REVIEW ARTICLE

Nuclear medicine and differentiated thyroid cancer

Sevastián S. Medina-Ornelas¹,* , Francisco O. García-Pérez¹ and Martín Granados-García²

¹Department of Nuclear Medicine and Imaging; ²Department of Head and Neck Surgery, Instituto Nacional de Cancerología, Ciudad de México, Mexico

Received on June 5, 2017; accepted on August 8, 2017
Available online: February 1, 2018

KEY WORDS
Thyroid cancer; Radioiodine; Nuclear medicine; Treatment

Abstract Those affected by differentiated thyroid cancer tend to have a favorable clinical course, but some may show an aggressive course with relapses. The optimal treatment is still controversial, especially regarding the extent of surgery, indications for radioiodine and suppression of thyroid-stimulating hormone. Correct risk assessment facilitates a selective approach to therapy. We present a review of the role of nuclear medicine in the evaluation, treatment and follow-up of patients affected by this interesting disease. (creativecommons.org/licenses/by-nc-nd/4.0/).

*E-mail for correspondence: dr.sevastian@outlook.com (S.S. Medina-Ornelas)
INTRODUCTION

According to GLOBOCAN, in Mexico there were 3,036 cases of thyroid cancer in 2012 (725 in men and 2,311 in women), accounting for 2.1% of total malignant neoplasms. Differentiated thyroid cancer (DTC) accounts for at least 85% of cases and includes papillary, follicular, and Hürthle cell types. Papillary cancer, which is the most common type, is associated with excellent survival, but some patients have a less favorable clinical course, with metastases or relapses that involve cervical lymph nodes and, less frequently, the lungs and bone.

Nuclear medicine makes use of DTC pathophysiology peculiarities and plays a highly important role both in adjuvant treatment and in follow-up and management of relapse. Treatment must be as efficacious as possible, with the least sequels and lowest cost; this is why individualized treatment is emphasized, according to the histological type, extent of disease and risk of relapse.

IODINE 131

Iodine 131([131]I) or radioiodine is produced in a nuclear reactor by tellurium dioxide neutron irradiation during uranium fission. Its physical half-life is 8.02 days. Iodine 131 atoms emit beta particles with several energies, the highest of which is 606 keV, which is fundamental for iodine 131 therapeutic effect. After the beta particle emission, it emits gamma rays with an energy of 364 to 637 keV, which is useful to obtain gammagraphic images or by means of single-photon emission computed tomography (SPECT). Iodine 131 is supplied as liquid iodide or in capsules for oral intake.

RADIOBIOLOGY

Most [131]I-emitted radiation occurs in the form of beta particles that disrupt chemical bonds and inflict devastating damage to the DNA, triggering cellular dysfunction and ultimately programmed cell-death activation. This occurs by means of two pathways: the first, or direct one, results from beta particles irradiation on DNA simple strand, whereas the second, or indirect one, occurs by means of interaction with water molecules forming free radicals, which damage the DNA; the latter pathway is the most important owing to the higher damage inflicted.

Beta particles penetrate tissues a couple of millimeters. The beta particle-delivered and absorbed dose for a particular radioactive dose increases within a tissue radius of up to 10 mm, and then it remains constant. Since beta particles virtually do not escape from large tumor deposits, large iodine 131 doses can be delivered without damaging the surrounding tissues. The lack of homogeneity in the radiation dose is due to iodine 131 irregular distribution in neoplastic foci and to beta particles small radius of action.

Gamma radiation contributes only with 10% of total radiation, and only a small fraction of gamma rays are absorbed by functional tissue, while most part abandons the patient through his/her surface; this radiation can be detected to be transformed into images and is responsible for the patient having to remain isolated when doses higher than 30 mCi are administered, according to current international legislation.

Iodine 131 efficacy is directly proportional to the uptake and retention by tumor tissue. Effective tumor uptake occurs if it reaches 0.5% of the iodine 131 dose per gram of tissue and has a biological half-life of 4 days. With a dose of 150 mCi (equivalent to 5.6 GBq) of iodine 131, the tumor can receive 25,000 cGy, which equates to 4-fold the dose released by external-beam radiotherapy.

BIOLOGY

Iodine is essential for the synthesis of thyroid hormones. After its ingestion, it is reduced to iodide at the proximal small intestine. More than 90% is absorbed during the first 60 min. It is distributed in the blood as an extracellular ion, similar to chloride, to be incorporated to cells thanks to the Na+/I- (NIS) co-transporter.

NIS is a protein of the follicular cell basolateral membrane that co-transport two sodium ions and one iodide ion. The sodium gradient provides the energy for this transfer, and it is maintained by the Na⁺/K⁺-ATPase pump. Within the cell, iodine penetrates the apical membrane until the colloid, thanks to transporters such as pendrin. Apical membrane thyroid peroxidase (TPO) acts on iodine by means of three sequential steps: first it oxidizes it, then it incorporates it to thyroglobulin (Tg) tyrosine residues, and finally it catalyzes the coupling of two iodinated tyrosine residues to form future hormones. This process is called iodine organification.

Subsequently, depending on the body’s needs with regard to thyroid hormones, Tg is endocytosed by the apical membrane in the form of colloid droplets that are degraded by lysosomal enzymes, thus releasing triiodothyronine and thyroxine (T3 and T4, respectively) into the bloodstream. This process is regulated by TSH, which, after binding to its receptor (TSH-r) at the basolateral membrane, activates AMPc-dependent pathways and induces iodine transportation by regulating both transcriptional and post-transcriptional NIS expression (Fig. 1).
**Na⁺/I⁻ co-transporter normal distribution**

In addition to thyroid tissue, NIS mRNA has also been detected in the salivary glands, the stomach, the thymus, the breasts and, at low levels, in the prostate, ovary, adrenal glands, lung and the heart. This is consistent with iodine 31 normal uptake at the salivary glands, the stomach, lactating breasts and the placenta. Occasionally, iodine 131 absorption is also observed in non-lactating breasts.

**Na⁺/I⁻ co-transporter expression in thyroid carcinoma**

Using immunohistochemistry with anti-NIS antibodies, NIS is detected at lower proportion in neoplastic thyroid tissue that in normal tissue, and heterogeneous expression is demonstrated in papillary or follicular carcinoma malignant cells. In neoplastic thyroid tissues, NIS mRNA expression is 10 to 1,200-fold lower than in normal thyroid tissue; TPO mRNA expression is 5-500-fold reduced, whereas Tg mRNA expression is 300-fold lower. Dohan et al. reported that 70% of thyroid tumors show an increase in NIS extracellular expression with regard to healthy thyroid tissue. These discordant results are explained by methodological differences, but also suggest that NIS is overexpressed in neoplastic cells, although malignant transformation interferes with NIS correct localization within the cell, which deteriorates its function.

In addition, most investigators document that HIS has an inverse relationship with neoplastic thyroid tissue that is normal tissue, and heterogeneous expression is demonstrated in papillary or follicular carcinoma malignant cells. In neoplastic thyroid tissues, NIS mRNA expression is 10 to 1,200-fold lower than in normal thyroid tissue; TPO mRNA expression is 5-500-fold reduced, whereas Tg mRNA expression is 300-fold lower. Dohan et al. reported that 70% of thyroid tumors show an increase in NIS extracellular expression with regard to healthy thyroid tissue. These discordant results are explained by methodological differences, but also suggest that NIS is overexpressed in neoplastic cells, although malignant transformation interferes with NIS correct localization within the cell, which deteriorates its function.

**ABLATION AND TREATMENT WITH IODINE 131**

Iodine 131-uptake occurs under TSH influence and AMPc activation, but other factors also have an influence: insulin, insulin-like growth factor 1 and epidermal growth factor.

**STRATEGIES TO ELEVATE THYROID-STIMULATING HORMONE**

To stimulate iodine 131 uptake by tumor cells, suppressive medication with levothyroxine is usually discontinued in order to elevate endogenous TSH or recombinant human TSH (rhTSH) (Thyrogen) is administered. This assumes that neoplastic cells preserve certain differentiation and response to hormones. Occasionally, thyroid cancer loses this capability and is associated with a considerably deteriorated prognosis.

After total thyroidectomy, T3, T4 and TSH levels are initially normal and, 2-3 weeks later, TSH levels begin to rise while those of T3 and T4 decrease. Hormone replacement treatment is generally avoided within the first 4-6 weeks after thyroidectomy if, based on risk assessment, iodine 131 administration has been decided. However, other institutions, owing to logistics, start hormone replacement therapy immediately.

TSH elevation above 30 mU/L is necessary to obtain iodine 131 sufficient concentration in NIS-expressing cells. Discontinuing or avoiding hormone replacement therapy for 4 weeks in thyroidectomized subjects reduces T3 and T4 levels and elevates those of TSH. Consequently, patients are exposed to a prolonged period of hypothyroidism and associated symptoms, with a deterioration of quality of life and probability of tumor growth.

An alternative to avoid the hypothyroid state caused by LT4 discontinuation includes the use of rhTSH, which has an identical structure to human TSH, but its glycosylation differs, and it has higher sialic acid content, which is associated with lower immune activity, less affinity for TSH-r and lower bioactivity in vitro than human TSH.

In patients with DTC and preserved renal function receiving 0.9 mg of rhTSH, it has a mean half-life of 22 h. T3 and T4 concentrations are increased by 54% and 89%, respectively, between 4 and 8 hours after rhTSH administration, while Tg peak occurs at 48 h. One study compared the rate of radiation exposure between individuals undergoing hormone suppression versus rhTSH administration and demonstrated that exposure to radiation is lower and shorter with the second procedure, which results in Tg lower concentration and less iodine 131 uptake by tumor cells.

rhTSH is highly efficacious, but relatively expensive. A third strategy consists in replacing LT4 with LT3, which has a much shorter half-life: 1-3 days (instead of 7 days of LT4), and thus it can be discontinued for less time to elevate TSH levels. Patients who discontinue LT4 and replace it with LT3 undergo only 2 weeks with hypothyroidism, whereas with LT4 it is 4 weeks.

The need to follow a low-iodine diet during the 2 weeks prior to iodine 131 administration, in order to obtain a < 50 µg/gCr ioduria, has been pointed out. This is based on old studies where iodine uptake by tumor cells was shown to increase to the double after a low-iodine diet; however, there are no studies examining if a low-iodine diet impacts on relapse or mortality rates.

rhTSH is reserved for special cases where the hypothyroid state can aggravate a subjacent medical condition such as poorly-controlled metabolic syndrome, chronic kidney disease (glomerular filtration rate [GFR] < 50 mg/mL), major depression, heart arrhythmia (particularly if on treatment with amiodarone and it is irreplaceable) or in patients with bulky residual and/or metastatic tissue that hinders TSH elevation owing to thyroid hormones continuous production.

The British Thyroid Association (BTA) guidelines suggest that the method of choice in patients with T1-T3, N0, N1a, M0 and R0 is rhTSH administration, but in high-risk patients (see below), on relapse, with metastatic disease, the
method of choice should be LT4 discontinuation; however, prospective studies are required to support this recommendation.

Regardless of the employed strategy, TSH levels have to be verified to be optimal when iodine 131 is received; i.e. above 30 mU/L; TSH is usually measured together with Tg and anti-thyroglobulin antibodies (anti-Tg Abs)\(^2\) (Fig. 2).

**RISK ASSESSMENT**

Ablation with radioiodine remains controversial, but it is argued that iodine 131 administration simplifies follow-up by eliminating normal or neoplastic Tg-producing thyroid tissue, which facilitates relapse identification by measuring Tg and preventing anti-Tg Abs continuous production\(^3\). The decision to administer ablative doses should be rational, based on risk assessments. The American Thyroid Association (ATA) (2015) and BTA (2014) guidelines propose similar systems, and even the National Comprehensive Cancer Network (NCCN) (V1.2016) concurs in several points\(^4\),\(^5\) (Table 1).

The ATA guidelines were prompted by the inability of other systems to establish the risk of relapse; previous systems are only useful to establish the mortality risk. It is a fact that a patient with low mortality risk can have high risk of relapse; for this reason, ATA, BTA and NCCN recommend for relapse-risk assessment to be performed in all patients.

**Who should receive iodine 131 and which is the appropriate dose?**

The purpose to administer iodine 131 is to eliminate any thyroid carcinoma and normal thyroid tissue microscopic deposit. NCCN and ATA propose three objectives for its administration: remnant thyroid tissue ablation (the term ablation should only be employed when the first dose of iodine 131 is administered in order to simplify follow-up); adjuvant therapy, to eliminate subclinical metastases, and therapeutic doses, the purpose of which is to treat local persistence or confirmed metastases. However, for practical purposes, iodine 131 application is usually classified as ablation and treatment. Iodine 131 efficiency is inversely proportional to the volume of residual thyroid tissue and directly proportional to TSH levels, and all macroscopic disease should therefore be surgically removed\(^6\).

Currently, there are three approaches to define the iodine 131 dose: fixed doses, dose determined by blood upper limit and qualitative tumor dosimetry. The two latter are often reserved for patients with metastasis or for unusual situations such as renal failure, children, elderly patients and patients with extensive lung metastases. Owing to the complexity of the two latter methods, the policy of fixed doses is favored\(^7\).

**Low-risk patients**

Prospective trials of the National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG) suggest that disease-specific progression-free survival and overall survival do not improve with iodine 131 treatment in stage I or II patients. A multicenter retrospective study, where 1,298 low-risk patients were evaluated, with an average follow-up of 10.3 years, failed to find benefits for ablation with iodine 131 as regards overall survival and progression-free survival\(^8\). In particular, there is little evidence supporting the use of iodine 131 in these patients.

Although there are no advantages in terms of survival, certain studies have demonstrated the convenience of low versus high doses in low-risk patients, regardless of the stimulation method\(^9\). Cheng et al.\(^10\) analyzed 9 randomized trials that included 2,569 low-risk patients and different TSH stimulation methods (rhTSH and hormone deprivation). They found no differences in iodine 131 efficacy between 30 and 100 mCi.

Ablation with 30 mCi or with 100 mCi are equivalent, regardless of the stimulation method, with the advantages that doses not higher than 30 mCi do not require hospitalization, quality of life is similar and iodine 131-related side

![Figure 2. Strategies to elevate TSH. In order to achieve optimal levels for iodine 131 to be received, three strategies can be followed: the first one consists in discontinuing Levothyroxine 4 weeks prior to iodine 131 administration; in the second one, levothyroxine is exchanged for liothyrone, which is discontinued 2 weeks prior to iodine 131; finally, administering rhTSH without discontinuing thyroid hormones can be an alternative.](image-url)
The concept of high, fixed doses was used, i.e., therapeutic effect, with the possibility for higher doses to be administered in case of recurrence. A dose of up to 100 mCi can provide the desired advantage in subjects older than 45 years, although follow-up time did not exceed 7 years. On the other hand, there was an advantage in subjects older than 45 years who received the treatment; although it didn’t surpass 73%, it was higher than the 59% obtained by the group that didn’t receive it. Lamartina et al. contributed to confusion, since in the review of 13 non-randomized trials they found no benefit, whereas 11 supported it. Further studies are required, with standardized and homogeneous criteria.

Recommended doses for this group of patients are 50 to 100 mCi, with higher doses being reserved for patients with more risk factors, i.e., high-risk patients (see below). Although there are no prospective studies involving this group of patients, a dose of up to 100 mCi can provide the desired therapeutic effect, with the possibility for higher doses to be administered in case of recurrence.

**HIGH-RISK PATIENTS**

Routine ablation is recommended in high-risk patients, and the first iodine 131 dose is suggested not to exceed 150 mCi, especially in patients older than 45 years. Different approaches have been proposed for the treatment of relapse or persistence. The concept of high, fixed doses was used, i.e., 100-150 mCi, if persistence or relapse was confined to the thyroid bed; 150-175 mCi if there was lymph node involvement; 200-250 mCi if there were lung metastases, and in case of bone metastases, 200-300 mCi were resorted to. However, iodine 131 efficacy is related to the radiation dose released to the neoplastic tissue and the radiosensitivity thereof, and radiosensitivity is therefore higher in younger individuals (<45 years) with small metastases (<10 mm) and well differentiated tumors (papillary and follicular), avid for iodine 131.

Currently, the maximum tolerated radiation dose (MTRD) is recognized to be 200 cGy in blood and with older age, renal function decreases, as it occurs with patients with renal or heart failure, which decreases iodine 131 clearance. In this sense, Tuttle et al. demonstrated that empirical doses of 140 mCi exceeded the MTRD by less than 7% in patients younger than 70 years; this percentage increased to 13% in subjects older than 80 years; on the other hand, doses of 200 and 250 mCi exceeded the MTRD in subjects younger than 70 years by 15 and 22%, respectively, and in those older than 70 years, by up to 38 and 50%, respectively. However, it is possible for doses higher than 200 mCi to be administered, as long as a dosimetric study is previously performed and patients are younger than 65 years of age.

Currently, administering iodine 131 at a dose higher than 200 mCi is not recommended, since its superiority has not been demonstrated; on the contrary, exposure to radiation is higher, side effects are more common and prolonged, and cumulative dose is higher with no better survival.

**Usefulness of pre- and post-treatment scan with iodine 131**

Some nuclear medicine centers perform a full-body scan prior to receiving ablative or therapeutic doses, in order to estimate the required iodine 131 dose. With the availability of SPECT/CT equipments, planar scan sensitivity and specificity have been increased. Planar scan sensitivity reaches 41%, and specificity, 68%, while SPECT specificity reaches 45%, and specificity, 89%, but with SPECT/CT, sensitivity increases to up to 50% and specificity is as high as 100%.

---

**Table 1. Risk groups according to ATA**

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All the following are present:</td>
<td>Any of the following is present:</td>
<td>Any of the following is present:</td>
</tr>
<tr>
<td>- No metastasis</td>
<td>- Microscopic extrathyroidal extension</td>
<td>- Macroscopic extrathyroidal extension</td>
</tr>
<tr>
<td>- Complete resection</td>
<td>- Iodine 131 uptake outside the thyroid bed after remnants’ ablation</td>
<td>- Incomplete tumor resection (R2)</td>
</tr>
<tr>
<td>- No extrathyroidal extension</td>
<td>- Aggressive histology (tall cell, insular cell, columnar cell, hobnail, Hürthle cell variants)</td>
<td>- Metastasis</td>
</tr>
<tr>
<td>- No aggressive histology</td>
<td>- Papillary carcinoma with vascular invasion</td>
<td>- Post-5x Tg elevated levels</td>
</tr>
<tr>
<td>- No vascular invasion</td>
<td>- Pathologic N1 (&gt; 5 pathologic lymph nodes) with overall dimension not larger than 3 cm</td>
<td>- Pathologic N1 with any number of metastatic lymph nodes or overall dimension larger than 3 cm</td>
</tr>
<tr>
<td>- No uptake outside the thyroid bed post-ablation with iodine 131</td>
<td>- Multifocal papillary carcinoma with minimal extrathyroidal extension and BRAFV600E mutation</td>
<td>- Follicular carcinoma with extensive vascular invasion (&gt; 4 foci)</td>
</tr>
<tr>
<td>- N0, N1 &lt; 5 micrometastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Encapsulated, intrathyroidal follicular variant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Well differentiated, intrathyroidal follicular carcinoma with minimal capsular invasion, and with or without minimal vascular invasion (&lt; 4 foci)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Iodine 131 uptake outside the thyroid bed after remnants’ ablation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Aggressive histology (tall cell, insular cell, columnar cell, hobnail, Hürthle cell variants)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Papillary carcinoma with vascular invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pathologic N1 (&gt; 5 pathologic lymph nodes) with overall dimension not larger than 3 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Multifocal papillary carcinoma with minimal extrathyroidal extension and BRAFV600E mutation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---
Avram et al., in a series of 320 patients who were practiced pre-iodine 131 ablation SPECT/CT, restaged 4% of patients younger than 45 years and 25% of those older than 45 years. With the widespread use of clinicopathological factors, pre-ablation scan is currently not recommended as a strategy to define the dose, but it may be necessary in patients in whom residual disease has not been evaluated with a histopathology study or by ultrasound.

“Thyroid stunning” is defined as a decrease in iodine 131 uptake by thyroid neoplastic cells after a diagnostic iodine 131 dose administration. It can be due to a reduction in the number of thyroid functional cells owing to iodine 131 beta radiation-produced cell death or to a decrease in viable thyroid cells’ capability to capture or retain iodine 131 during a time interval. Guiraud-Vitaux et al. noted that there can be infra-therapeutic necrosis owing to high doses of iodine 131, which would imply therapeutic doses efficacy reduction after an imaging diagnosis. However, research on this phenomenon has led to conflicting conclusions.

Recent investigations have demonstrated that it is a radiobiological phenomenon that is closely related to absorbed radiation, rather than to the administered dose, and that stunning is often observed 48 h after a dose of iodine 131 administration.

In another line of thought, practicing a body scan 5-8 days after ablation or therapeutic dose is recommended, since it identifies additional metastatic foci in 10-26% of patients when compared with a diagnostic scan, although some series of studies have reported new foci in up to 31%, SPECT/CT increases sensitivity to up to 78% and specificity to up to 100%, thus reducing the need for sectional studies in 20% of cases (Fig. 3).

**FOLLOW-UP**

Full-body scan plus SPECT/CT with iodine 131 is used for follow-up at least 6 months (according to ATA) or at least 9 months (according to BTA) after the ablation or therapeutic dose in three scenarios: patients with abnormal uptake beyond the thyroid bed after post-treatment or post-ablation scan; patients with scarce information at post-ablation scan owing to large remnants that hinder defining if there has been uptake beyond the thyroid bed and patients with presence or de novo appearance of anti-Tg Abs, even in the absence of findings suspicious of residual disease by ultrasound.

Clinical, biochemical and imaging findings should be put together during follow-up in order to redefine treatment, to provide the most appropriate therapy and to define the response. Tuttle et al. and Vaisman et al. have contributed to a better evaluation by defining 4 response categories:

- **Excellent response:** which is obtained when there is no evidence of structural (by imaging with ultrasound

![Figure 3](image.png)

Figure 3. A: anterior projection planar scan practiced 48 h after 5 mCi iodine 131 administration. Intense abnormal focal uptake limited to the thyroid bed is observed. Owing to respiratory symptoms, a non-contrasted CT scan was practiced, where multiple nodular images consistent with lung metastases are observed in both lungs (C and D); therefore, administering 200 mCi of iodine 131 was decided and, 7 days later, planar scan anterior projection shows intense uptake in the thyroid bed and in both lungs (B). Subsequently to the scan, SPECT/CT revealed pulmonary infiltrate and iodine 131 uptake, not visualized in the pre-ablation planar scan (E).
or SPECT/CT) and clinical or biochemical disease (Tg suppressed < 0.2 ng/mL or stimulated < 1 ng/mL). It occurs in 86-91% of low-risk patients, in 57-63% of intermediate-risk patients and in 14-16% of high-risk patients.

- Incomplete biochemical response: it results when there is a negative imaging test, but > 1 ng/mL suppressed Tg levels, > 10 ng/mL stimulated Tg or anti-Tg Abs elevation. This response is shown by 11-19% of low-risk patients, 21-22% of those with intermediate risk and 16-18% of those with high risk.

- Incomplete structural response: it refers to those patients with structural or functional disease by any imaging method with any level of Tg and/or anti-Tg Abs; it is present in 2-6% of low-risk patients, 19-28% of intermediate-risk patients and in 67-75% of those with high risk.

- Indeterminate response: it refers to imaging unspecif findings, < 1 ng/mL suppressed Tg levels, < 10 ng/mL stimulated Tg levels or anti-Tg Abs stable levels. This response is present in 12-29% of low-risk patients, 8-23% of intermediate-risk patients and in 0-4% of high-risk patients.

Performing SPECT/CT full-body scans is not sufficient, but they have to be correlated with the specific markers, Tg and anti-Tg Abs. Tg levels’ measurements are well known to be of particular importance to monitor patients with residual disease and relapse. In the absence of anti-Tg Abs, Tg has high sensitivity and specificity to document disease relapse or persistence. Many authors recommend its measurement with stimulated TSH, since it can increase Tg levels up to 5-10-fold. Tg stimulated levels < 1 ng/mL, in the absence of anti-Tg Abs, have a probability of 98% to identify disease-free patients.

On the other hand, anti-Tg Abs can be present or appear de novo in up to 25% of patients, particularly in those with Hashimoto’s thyroiditis. Thyroid autoimmune diseases are associated with the production of antibodies in intrathyroid lymphocytes and, after total thyroidecomy, their levels remain elevated for years with no evidence of disease. The reason is that the autoimmune response in reaction to Tg response in antigen-presenting cells is initiated and spread in cervical lymph nodes. Anti-Tg Abs half-life after total thyroidectomy is 10 weeks. This rapid decrease is due to the formation of Tg-anti-Tg Abs complexes in response to Tg elevation after surgery.

Surgery can initiate or favor anti-Tg Abs de novo appearance, which tend to decline over the course of months. Patients may not reach an anti-Tg Abs negative status within the first postoperative year and even exhibit an increase (de novo appearance) within the first 6 months after treatment with iodine 131 when there is Tg release secondary to thyroid tissue radiolytic damage.

For anti-Tg Abs efficacious long-term follow-up, it is essential for a sensitive method to be used every 6-12 months. Kim et al. found that, in patients with anti-Tg Abs levels decrease higher than 50% within 6-12 months after iodine 131, < 1% developed relapse; conversely, 19% of patients with a decrease lower than 50% in the same interval experienced relapse, whereas 37% of those who had increased levels experienced relapse.

Role of PET/CT with 2-[18F]-fluoro-2-deoxy-D-glucose

PET/CT with 2-[18F]-fluoro-2-deoxy-D-glucose (FDG PET/CT) is a valuable tool in patients with Tg and/or anti-Tg Abs levels elevation and negative iodine 131 scan. In thyroid neoplasms, radio-drug 18F-FDG uptake is restricted to the most aggressive or high-grade tumors, with limited or no uptake by well-differentiated tumors; Feine et al. named this the “flip-flop” phenomenon.

Owing to its hydrophilic nature, glucose requires transmembrane glucose-transporting (GLUT) proteins, which enable for it to cross the cell membrane. GLUT1 overexpression in thyroid neoplasms cell membrane is closely related to tumors with more aggressive biological behavior. Furthermore, TSH plays an important role, since it stimulates glucose transportation and thyrocyte glycolytic activity through GLUT1 translocation, as well as GLUT1 neosynthesis by activation of its gene expression, which indicates that FDG PET/CT sensitivity is influenced by TSH levels.

Salvatori et al. suggest that the indications to practice FDG PET/CT should be divided into strongly defined and not completely defined indications. The former include patients with Tg elevated levels (> 10 ng/mL) and a negative imaging test (ultrasound, scan with iodine 131). Anti-Tg Abs elevation or de novo appearance can drastically alter Tg values. Therefore, anti-Tg Abs elevation or de novo appearance in the presence of Tg levels < 2 ng/mL is also an indication.

FDG PET/CT prognostic importance lies in that most patients with metastatic disease have 18F-FDG avidity, which suggests higher aggressiveness, dedifferentiation and metabolically active cells, whereas a negative FDG PET/CT predicts a favorable prognosis. In a multivariate analysis carried out by Wang et al., 400 patients with high-risk characteristics were analyzed, with age and FDG PET/CT being observed to be the most important prognostic factors, since there was an inverse relationship between survival and the number of metabolically-active lesions.

Sensitivity and specificity are related to Tg levels. In a meta-analysis conducted by Lebolleux et al., sensitivity and specificity were shown to be strongly influenced by a Tg cutoff value > 10 ng/mL, and to be 83% and 84%, respectively, in patients with non-iodine-avid disease. Another analysis demonstrated that sensitivity at Tg levels < 10 ng/mL, > 10 ng/mL, but < 100 ng/mL and > 100 ng/mL was 10.5, 75.6 and 91%, respectively. In addition, sensitivity also depends on metastases site and size. For < 10 mm lymph node metastases, sensitivity is 69.7% and specificity 83.3%, whereas for those larger than 11 mm, sensitivity is 95.7% and specificity 80%. On the other hand, with < 10 mm lung metastases, sensitivity is 41% and specificity 80%, while for those larger than 11 mm, sensitivity is 94% and specificity 89%.

As previously mentioned, SPECT/CT sensitivity is higher and, in the absence of findings with Tg or anti-Tg Abs elevated levels, the need for SPECT/CT is therefore also indicated (Fig. 4).

Owing to BRAF (V600E)-related oncogenic mutations recent implementation in some centers, there are some studies demonstrating the existence of a correlation with hypermetabolism in patients with such mutation. In the study carried out by Nagarajah et al., with a sample of 48 patients...
with DTC, 24 of them with BRAF (V600E) mutation and 24 with wild type BRAF, a significantly higher correlation of metabolic activity was observed in patients with the BRAF (V600E) mutation, and it was concluded that a high metabolic rate can be associated with mutation of the gene, which entails higher tumor aggressiveness and worse prognosis; however, further studies are required in order to correlate these findings.

Not-completely-defined indications include PET/CT practice in patients with refractory disease, in order to assess the response to treatment with targeted therapies, for high-risk histology staging and follow-up, in indeterminate thyroid lymph nodes after aspiration biopsy and, recently, for radio-guided surgery.

To better illustrate iodine 131-managed DTC patients follow-up and treatment, please refer to Fig. 5.

Figure 4. A: anterior projection planar scan practiced 48 h after 5 mCi iodine 131 administration. Biodistribution and usual elimination routes, without abnormal uptake focal zones, are observed in a patient with stimulated TSH and Tg > 100 ng/mL. B: seven days later, FDG PET/CT was practiced, where abnormal focal uptake is observed at the right parasternal midline. C and D: Two nodules with intense radiotracer uptake at level VI right cervical lymph nodes and level 1R and 3A mediastinal lymph nodes are observed on axial and coronal sections.

<table>
<thead>
<tr>
<th>Tg</th>
<th>Anti-Tg antibodies</th>
<th>$^{131}$I Scan &amp; SPECT/CT</th>
<th>FDG PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>no</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>no</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>+</td>
<td>no</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 5. Recommendations according to post-radioliodine administration clinical scenario.
ACKNOWLEDGEMENTS

To Dr. Claudia Mosqueda and Dr. Angélica Arellano, for their collaboration in the generation and edition of illustrations.

REFERENCES

35. Sabra M, Grewal R, Ghossein RM, Tuttle RM. Higher administered ac-tivities of radioactive iodine are associated with less structural persistent response in older, but not younger, papillary thyroid cancer patients with lateral neck lymph node metastases. Thyroid. 2014;24(7):1088-95.

Nuclear medicine and differentiated thyroid cancer 238


55. Vaisman F, Shaha A, Fish S, Michael Tuttle R. Initial therapy with either thyroid lobectomy or total thyroidectomy without radioactive iodine remnant ablation is associated with very low rates of structural disease recurrence in properly selected patients with differentiated thyroid cancer. Clin Endocrinol (Oxf). 2011;75(1):112-9.


59. Spencer CA. Clinical review: Clinical utility of thyroglobulin antibody (TgAb) measurements for patients with differentiated thyroid cancers (DTC). J Clin Endocrinol Metab. 2011;96(12):3615-27.


