42	0.56	0.6	2.2	1.36	0.38	0.9	1.8	0.621
At 6th months	1.48	0.51	0.9	2.2	1.56	0.4	1.1	2.2	0.328
At 12th months	1.46	0.35	1.1	2	1.54	0.33	1.1	1.9	0.623
At 18th months	1.52	0.4	1	2.2	1.58	0.31	1.1	1.9	0.321
At 24th months	1.56	0.33	1.2	2	1.4	0.29	1.0	1.8	0.082
p– value*	**0.377**				**<0.001**				

p>0.05 is non–significant; p≤0.05 is significant. ‡ Mann– Whitney U test. G1: Group 1 and G2: group 2.

Table 5. Thyroid 99m–Tc Uptake at baseline (0–h) and at 6 months at 6 months interval follow–up for G1 and G2

I131 uptake		Group (1) 0.3 mg rhTSH (n=25)				Group (2) 0.1 mg rhTSH (n=25)				p– value‡
		Mean	± SD		Range	Mean	± SD		Range	
Before Treatment	0 hr.	8.90	2.45	5.10	11.53	8.24	1.74	6.0	10.0	0.142
	24 hr.	23.38	4.20	18.00	28.70	16.34	3.00	9.0	19.7	<0.001
	Change difference	14.48	1.75	12.9	17.17	8.10	1.26	3.0	9.7	<0.001
Percent Change From Baseline, %		162.70	71.42	252.94	153.51	98.30	72.41	50.0	97.0	0.028
After Treatment	0 hr.	11.04	3.75	4.90	15.00	11.20	2.27	11.0	17.0	0.222
	24 hr.	41.74	6.27	32.40	51.00	34.80	3.84	29.0	39.0	<0.001
	Change difference	30.70	2.52	27.50	36.0	21.60	1.57	18.0	22.0	<0.001
Percent Change From Baseline, %		278.10	67.56	562.10	240.0	192.85	70.0	163.60	129.4	0.028

p>0.05 is non–significant; p≤0.05 is significant. ‡ Mann– Whitney U test. G1: Group 1 and G2: group 2.

Table 6. Thyroid 131–I uptake – comparison between G1 and G2 at 6 months interval

	Sensitivity	Specificity	PPV	NPV	AUC	P–value
I131 uptake % change	100%	60%	71.4%	100%	0.680	0.037
Thyroid volume after treatment	80%	100%	100%	83.3%	0.960	<0.001

Table 7. Receiver operating characteristic of I131 uptake change (%) and thyroid volume after treatment in differentiation between different dose levels of recombinant human TSH

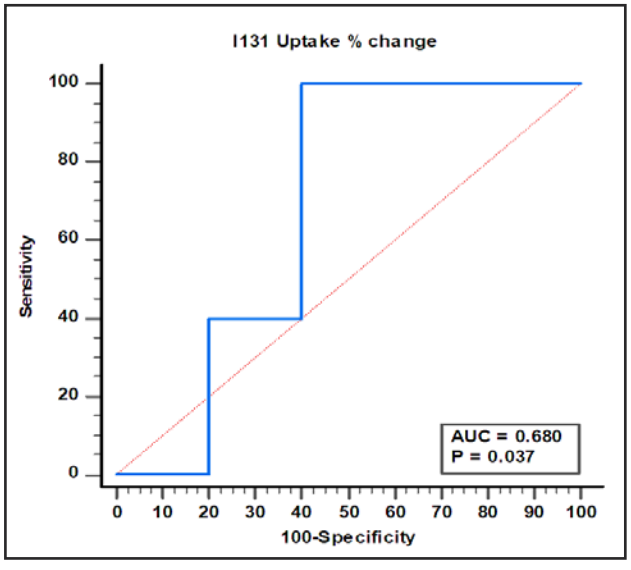


Figure 3. ROC curve of I131 uptake % change in differentiation between different dose levels of recombinant human TSH.

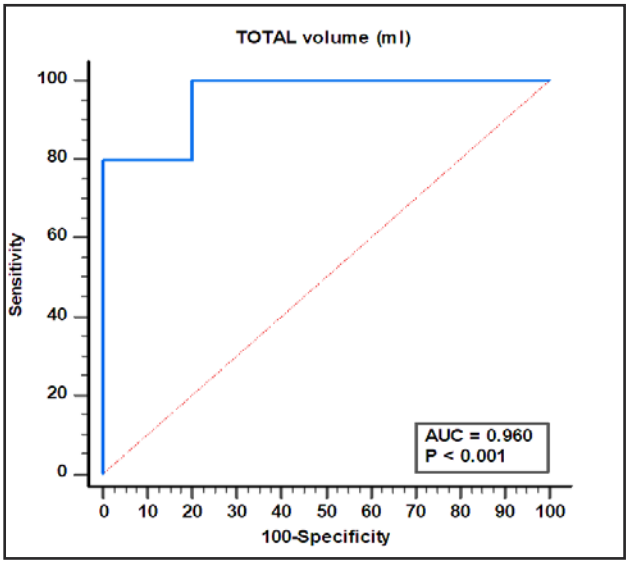


Figure 4. ROC curve of thyroid TV after treatment in differentiation between different dose levels of recombinant human TSH.

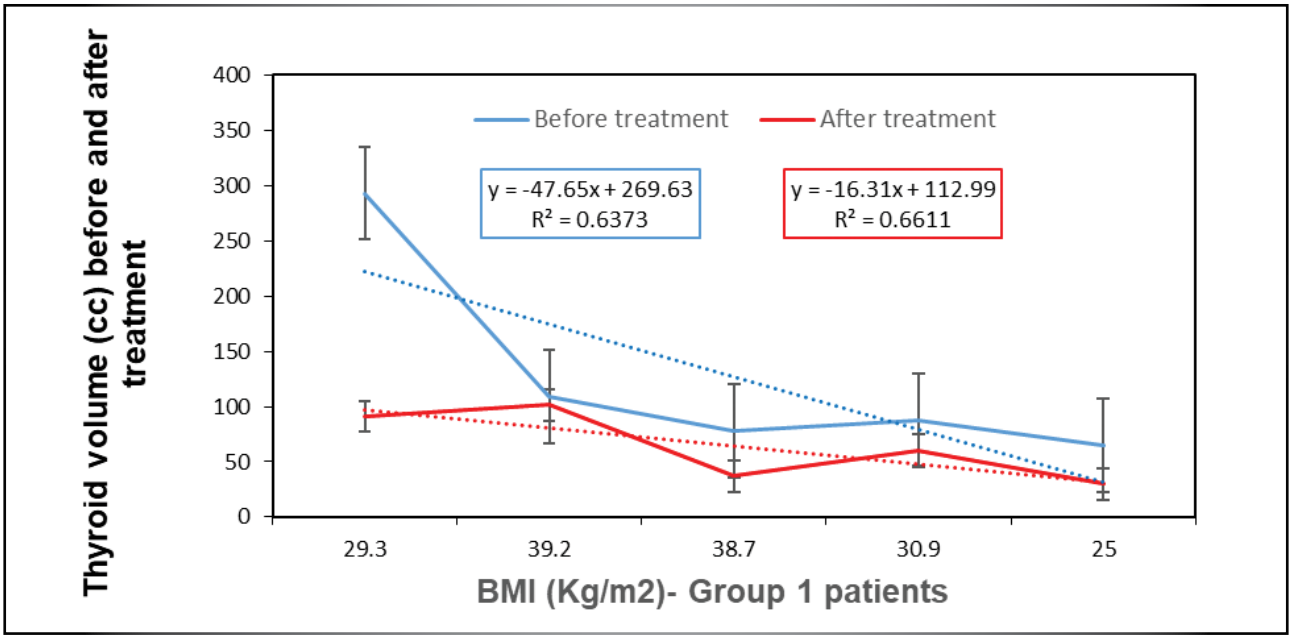


Figure 5. Correlation between BMI and thyroid volumes for group 1 patients

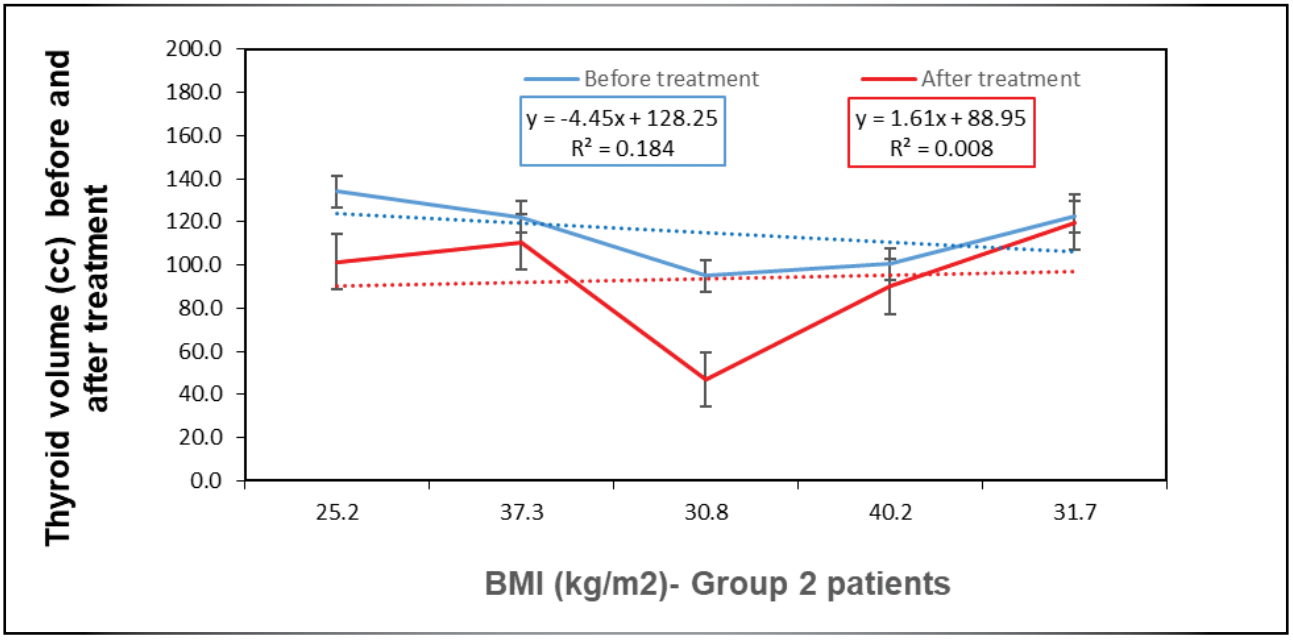


Figure 6. Correlation between BMI and thyroid volumes for group 2 patients

Figures 7–8 presents multiple images of a 45–year–old male patient (group 1) who was suffering from a swelling neck with difficulty to breath and had CT incidental findings of nodular thyroid goiter. His thyroid function test was normal. The U/S scan revealed the whole thyroid is diffusely enlarged with heterogeneous echo patterns and multiple nodules in both lobes. It also showed a retrosternal extension on the left lobe. Radionuclide heterogeneous tracer uptake was seen in both thyroid lobes uptake at baseline and 24 intervals post intramuscular (buttock) administration of rhTSH using the (NaI) scintillation gamma probe detector. SPECT/CT showed an enlarged multinodular thyroid lobe with dominated cold nodules, with the largest seen in the right lobe. Radioiodine thyroid uptake was measured to be 7.2% (3h) and 18.10% (24h), where 99mTc uptake was in the lower normal range (0.6%). The patient was treated with an intramuscular injection of 0.3 mg rhTSH and an oral dose of 25 mCi of 131–I. SPECT/CT scan post–therapy follow–up (24 months) showed a regressive size of the MNG by two folds and 24 hours thyroid iodine uptake measured to be 4.9% (3h) and 12.94% (24h).

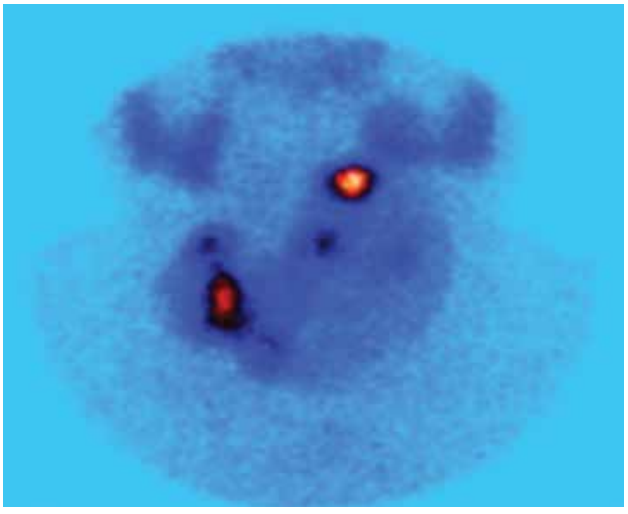
Discussion

The expression of the progressive and the nodular increase of the thyroid in non–toxic benign goiters are the results of a combination of genetic and environmental factors, of which iodine deficiency is the most important [9]. Treatment strategies differ greatly among teams worldwide because of the environmental fluctuated effects, including chemical, toxic gases, radiation and genetic factors and their long–term effect, according to the type of management (surgery or medical treatment) as stated earlier. An increased prevalence of nodular disease has been associated with exposure to radio nuclear fallouts and therapeutic external radiation [15]. The choice of treatment in patients with benign non–toxic goiter can be challenging, considering that the size of the goiter and the occurrence of symptoms often follow a nonlinear association. The ideal treatment for MNG is controversial [25], in part due to the variation in the natural history of these goiters. Multinodular nontoxic goiter (MNG), causing compression symptoms or cosmetic complaints, is a very prevalent disease in iodine–deficient regions, and prevention of goiter is a major goal of iodine fortification programs. For many years, treatment of the MNG was confined to either thyroid hormone suppressive therapy or thyroidectomy.

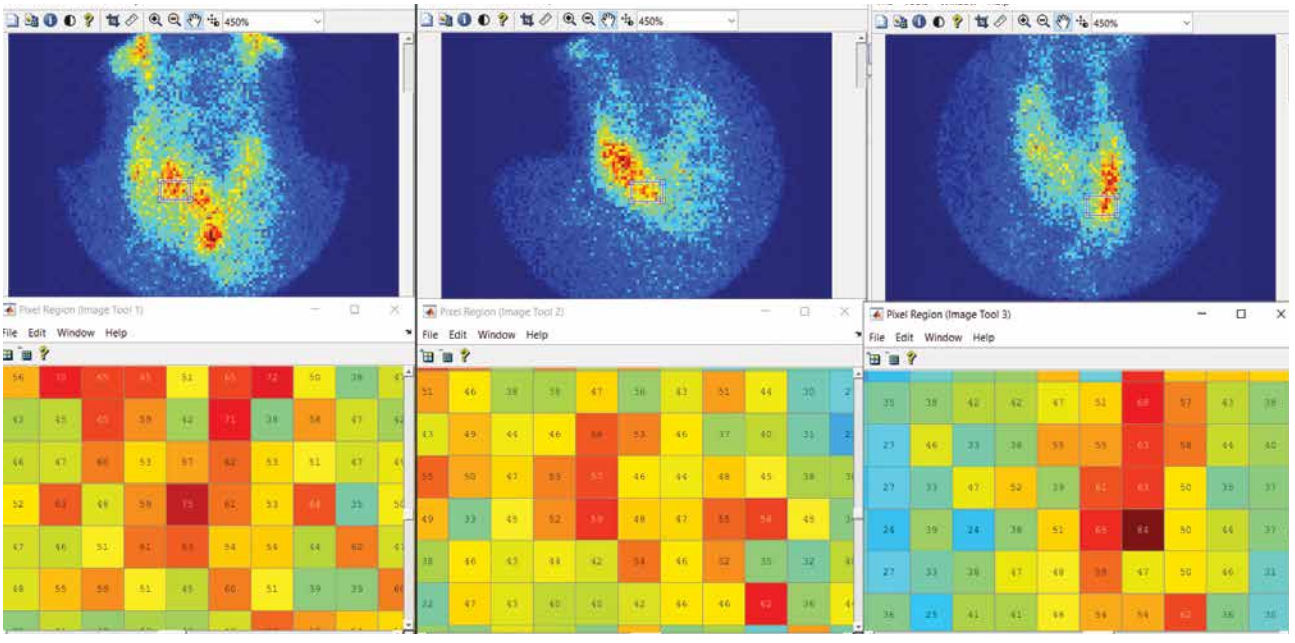
Most [24] but not all studies have demonstrated that there is an inverse relationship between non–toxic goiter reduction and the pretreatment thyroid volume, using 131–I therapy, despite the application of similar thyroid doses. Such a correlation seems logical because the relative amount of degenerated fibrous tissue and hibernating thyrocytes—not being affected by radiation to any greater extent—probably increases with goiter size. A quantitative analysis of how the amount of degenerated thyroid tissue affects the goiter reduction after 131–I therapy remains to be performed. The subsequent studies have unanimously demonstrated that 131–I therapy reduces the MNG volume by approximately 40% after 1 year and by 50–60% after 2–5 year [25]. Our investigating results and outcome are in line with their finding, where our results suggest 42.1% thyroid volume reduction for group 1 and 20% for group 2.

However, a major limitation of 131–I therapy for MNG is a low thyroid RAIU. Facing a patient with a low thyroid RAIU, treatment of MNG is usually restricted to surgery—unless the target tissue can regain its ability to trap 131–I. Many studies have demonstrated that rhTSH has a marked effect in patients with MNG, increasing the thyroid RAIU 2– to 4–fold [26]. There are, however, large interindividual variations, as seen also in healthy subjects. This means that patients with MNG, in whom therapy previously was restricted to thyroidectomy due to a low RAIU, may benefit from 131–I therapy if combined with rhTSH prestimulation.

a)



b)



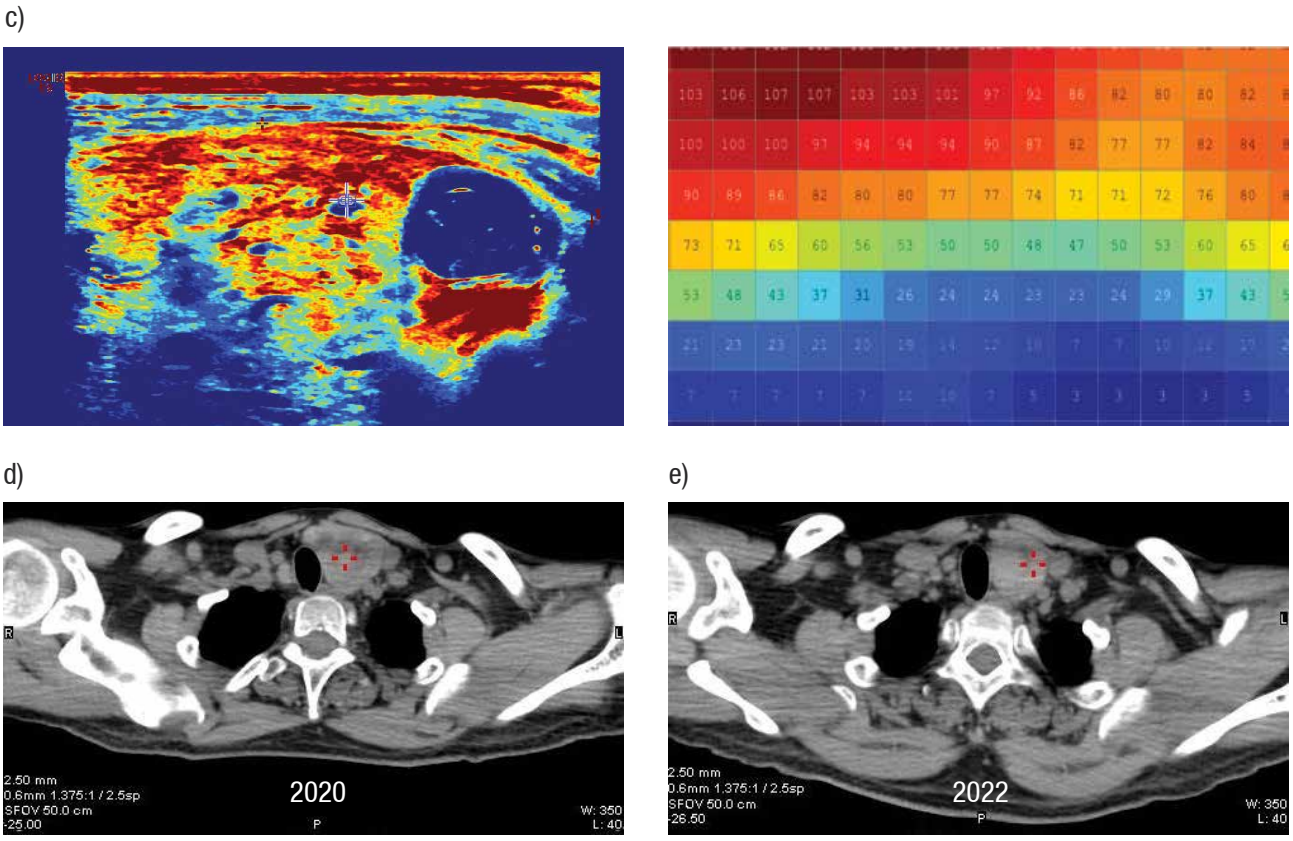
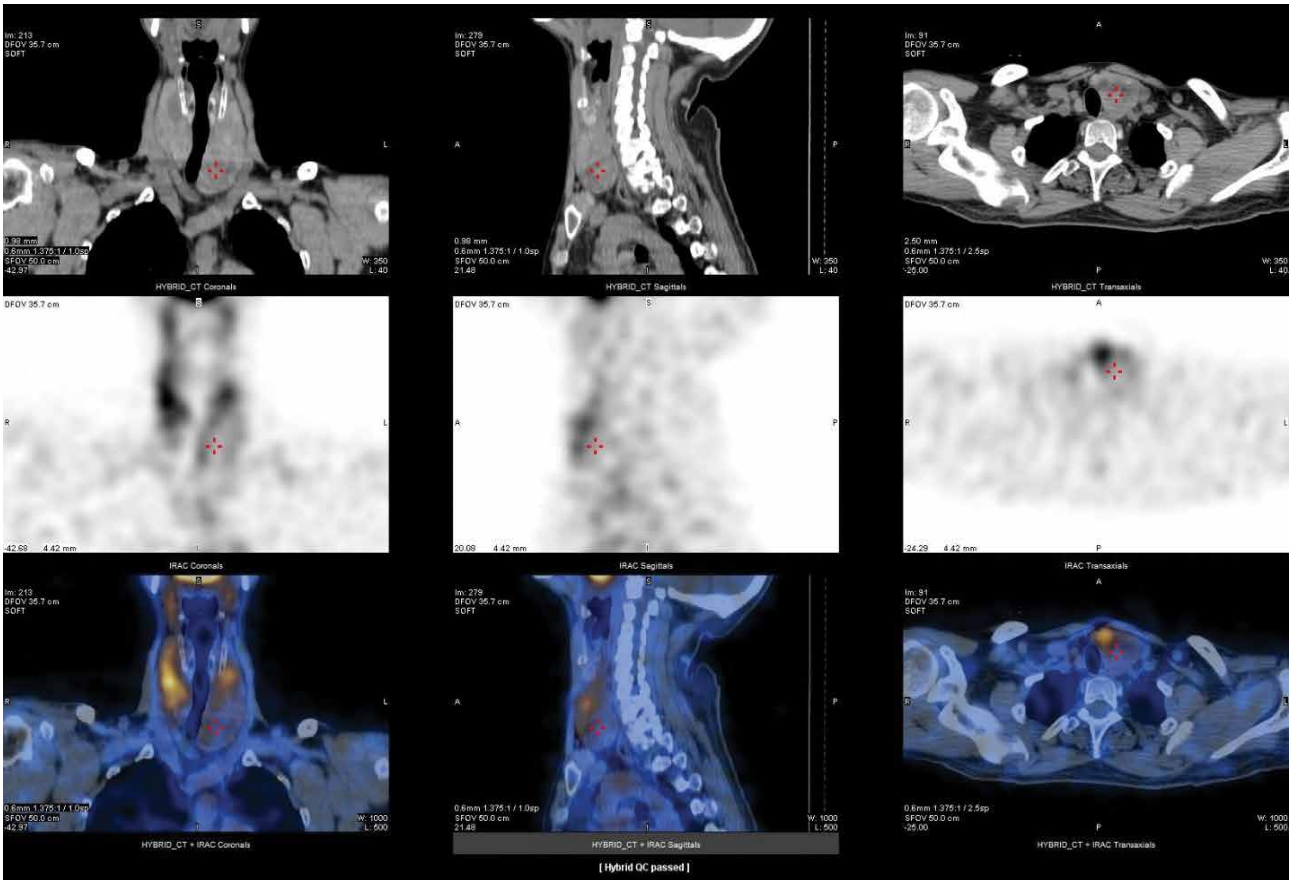


Figure 7. Presenting static images: (a) parallel hole & (b) pinhole and generated MATLAB color maps, (c) U/S images and the MATLAB–produced color maps, (d–e) a CT transaxial image prior to treatment on 2020 and post treatment on 2022, of a 45–year–old male patient neck, showing a huge cold nodule reaching the suprasternal region, which had an intramuscular injection of 0.3 mg rhTSH and an oral dose of dose of 25 mCi of 131–I.

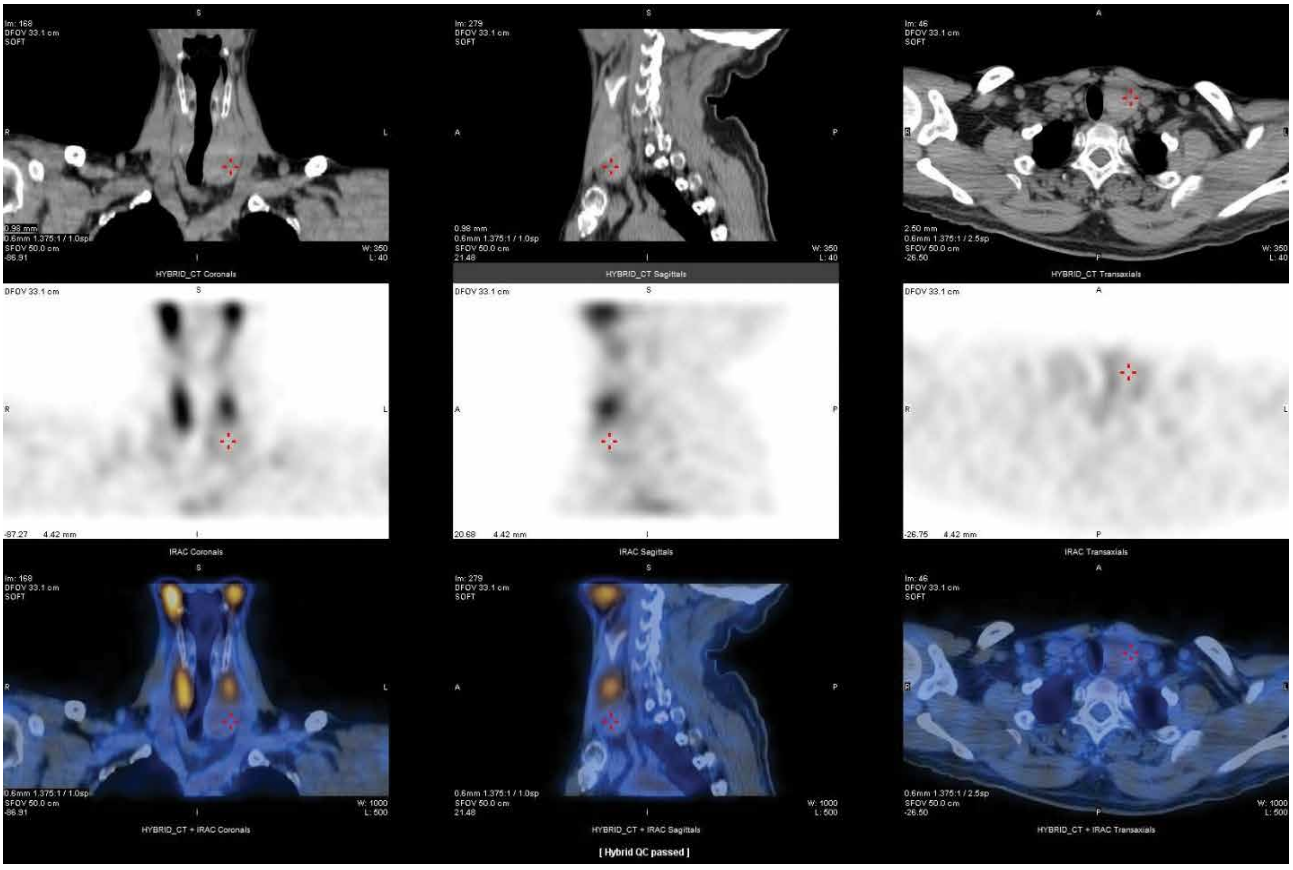
The optimal applied thyroid dose for reduction of nodular goiter is not established, and no prospective dose response study has been performed. As underlined earlier, most rhTSH studies have used fixed doses, with the consequence that the goiters were irradiated to a varying degree due to differences in the thyroid RAIU and goiter size. In other studies [27], the thyroid dose was based on thyroid dosimetry, and with rhTSH stimulation the applied thyroid dose reached 150–300 Gy, much more than the targeted 100 Gy in the placebo–stimulated patients. In our study, thyroid dose post rhTSH +I–131 was in the range of 87–203 Gy (mean value=127.6+/– 40.7) for both groups (G1: 0.3 mg rhTSH) received the higher dose to thyroid (153.54+/–43.2 Gy) in comparison to the group 2 (0.1 mg rhTSH) who had 101.57+/–13.3 Gy) which is in line with the other studies. This strongly supports the view that rhTSH has a preconditioning effect on 131–I therapy; the important implication is that a much lower amount of 131–I may suffice without loss of efficacy.

The long–term effect and the risk of goiter recurrence is an important issue that has only sparsely been evaluated. A few studies including a limited number of patients [28] have evaluated the effect of rhTSH–stimulated 131–I therapy beyond one year, with conflicting results. In the uncontrolled study by Paz–Filho *et al.* [29], no further goiter reduction was achieved in the second year (48% goiter reduction during the first year). In contrast, Cardia *et al.* [30] found that the goiter reduction continued during the additional 3 years of follow–up, to the same extent as in patients who received conventional 131–I therapy. A few patients in both studies experienced thyroid regrowth during follow–up. The outcome of our investigation suggests goiter reduction in both groups are in the range of 20% to 42% considering local environment and genetic factors. Several studies suggest that thyroid volume is also significantly correlated with body weight and body mass index. In agreement with this, a recent study has shown that in obese women, weight loss of more than 10% may result in a significant decrease in thyroid volume [31]. Our study also revealed that there was a much higher correlation post–treatment between BMI and thyroid volume for group 1 than for group 2 (R^2 for G1: 0.661 and R^2 for G2: 0.008). The nodular thyroid disease is more frequent (5– to 15–fold) [13] in women, but the reasons for this are poorly understood. Thus, at present, one can only speculate as to genetic susceptibility for thyroid disease.

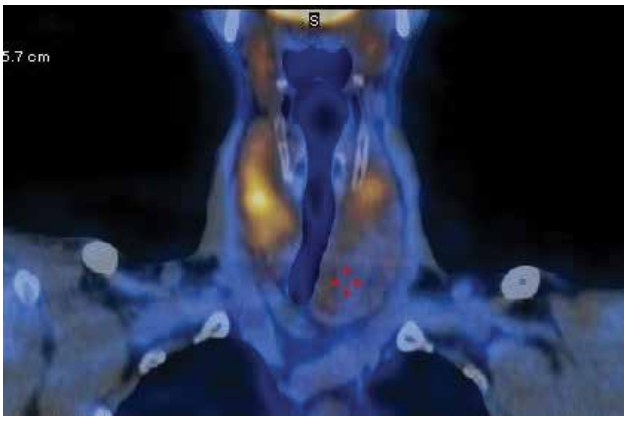
a):2020


HYBRID_CT Coronals
HYBRID_CT Sagittals
HYBRID_CT Transaxials
IRAC Coronals
IRAC Sagittals
IRAC Transaxials
HYBRID_CT + IRAC Coronals
HYBRID_CT + IRAC Sagittals
HYBRID_CT + IRAC Transaxials
[Hybrid QC passed]

b):2022


HYBRID_CT Coronals
HYBRID_CT Sagittals
HYBRID_CT Transaxials
IRAC Coronals
IRAC Sagittals
IRAC Transaxials
HYBRID_CT + IRAC Coronals
HYBRID_CT + IRAC Sagittals
HYBRID_CT + IRAC Transaxials
[Hybrid QC passed]

c):2020



d):2022

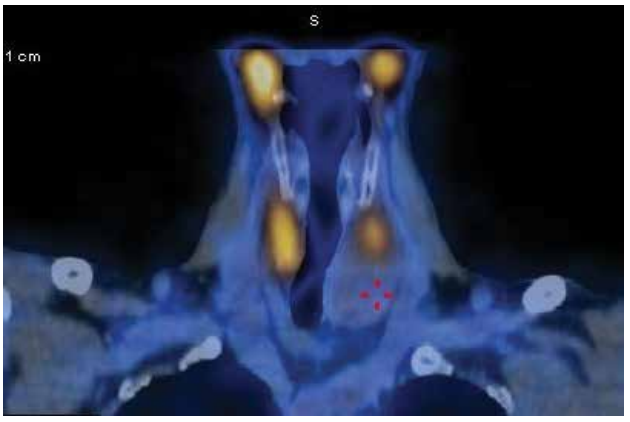


Figure 8. SPECT/CT scan images of the 45–year–old patient neck: a–b) transaxial, coronals and sagittal prior to treatment (2020) and post treatment (2022) and c–d) enlarged sagittal images of the multinodular thyroid lobes with dominant cold nodules in the left lobe – before treatment (2020) and after treatment (2022) with an intramuscular injection of 0.3 mg rhTSH and an oral dose of 25 mCi of 131–I, showing regressive size of both thyroid lobes.

A previous study highlighted the trade–off, revealing significantly higher adverse effects and hypothyroidism with high dose rhTSH pretreatment. In this research we did not extensively address adverse effects but focused on thyroid function and radiological outcomes. The comparison between our two studies underscores the need to carefully balance therapeutic benefits with potential side effects when considering rhTSH–stimulated 131–I treatment for non–toxic MNG [28]. However, our study did not explicitly explore patient satisfaction, but the alignment in reduced goiter volume and the lower risk of requiring additional therapy resonates with the external findings. One shortfall in this study was the lack of normal control group due to difficulty recruiting the patients. In summary, the project's specific clinical and scientific impacts and beneficiary encompass improvements in individualized patient care, advancements in medical imaging and biomarker research, optimization of healthcare delivery, refinement of national guidelines, potential pharmaceutical innovations, and contributions to the global understanding of thyroid disorders.

Conclusion

The results consistently favor Group 1 (0.3 mg rhTSH), suggests that this higher dose is more effective in suppressing thyroid function, inducing regression in multinodular goiter size, and reducing total thyroid volume compared to the lower dose in Group 2 (0.1 mg rhTSH). The study underscores the potential benefits of the higher rhTSH dose in managing multinodular goiter for the Kuwaiti population and the region considering the impact of dietary, and experience to the drastic environmental exposure, emphasizing the importance of dose selection in clinical practice. However, further research with a larger sample size could strengthen the robustness of these findings.

Ethics Approval

The study was performed in compliance with the requirements of the regulatory authorities. Ethical approval: M2019–1–29/351 was granted by the Standing Committee for Coordination of Health and Medical Research at the Ministry of Health– Kuwait.

Funding and Conflict of Interest

This study was funded by the Kuwait Foundation for the Advancement of Sciences (KFAS) under the project code PN20–13MN–02.

There is no conflict of interest.

References

1. Hedinger C, Williams ED, Sobin LH. The WHO histological classification of thyroid tumors commentary on the second edition. Cancer 1989; 63:908–911.
2. Belfiore A, La Rosa GL, La Porta GA, Giuffrida D, Milazzo G, Lupo L, Regalbuto C, Vigneri R. Cancer risk in patients with cold thyroid nodules: relevance of iodine intake, sex, age, and multilocularity. Am J Med .1992; 93:363–369.
3. Knudsen N, Perrild H, Christiansen E, Rasmussen S, Dige–Petersen H, Jorgensen T. Thyroid structure and size and two–year follow–up of solitary cold thyroid nodules in an unselected population with borderline iodine deficiency. Eur J End 2000; 142:224–230.
4. Berghout A, Wiersinga WM, Smits NJ, Touber JL. Interrelationships between age, thyroid volume, thyroid nodularity, and thyroid function in patients with sporadic nontoxic goiter. Am J Med 1990; 89:602–608.

5. Studer H, Peter HJ, Gerber H. Natural heterogeneity of thyroid cells: the basis for understanding thyroid function and nodular goiter growth. Endocr Rev 1989; 10:125–135.
6. Wiersinga WM. Determinants of outcome in sporadic nontoxic goiter. Thyroidology 1992; 4:41–43.
7. Aghini–Lombardi F, Antonangeli L, Martino E, Vitti P, Maccherini D, Leoli F, Rago T, Grasso L, Valeriano R, Balestrieri A, Pinchera A. The spectrum of thyroid disorders in an iodine deficient community: the Pescopagano survey. J Clin End Metab 1999; 84:561–566.
8. Hampel R, Kulberg T, Klein K, Jerichow JU, Pichmann EG, Clausen V, Schmidt I. [Goiter incidence in Germany is greater than previously suspected]. Med Klin (Munich) 1995; 90:324–329.
9. Krohn K, Fuhrer D, Bayer Y, et al. Molecular pathogenesis of euthyroid and toxic multinodular goiter. Endo Rev 2005; 26:504–24.
10. Jarlov AE, Nygaard B, Hegedus L, Hartling SG, Hansen JM. Observer variation in the clinical and laboratory evaluation of patients with thyroid dysfunction and goiter. Thyroid 1998; 8:393–398.
11. Hegedus L. Thyroid ultrasound. Endocrinol Metab Clin North Am 2001; 30:339–344.
12. Knudsen N, Laurberg P, Perrild H, Bulow I, Ovesen L, Jorgensen T. Risk factors for goiter and thyroid nodules. Thyroid 2002;12: 879–888.
13. Hegedu¨ s L, Bonnema SJ, Bennedbaek FN. Management of simple nodular goiter: current status and future perspectives. Endocr Rev 2003; 24:102–132.
14. Furlanetto TW, Nguyen LQ, Jameson JL. Estradiol increases proliferation and down–regulates the sodium/iodide symporter gene in FRTL–5 cells. Endocrinology 1999; 140:5705–5711.
15. Nagataki S, Nystrom E. Epidemiology and primary prevention of thyroid cancer. Thyroid 2002; 12:889–896.
16. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty–year follow–up of the Whickham Survey. Clin Endocrinol (Oxf) 1995; 43:55–68. doi:10.1111/j.1365–2265. 1995.tb01894.
17. Bonnema SJ, Fast S, Hegedüs L. The role of radioiodine therapy in benign nodular goiter. Best Pract Res Clin Endocrinol Metabol 2014; 28:619–31.
18. Bonnema SJ, Hegedüs L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. Endocrinol Rev 2012; 33:920–80. doi:10.1210/er.2012–1030.
19. Fast S, Nielsen VE, Bonnema SJ and Hegedu L. Dose–dependent acute effects of recombinant human TSH (rhTSH) on thyroid size and function: comparison of 0.1, 0.3 and 0.9 mg of rhTSH. Clinical Endocrinology 2010; 72, 411–416.
20. The Petkau Effect, Revised Edition 1990 by Ralph Graeub, translated from German by Phil Hill, and Published by Four Walls Eight Windows, New York, 1994; ISBN: 1–56858–019–3.
21. Nielsen VE, Bonnema SJ, Boel–Jørgensen H, etal. Stimulation with 0.3–mg recombinant human thyrotropin prior to iodine 131 therapy to improve the size reduction of benign nontoxic nodular goiter: a prospective randomized double–blind trial. Arch Intern Med 2006; 166:1476–1482.
22. Bonnema SJ and Hegedus L. Radioiodine Therapy in Benign Thyroid Diseases: Effects, Side Effects, and Factors Affecting Therapeutic outcome. Endocrine Reviews 2012; 33(6):920–980.
23. Stabin MG and Siegel JA. Physical Models and Dose Factors for Use in Internal Dose Assessment. Health Physics 2003; 85(3): 294.
24. Le Moli R, Wesche MF, Tiel–Van Buul MM, Wiersinga WM. Determinants of long–term outcome of radioiodine therapy of sporadic non– toxic goitre. Clin Endocrinol (Oxf) 1999; 50:783–789.
25. Diehl LA, Garcia V, Bonnema SJ, Hegedüs L, Albino CC, Graf H, et al. Management of the nontoxic multinodular goiter in Latin America: comparison with North America and Europe, an electronic survey. J Clin End Metab 2005; 90:117–23.
26. Nielsen VE, Bonnema SJ, Boel–Jørgensen H, Veje A, Hegedus L. Recombinant human thyrotropin markedly changes the 131–I kinetics during 131–I therapy of patients with nodular goiter: an evaluation by a randomized double–blinded trial. J Clin Endocrinol Metab 2005; 90:79–83.
27. Bonnema SJ, Nielsen VE, Boel–Jørgensen H, Grupe P, Andersen PB, Bastholt L, Hegedus L. Improvement of goiter volume reduction after 0.3 mg recombinant human thyrotropin–stimulated radioiodine therapy in patients with a very large goiter: a double–blinded, randomized trial. J Clin Endocrinol Metab 2007; 92:3424–3428.
28. Limin T, Tiekun Ma, Wu F. Recombinant human thyrotropin stimulated 131–I treatment for multinodular goiter. Nuklear medizin–nuclear Medicine 2016; 55(6):228–235. doi: 10.3413/NUKMED–0808–16–03.
29. Paz–Filho GJ, Mesa CO, Carvalho GA, Goedert CA, Graf H. Recombinant human TSH associated with radioiodine does not have further effects on thyroid volume and function after 2 years. Clin Endocrinol (Oxf) 2008; 69:345–346.
30. Cardia MS, Rubio IG, Medeiros–Neto G. Prolonged follow–up of multinodular goitre patients treated with radioiodine preceded or not by human recombinant TSH. Clin Endocrinol (Oxf) 2006; 64:474.
31. Sari R, Balci MK, Altunbas H, Karayalcin U. The effect of body weight and weight loss on thyroid volume and function in obese women. Clin Endocrinol (Oxf) 2003; 59:258–262.