Chapter 4

Nuclear Medicine in the Assessment of Thyrotoxicosis Associated with Increased Thyroid Function and Radioiodine 131 Ablative Therapies

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Additional information is available at the end of the chapter

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Abstract

Nuclear medicine is directly involved in both the diagnosis and treatment of benign thyroid disease. Thyroid scintigraphy (most commonly with technetium-99 m pertechnetate) should be used as the imaging modality of choice for assessment of thyrotoxicosis, since it demonstrates the functional state of the thyroid gland. An adequate understanding of the pathophysiological mechanisms and characteristics of the patient is essential, as well as the different treatments of thyroid disorders that present with hyperthyroidism (*Graves' disease*, toxic multinodular goiter, and toxic adenoma-Plummer's disease). Therapeutic modalities include antithyroid drugs, radioiodine and surgery. Antithyroid drugs are the first line of therapy and regarding the use of radioiodine, current recommendations consider it a safe and effective therapeutic alternative in hyperthyroidism. Finally, we highlight the existence of some special situations (children, pregnancy, thyroid eye disease, chronic renal failure and dialysis patients) and the importance of radiation protection measures to the patient, the public and professionals.

Keywords: nuclear medicine, thyrotoxicosis, thyroid hyperfunction, radioiodine 131

1. Introduction: thyroid anatomy and physiology

Thyroid gland is the first organ to develop in human embryo. Its development begins 22 days after conception. The thyroid gland develops in the floor of the primitive foregut, between the first and second pharyngeal pouches from the endoderm. It descends to its habitual position, by the anterior neck to the level of the trachea, connecting to the tongue's base by the thyroglossal duct. The thyroglossal duct starts from the foramen caecum and normally involutes

throughout the development of the embryo when the thyroid occupies its final position in the neck, but sometimes becomes into a pyramidal lobe which is contiguous with the thyroid isthmus [1].

The TSHR is a G-protein coupled receptor present in thyroid, lymphocytes, fibroblasts and adipocytes. The binding of TSH to TSHR results in signaling pathway downstream that results in actions of thyroid hormone production [2].

Approximately 94% of thyroid hormones are secreted by the thyroid gland as tetraiodothyronine (T4) and 6% as triiodothyronine (T3). T4 is catalytically converted to T3 (more metabolically active) in peripheral tissues by deiodinases enzymes. Both T4 and T3 are mostly bound to carrier thyroxine-binding globulin proteins (TBG) in the serum [3].

At the cellular level, the function of thyroid hormones is mediated by the free hormones (free T4 (fT4) and free T3 (fT3)), principally by the binding of triiodothyronine (T3) to its receptors. In addition, the subsequent expression of genes is regulated by the binding of the T3-receptor complexes to DNA. This is specifically important, for example, for those genes that regulate the calcium cycling in cardiac cells [3, 4].

2. Radiopharmaceuticals principles

Radiopharmaceuticals are substances that contain one or more radioisotopes (radionuclides). They are nonencapsulated sources of artificial ionizing radiation, which are used for both diagnostic and therapeutic medical applications in the field of nuclear medicine.

It is important to mention certain general characteristics, such as the type of radioactive emission (gamma photons, alpha or beta particles and mixed, with emission of gamma photons and charged particles), the emission energy measured in KeV and the physical half-life (T ½ f), that help us to know and properly choose the type of radiotracer that we should use at all times. Radioiodine isotopes and ^{99m}Tc-pertechnetate (TCO4-) are the most commonly used radiopharmaceuticals for thyroid imaging.

^{99m}Tc-pertechnetate is used worldwide to study the thyroid function because of its advantages, such as a short retention in the gland due to half-life (6 h) and no beta-radiation, thus providing low dosimetry to the thyroid gland and the rest of the body. Its gamma photon of 140 keV is ideal for imaging using scintillation cameras, really cost effective and it can be done fast (readily available), safe and no side effects [5, 6]. A disadvantage is that ^{99m}Tc is only trapped and not organified in the follicles [7].

Iodine-123 (^{123}I) is both trapped and organified by the thyroid gland, it has a relatively short half-life of 13.6 h, a gamma photon suitable for imaging using conventional scintillation cameras (159 keV) and no beta-radiation [5, 7]. Therefore, it is considered the ideal agent for thyroid imaging. However, the reality is that its availability is limited and costly due to its expensive and complex production in a cyclotron. As the information is mostly the same as that obtained by ^{99m}Tc-pertechnetate scintigraphy, specific indications include evaluation of organification defects [5–7].

Iodine-131 (^{131}I) was frequently used in the past in thyroid diagnosis imaging because of both gamma emission (364 keV) and beta particle emission [7]. Its special characteristics of energy emission, its long half-life (approximately 8.1 days) and high radiation doses to the gland (1–3 rad/mCi) makes 131-Iodine less satisfactory for thyroid imaging (poor quality images are produced) [5]. Currently, 131-Iodine is a radiopharmaceutical used mainly for metabolic therapy in benign thyroid disorders (thyroid hyperfunction) and ablation of tumor remnants of differentiated thyroid carcinomas, in addition to the staging and follow-up of patients with such tumors (using a lower dose of ^{131}I than in the ablation of possible thyroid remnants) [6].

3. Clinical presentation

A thorough cervical examination is important. The palpation of the thyroid gland should be done with the patient sitting (never in supine position) and helping with swallowing movements. We must be careful in the search for possible goiters and their correlation with size (from small goiters, grade-I, to large goiters of endothoracic clinical characteristics, grade-IV), palpation of thyroid nodules and/or adjacent adenopathies (mobile/fixed, painful/not painful, reactive, etc.).

In addition, it is necessary to pay special attention to the size and weight of the patient, heart rate and blood pressure, body temperature, skin adnexa such as hair and nails, skin characteristics or menstrual changes in cases of women of childbearing age.

In patients with thyroid hyperfunction, there is usually weight loss (accompanied by nausea, vomiting, diarrhea and often an increased appetite), excessive urination and thirst, along with remarkable associated hyperactivity.

The cardiovascular system is altered by thyroid hormones which have important effects on cardiac muscle, the peripheral circulation, and the sympathetic nervous system. There is an important correlation between the hyperthyroid state and cardiac morbidity, with cause–effect determination. Cardiac symptoms such as tachycardia, heart failure, or arrhythmia and atrial fibrillation are most frequent [3, 4].

About psycho-neurological manifestations, we have to highlight detected cases of tremors, chorea, myopathy, myasthenia gravis, ophthalmopathy (exophthalmos), delirium, emotional lability, psychosis, paranoia, irritability, exhaustion, depression and panic attacks among others.

Fine and brittle hair or a diffuse hair loss due to an acceleration of capillary cycles is common. The skin is usually smooth, thin, moist and hot, with marked redness of the palms of the hands and tendency to facial flushing, due in large part to heat intolerance. Loss of libido and amenorrhea are other alterations that can be generated over time.

Some laboratory alterations in addition to the thyroid profile such as high blood sugar, low cholesterol or calcium-phosphorus metabolism's alterations (with osteoporosis tendency) can be visualized.

Regarding pediatric age, a high index of suspicion is required due to its important effects on the organism. Thyroid hormones play an important role in the development of the central nervous system and growth. A situation of thyroid hyperfunction can interfere with growth

and development, result in growth retardation, brain damage due to craniosynostosis and cognitive impairment [8].

Although the manifestations are mostly similar to adults, the initial clinical presentation may be different in the pediatric age and even the symptoms may vary within this age group according to (prepubertal or pubertal population). A highlight of certain symptoms as an example of such atypical presentation and that are subject to confusion are mood changes and emotional lability, fatigue, sleep disturbance and increased appetite (prepubertal children more commonly present with poor weight gain and frequent bowel movements), attention-deficit hyperactivity disorder, poor school performance, irritability, fatigue, palpitations, heat intolerance, fine tremor and a goiter [2].

Definitive diagnosis can be more challenging in pregnancy. A diffuse goiter, ophthalmopathy, hyperthyroid symptoms prior to pregnancy and serum thyroid hormone receptor antibody (TRAb) positivity favor the diagnosis of *Graves' disease*. Transient gestational thyrotoxicosis is more common in women with morning sickness, especially those with the most severe form, hyperemesis gravidarum [9].

4. Diagnostic methods in the evaluation of hyperthyroidism

The normal thyroid gland and anatomic variants can be visualized by numerous imaging modalities including scintigraphy, ultrasound and computed tomography. Although magnetic resonance imaging (MRI) is capable of providing excellent anatomic detail of the thyroid gland using proton density imaging, it is not usually used in routine clinical practice [7].

Thyroid ultrasonography utilizes reflected sound waves that allow to identify and evaluate gland size, location, the presence of nodules and to differentiate between cystic and solid lesions [7].

There are certain echographic characteristics such as echogenic behavior of the thyroid nodule (as purely cystic or hyperechoic nodules), good demarcation and external vascularization suggesting signs of benign course (e.g., a thyroid adenoma). On the contrary, solid hypoechogenic nodules, irregular borders, internal vascularization, presence of microcalcifications or recent increase in size on follow-up are associated with malignancy [10].

Ultrasound is, therefore, an image modality from which morphological information of the thyroid gland is obtained. On the other hand, thyroid scintigraphy is a functional imaging test that visualizes the distribution of active thyroid tissue and is used as a complementary test for definite diagnosis [6, 10].

American Thyroid Association (ATA) and other guidelines have published their recommendations suggesting that thyroid scintigraphy is useful in the assessment of diffuse goiter *(Graves' disease)*, the simple thyroid nodule and multinodular goiter, acute or chronic local inflammation (thyroiditis), suspected ectopic thyroid (such as lingual thyroid), the study of cervical embryonic development anomalies of thyroid origin (thyroglossal cysts) to evaluate the extent of retroesternal goiter and patients undergoing treatment with radioactive iodine, which is important to know about the anatomical distribution, active thyroid tissue information and select the appropriate therapeutic dose/activity of 131-Iodine [6].

Regarding the evaluation of thyroid nodules by thyroid scintigraphy, it plays an important role in the identification of the functional state of the nodule. Non-functioning thyroid nodules do not present radiotracer uptake ("cold nodules") and present a higher risk of malignancy, while functioning thyroid nodules have tracer uptake ("hot nodules") and are usually benign nodules [10].

Laboratory tests play a fundamental role in the initial diagnosis and follow-up of thyroid hyperfunction, in the assessment of possible autoimmunity associated with thyrotoxicosis, in the control and adjustment of adequate pharmacological dose to each patient, as well as in the detection of pharmacological response (drug resistance) or clinical relapse.

In the presence of typical signs and symptoms, a TSH suppressed with excess thyroid hormone production—thyroxine (T4), free thyroxine (FT4) and/or triiodothyronine (T3)—indicates clinical-analytic findings of hyperthyroidism. In the case of *Graves' disease*, these hormonal alterations are attributed to the presence of thyroid stimulating antibodies (TSHR-Ab), specifically thyroid stimulating immunoglobulins (TSI) [2, 11]. This existence of antibodies in the bloodstream explains the autoimmune and genetic component of this syndrome, as well as its relationship with other autoimmune entities.

5. Thyroid scintigraphy: patient preparation, instrumentation and image acquisition. Evaluation of thyrotoxicosis associated with thyroid hyperfunction (clinical examples)

5.1. Patient preparation, instrumentation and image acquisition

Usually no prior patient preparation is needed for thyroid scintigraphy [6]. It is not necessary to carry out any special diet or suspend the usual medication. In case the patient is taking thyroid hormone replacement therapy (levothyroxine), it is necessary to stop taking such medication at least 30 days before the imaging study.

That medication can be restarted as usual once the image is acquired. If the patient is taking an iodine supplement or has recently had an intravenous iodine test (such as a CT scan with intravenous contrast), the study should be delayed 4–6 weeks later [6].

On the other hand, women who are pregnant or breastfeeding should inform the nuclear medicine physician before any testing of the service. Although the exposure to the radiation involved is very low with ^{99m}Tc-pertechnetate, the benefit/risk of the test must be compared, using the lowest possible dose to obtain an adequate image (optimization criterion) [6].

Breastfeeding will be suspended for 24 h after performing the thyroid scan and the importance of drinking plenty of water for an early elimination of the radiotracer will be reported, which will reduce the exposure time of the embryo/fetus to radiation.

About radiation protection measures, it is recommended not to be in contact with pregnant women or young children for 24 h after the scintigraphy. If this condition cannot be met, a distance of at least 1 m from the patient should be maintained.

Regarding scintigraphic technique, the images begin 20 min after the intravenous injection of 5 mCi (185 MBq) of ^{99m}Tc-pertechnetate [12]. In pediatric population, these fixed doses are not used (5–10 mCi [185–370 MBq]); the dose administered to make the image is adjusted to the weight of the patient.

The acquisition is done with gamma cameras, which are composed of collimators of scintillation crystals and photomultipliers, which allow the image obtained to be the projection of the radiotracer distribution. In our department, we use a pinhole collimator with a 3.5 mm opening, as well as an energy setting of 140 keV photopeak for ^{99m}Tc. Images are obtained on a 128 x 128 matrix with a zoom 5 and at 100,000 counts in the anterior and 30° anterior oblique views (right and left anterior oblique) with the collimator placed as close as possible to the patient's extended neck [5, 12]. The duration of the image is usually about 5 min.

In cases where we want to visualize more specifically the thyroid gland and adjacent structures (as in the case of intrathoracic goiters), we can perform the SPECT/CT hybrid technique *(Tomography by Emission of a Single Photon)*. Several rotating gantry are incorporated to the gamma cameras and they rotate around a central axis of the patient, what allows a rotation arc of 180° to 360°. Finally three-dimensional images are obtained, unlike the two-dimensional planar images of the scintigraphy.

5.2. Evaluation of thyrotoxicosis associated with thyroid hyperfunction (clinical examples)

The biodistribution of ^{99m}Tc-O4 in the body is taken up by the thyroid, but this is also taken up by other structures such as salivary glands. Its secretion by saliva, sweat or urine may give false positive image [10].

Therefore, in a normal thyroid scintigraphy, the gland is symmetrical and the lateral borders of lobes are straight to convex. Tracer is normally seen in salivary glands and in capillary network of the neck tissue also, called as 'blood pool' (i.e., seen as a light background along the neck contour) [6].

In the case of diffuse goiter due to *Graves' disease*, thyroid scintigraphy shows a diffuse enlargement of thyroid with a homogeneous distribution of the radiotracer and markedly increased uptake of both thyroid glands suggestive of hyperfunction [8]. Activity throughout the gland is increased relative to the background due to both increased stimulation and function of the gland (**Figure 1**). Such stimulation at times results in visualization of the pyramidal lobe (a remnant of the thyroglossal duct). Owing to its relatively small size, the pyramidal lobe is normally not seen unless the gland is overly stimulated [12].

The toxic multinodular goiter is shown as an enlarged thyroid with a heterogeneous distribution of the radiotracer. Non-functioning and uptake-tracer thyroid nodules are both present, whose activity is above normal (hyperfunction) (**Figure 2**).

With respect to the pretoxic nodular goiter, the thyroid gland usually presents a hyperfunctioning nodulation in one of its thyroid lobes, while the rest of the thyroid parenchyma presents a slight decrease in the uptake of the radiotracer, which suggests the existence of braking phenomena (**Figure 3**).

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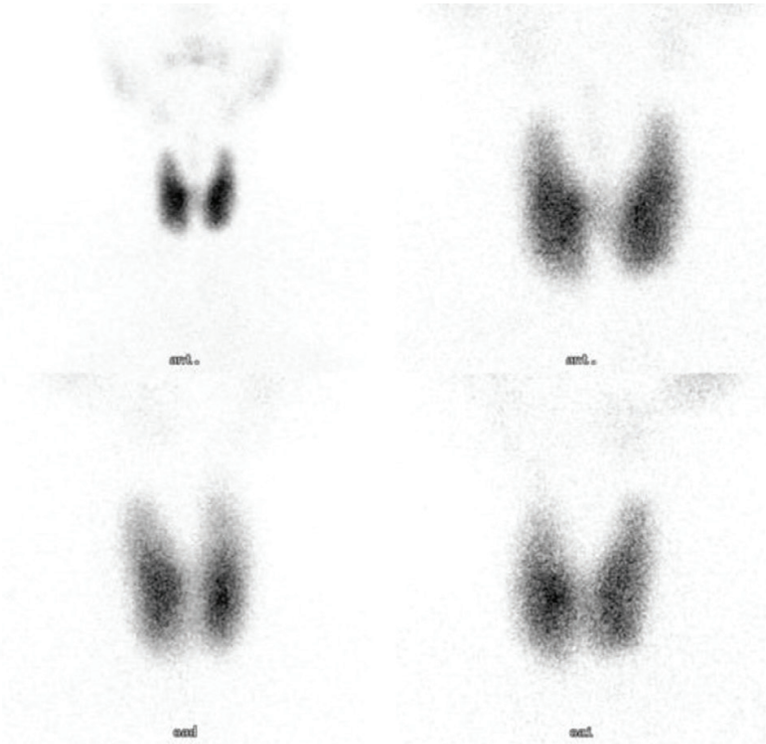

Figure 1. It is noted a diffuse enlargement of thyroid with a homogeneous distribution of the radiotracer and markedly increased uptake of both thyroid lobes, suggestive of hyperfunction. *Courtesy of H.R.U. Málaga, Spain. Nuclear Medicine Department.*

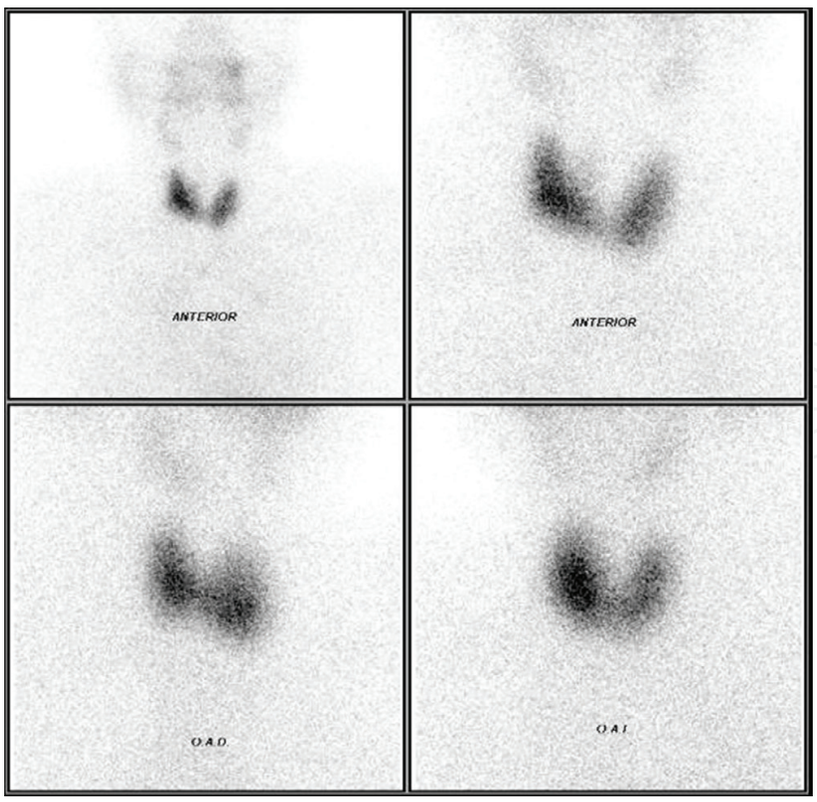

Figure 2. Thyroid scintigraphy shows an uptake-tracer nodule at the base of the right thyroid lobe and another non-functioning nodule at the base of the left thyroid lobe. *Courtesy of H.R.U. Málaga, Spain. Nuclear Medicine Department.*

Figure 3. Hyperfunctioning nodulation is seen at the base of the right thyroid lobe. *Courtesy of H.R.U. Málaga, Spain. Nuclear Medicine Department.*

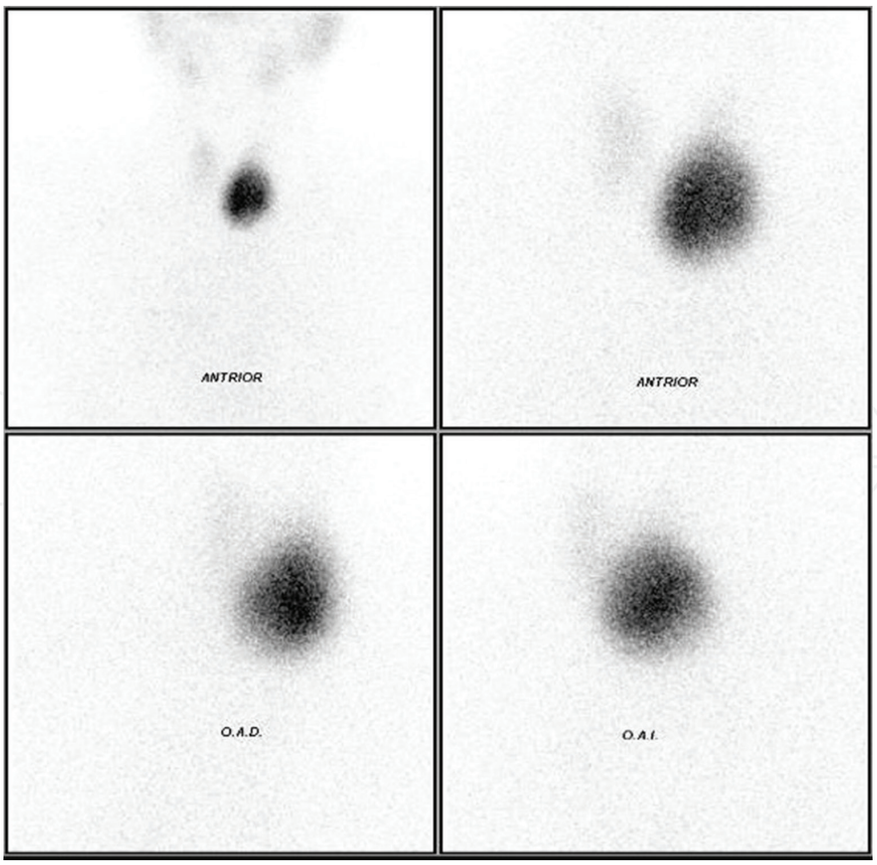

Figure 4. We can see the existence of a large hyperfunctioning nodulation that occupies the left thyroid lobe. *Courtesy of H.R.U. Málaga., Spain. Nuclear Medicine Department.*

As for the toxic adenoma, the thyroid gland appears enlarged at the expense of a thyroid lobe, which is occupied by a hyperfunctioning nodulation. The contralateral thyroid shows a notable decrease in uptake, due to more advanced braking phenomena than in the previous case (**Figure 4**).

The most common reason for hyperthyroidism is *Graves' disease*. Toxic nodular goiter is a clinical situation that includes toxic multinodular goiter and toxic adenoma and is the second most common reason of hyperthyroidism [13].

6. Treatment in hyperthyroidism: different therapeutic options. Radioiodine (^{131}I) administration protocol in our center

6.1. Different therapeutic options in hyperthyroidism

Current therapeutic options for these pathologies include antithyroid drugs (ATD), radioactive iodine and thyroidectomy. The choice of treatment depends on the type of pathology (*Graves' disease*, toxic multinodular goiter, pretoxic or toxic adenoma), physiological characteristics of the patient (age, pregnancy, breastfeeding), co-morbidities (advanced age, heart failure, large compressive intrathoracic goiters, thyroid ophthalmopathy), as well as refractoriness to the treatment administered [8, 14].

Antithyroid drugs (ATD) therapy is usually recommended as the initial treatment for hyperthyroidism (especially in *Graves' disease*), achieving normalization of thyroid function in 4–6 weeks [8].

There are several antithyroid drugs, the most used in our environment are methimazole and propylthiouracil. For several reasons, propylthiouracil is preferred during pregnancy. Avoidance of the use of propylthiouracil (PTU) was recently recommended in childhood because of the high risk of PTU-induced hepatitis. Because methimazole (active metabolite of carbimazole) has a longer half-life and is effective as a single daily dose, it is particularly helpful in younger children. Daily loading doses of 10–30 mg of methimazole or 100–300 mg of propylthiouracil are appropriate for most patients [15, 16].

The medication is prescribed for 12–18 months normally, with the aim of achieving remission of the disease. However, the frequency of recurrences (more frequently in young males) and severe side effects like cytopenias, vasculitis, liver failure or agranulocytosis (higher in pediatric patients than adults) are a main limitation of ATD treatment [8, 14, 16].

Radioiodine therapy and surgery are usually the second-line treatments in *Graves' disease*. It does not happen in the case of toxic nodular goiter (toxic multinodular goiter and toxic adenoma), where definite and effective treatment can be achieved only with radioiodine or surgery [13]. So, both are considered as the first line of treatment for these pathologies and not the second line as in *Graves' disease* [17].

The use of 131-Iodine in the treatment of hyperthyroidism is increasing, as it is easy to administer, relatively inexpensive, safe and highly effective with a cure rate approaching 100% after one or more activity [18].

In our department, we administer single doses of radioiodine, which are prepared in individual capsules to be taken orally. The said capsules are specifically detailed with the data of the patient who is going to receive the metabolic treatment, as well as the amount of dose that the capsule carries. That way, it is possible to reduce failures in the administration of doses between patients.

There is no consensus regarding the optimum dose of radioiodine [17]. There are fixed doses regimens of 10 mCi (370 MBq) generally used to treat *Graves 'disease*, in addition to capsules with a dose of 12 mCi (444 MBq) at 15 mCi (555 MBq), for cases of pretoxic and toxic multinodular goiter and adenoma, respectively. Also, calculated-dose strategies (doses adjusted to patient's weight) can be used, which is considered the most specific option, since the patient is prevented from receiving a higher or lower dose than necessary. In a study conducted by Rokni H et al., it was observed that, interestingly, permanent hypothyroidism was not significantly different between calculated and fixed dose regimens [17].

Once the dose of ^{131}I is administered, the patient may present three situations. The goal of treatment of hyperthyroidism is to bring patients to the euthyroid state.

Hypothyroidism is recognized as an important and more frequent side effect of treatment for hyperthyroidism. Hypothyroidism may be transient (usually 2–4 months after therapy) or permanent [17, 18]. Patients with permanent hypothyroidism usually need additional treatment with thyroid hormones (levothyroxine), whose doses are increased or decreased according to clinical and analytical controls.

On the other hand, it may happen that once the dose of 131-Iodine is administered, the patient persists in hyperthyroidism. In this case, refractoriness is discussed at the initial dose of metabolic therapy and it may be necessary to administer a second dose of ^{131}I after 6 months from the initial dose.

Risk factors such as the presence of thyroid antibodies, age and sex of the patient, etiology of hyperthyroidism, administration of antithyroid drugs and goiter size can influence the outcome of ^{131}I treatment [18]. Patients with antithyroid antibodies, young males, *Graves' disease* (more frequent than multinodular goiter and pretoxic/toxic adenoma), long period of time with high doses of antithyroid drugs or relapse after its suspension, large intrathoracic compressive goiters or *Graves´ophthalmopathy*, have more risk of failure to the initial treatment with 131-Iodine.

These fixed dose regimens of 131-Iodine (^{131}I) for each pathology: 10 mCi [370 MBq] *(Graves' disease)*, 12 mCi [444 MBq] (multinodular goiter and adenoma in "pre-toxic situation"), 15 mCi [555 MBq] (toxic multinodular goiter and toxic adenoma) have been previously studied, increasing the probability of healing and providing the lowest possible radiation to the rest of the body. Calculated-dose strategies (doses adjusted to patient's weight) have the advantage that they are individualized for each patient. In our department, calculated-dose strategies are used in childhood and adolescent patients, as well as in adults of low weight. However, the optimal way is to use adjusted doses to the weight of the patient and to a lesser extent the fixed doses.

Surgery (total thyroidectomy) is recommended when there are side effects of antithyroid drugs, non-adherence to pharmacological treatment, non-remissions in hyperthyroidism's recurrences after prolonged medical treatment, patients with severe exophthalmos, very large

goiters, multinodular goiters, large nodules on thyroid or refuse treatment with 131-Iodine. Although the treatment rate is high with surgery, serious complications such as recurrent laryngeal nerve injury and hypoparathyroidism may be seen [8, 13].

6.2. Radioiodine (^{131}I) administration protocol in our center

In all cases of treatment with 131-Iodine (*Graves' disease*, pretoxic/toxic multinodular goiter or pretoxic/toxic adenoma), treatment is performed in our department on an outpatient basis if the dose of ^{131}I is less than 30 mCi (1110 MBq).

Prior to the administration of the radioiodine dose, metabolic treatment is explained, as well as all the radiological protection measures to be followed, possible side effects such us fever due to radiation-thyroiditis (which usually remits at 48 h); cervical/pharyngeal complaints, that usually remit with analgesics or tachycardia. Additional treatment with β-blockers (except in patients with asthma or cardiac failure) during the first 2 weeks of management may help to reduce the patient's symptoms. This treatment can be given orally twice daily, at a dose of 2 mg/kg/day, and stopped when the patient becomes euthyroid [15]. After a detailed explanation, informed consent is signed.

If there are women of childbearing age, it is mandatory to ask the date of last menstruation and request pregnancy tests. To receive a therapeutic dose of ^{131}I, it is also necessary to have a thyroid scintigraphy in the last year.

As for the preparation, the patient should come fasting for at least 4 h and have stopped the medication with antithyroid drugs 2 days before. The medication with antithyroid drugs will be reintroduced 72 h after taking the radioiodine and half the dose scheduled until the next revision by endocrinology. There is another option such as discontinuing antithyroid drugs 1 week before treatment and starting again 1 week after treatment [13].

Once the patient has ingested the capsule, it is not necessary to carry out any diet low in iodine. However, it is mandatory that the patient stays for 2 more h fasting and performs the radiological protection measures (already explained previously) for 7–10 days following the administration of ^{131}I. This is due to a reasonable 131-Iodine half-life of 8 days [8, 13].

Following treatment, patients must be evaluated at 1, 3, 6 and 12 months for thyroid function tests, clinical symptoms and physical examination by endocrinology physicians to observe the response to metabolic therapy. Patients who develop euthyroidism and hypothyroidism in the sixth month are accepted as cured [13].

7. Radiation protection: ionizing radiation and radiobiology. Objective, pillars and radiological protection measures

7.1. Ionizing radiation and radiobiology

Nuclear medicine is the medical speciality that uses non-encapsulated sources of artificial ionizing radiation with diagnostic-therapeutic use and research. In these cases, the patient is the source of radiation. For these reasons, there is a risk of external radiation to health personnel,

patients' relatives and the general public. In addition, special attention is paid to the possibility of contamination because these tracers are excreted physiologically by tear secretions, saliva, sweat, urine, feces, genital fluids or breastfeeding.

Radiobiology studies the effects of ionizing radiation on cells. These effects are diverse and are classified into three large groups:

- According to the time of appearance: early or late effects.
- Depending on its action on cells: direct effects on DNA (breakage of DNA strands) or indirect effects (cellular damage by free radicals).
- From a point of view of dose dependence: deterministic effects ("dose-dependent", which can be prevented if this dose threshold is not exceeded) and stochastic effects (due to chance, cannot be prevented since they do not present dose threshold).

7.2. Objective, pillars and radiological protection measures

The main objective of radiation protection is to prevent the appearance of deterministic effects and limit the possibility of stochastic effects. The pillars of radiological protection are based on:

- Justification: obtain positive net benefit. Benefit/risk balance, where the benefit of the test must be greater than the risk.
- Optimization: exposure to ionizing radiation should be as low as reasonably achievable *("ALARA principle")*. It is because of that calculated-dose method may be more acceptable, due to considering that principle and an increasing desire for lowering annual dose of the general population [17].
- Limitation of doses: use the lowest possible dose to obtain good image quality and limit the radiological tests to be performed. Maximum doses (mSv) are established for members of the public, caregivers of the patient and health personnel, as well as specifically for the lens, skin and limbs.

The general measures in radiological protection are:

- Time: the shorter the time in contact with the radiation source (patient), the lower the received dose.
- Distance: it must be as far as possible from the radiation source (patient), since the dose received will be lower. The physical law of the *"inverse of the square of the distance"* is applied in such a way that if we move away twice the distance of the patient, we will decrease the dose 1/22 (1/4); if we go three times, the received dose will decrease 1/33 (1/9), and so on.
- Shielding: separation between the issuing source (patient) and the rest of people (operators / public). There are "primary shields" such as lead tubes used as a protector for the injection of the radiotracer. Also, mention the existence of "secondary shields", such as leaded aprons, thyroid protectors, eye protectors for lenses, gloves, glass or special screens.

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When a patient is treated with ^{131}I and released, it is important that members of the public, including the family, are not exposed to significant radiation. The regulations vary between countries, but there are certain general conditions under which outpatient therapy can be arranged. Between them, no adult can be exposed to 5 mSv (500 mrem), patients can be released when the administered dose is <1.22 GBq (33 mCi) [1221 MBq] and the emitted radiation must be <7 mrem/h at 1 m [16].

Several studies have measured radiation rates to family members and have confirmed that simple measures, such as sleeping in a separate bedroom and remaining more than 2 m from family members for a few days, ensure that the regulations are fulfilled [16]. In our nuclear medicine department of the *Regional University Hospital of Málaga*, we have prepared an informative document with the recommendations and precautions that patients should follow in treatment with radioiodine, which is explained and delivered to each of these patients (Appendix 1).

8. Special situations in nuclear medicine and radiation protection

8.1. Pregnancy and breastfeeding

"In nuclear medicine, a woman of childbearing age is considered pregnant until proven otherwise". In the nuclear medicine services, there are visible information leaflets to the public, especially for women of childbearing age who may be pregnant and whose duty it is to inform the center's health personnel.

In addition, it is mandatory to ask the date of last menstruation and about the possibility of pregnancy in the clinical history. Also, all women in this age group who are to be treated with radionuclides of iodine must have a negative pregnancy test, prior to the administration of the radiopharmaceutical as therapy [16]. The result of the pregnancy test will be recorded in the patient's health history.

Pregnant women with untreated overt hyperthyroidism are at increased risk for spontaneous miscarriage, congestive heart failure, thyroid storm, preterm birth, pre-eclampsia, fetal growth restriction, and increased perinatal morbidity and mortality [9].

Regarding the use of radioiodine, fertility could be reduced and abnormalities offspring will be increased. Several studies are related to larger doses of ^{131}I that are used to treat thyroid cancer [16]. Medical personnel should warn patients to avoid becoming pregnant during the time following the procedure with radionuclides. The time required depends on the type of radiopharmaceutical used; in the case of ^{131}I (either used for the treatment of hyperthyroidism or as ablative therapy of possible thyroid remnants in differentiated thyroid carcinoma) the consensus is that the conception should be deferred for 12 weeks (minimum 6 months) and that maternal thyroid function should be normal [16].

By avoiding pregnancy during this period, the objective is achieved to reduce the probability that the dose received to an embryo or fetus is greater than 1 mSv (dose limit to the public). Keep in mind that these compounds cross the placental barrier and there is a risk of an exposure of the fetus that can reduce the intelligence quotient by 30 points per gray (100 rads), and

may be associated with attention deficit disorders and impairment of figurative memory in the offspring and also a slightly increased cancer-risk possibility. According on the gestation period the patient is in, there is a greater probability of risk of [3, 16]:

- Pre-implantation stage (second week): abortions *("all-or-nothing law")*.
- Stage of organogenesis (second–eighth week): congenital malformations.
- Early fetal stage (8th–15th week): neurological alterations such as decrease of the intellectual coefficient.
- Late fetal stage (15th–25th week): neurological alterations and risk of developing radioinduced cancer that will be suffered before the age of 15 years.
- Special mention with the use of ^{131}I, therapeutic administration of radioiodine to the mother after the fetal gland is formed (after about 10 weeks into gestation) can result in fetal hypothyroidism. This is because after the eleventh week, the fetal thyroid concentrates iodine, and if the fetus is exposed, it will be born athyrotic.

For these reasons, radioiodine therapy is contraindicated in pregnancy, being the pharmacological treatment with oral antithyroid drugs the first line of therapy, mainly with propylthiouracil. Radioiodine would be acceptable when pregnancy is contemplated after at least 6 months, and thyroidectomy if conception is envisaged within a 6 month interval and/or if there is a large goiter [3]. It must also be borne in mind that these possibilities of therapy are considered second line, in the case of contraindication, refractoriness or failure to adherence to pharmacological therapy with anti-thyroid drugs.

Regarding breastfeeding, there are general guidelines on the time of interruption depending on the radiopharmaceutical used. In the case of ^{131}I for therapeutic purposes, breastfeeding should be completely suppressed after administration of ^{131}I. This condition does not occur with antithyroid drugs, since studies have shown that only limited amounts of propylthiouracil or carbimazole are secreted in breast milk, which explains that the neonatal exposure to these drugs is insignificant. Therefore, the use of low-moderate doses of carbimazole (<20 mg) or propylthiouracil (<300 mg) during breastfeeding is recommended [3].

8.2. Chronic renal failure and dialysis

Patients with chronic renal failure do not have a contraindication to receive treatment with 131-Iodine.

Holst et al. reviewed the medical literature and concluded that the ^{131}I dose does not need to be adjusted in patients who have end-stage renal disease and who are referred for the therapy of hyperthyroidism. However, they recommended ^{131}I administration as soon as possible after dialysis and a delay in subsequent dialysis until the maximum ^{131}I uptake has occurred in the thyroid [16].

Some cases of contamination of dialysis machines have been reported. In these cases where there may be a slight contamination with 131-Iodine in disposable items such as syringes or waste bags, these can be stored for several half-life periods until activity declines. Also these

patients should undergo dialysis in a private room and monitored by radiophysics personnel. Apart from this, no additional precaution is needed.

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2. Data collection: Elena Espinosa Muñoz.

3. Analysis and interpretation of data: Elena Espinosa Muñoz.

4. Drafting, revision, approval of the manuscript: Elena Espinosa Muñoz.

Conflict of interest

The authors declare that they have no conflict of interest.

The authors declare that the protocols established by their respective health centers have been followed to access the data of the clinical histories in order to be able to carry out this type of publication with the purpose of research/dissemination for the scientific community.

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A. Appendix 1

Nuclear medicine service.

Regional university hospital of Málaga.

Patients in radioiodine treatment.

Name and surname:

Dear SR / SRA:

For the treatment of your illness, we have given you a radioactive substance called 131-Iodine. This substance will remain in your body for several days until it disappears completely through the urine, because it eliminates itself. While this is beneficial for you, certain precautions must be taken in order to protect the people with whom you live. Therefore, we recommend that you follow these instructions for the next 7–10 days (from xx-xx-xxxx to xx-xx-xxxx):

- Avoid being around pregnant women and young children.
- If you stay in a room with your family for a long time, try to be as far away from them as possible (at least 1 meter away).

- When using the toilet, you must pull the cistern several times (approximately 4 times).
- Use your own napkin, towel, toothbrush, glass, plate, cutlery, and so on.
- Drink plenty of fluids.
- Daily shower and brushing of teeth after each meal.
- Wash your underwear and bedding in a different laundry from your family.
- Avoid having sex during these days.
- Sleep in a different room from the rest of your family.
- If you are of childbearing age, avoid becoming pregnant during the next 12 months.
- If you are the one who cooks at home, do it with rubber gloves (to avoid touching the food with your own skin).
- You can go out to the street only to walk and away from places with crowds of people. You should not enter closed places such as cafes, bars, shops, cinemas, and so on.

If you have any questions, do not hesitate to contact us by calling 0–00-000000. Thank you very much for your help.

Remember that you must continue fasting for 2 h after the administration of the dose of iodine.

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