Nuclear medicine impact on differentiated thyroid cancer diagnosis and treatment

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Abstract

Patients affected by differentiated thyroid cancer usually have a favorable clinical course, since the cornerstone of treatment is surgery; despite this, some patients may develop an ominous outcome, due to the clinical-pathological features of this disease. Optimal treatment remains controversial, especially regarding the extent of surgery, indications for radioiodine and thyroid-stimulating hormone. The correct evaluation of risks before and after surgery facilitates a selective treatment approach; highlighting the importance of reviewing the impact of nuclear medicine on the correct evaluation, treatment and follow-up of patients suffering from this neoplasm.

KEY WORDS: Thyroid cancer. Radioiodine. Nuclear medicine.

Introduction

According to Globocan, in 2012, in Mexico there were 3036 cases of thyroid cancer (725 in men and 2311 in women), which accounted for 2.1 % of total malignant neoplasms.¹ Differentiated thyroid cancer (DTC) represents at least 85 % of cases and includes the papillary, follicular and Hürtle-cell types. Papillary cancer, the most common type, is associated with an excellent survival, although some patients have a less favorable clinical course, with metastasis or relapses that affect the cervical lymph nodes, and less frequently, lungs and bone.^{2,3}

Nuclear medicine uses the peculiarities of DTC pathophysiology and plays a highly important role, both in adjuvant treatment and in follow-up and management of relapses. Treatment should be the most efficacious, with the least sequels and lower cost; for this reason, emphasis is made on individualization according to histological type, extension of the disease and risk of relapse.

Iodine 131

Iodine 131 (¹³¹I, radioiodine or RAI) is produced in a nuclear reactor by neutron irradiation of tellurium dioxide during uranium fission. Physical half-life is 8.02 days. Iodine 131 atoms emit β particles with several energies, the maximum being 606 keV, essential for iodine 131 therapeutic effect; after the β particle emission, it emits γ rays with energy ranging from 364 to 637 keV, which are useful to obtain scintigraphy images or by single photon emission computed tomography (SPECT). Iodine 131 is supplied in the form of liquid iodide or in capsules for oral intake.⁴

Radiobiology

The highest radiation emitted by iodine 131 occurs in the form of β particles that interrupt chemicals bonds and inflict devastating damage to the DNA, which causes cell dysfunction and programmed cell death activation. This occurs in two ways: the first one or direct results from β particles irradiation on single-strand

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DNA, while the second, or indirect, occurs through interaction with water molecules, which forms free radicals that damage the DNA; the latter is the most important due to the larger inflicted damage.⁵

The β particles penetrate the tissue a few millimeters. The dose absorbed and delivered by the β particles for a given radioactive dose increases with the tissue radius up to 10 mm and then it remains constant. Since β particles virtually do not escape from large tumor deposits, large doses of iodine 131 can be supplied 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 β particles' small radius of action.

The γ radiation provides only 10% of total radiation, and only a small fraction of γ rays are absorbed by functional tissue, while the largest part leaves through the body surface; this radiation can be detected to be transformed into images and is responsible for the patient to have to remain isolated when doses higher than 30 mCi are administered, according to current international legislation.⁶

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 four days. With a 150 mCi dose (equivalent to 5.6 GBq) of iodine 131, the tumor can receive 25,000 cGy, which equals four times the dose released in an external beam radiation session.⁷

Biology

Iodine is essential for thyroid hormones synthesis. After its intake, it is reduced to iodide in the proximal small intestine. More than 90 % is absorbed during the first 60 minutes. It is distributed in blood as an extracellular ion, similar to chloride, to be incorporated into the cells thanks to the Na^+/I^- symporter (NIS).⁸

NIS is a follicular cell basolateral membrane protein. NIS cotransports two sodium ions and one iodide ion. The sodium gradient provides the energy for this transfer and is maintained by the Na^+/K^+ -ATPase pump. Within the cell, iodine penetrates the apical membrane to the colloid, thanks to transporters such as pendrin. Apical membrane thyroperoxidase (TPO) acts on iodine in 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 the future thyroid hormones. This process is called iodine organification.⁹

Then, depending on the need for thyroid hormones by the body, Tg is endocytosed by the apical membrane in the form of colloid drops that are degraded by lysosomal enzymes, releasing triiodothyronine and thyroxine (T3 and T4, respectively) into the bloodstream. This process is regulated by thyroid stimulating hormone (TSH), which after binding to its receptor (TSH-r) in the basolateral membrane, activates cAMP-dependent pathways and induces the transport of iodine by regulating NIS both transcriptional and posttranscriptional expression (Fig. 1).

NIS normal distribution

In addition to thyroid tissue, mRNA-NIS has been detected in salivary glands, the stomach, thymus and breast, and at low levels in the prostate, ovary, adrenal glands, lung, and heart.¹⁰ This is consistent with iodine 131 normal uptake in salivary glands, stomach, lactating breast and placenta. Occasionally, iodine 131 absorption is also observed in non-lactating breasts.¹¹

NIS expression in thyroid carcinoma

Using immunohistochemistry with anti-NIS antibodies, NIS is detected at a lower proportion in neoplastic thyroid tissues in comparison with normal tissues, and heterogeneous expression is demonstrated in papillary or follicular carcinoma malignant cells. In neoplastic thyroid tissues, mRNA-NIS expression is 10 to 1200 times lower with regard to normal thyroid tissue; mRNA-TPO expression is reduced 5 to 500 times, while mRNA-Tg expression is 300-fold lower.¹² Notwithstanding, Dohan et al.¹³ reported that 70 % of thyroid tumors show an increase in NIS intracellular expression with regard to healthy thyroid tissue. These discordant results are explained by methodological differences, but it also suggests that although NIS is overexpressed in neoplastic cells, malignant transformation interferes with its correct location within the cell, which impairs its function.¹⁴

In addition, most researchers document that NIS expression has an inverse relationship with neoplastic cells differentiation. NIS is always expressed in the most differentiated cancers, while it is negative in most poorly differentiated neoplasms.¹⁵ The location of the transporter on the membrane is indispensable for it to be functional and capture iodine. It is not enough for NIS to be expressed, it has to be located in the cell membrane in order to be entirely functional.¹⁶

Figure 1. Na^+/I^- symporter (NIS) actively transports iodine together with two sodium atoms into the cell through the basolateral membrane; once inside, iodine crosses the apical membrane towards the colloid thanks to pendrin. The process is regulated by thyroid stimulating hormone.

Ablation and treatment with iodine 131

Iodine 131 uptake occurs mainly by the influence of TSH and cAMP activation, which increases NIS biosynthesis, but other factors also involved: insulin, insulin-like growth factor 1 (IGF-1) and epidermal growth factor (EGF).

An effective measure is to avoid radioiodinated contrasts for three months and any medication with high iodine content, such as amiodarone, multivitamins, antibiotics (penicillin), cough syrups (ambroxol/dextromethorphan), even some cosmetics contain high amounts of iodine, since they can interfere with iodine 131 action.¹⁷

Strategies to elevate TSH

To stimulate iodine 131 uptake by tumor cells, the suppressing medication with levothyroxine is usually eliminated in order to raise endogenous TSH, or recombinant human TSH (Thyrogen®) is administered. This assumes that neoplastic cells preserve certain differentiation and hormonal response. Occasionally thyroid cancer loses this capacity, being associated with a considerably deteriorated prognosis.¹⁸

After total thyroidectomy, T3, T4 and TSH levels are initially normal and, 2 to 3 weeks later, TSH levels begin to rise, while those of T3 and T4 decrease. Usually, hormone replacement therapy is avoided the first 4 to 6 weeks after thyroidectomy if, based on risk assessment, administering iodine 131 has been

decided. However, hormone replacement therapy is started immediately in some places.¹⁹

TSH elevation above 30 mU/L is necessary to obtain sufficient iodine 131 concentration in NIS-expressing cells. Discontinuing or avoiding hormone replacement therapy for 4 weeks in thyroidectomized individuals reduces T3 and T4 levels and elevates TSH levels.²⁰ Consequently, patients are exposed to a prolonged period of hypothyroidism and associated symptoms, with quality of life deterioration, and probability of tumor growth.²¹

Alternatives to avoid the hypothyroid state caused by LT4 discontinuation include the use of recombinant human TSH (rhTSH), which has an identical structure to human TSH, but its glycosylation differs; it has a higher sialic acid content, which is associated with less immune activity, lower affinity for the TSH receptor and lower bioactivity in vitro with regard to human TSH. In patients with DTC and preserved renal function who receive 0.9 mg of rhTSH, it has a half-life of 22 hours. T3 and T4 concentrations increase to 54 and 89 %, respectively, between 4 and 8 hours after rhTSH administration, while thyroglobulin peak occurs at 48 hours.²² In one study, the radiation exposure rate was compared between individuals undergoing hormone suppression versus rhTSH administration; exposure to radiation was shown to be lower and shorter with the latter, which results in lower thyroglobulin concentration and lower iodine 131 uptake by tumor cells.^{23,24} However, although rhTSH is highly effective, it is relatively expensive.

Figure 2. Strategies to increase thyroid-stimulating hormone. To achieve optimal levels for receiving iodine 131, 3 strategies can be followed: discontinuing levothyroxine 4 weeks prior to iodine 131 administration, exchanging levothyroxine for liothyronine, which is to be discontinued 2 weeks prior to iodine 131, and choosing to administer TSH without thyroid hormones being discontinued.

A third strategy is to replace LT4 with LT3; the latter has much shorter half-life: 1 to 3 days (instead of 7 days of LT4), and for this reason it can be discontinued for less time to elevate TSH levels.²⁵ Patients who discontinue LT4 and replace it with LT3, undergo only 2 weeks of hypothyroidism, while with LT4 it is 4.

The need to follow a low iodine diet two weeks prior to iodine 131 administration to obtain a $<50 \mu\text{g/gCr}$ ioduria has been pointed out;²⁶ previously, uptake by tumor cells had been shown to increase to the double after a low-iodine diet. Nevertheless, there are no studies examining whether a low iodine diet impacts on the rate of relapse or mortality.²⁷

rhTSH is reserved for patients in whom a hypothyroid status can worsen an underlying medical condition, such as poorly controlled metabolic syndrome, chronic kidney disease ($\text{GFR} < 50 \text{ mL/min}$), major depression, cardiac arrhythmia (particularly if the patient is on treatment with amiodarone and it is irreplaceable) or in patients with voluminous residual or metastatic tissue that prevents TSH elevation owing to continuous production of thyroid hormones.²⁸

The BTA guidelines suggests that, in patients with T1-T3, N0, N1a, M0 and R0, the method of choice is to administer rhTSH; but in high-risk patients, on relapse or with metastatic disease, the method of choice should be to discontinue LT4; however, prospective studies are required to support such recommendation.

Regardless of the strategy, TSH levels should be corroborated to be optimal when receiving iodine 131, i.e., above 30 mU/L ; usually, TSH is measured together with thyroglobulin (Tg) and anti-thyroglobulin antibodies (anti-Tg-Ab) (Fig. 2).²⁹

Risk assessment

Controversies still exist regarding ablation with RAI, but it is claimed that iodine 131 administration simplifies follow-up by eliminating Tg-producing normal or neoplastic thyroid tissue, which facilitates relapse identification by measuring Tg and avoiding anti-Tg antibodies (anti-Tg-Ab) continuous production.³⁰ The decision to administer ablative doses should be rational, based on risk assessment. The American Thyroid Association (ATA 2015) and the British Thyroid Association (BTA, 2014) guidelines propose similar systems, even the National Comprehensive Cancer Network (NCCN V1.2016) agrees on several points (Table 1).^{31,32}

The ATA guidelines arose from the inability of other systems to establish the risk for relapse; previous systems are only useful to establish mortality risk. It is a fact that a patient with low mortality risk can be at high risk of relapse; for this reason, ATA, BTA and NCCN recommend assessing the risk for relapse in all patients.

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

The purpose of administering iodine 131 is to eliminate any thyroid carcinoma and normal thyroid tissue microscopic deposit. NCCN and ATA propose 3 goals:

- Remnant thyroid tissue ablation (the term ablation should only be used when the first iodine 131 dose is administered in order to simplify follow-up).
- Adjuvant therapy, to eliminate subclinical micrometastases.

Table 1. Thyroid cancer risk groups according to the American Thyroid Association

Low risk	Intermediate risk	High risk
<p>All the following are present:</p> <ul style="list-style-type: none"> – No metastasis. – Complete resection. – No extrathyroidal extension. – No aggressive histology. – No vascular invasion. – No uptake outside the thyroid bed post-ablation with iodine 131. – N0, < 5 N1 micrometastases. – Intrathyroidal, encapsulated follicular variant. – Intrathyroidal, well differentiated follicular carcinoma with minimal capsular invasion and no or minimal vascular invasion (< 4 foci). – Uni- or multifocal intrathyroidal papillary microcarcinoma without <i>BRAF V600E</i> mutation. 	<p>Any of the following is present:</p> <ul style="list-style-type: none"> – Microscopic extrathyroidal extension. – Iodine 131 uptake outside the thyroid bed after remnants ablation. – Aggressive histology (tall cells, insular, columnar, hobnail variants, Hurthle cells). – Papillary carcinoma with vascular invasion. – Pathologic N1 (> 5 pathologic lymph nodes) with global dimension no larger than 3 cm. – Multifocal papillary carcinoma with minimal extrathyroidal extension and <i>BRAF V600E</i> mutation. 	<p>Any of the following is present:</p> <ul style="list-style-type: none"> – Macroscopic extrathyroidal extension. – Incomplete tumor resection (R2). – Metastases. – Post-surgery Tg elevated levels. – Pathologic N1 with any number of metastatic lymph nodes or global dimension larger than 3 cm. – Follicular carcinoma with extensive vascular invasion (> 4 foci).

- Therapeutic dose to treat local persistence or confirmed metastases.

However, for practical purposes, iodine 131 administration 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 must therefore be surgically removed.³³

To date, there are three approaches to define the iodine 131 dose: fixed dose, dose determined by blood upper limit and quantitative tumor dosimetry, with the latter two being often reserved for patients with metastases or for unusual situations, such as kidney failure, children, older patients, and those with extensive pulmonary metastases; due to its complexity, the fixed doses strategy is favored.³⁴

Patients with low risk

Prospective studies of the National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG) suggest that progression-free survival and overall disease-specific survival do not improve with iodine 131 treatment in stage I or II patients. A retrospective multicenter study, where 1298 low-risk patients were assessed with a mean follow-up of 10.3 years, failed to find benefits from iodine 131 ablation in terms of overall survival and progression-free survival.³⁵ Specifically, there is scant evidence that supports the use of iodine 131 in these patients.

Although there are no advantages in terms of survival, certain studies have shown the convenience of low versus high doses in patients with low risk, regardless of the stimulation method.³⁶ Cheng et al.³⁷ analyzed 9 randomized studies that included 2569 low-risk patients and different TSH stimulation

methods (rhTSH and hormone withdrawal). They found no differences in iodine 131 efficacy between 30 mCi and 100 mCi.

Ablation with 30 versus 100 mCi is equivalent, regardless of the stimulation method; the advantage of doses not exceeding 30 mCi lies in that patients do not require hospitalization, there is similar quality of life and iodine 131-related side effects, such as sialadenitis, edema, nausea and vomiting are lower; in addition, there is a lower radiation exposure rate and lower cumulative dose. Recent analyses and systematic reviews support these conclusions.³⁸

Patients with intermediate risk

Regarding this category, there are discrepancies in the literature.³⁹ Iodine 131 administration in patients with histologically aggressive tumors (tall cells, diffuse sclerosing, etc.), overall survival is improved; however, in studies with patients with positive lymph nodes, microscopic extrathyroidal extension or tumor > 4 cm, survival is similar if patients are younger than 45 years, although follow-up time did not exceed 7 years. On the other hand, there is an advantage in > 45-year individuals who received treatment; although it did not exceed 73 %, it was higher than 69 % of the group that did not receive it.⁴⁰ Lamartina et al.,⁴¹ in the review of 13 nonrandomized studies, did not find any benefits, whereas 11 supported its use. We consider that further studies are required, with standardized and homogeneous criteria.

Patients with high risk

Routine ablation is recommended in patients with high risk, and it is suggested that the first dose of iodine

¹³¹I should not exceed 150 mCi, especially in > 45-year individuals.⁴² 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 was metastasis to the lung; in case of bone metastases, 200-300 mCi were resorted to.⁴³ However, iodine ¹³¹I effectiveness is related to the dose of radiation released into neoplastic tissue and its radiosensitivity. Thus, radiosensitivity is higher in young people (< 45 years), with small metastases (<10 mm), well-differentiated (papillary and follicular) and iodine ¹³¹I-avid tumors.

Currently, it is recognized that the maximum tolerated radiation dose (MTRD) absorbed in blood is 200 cGy,⁴⁴ and at older age renal function decreases, as it occurs in patients with kidney failure or heart failure, and thereby iodine ¹³¹I clearance decreases.⁴⁵ In this regard, Tuttle et al.⁴⁶ demonstrated that empirical doses of 140 mCi exceeded the MTRD by less than 7 % in patients < 70 years; this percentage increased to 13 % in patients > 80 years; on the other hand, the 200 and 250 mCi doses exceeded the MTRD in 15 and 22 % of subjects < 70 years, respectively, while in patients > 70 years, in up to 38 and 50 %, respectively. Administering doses > 200 mCi is possible as long as a previous dosimetric study is performed and patients are < 65 years of age.

Currently, administering iodine ¹³¹I at doses > 200 mCi is not recommended, since its superiority has not been demonstrated and, conversely, radiation exposure is higher, side effects are more common and prolonged and cumulative dose is higher without better survival.

Usefulness of pre- and post-iodine ¹³¹I treatment scanning

Some nuclear medicine centers perform a full body scan before an ablative or therapeutic dose in order to estimate the iodine ¹³¹I required dose. With the availability of SPECT/CT equipment, sensitivity and specificity with regard to planar imaging has increased. Planar imaging reaches a sensitivity of 41 % and specificity of 68 %, whereas SPECT sensitivity is 45 % and specificity 89 %. With SPECT/CT, sensitivity is increased to up to 50 % and specificity reaches 100 %.⁴⁷

Avram et al., in a series of 320 patients who underwent SPECT/CT pre-iodine ¹³¹I ablation, re-staged 4 % of patients < 45 years of age and 25 % of those

> 45 years old.⁴⁸ With the widespread use of clinico-pathological factors, pre-ablation imaging is currently not recommended as a strategy to define the dose, however, it may be necessary in patients in whom residual disease has not been evaluated with histopathological study or ultrasound.

“Stunning” is defined as a decrease in iodine ¹³¹I uptake by neoplastic thyroid cells after administration of a iodine ¹³¹I diagnostic dose.⁴⁹ It may be due to a reduction in the number of functional thyroid cells owing to cell death produced by iodine ¹³¹I β radiation or by a decrease in the capability of viable thyroid cells to trap or retain iodine ¹³¹I during a time interval. Guiraud-Vitoux et al.⁵⁰ point out that there may be infra-therapeutic necrosis due to high doses of iodine ¹³¹I, which would imply a reduction in the efficacy of therapeutic doses after diagnostic imaging. However, investigation of this phenomenon has led to contradictory conclusions.⁵¹ Recent investigations have demonstrated that it is a radiobiological phenomenon that is closely related to the absorbed radiation, rather than to the administered dose, and that stunning is often observed 48 hours after a iodine ¹³¹I dose.⁵²

In a different train of thought, practicing a body scan 5 to 8 days after ablation or therapeutic dose is recommended, as it identifies additional metastatic foci in 10 to 26 % of patients when compared to a diagnostic scan.

SPECT/CT improves sensitivity to up to 78% and specificity to up to 100%, thus reducing the need for sectional studies in 20 % (Fig. 3).⁵³

Follow-up

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

Clinical, biochemical and imaging findings during follow-up must be put together in order to redefine the treatment, provide the most appropriate therapy and define the response. Tuttle et al.⁵⁴ and Vaisman et al.⁵⁵ have contributed to a better evaluation by defining four response categories:

Figure 3. (A) Anterior projection planar scan performed 48 hours after administering 5 mCi of iodine 131. Intense abnormal focal uptake limited to the thyroid bed is observed. Owing to respiratory symptomatology, a non-contrasted computed tomography was performed, where multiple nodular images consistent with pulmonary metastases were observed in both lungs (C and D); therefore, administering 200 mCi of iodine 131 was decided; seven days later, on anterior projection planar scan, intense uptake was observed in the thyroid bed in both lungs (B). After the scan, SPECT/CT revealed pulmonary infiltrate and iodine 131 uptake, not visualized in pre-ablation planar scan (E).

- *Excellent response*, which is obtained when there is no evidence of structural disease by imaging (with ultrasound or SPECT/CT imaging), as well as clinically or by biochemistry (Tg suppressed < 0.2 ng/mL or stimulated < 1 ng/mL). It occurs in 86 to 91 % of patients with low risk, in 57 to 63 % of patients with intermediate risk and in 14 to 16 % of those with high risk.
- *Incomplete biochemical response*, which occurs when there is a negative imaging method, but suppressed Tg levels > 1 ng/mL, stimulated Tg > 10 ng/mL or anti-Tg-Ab elevation. This response is presented by 11 to 19 % of low-risk patients, 21 to 22 % of those with intermediate risk and 16 to 18 % of those with high risk.
- *Incomplete structural response*, which refers to patients with structural or functional disease by any imaging method, with any levels of Tg or anti-Tg-Ab, and it occurs in 2 to 6 % of patients with low risk, 19 to 28 % with intermediate risk and 67 to 75 % with high risk.
- *Indeterminate response*, which refers to nonspecific findings in imaging studies, suppressed Tg levels

< 1 ng/mL, stimulated Tg levels < 10 ng/mL or anti-Tg-Ab stable levels. This response is present in 12 to 29 % of patients with low risk, 8 to 23 % with intermediate risk and 0 to 4 % with high risk.

Performing full scans with SPECT/CT is not enough, they must be correlated with specific markers, Tg and anti-Tg antibodies. It is well known that Tg levels measurements are of particular importance for the monitoring of patients with residual disease and relapse. In the absence of anti-Tg-Abs, Tg has elevated sensitivity and specificity to document relapse or persistence of the disease. Numerous authors recommend its measurement with stimulated TSH, since it can increase Tg levels between 5 and 10 times. Stimulated Tg levels < 1 ng/mL or absence of anti-Tg antibodies have 98 % probability to identify patients with absence of disease.⁵⁶

On the other hand, anti-Tg-Abs may be present or appear de novo in up to 25 % of patients, particularly in those with Hashimoto's thyroiditis.⁵⁷ Thyroid autoimmune diseases are associated with the production of antibodies in intrathyroidal lymphocytes and, after total thyroidectomy, levels remain elevated for years without evidence of disease. The reason is that

Figure 4. (A) Anterior projection planar scan performed 48 hours after the administration of 5 mCi of iodine 131. Usual biodistribution and elimination pathways were observed, without abnormal uptake focal areas in a patient with stimulated TSH and Tg > 100 ng/mL. (B) Seven days later, a PET/CT-FDG was practiced, where abnormal focal uptake was observed on the right parasternal midline. (C and D) On axial and coronal slices, two nodules with radiotracer intense uptake at level VI right cervical lymph nodes and level 1R and 3A mediastinal lymph nodes were appreciated.

autoimmune response starts and spreads in the cervical lymph nodes in response to Tg in antigen-presenting cells. Anti-Tg-Abs half-life after total thyroidectomy is 10 weeks, with rapid decrease due to the formation of Tg-anti-Tg antibody complexes in response to Tg elevation after surgery.⁵⁸

Surgery can trigger or promote anti-Tg-Abs de novo appearance, which tend to decline in the course of months. Patients may not reach an anti-Tg-Ab negative status during the first postoperative year and even exhibit an increase (or de novo appearance) within the 6 months following iodine 131 treatment when there is Tg release secondary to thyroid tissue radiolytic damage.⁵⁹

For an efficacious anti-Tg-Ab long-term follow-up, it is essential for a sensitive method to be used every 6 to 12 months. Kim et al.⁶⁰ found that in patients with a decrease higher than 50 % in anti-Tg-Ab between 6 and 12 months after iodine 131, < 1 % developed relapse. In contrast, 19 % of patients with less than 50 % decrease in the same interval experienced relapse, while 37 % of those in whom levels were increased showed relapse.

The role of PET/CT with 2-deoxy-2-[18F]-fluoro-D-glucose (PET/CT-FDG)

PET/CT-FDG is a valuable tool in patients with Tg levels elevation or anti-Tg antibodies and negative

iodine 131 scan.⁶¹ In thyroid neoplasms, radiopharmaceutical 18F-FDG uptake is limited to more aggressive or high-grade tumors, with no or poor uptake by well-differentiated tumors, a phenomenon that Feine et al.⁶² named “flip-flop”.

Owing to its hydrophilic nature, glucose requires GLUT (glucose-transporting transmembrane proteins) to enable for it to cross the cell membrane. GLUT1 overexpression in the cell membrane of thyroid neoplasms is closely related to tumors with more aggressive biological behavior. In addition, TSH plays an important role, since it stimulates glucose transport and glycolytic activity in thyrocytes by means of GLUT1 translocation, as well as GLUT1 neosynthesis by activation of its gene expression, which indicates that PET/CT-FDG is influenced by TSH levels.⁶³

Salvatori et al.⁶⁴ suggest that the indications to practice PET/CT-FDG should be divided into strongly defined and not completely defined. In the former, patients with high levels of Tg (> 10 ng/mL) and negative imaging study (ultrasound, iodine 131 scan) should be included. Anti-Tg-Ab elevation or de novo appearance can drastically alter Tg values; therefore, anti-Tg-Ab elevation or de novo appearance in the presence of Tg levels < 2 ng/mL is also an indication.

The prognostic importance of PET/CT-FDG lies in that most patients with metastatic disease show avidness for 18F-FDG, which suggests higher aggressiveness, dedifferentiation and metabolically active cells;

Figure 5. Recommendations according to post-radioiodine administration clinical scenario, based on the reviewed literature and with no unification of established criteria for intermediate and high risk groups.

a negative PET/CT-FDG predicts a favorable prognosis.⁶⁵ In a multivariate analysis, Wang et al.⁶⁶ analyzed 400 patients with high-risk characteristics; they observed that age and a PET/CT-FDG are the most important prognostic factors, since there is an inverse relationship between survival and the number of metabolically active lesions.

Sensitivity and specificity are related to Tg levels. In a meta-analysis, Leboulleux⁶⁷ demonstrated that sensitivity and specificity are strongly influenced by a Tg cut-off point of > 10 ng/mL, with the values being 83 and 84 %, respectively, in patients with disease with no iodine uptake. Another analysis showed that sensitivity at Tg levels < 10 ng/mL, > 10 but < 100 ng/mL and > 100 ng/mL was 10.5, 75.6 and 91 %, respectively. In addition, sensitivity also depends on the site and size of metastases. For lymph node metastases < 10 mm, sensitivity is 69.7 % and specificity 83.3 %, whereas for > 11 mm, sensitivity was 95.7 % and specificity 80 %. On the other hand, with pulmonary metastases < 10 mm, sensitivity was 41 % and specificity 80 %; for > 11 mm, sensitivity was 94 % and specificity 89 %.⁶⁸

As previously mentioned, SPECT/CT sensitivity is higher, so that the absence of findings with Tg elevated levels or anti-Tg-Ab also indicates the need for PET/CT-FDG (Fig. 4).

Owing to the recent implementation in some centers with regard to oncogenic mutations related to BRAF (V600E), there are some studies that demonstrate the existence of a correlation with hypermetabolism in patients with this mutation.⁶⁹ Nagarajah et al.⁷⁰ showed that in a sample of 48 patients with DTC, 24 had BRAF mutation (V600E) and 24, wild-type BRAF; they observed a significantly higher correlation of

metabolic activity in patients with BRAF mutation (V600E), and concluded that a high metabolic rate may be related to gene mutation, which entails higher tumor aggressiveness and worse prognosis; however, further studies are required to correlate these findings.

Indications that are not completely defined include the practice of PET CT in patients with refractory disease, to assess the response to treatment with targeted therapies, in staging and monitoring of high-risk histologies, in indeterminate thyroid nodules after aspiration biopsy and, recently, for radio-guided surgery.⁷¹

Figure 5 illustrates the follow-up and treatment of patients with DTC managed with iodine 131.

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