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PROTOCOL PENTRU TERAPIA CU I-131 IN AFECTIUNI BENIGNE SI MALIGNE TIROIDIENE

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1. Radioiodine Therapy in Benign Thyroid Diseases

Radioiodine (*I-131*) has been used to treat benign conditions of the thyroid gland since the 1940s. This therapy may be used for patients with hyperthyroidism, which is a consequence of excessive thyroid hormone action (ATA/AACE, 2011 and ATA 2016):

- Autoimmune hyperthyroidism (Graves' disease)
- Solitary hyperfunctioning thyroid nodule
- Toxic multinodular goiter

Also patients with a large nontoxic goiter who are euthyroid may benefit from a reduction in thyroid volume after radioiodine therapy.

In patients with hyperthyroidism, the aim of the treatment with I-131 is to achieve a nonhyperthyroid status, which can be euthyroid or hypothyroid, consequently treated by LT4 (levothyroxine) medication. In patients with nontoxic large goiter, the aim of the treatment with I-131 is to diminish the size of the goiter and, consequently, to reduce the symptoms related to gland enlargement and nodule formation.

According to different pathophysiological conditions, the treatment options of hyperthyroidism are:

- Antithyroid drugs
- Radioiodine
- Surgery

Indications of I-131 Therapy:

- Graves' disease
- Toxic multinodular goiter
- Solitary hyperfunctioning nodule
- Nontoxic multinodular goiter
- Goiter recurrence
- Ablation of residual thyroid tissue in case of malignant ophthalmopathy after surgery, but during an inactive state of the orbitopathy

Contraindications of I-131 Therapy:

Absolute

- Pregnancy
- Breastfeeding

Relative

- Uncontrolled hyperthyroidism
- Active thyroid orbitopathy (especially at smokers)

Procedure

The national regulations may request the therapy being done only in inpatients conditions even though the doses are not high; there are also countries that allow the treatment in ambulatory conditions.

The facility requirements for the unit performing therapy for thyroid disease according to national legislation must be a nuclear unit, with appropriate authorization for using therapy doses of radioiodine. The facility in which treatment is performed has appropriate personnel, radiation safety equipment and procedures for waste handling and disposal, handling of incidental contamination and monitoring of personnel for accidental contamination and controlling/limiting its spread. This facility may be easily achieved either in an endocrinology department or nuclear medicine unit.

Patient Preparation

Patient evaluation before radioiodine therapy should include (Stokkel et al. 2010):

- Patient history with special emphasis on previous treatments (e.g., use of ATS, contrast media, amiodarone, other iodine-containing medication and iodine-containing food).
- Laboratory testing, including FT4, FT3, TSH, Anti-TPO, and TRab.
- Thyroid Tc-99m scintigraphy or radioiodine scan + radioiodine 24-h uptake (RAIU); according to the availability in the department. The RAIU at 24 should be >20%, if lower other treatment modalities should be considered. Uptake measurements are not absolutely required when fixed activities are used.
- Assessment of thyroid target volume (ultrasonography) and intra-thoracic extension in those with a large goiter (magnetic resonance imaging/computed tomography). However, we have to note that assessment of the target volume by computed tomography using contrast agents impair the radioiodine uptake for weeks to months, making therapy with I-131 impossible during that time.
- Fine needle aspiration biopsy (FNAB) of nodules larger than 1–1.5 cm with a suspicious ultrasound appearance and hypo/iso-functioning on scan. In autonomously functioning nodules, as the risk of malignancy is very low, FNAB should only be considered in those with suspicious ultrasound features.
- In female patients of childbearing potential, a routine testing for pregnancy is performed within 72 h before the administration of I-131. When the patient history clearly indicates that pregnancy is excluded, a pregnancy test may be omitted at the discretion of the treating physician. In case of suspicious situation, a serologic analysis of beta HCG may be requested.
- In patients with Graves' ophthalmopathy, establishment of the status of thyroid eye disease activity by an experienced ophthalmologist.
- Informed consent is required for every patient.
- All documents including identity data, medical information, activity administered, indication about medication needed to be restarted, radioprotection aspects, contact data and physician identification are provided to patients.

Special Considerations

- If the antithyroid drugs (ATS) are used in the initial treatment of patients with hyperthyroidism, the procedure is to be stopped 5–7 days before radioiodine and the beta blockers within 24 h before. Propylthiouracil is stopped at least 2 weeks before therapy.
- ATS are restarted after I-131 only if a previous treatment was applied before therapy and there were no side effects on ATS.
- In patients with Graves' ophthalmopathy, if they are already on steroid therapy, orally prednisolone is administered. It is not a routine to start the corticotherapy.
- In patients with thyrotoxicosis induced by amiodarone or in those receiving compounds that contain iodine (e.g., radiographic contrast agents), radioiodine can be administered as definitive therapy, if the drug has been stopped sufficiently long enough. In amiodarone-induced thyrotoxicosis the excess of iodine is eliminated during at least 3-6 months, after withdrawal the drug. In this respect, the assay of urinary iodine excretion can be used as an indicator of normalization of iodine upload.
- The use of other drugs in preparing the therapy, such as lithium, is not a routine and is reserved to the specific conditions of some patients.

Patient Information and Instruction

Patients receive both written and verbal information about the procedure before receiving therapy.

A written informed consent from the patient is obtained. Radiation protection measures are detailed in the leaflets given to the patient in order to reduce radiation doses to children, family members and other people in the general population, according to national rules. Contraception for 4 months after I-131 therapy is also recommended. As the result is evaluated 6 months after therapy, this interval is necessary in clinical practice to avoid interference with retreatment in the event of recurrent disease. The American Thyroid Association Taskforce on Radioiodine Safety (2011).

Radiopharmaceutical and Administration

Radioiodine is orally administered. Patients should be encouraged to drink a large volume of fluids (1.5–2 L) for a 24-h period following radioiodine therapy to lower the radiation dose to the bladder.

Two procedures are in use:

- Empirically established doses
- Calculated doses, especially in young patients and with less severe symptoms

Currently, an absorbed radiation dose of 100–150 Gy is recommended, requiring about 3.7–5.5 MBq (0.1–0.15 mCi) per gram of thyroid tissue corrected for the 24-h I-131 uptake. In patients with autonomously functioning nodules, the recommended dose is of 300–400 Gy.

In patients with Graves' disease, the dose with the aim of restoring a euthyroid status is approximately 150 Gy, whereas the dose to achieve complete ablation is in the range of 200–300 Gy.

The fixed dose approaches are usually based on an estimation of the size of the gland realized by palpation or by the measurement on ultrasonography or scintigraphy.

The range of activities currently prescribed, vary in the range of 200–800 MBq (5–21 mCi), with the majority of patients receiving 200–500 MBq (5–15 mCi). The amount of activity is prescribed according to clinical features, volume of gland, disease.

Radioiodine therapy for children younger than 5 years old is done only in exceptionally cases.

For children between 5 and 15 years of age, radioiodine therapy may be considered. The side effects should be clearly discussed by all the staff involved in the treatment of a young patient with Graves' disease.

The calculated doses are decided according to the Marinelli's following formula (Eq. 7.1):

$$\text{MBq} = \frac{V \times 25 \times (100 - 300\ \text{Gy})}{\text{RAIU 24 h} \times T_{\text{ef}}} \tag{7.1}$$

MBq – the calculated activity in MBq

V – the gland volume estimated at ultrasound in ml (cm^3)

100–300 Gy – estimated required dose at thyroid level, between 100 and 300 Gy

RAIU 24 h – % of thyroid uptake at 24 h

T_{ef} – effective half-time, estimated in hyperthyroidism at 4.5 days and in euthyroidism at 6 days.

25 – constant

Example (Eq. 7.2):

Thyroid gland volume – 30 mL

Constant – 25

Estimated dose – 200 Gy

RAIU 24 h – 67%

T_{ef} – 4.5

$$\text{MBq} = \frac{30 \times 25 \times 200}{67 \times 4.5} = \frac{150{,}000}{301.5} = 497.5 \qquad (7.2)$$

37 MBq = 1 mCi
497.5 MBq = 13.44 mCi
Result: the necessary dose for therapy is of 13.5 mCi

Side Effects of I-131 Therapy

Acute patients with a large goiter may notice transient edema of the goiter and dyspnea. This symptom may last several days following therapy and some discomfort or dyspnea may be associated with it. Slight discomfort of the salivary glands may be present. In some patients a thyroid storm may develop. This rare condition must be treated with intravenous infusion of ATS, corticosteroids, and β-blockers. This situation is extremely rare and does not represent a reason to not recommending the therapy.

Hypothyroidism is the main side effect of radioiodine treatment. Its rate varies and its incidence continues to increase over time, so that life-long follow-up is essential. According to all published data in the literature the rate of hypothyroidism at 1 year after radioiodine therapy is very similar to the rate from the surgery approach.

The administration of prednisone helps prevent exacerbation of ophthalmopathy, and this is now the standard approach in patients who have clinically active ophthalmopathy at the time of treatment. The determination of periorbital inflammation tissue by nuclear test with Tc-99m DTPA may identify the cases that will benefit from steroid treatment.

Follow-up After Radioiodine Treatment

Regular review of thyroid function tests in patients who have undergone radioiodine treatment for thyroid disease is essential to assess the efficacy of the treatment and for timely detection of developing hypothyroidism or posttreatment immunogenic hyperthyroidism. First, TSH and FT4 examination is performed not longer than 4–6 weeks after radioiodine therapy. Shorter intervals of about 2–3 weeks are recommended for patients who have received ATS or who have an increased risk of endocrine ophthalmopathy because of hypothyroidism.

The level of TSH serum is slowly increasing so the determination of TSH is less useful in the monitoring in the first 3–6 months, than FT4 is. If the treatment was performed for (overt) hyperthyroidism, ATS is restarted, about 3–5 days after the radioiodine administration. In those with persistent hyperthyroidism, the radioiodine treatment can be repeated after 6–12 months. In those with posttherapy immunogenic hyperthyroidism, ATS for some months appears to be adequate, and a second radioiodine treatment is not necessary in most patients. Annual laboratory tests (at least including TSH) are necessary for life even in patients with euthyroidism after I-131 therapy.

2. Radioiodine Therapy in Malignant Thyroid Diseases

Overview

The thyroid cancer is a possible aggressive thyroid condition, which continues to be the most frequent endocrine tumor. The incidence of thyroid cancer, mainly differentiated, is one of the most rapidly increasing human cancers, especially in the last decade (ATA 2015, Gaengler 2017, Hodgson 2004, Pacini 2004, Perros 2016, Piciu 2014, Sassolas 2009). Despite this situation, it is still considered to be one of the rare cancers. According to the European surveillance of rare cancers project (rare cancers list), a rare cancer is defined as a tumor with an annual incidence lower than 6 cases per 100,000 persons.

Thyroid cancer can be identified as a thyroid nodule detected by palpation, and, more frequently nowadays, by neck ultrasound. Thyroid ultrasound is a widespread technique that is used as a first-line diagnostic procedure for detecting and characterizing nodular thyroid disease. There are some special patterns of ultrasound image, which may suggest the malign transformation. These features relate to a previous neck irradiation or a family history of thyroid cancer, and the presence of cervical lymph nodes leads to the cytology evaluation of the nodule despite its size. Otherwise, the limit of 1 cm in maximum diameter of the highly suspicious thyroid nodule is the one recommending as routine the fine needle aspiration biopsy (FNAB) (Braga 2001; Goldstein 2002; Pacini 2010; ATA 2015, Haugen 2017). The FNAB sensitivity may be of 83% and its specificity could be 72–100%.

According to the latest studies, the use of various immunohistochemical markers in cytological samples (such as BRAF, RAS, RET/PTC, etc.) might increase the accuracy of the positive diagnosis diagnosis (Bongiovanni 2010, ATA 2015).

The serum hormonal tests and scan images will be indicated according to the protocols of thyroid nodule diagnosis (AACE/AME/ETA 2010; AACE 2002; Hegedus 2001; Guarino 2005; Frates 2005; Margusee 2000; Dunn 1994; Pacini 2004; ATA guidelines 2015, BTA 2014) all investigations are made with the aim of limiting the unjustified surgery and to improve the positive diagnosis of malignancy prior surgery.

The papillary type is the most frequent form (Hay 1993; Hay 2002; AACE/AME/ETA 2010; Leger 2005, Machens 2005; Shah 1992, ATA 2015) (nearly 80%) and its microscopic presentation (thyroid microcarcinoma) is by far the most challenging problem regarding the increasing frequency.

There is a need for a uniform diagnosis and treatment strategies for thyroid nodules and differentiated thyroid cancer (DTC), since the disease requires a multidisciplinary approach. Thyroid cancer comprises 0.5–1.5% of all childhood tumors and represents the most common head and neck malignant tumor in young people (Robbins 1992; Zimmerman 1988, Piciu 2012, Francis 2015).

An accurate treatment strategy can cure this disease, can minimize recurrence risks and can give an excellent prognosis to these patients.

2.1 Classification of Thyroid Tumors

WHO Classification of Carcinoma of the Thyroid (2004).

Papillary carcinoma

Variants (in alphabetical order):

- Classical (usual)
- Clear cell variant
- Columnar cell variant
- Cribriform-morular variant
- Diffuse sclerosing variant
- Follicular variant
- Macrofollicular variant
- Microcarcinoma (occult, latent, small, papillary microtumor)
- Oncocytic or oxyphilic variant (follicular variant, non-follicular variant)
- Solid variant
- Tall cell variant
- Warthin-like variant

- Hobnail variant of papillary thyroid cancer
- Cribriform morular variant of papillary thyroid cancer

Follicular carcinoma

Variants:

- Clear cell variant
- Oncocytic (Hürthle cell) variant
- Poorly differentiated thyroid carcinomas including insular carcinoma

Medullary Carcinoma

Undifferentiated (anaplastic) Carcinoma

Carcinoma, type cannot be determined

Others:

- Squamous cell carcinoma
- Mucoepidermoid carcinoma
- Sclerosing mucoepidermoid carcinoma with eosinophilia
- Mucinous carcinoma
- Mixed medullary and follicular cell carcinoma
- Spindle cell tumor with thymus-like differentiation (SETTLE)
- Carcinoma showing thymus-like differentiation (CASTLE)

Other thyroid tumors:

- Teratoma
- Primary lymphoma and plasmacytoma
- Ectopic thymoma
- Angiosarcoma
- Smooth muscle tumors
- Peripheral nerve sheath tumors
- Paraganglioma
- Solitary fibrous tumor
- Follicular dendritic cell tumor
- Langerhans' cell histiocytosis
- Secondary tumors of the thyroid

Well-differentiated malignant neoplasms (85% of the thyroid cancers)

- Papillary thyroid carcinoma (PTC)
- Follicular thyroid carcinoma (FTC)

Poor differentiated malignant neoplasms:

- Medullary thyroid carcinoma (MTC)
- Anaplastic thyroid carcinoma (ATC)

These images were obtained with the courtesy of the colleagues from the pathology department of the Institute of Oncology "Prof. Dr. I. Chiricuţă" Cluj-Napoca.

From a clinical perspective, molecular studies are being used to guide management of thyroid nodules with indeterminate FNAB and to better define prognosis. Also, the genetic profile aids to more rationale selection of novel therapeutic agents that are able to target the aggressive and advanced disease. A summary of most common genotypes found in DTC is presented in Table 1.

Table 1. Genotype in differentiated thyroid carcinoma (DTC) (Adapted from Schlumberger, 2016)

Genotype	DTC histological variant
RET/PTC1, RET/PTC 3	PTC, PTC solid variant
TRK	PTC, radiation induced
ALK	ATC, poorly DTC
BRAF V600E	PTC, tall cell PTC
RAS	FTC, ATC, poorly DTC, follicular variant of PTC, follicular adenoma
PAX8-PPARγ	FTC, follicular variant of PTC, follicular adenoma
PI3K/AKT	FTC, ATC, poorly DTC
PTEN	ATC, poorly DTC
TERT	ATC, PTC, poorly DTC

2.2 The TNM Staging System

The majority of thyroid cancer forms is not aggressive and has an excellent prognosis. In order to select the best therapeutic options many scientific committees proposed during the years the prognostic factors for thyroid cancer.

Prognostic factors:

- Age
- Sex
- Tumor size
- Extrathyroidal extension
- Distant metastases
- Lymph node involvement
- Histological grade
- Histological type
- Multicentricity
- Incomplete resection

According to these factors some prognostic scores were proposed as follows:

- *AGES*: Patient age, histologic grade of tumor, tumor extent and size of primary tumor
- *AMES*: Patient age, presence of distant metastases, extent and size of primary tumor
- *EORTC*: European Organization for Research and Treatment of Cancer; age, sex, extrathyroidal extension, distant metastases and histological type
- *MACIS*: Metastasis, patient age, completeness of resection, local invasion and tumor size
- *MSKCC*: Memorial Sloan-Kettering Cancer Center; age, tumor size, extrathyroidal extension, distant metastases, lymph node involvement, histologic grade and histological type
- *NTCTCS*: National Thyroid Cancer Treatment Cooperative Study; age, tumor size, extrathyroidal extension, distant metastases, lymph node involvement, histological type and multicentricity
- *OSU*: Ohio State University; tumor size, extrathyroidal extension, distant metastases, lymph node involvement and multicentricity
- *TNM*: Tumor–node–metastasis (American Joint Committee on Cancer staging system)

The most common system used to describe the stages of thyroid cancer is the American Joint Committee on Cancer (AJCC) TNM system. American Joint Committee on Cancer (AJCC) TNM Staging for Thyroid Cancer (7th ed., 2010)

T indicates the size of the main (primary) *tumor* and whether it has grown into nearby areas.

N describes the extent of spread to nearby (regional) lymph *nodes*.

M indicates whether the cancer has spread (*metastasized*) to other organs of the body. (The most

common sites of spread of thyroid cancer are the lungs, the liver, and the bones.)

T categories for thyroid cancer (other than anaplastic thyroid cancer)

Primary Tumor (T)

Note: All categories may be subdivided:

- (s) Solitary tumor
- (m) Multifocal tumor (the largest determines the classification):

TX: Primary tumor cannot be assessed.

T0: No evidence of primary tumor.

T1: The tumor is 2 cm or smaller and has not grown out of the thyroid.

T1a: The tumor is 1 cm or smaller and has not grown outside the thyroid.

T1b: The tumor is larger than 1 cm but not larger than 2 cm across and has not grown outside of the thyroid.

T2: The tumor is between 2 and 4 cm across and has not grown out of the thyroid.

T3: The tumor is larger than 4 cm or it has begun to grow into nearby tissues outside the thyroid. Tumor more than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroidal extension (e.g., extension to the sternothyroid muscle or perithyroid soft tissues).

T4a: The tumor is of any size and has grown extensively beyond the thyroid gland into the nearby tissues of the neck, such as the larynx, trachea, esophagus, or the nerve to the larynx. This is also called moderately advanced disease.

T4b: A tumor of any size that has grown either back towards the spine or into nearby large blood vessels. This is also called very advanced disease.

T categories for anaplastic thyroid cancer

All anaplastic thyroid cancers are considered T4 tumors at the time of diagnosis.

T4a: Tumor is still within the thyroid.

T4b: Tumor has grown outside of the thyroid.

N categories for thyroid cancer:

NX: Regional (nearby) lymph nodes cannot be assessed.

N0: No spread to nearby lymph nodes.

N1: The cancer has spread to nearby lymph nodes.

N1a: Spread to lymph nodes pretracheal, paratracheal, and prelaryngeal.

N1b: Spread to other cervical lymph nodes or to lymph nodes behind the throat (retropharyngeal) or in the upper mediastinum.

M categories for thyroid cancer:

M0: No distant metastasis.

M1: Spread to other parts of the body, such as distant lymph nodes, brain, internal organs, bones, etc.

2.3 Thyroid Cancer Staging

Papillary or follicular (differentiated) thyroid cancer in patients younger than 45 years old

All people younger than 45 years old having these types of cancers are considered to have a *stage I* cancer if they have no distant spread, and a *stage II* cancer if they have distant spread.

Stage I (any T, any N, M0):

The tumor can be of any size (any T) and may or may not have spread to nearby lymph nodes (any N). It has not spread to distant sites (M0).

Stage II (any T, any N, M1):

The tumor can be of any size (any T) and may or may not have spread to nearby lymph nodes

(any N). It has spread to distant sites (M1).

Papillary or follicular (differentiated) thyroid cancer in patients of 45 years old and older

Stage I (T1, N0, M0):

The tumor is of 2 cm or less across and has not grown outside the thyroid (T1). It has not spread to nearby lymph nodes (N0) or distant sites (M0).

Stage II (T2, N0, M0):

The tumor is more than 2 cm but not larger than 4 cm across and has not grown outside the thyroid (T2). It has not spread to nearby lymph nodes (N0) or distant sites (M0).

Stage III - one of the following applies:

T3, N0, M0: The tumor is larger than 4 cm or has grown slightly outside the thyroid (T3), but it has not spread to nearby lymph nodes (N0) or distant sites (M0).

T1 to T3, N1a, M0: The tumor is of any size and may have grown slightly outside the thyroid (T1 to T3). It has spread to lymph nodes around the thyroid in the neck (N1a) but not to distant sites (M0).

Stage IVA - one of the following applies:

T4a, any N, M0: The tumor is of any size and has grown beyond the thyroid gland and into nearby tissues of the neck (T4a). It may or may not have spread to nearby lymph nodes (any N). It has not spread to distant sites (M0).

T1 to T3, N1b, M0: The tumor is of any size and may have grown slightly outside the thyroid gland (T1 to T3). It has spread to certain lymph nodes in the neck (cervical nodes) or to lymph nodes in the upper chest (superior mediastinal nodes) or behind the throat (retropharyngeal nodes) (N1b) but not to distant sites (M0)

Stage IVB (T4b, any N, M0):

The tumor is of any size and has grown either back to the spine or into nearby large blood vessels (T4b). It may or may not have spread to nearby lymph nodes (any N), but it has not spread to distant sites (M0).

Stage IVC (any T, any N, M1):

The tumor is any of size and may or may not have grown outside the thyroid (any T). It may or may not have spread to nearby lymph nodes (any N). It has spread to distant sites (M1).

Medullary thyroid cancer

Age is not a factor in the stage of medullary thyroid cancer.

Stage I (T1, N0, M0):

The tumor is of 2 cm or less across and has not grown outside the thyroid (T1). It has not spread to nearby lymph nodes (N0) or distant sites (M0).

Stage II - one of the following applies:

T2, N0, M0: The tumor is more than 2 cm but not larger than 4 cm across and has not grown outside the thyroid (T2). It has not spread to nearby lymph nodes (N0) or distant sites (M0).

T3, N0, M0: The tumor is larger than 4 cm or has grown slightly outside the thyroid (T3), but it has not spread to nearby lymph nodes (N0) or distant sites (M0)

Stage III (T1 to T3, N1a, M0):

The tumor is of any size and may have grown slightly outside the thyroid (T1 to T3). It has spread to lymph nodes around the thyroid in the neck (N1a) but not to distant sites (M0).

Stage IVA-one of the following applies:

T4a, any N, M0: The tumor is of any size and has grown beyond the thyroid gland and into nearby tissues of the neck (T4a). It may or may not have spread to nearby lymph nodes (any N). It has not spread to distant sites (M0).

T1 to T3, N1b, M0: The tumor is of any size and may have grown slightly outside the thyroid gland (T1 to T3). It has spread to certain lymph nodes in the neck (cervical nodes) or to lymph nodes in the upper chest or behind the throat (retropharyngeal nodes) (N1b) but not to distant sites (M0).

Stage IVB (*T4b, any N, M0*):

The tumor is of any size and has grown either back towards the spine or into nearby large blood vessels (T4b). It may or may not have spread to nearby lymph nodes (any N), but it has not spread to distant sites (M0).

Stage IVC (*any T, any N, M1*):

The tumor is of any size and may or may not have grown outside the thyroid (any T). It may or may not have spread to nearby lymph nodes (any N). It has spread to distant sites (M1).

Anaplastic (*undifferentiated*) *thyroid cancer*

All anaplastic thyroid cancers are considered to be a stage IV, reflecting the poor prognosis of this type of cancer.

Stage IVA (*T4a, any N, M0*):

The tumor is still within the thyroid (T4a). It may or may not have spread to nearby lymph nodes (any N), but it has not spread to distant sites (M0).

Stage IVB (*T4b, any N, M0*):

The tumor has grown outside the thyroid (T4b). It may or may not have spread to nearby lymph nodes (any N), but it has not spread to distant sites (M0).

Stage IVC (*any T, any N, M1*):

The tumor is of any size and may or may not have grown outside of the thyroid (any T). It may or may not have spread to nearby lymph nodes (any N). It has spread to distant sites (M1).

The last years brought a more conservative approach of the non-aggressive histologies of thyroid cancer. In this light, some guidelines were revised and endorsed their recommendations. An example is ATA 2015 guidelines, that re-defined in 2017 (Haugen 2017) the histopathologic nomenclature for Encapsulated Follicular Variant Papillary Thyroid Carcinoma (EFVPTC) without invasion as a NIFTP, given the excellent prognosis of this neoplastic variant. Nevertheless, it is recommended to validate the observed patient outcomes (and test performance in predicting thyroid cancer outcomes), as well as implications on patients' psychosocial health and economics.

Nikiforov et al in 2016 published the results of an international, multidisciplinary, retrospective study of patients with thyroid tumors currently diagnosed as noninvasive EFVPTC; the authors concluded that EFVPTC have a very low risk of adverse outcome and should be termed NIFTP. This reclassification will affect a large population of patients worldwide and result in a significant reduction in psychological and clinical consequences associated with the diagnosis of cancer.

According to histology and the stage thyroid carcinoma has different therapy approaches. There are multiple guidelines of diagnosis and therapy, many of them published by national and international committees of experts in endocrinology, endocrine surgery, nuclear medicine, and oncology. All these algorithms were frequently reviewed with the intention to minimize the inadequate diagnosis, surgery, and to provide the best option for surgery and complementary therapies.

The European Thyroid Association (ETA), the American Thyroid Association (ATA 2009 and 2015), the American Association of Clinical Endocrinologists (AACE/AME/ETA 2010) the American Association of Endocrine Surgeons (AAES), the Associazione Medici Endocrinologi (AME), the British Thyroid Association (BTA 2007, 2014) the National Cancer Comprehensive

Network (NCCN 2016) have produced the most comprehensive guidelines of diagnosis and treatment of thyroid cancer, many completed and renewed in the last 2 years.

2.6.4 Treatment Recommendations

Stage I and II Papillary and Follicular Thyroid Cancer

- Surgery is the therapy of choice for all primary lesions. Surgical options include total thyroidectomy or lobectomy. The choice of procedure is influenced mainly by the age of the patient and the size of the nodule.
- Total thyroidectomy: Preferred due to the high incidence of multicentric involvement of both lobes of the gland and the possibility of dedifferentiation of any residual tumor to the anaplastic cell type.
- Lobectomy: This term represents the total ablation of one lobe including the isthmus.

- I-131: A therapeutic ablative dose of I-131 results in a decreased recurrence rate among high-risk patients with papillary and follicular carcinomas (NCCN 2016, ATA 2015, Pacini 2006a, 2010, Schlumberger 2016, Chianelli 2009, Franzius 2007). Patients presenting with papillary thyroid microcarcinomas (tumors <10 mm) have an excellent prognosis when treated surgically and additional therapy with I-131 is limited (Verburg 2010).
- Following surgery and radioiodine therapy procedure, patients should receive postoperative treatment with exogenous thyroid hormone in doses sufficient to suppress the thyroid-stimulating hormone (TSH); the suppression is not long life, except the group of persistent/aggressive disease (Biondi 2005, ATA 2015, BTA 2014, Mitchell 2016).

Stage III Papillary and Follicular Thyroid Cancer

- Total thyroidectomy including removal of involved lymph nodes or other sites of extrathyroidal disease.
- I-131 ablation following total thyroidectomy if the tumor demonstrates uptake of this isotope.
- External-beam radiation therapy if I-131 uptake is minimal (Clark 1990; Braverman et al. 2000, ATA 2015).

Stage IV Papillary and Follicular Thyroid Cancer

The most common sites of metastases are the lymph nodes, the lung and the bone. The treatment of lymph node metastases alone is often curative. Treatment of distant metastases is usually not curative but may produce significant palliation (DeVita 2001; Pacini et al. 2006b).

Standard treatment options:

- I-131: Metastases that demonstrate uptake of this isotope may be ablated by therapeutic doses of I-131.
- External-beam radiation therapy for patients with localized lesions which are unresponsive to I-131.
- Resection of limited metastases, especially symptomatic metastases, should be considered when the tumor has no uptake of I-131.
- Thyroid-stimulating hormone suppression with thyroxin is also effective in many lesions not sensitive to I-131.

Patients unresponsive to I-131 should also be considered candidates for systemic therapies and clinical trials testing new approaches to this disease (Haugen 2017, ATA 2015, NCCN 2012, Pacini 2010).

According to actual knowledge, 1/3 of metastatic DTC are definitely cured by radioiodine, the others being difficult to be managed regarding tumor progression. In France, 350 cases/year of refractory differentiated thyroid carcinoma (RDTC) (Sassolas et al. 2009) and metastatic RDTC

refractory about 200 cases/year were reported.

Radiosensitivity to classic therapy with radioiodine is related to the following factors:

- Young patient
- Small foci
- Low FDG uptake at PET
- Well differentiation of tumor

Differentiated thyroid carcinoma is generally indolent in nature and, even though it metastasizes to distant organs, the prognosis is frequently excellent. In contrast, the overall survival of patients with radioactive iodine refractory and progressive metastases is unpredictable. Until recently, treatment options for patients with progressive, radioactive iodine-resistant differentiated thyroid cancer (DTC) have been limited. However, the last years demonstrated consistent data about the administration of tyrosine-kinase inhibitors (TKIs); the drug has become a new line of therapy for RAI-refractory and progressive metastases. Previous studies have reported significant improvement regarding the progression-free survival rates of patients with metastatic lesions. However, TKIs cause various severe adverse effects that damage patients' quality of life and can even be life-threatening. Additionally, metastatic lesions may progress significantly after stopping TKI therapy. Therefore, it is difficult to determine who is a candidate for TKI therapy, as well as how and when physicians start and stop the therapy. Among other professionals the Committee of pharmacological therapy for thyroid cancer of the Japanese Society of Thyroid Surgery (JSTS) and the Japan Association of Endocrine Surgeons (JAES) summarized in the review published in 2016 (Ito et al 2016) how to appropriately use TKIs by describing what they recommend to do and not in the treatment using TKIs.

The molecular pathogenesis of thyroid cancer has led to the discovery of driving somatic genetic alterations and suggested better methods to risk-stratify patients prior to surgery, and also identifying patients at risk for recurrence and dedifferentiation, into a more aggressive thyroid cancer. Molecular profiling offers tremendous benefit in the refractory metastatic disease and identification of targetable pathogenic lesions may select for more precise therapeutic options, such as the molecular kinase inhibitors. Fig. 1 summarizes the most important molecular pathways that might me targeted by these therapies.

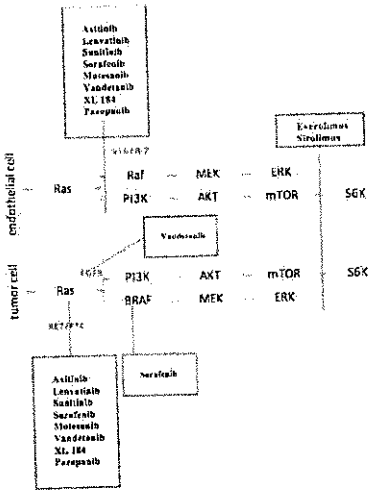

Fig. 1. Systemic therapy in refractory radioactive iodine DTC

Selection criteria (Brose, 2014):

- L-T4: TSH < 0.1 mUI/L
- Radical treatment of DTC
- WBS I-131 negative, no I-131 uptake in the lesions
- No resectability of the tumor
- No indication for external irradiation
- Significantly progression of the disease in the last 6-12 months, according to RECIST criteria

Radiological evaluation at 6 months:

- Stable disease- monitoring
- Progression of the disease – systemic therapy

Rates of response:

- 0-35% Motesanib, Axitinib, Sunitinib, Vandetanib, Vemurafenib
- ≥50% Lenvatinib, Pazopanib, Cabozantinib

Progression free survival (PFS) vs placebo

- Vandetanib –phase II random- 11.1 vs 5.9 months
- Sorafenib- phase III- DECISION trial– 10.8 vs 5.8 months
- Lenvatinib-phase III- SELECT trial -18.3 vs 3.6 months

Brose et al published in 2014 the results of the trial DECISION. This multicentre, randomized (1:1), double-blind, placebo-controlled, phase III study investigated sorafenib (400 mg orally twice-daily) in patients with RAI-refractory locally advanced or metastatic DTC progressing within the past 14 months. The primary endpoint was progression-free survival (PFS) by central independent review. Patients receiving placebo could crossover to open-label sorafenib upon progression. Archival tumour tissue was examined for BRAF and RAS mutations. Serum thyroglobulin was measured at baseline and each visit. Sorafenib significantly improved PFS compared with placebo in patients with progressive RAI-refractory DTC. Adverse events were consistent with the known sorafenib safety profile. These results suggest that sorafenib represents a new treatment option for patients with progressive RAI-refractory DTC.

A novel area of development is usage of TKIs as radioiodine re-sensitizing agents. A pilot study evaluated the role of Selumetinib, a MEK inhibitor. Selumetinib increased iodine uptake in 12 patients, and 8 were retreated with RAI (Ho AL, 2013), suggesting that MEK inhibition therapy can lead to re-sensitization. The use of Dabrafenib, a selective BRAF inhibitor, was also evaluated; the study demonstrated new radioiodine uptake following treatment (Schlumberger M, 2016).

Medullary Thyroid Cancer

Medullary thyroid cancer (MTC) comprises less than 5% of all the thyroid cancers. MTC may be diagnosed through screening family members, determining serum calcitonin in basal or stimulated conditions or determining RET proto-oncogene mutation (Dunn 1994; Mayr et al. 1999; Elisei 2004, Schlumberger 2016). MTC may be also diagnosed by evaluation of thyroid nodule or lymph nodes. Approximately 25% of the reported cases of MTC are familial, others being sporadic MTC. Familial MTC syndromes include MEN 2A, MEN 2B; and familial non-MEN syndromes. Any patient with a familial variant should be screened for other associated endocrine tumors, particularly parathyroid hyperplasia and pheochromocytoma (Sipple 1961). MTC can secrete calcitonin and other peptide substances. Family members who are gene carriers should undergo prophylactic thyroidectomy at an early age.

Treatment options (AACE 2002; Pacini et al. 2010; ATA 2009; Pacini 2006b):

- Thyroidectomy: Patients with medullary thyroid cancer should be treated by total

thyroidectomy, unless there is evidence of distant metastasis. In patients with clinically palpable medullary carcinoma of the thyroid, the incidence of microscopically positive nodes is more than 75%; routine central and bilateral modified neck dissections have been recommended. When cancer is confined to the thyroid gland, the prognosis is excellent.

- External radiation therapy: External radiation therapy has been used for palliation of locally recurrent tumors, without evidence that it provides any survival advantage.
- Radioactive iodine has no place in the treatment of patients with MTC.
- Chemotherapy: Palliative chemotherapy has been reported to produce occasional responses in patients with metastatic disease. No single drug regimen can be considered standard. Some patients with distant metastases will experience prolonged survival and can be managed expectantly until they become symptomatic.

Anaplastic Thyroid Cancer

Standard treatment options (Braverman 2000; NCCN 2016):

- Surgery: Frequently surgery is resumed to biopsy because of the aggressive extent of the tumor. If the disease is confined to the local area, which is rare, total thyroidectomy is warranted to reduce symptoms caused by the tumor mass.
- Radiation therapy: External-beam radiation therapy may be used in patients who are not surgical candidates or whose tumor cannot be surgically excised.
- Chemotherapy: Anaplastic thyroid cancer as MTC is not responsive to I-131 therapy; the treatment with individual anticancer drugs has been reported to produce partial remissions in some patients. Single or in combination with other drugs, the doxorubicin appears to be active and has been reported to produce an improvement of the disease.

2.5 European Thyroid Association (ETA) and American Thyroid Association (ATA): Indications for Postsurgical Radioiodine Thyroid Ablation, Procedure and Follow-up

As the trend in thyroid cancer management continues to move toward a personalized therapy and monitoring, it is even more important that the professionals involved in this pathology be able to accurately assess the risk of recurrence and risk of disease specific mortality in order to ensure that the recommendations are specific tailored for each patient and the quality of life is appropriate.

In this light, the former guidelines referring the therapy and follow-up of thyroid cancer, presented in the first edition of this book are still available, but there are new tendencies worldwide to improve quality of life and to adjust every single recommendation to specific particularities of each patient, having a more conservative approach for the indolent forms, and a clearer defined systemic approach in the aggressive forms.

The next paragraphs will cover both the former and the newest guidelines, in order to have an overview about the changes that were made. From the personal point of view, the authors' opinion is that one of the major attention in this new approach was focused on patients' perspective and quality of life, considering that this pathology is in the majority of cases, a curable and long-life threatening and monitoring disease, completely different compared with other cancers.

As in the previous edition, we will focus on the recommendations made by the most important opinion leaders which continue to be the European Thyroid Association (ETA) and the American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE). The latest guidelines will be also summarized from ETA (2010), ATA (2015) and completed with the endorsements from other professional associations involved in this pathology: European Association of Nuclear Medicine (EANM, 2010), UK National multidisciplinary

guidelines (2016), British Thyroid Association (2014), Italian (2016), South Korea (2017), Japanese (2014), Latin-American Thyroid Society (LATS, 2009) revised guidelines.

European Thyroid Association (ETA) (Pacini 2006b; Pacini 2010)

Very Low-Risk Group NO INDICATION for POSTOPERATIVE I-131

- Unifocal microcarcinoma (≤1 cm)
- No extension beyond the thyroid capsule
- No lymph node metastases
- Complete surgery

Low-Risk Group PROBABLE INDICATION for I-131: NO CONSENSUS

- Less than total thyroidectomy, no lymph node dissection
- Age <18 years
- Unfavorable histology, T1 > 1 cm, T2, N0, M0

High-Risk Group DEFINITE INDICATION for I-131

- T3, T4, N1, M1
- Incomplete surgery
- High risk of recurrence

American Thyroid Association (ATA 2009)

The American guidelines has a classification of recommendations in six groups: A; B; C; D; E; F; I related to the strength of medical evidence-based studies.

A. *Strongly recommends*. The recommendation is based on good evidence and includes consistent results from well-designed, well-conducted studies in representative populations.
B. *Recommends*. The recommendation is based on fair evidence that the service or intervention can improve important health outcomes. The evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited.
C. *Recommends*. The recommendation is based on expert opinion.
D. *Recommends against*. The recommendation is based on expert opinion.
E. *Recommends against*. The recommendation is based on fair evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits.
F. *Strongly recommends against*. The recommendation is based on good evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits.
G. *Recommends neither for nor against.*

Recommendation R 32 – radioiodine ablation is recommended for:

- Patients with stage III and IV (AJCC 7th edition, TNM classification)
- All patients with stage II younger than 45 years old
- Most patients with stage II 45 years old or older
- Selected patients with stage I, with multifocal (>2 foci) disease, nodal metastases, extrathyroidal and vascular invasion and/or aggressive histology. Recommendation B

ETA – staging and recommendations after thyroidectomy and radioiodine therapy *(Pacini 2006b)*

Very low risk

- Unifocal T1a (≤1 cm) N0M0 and no extension beyond thyroid capsule
- LT4 replacement: TSH −0.5–1 mIU/L

Low risk

- T1b (>1cm, but less 2 cm) N0M0 or T2N0M0 or multifocal T1aN0M0
- LT4 replacement: TSH – 0.5–1 mIU/L for 6–12 months

High risk

- Any T3 and T4 or any T, N1 or M1.
- LT4 suppressive dose TSH < 0.1 mIU/L for 3–5 years

ATA – staging and recommendations after thyroidectomy and radioiodine therapy *(2009)*

Low risk

- No local or distant metastases
- All macroscopic tumor removed
- No tumor invasion of locoregional tissues or structures
- No aggressive histology (e.g., tall cell, insular, columnar carcinoma)
- TSH must be between 0.3 and 2 mIU/L. Recommendation C

Intermediate risk

- Microscopic invasion in perithyroidal soft tissues
- Aggressive histology or vascular invasion

High risk

- Macroscopic tumor invasion
- Incomplete tumor resection
- Distant metastases
- I-131 uptake outside the thyroid bed after the post-treatment WBS scan.
- TSH must be between 0.1 and 0.5 mIU/L for 5–10 years. Recommendation C

LATS (Pitoia, 2009) proposed a disease staging system based on 3 categories:

Very low risk

- Unifocal T1a (<1 cm) N0M0 and no extension beyond thyroid capsule

Low risk

- T multifocal 1-4 cm N0M0

High risk

- T > 4 cm (> 45 years)
- Macroscopic extrathyroidal extension (>45 years)
- N1
- M1
- Residual disease
- Aggressive histology

According to **BTA 2014,** the following algorithm of disease staging should be used:

No indications of I-131 therapy

All criteria below should be met

- Tumour <1cm unifocal or multifocal
- Histology classical papillary or follicular variant of papillary carcinoma, or follicular carcinoma
- Minimally invasive without angioinvasion
- No invasion of thyroid capsule (extra thyroidal extension)

Definite indications of I-131 therapy

Any one of the criteria below should be met

- Tumour >4cm
- Any tumour size with gross extra thyroidal extension
- Distant metastases present

Uncertain indications; selective use of I-131

All other cases

One or more of the following risk factors may identify patients at higher risk of recurrence who may benefit from RRA:

- Large tumour size
- Extra-thyroidal extension
- Unfavorable cell type (tall cell, columnar or diffuse sclerosing papillary cancer, poorly differentiated elements)
- Widely invasive histology
- Multiple lymph node involvement, large size of involved lymph nodes, high ratio of positive to negative nodes, extracapsular nodal involvement.
- WBS post therapy at 3–5 days

ETA/ATA – management of metastatic and recurrent disease *(Pacini 2006b,2009)*

Local and Regional Recurrence

- Surgery and I-131
- External beam therapy of 40–45 Gy in 25–30 sessions only if surgery is not possible and there is no I-131 uptake

Distant Metastases

- Lungs: 100–200 mCi every 4–8 months during the first 2 years
- Bones: surgery and I-131, external beam therapy
- Brain: surgery and external beam therapy, I-131 only after external radiotherapy

Second Malignancies

- ETA – over 600 mCi I-131, the risk is significantly higher for second malignancy (Canchola 2006; Pacini et al. 2006a; Rubino et al. 2003)
- ATA – the risk of second malignancy is dose related, long term follow- up studies demonstrate a very low risk. There appears to be an increased risk of breast cancer, unclear whether this is a result of screening basis, radioiodine therapy, or other factors – recommendation C

We strongly suggest having cancer-screening programs to all the patients with thyroid malignancy, most of them women, who have the opportunity of regular breast examination and genital control.

In order to do our best for this disease, there has to exist a close relation between all the specialists involved in the diagnostic and treatment of this pathology.

The prognosis of these patients strongly depends on some pre-surgical, intra-operative and post-operative criteria, as were synthetized by Schlumberger, 2016 and are presented below in Fig. 2.

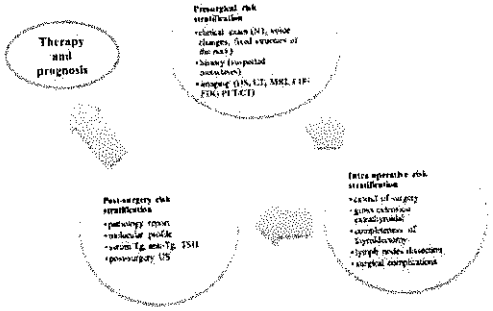

Fig. 2 Initial risk stratification factors, adapted from Schlumberger, 2016

The new ATA 2015 guidelines proposed a new risk stratification, summarized in Table 2; to be noted, compare to the previous guideline, the introduction of genotype criteria and of number and/or sizes of metastatic vessels or lymph nodes.

Table 2. Risk stratification system ATA 2015

LOW RISK	INTERMEDIATE RISK	HIGH RISK
1.Papillary thyroid cancer, with all of the following: ▪ No local or distant metastases; ▪ All macroscopic tumor has been resected ▪ No tumor invasion of loco-regional tissues or structures ▪ The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) ▪ If I-131 is given, there are no I-31-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan ▪ No vascular invasion ▪ Clinical N0 or ≤5 pathologic N1 micrometastases (<0.2 cm in largest dimension) 2.Intrathyroidal papillary microcarcinoma, unifocal or multifocal, including BRAF^{V600E} mutated (if known) 3.Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer 4.Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion	1. Microscopic invasion of tumor into the perithyroidal soft tissues 2. I-131-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan 3. Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) 4. Papillary thyroid cancer with vascular invasion 5. Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension 6. Multifocal papillary microcarcinoma with extrathyroidal extension and BRAF^{V600E} mutated (if known)	1. Macroscopic invasion of tumor into the perithyroidal soft tissues (gross extension) 2. Incomplete tumor resection 3. Distant metastases 4. Postoperative serum thyroglobulin suggestive of distant metastases 5. Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension 6. Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)

Recommendations for radioiodine ablation according to **ATA 2015** are summarized in Table 3.

Table 3. Characteristics according to the ATA risk stratification system and AJCC/TNM staging system with postoperative radioiodine decision-making

Risk staging ATA, 2015	Features	Radioiodine indication (RAI)
ATA low risk T1a,N0/Nx,M0/Mx	Tumor size ≥1 cm (uni- or multifocal)	No
ATA low risk T1b,T2,N0/Nx,M0/Mx	Tumor size >1–4 cm	Not routine—May be considered for patients with aggressive histology or vascular invasion
ATA low to intermediate risk T3,N0/Nx,M0/Mx	Tumor size >4 cm	Consider—Need to consider presence of other adverse features. Advancing age may favor RAI use in some cases, but specific age and tumor size cutoffs subject to some uncertainty.
ATA low to intermediate risk T3,N0/Nx,M0/Mx	Microscopic ETE, any T	Consider—Generally favored based on risk of recurrent disease. Smaller tumors with microscopic extension may not require RAI.

ATA low to intermediate risk T1-3,N1a,M0/Mx	Central compartment neck lymph node metastases	Consider—Generally favored, due to somewhat higher risk of persistent or recurrent disease, especially with increasing number of large (>2–3 cm) or clinically evident lymph nodes or presence of extra- nodal extension. Advancing age may also favor RAI use. However, there is insufficient data to mandate RAI use in patients with few (<5) microscopic nodal metastases in central compartment in absence of other adverse features.
ATA low to intermediate risk T1-3,N1b,M0/Mx	Lateral neck or mediastinal lymph node metastases	Consider—Generally favored, due to higher risk of persistent or recurrent disease, especially with increasing number of macroscopic or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.
ATA high risk T4 Any N, Any M	Any size, gross ETE	Yes
ATA high risk M1, Any T, Any N	Distant metastases	Yes

A novelty proposed by the new guidelines was the response classification to therapy. The response to therapy restaging system was designed and specifically developed to guide specific therapeutic decisions after primary therapy is completed. Prospective studies of the value of this system for guiding extent of primary treatment, including adjuvant treatment decisions, are needed. However, given that there is emerging evidence that such a reclassification system has potential to be of great importance in the management of DTC patients after primary treatment, there will be presented the systems proposed by BTA 2014 (Table 4) and ATA 2015 (Table 5).
BTA proposed the following terminology:

Table 4 Dynamic Risk Stratification: definitions of response to initial therapy of DTC (9–12 months after total thyroidectomy with and subsequent radioiodine therapy, adapted BTA 2014

Excellent response	*All the following:* ▪ Suppressed and stimulated Tg <1 ng/mL (anti-Tg negative) ▪ Neck US without evidence of disease ▪ Cross-sectional and/or nuclear medicine imaging negative (if performed)	***Low risk***
Indeterminate response	*Any of the following:* ▪ Suppressed Tg < 1 ng/L and stimulated Tg ≥1 and <10 ng/L (anti-Tg negative) ▪ Neck US with nonspecific changes or stable < 1 cm lymph nodes ▪ Cross-sectional and/or nuclear medicine imaging with nonspecific changes, although not completely normal	***Intermediate risk***
Incomplete response	*Any of the following:* ▪ Suppressed Tg≥1 ng/mL or stimulated Tg ≥ 10 ng/L (anti-Tg negative) ▪ Rising Tg values ▪ Persistent or newly identified disease on cross-sectional and/or nuclear medicine imaging	***High risk***

ATA proposed the following terminology, for the assessment of therapy response:

1. **Excellent response**: no clinical, biochemical, or structural evidence of disease after initial therapy; <1% disease specific death.
2. **Biochemical incomplete response**: abnormal Tg /anti-Tg values in the absence of localizable disease; <1% disease specific death.
3. **Structural incomplete response**: persistent or newly identified loco- regional or distant metastases; 11% disease specific death (loco-regional metastases), 50% disease specific death (distant metastases).
4. **Indeterminate response**: biochemical or structural findings that cannot be classified as either benign or malignant; <1% disease specific death.

Table 5. Proposed terminology to classify response to therapy and clinical implications (adapted from ATA,2015)

Excellent response	*Negative imaging* and either ▪ Suppressed Tg <0.2 ng/mL or ▪ TSH-stimulated Tg <1 ng/mL	An excellent response to therapy should lead to: ▪ an early decrease in the intensity and frequency of *follow up* ▪ and the *degree of TSH suppression*
Biochemical incomplete response	*Negative imaging* and ▪ Suppressed Tg ≥1 ng/mL or ▪ Stimulated Tg ≥10 ng/mL or ▪ Rising anti-Tg antibody levels	A biochemical incomplete response should lead to: ▪ If associated with *stable or declining serum Tg values*, continued observation with ongoing TSH suppression in most patients. ▪ *Rising Tg or anti-Tg antibody values* should prompt additional investigations and potentially additional therapies.
Structural incomplete response	*Structural or functional evidence of disease* with any Tg level, with or without anti-Tg antibodies	A structural incomplete response may lead to: ▪ additional treatments or ongoing observation depending on multiple clinico-pathologic factors including the size, location, rate of growth, RAI avidity, F18-FDG avidity, and specific pathology of the structural lesions.
Indeterminate response	▪ Nonspecific findings on imaging studies ▪ Faint uptake in thyroid bed on RAI scanning ▪ Nonstimulated Tg detectable, but <1 ng/mL ▪ Stimulated Tg detectable, but <10 ng/mL or ▪ Anti-Tg antibodies stable or declining in the absence of structural or functional disease	An indeterminate response should lead to: ▪ *continued observation* with appropriate serial imaging of the nonspecific lesions and serum Tg monitoring. ▪ Nonspecific findings that become suspicious over time can be *further evaluated* with additional imaging or biopsy.

ETA/ATA – radioiodine procedure *(Pacini 2006a,2006b,2009)*

- High- risk group > 100 mCi I-131 after withdrawal
- Low-risk group – 30–100 mCi I-131 after withdrawal or 100 mCi I-131 in the third day

after an rhTSH 0.9 mg day 1 and 2
- Scan before ablation may be avoided
- TSH must be >30 mIU/L, Tg before ablation

A low iodine diet for approximately 1–2 weeks should be considered for patients undergoing RAI remnant ablation or treatment, even if there are no clear evidences about the benefit of strict diet. Surely, the patient should avoid medication with iodine content, contrast media; the specific region profile diet should know and adapted. A patient coming from a region with high intake of seafood needs to know about the supplementary tests or diet restriction prior to therapy. A special attention should be considering about the use of Amiodarone, where the impact on iodine uptake may influence significantly the possibility of favorable outcome; the blockade may take sometimes more than one year.

2.6 Radioactive Iodine Therapy

Radiopharmaceutical:
(I-131)NaI – sodium iodide capsules for oral administration with specific activity of 1.11, 1.85, 2.59, 3.7, and 5.55 GBq at calibration time, clearly mentioned by the producer and strictly scheduled for arriving in the department.

Principle:
This is a systemic administration of I-131 sodium iodide for selective irradiation of thyroid postsurgical remnants of differentiated thyroid carcinoma (DTC) or other nonresectable DTC, or for irradiation of metastatic iodine-avid structures.

Patient Preparation:
The patient should be:
- After total or near total thyroidectomy with histopathological diagnostic of differentiated thyroid carcinoma
- With a TSH value >30-40 mIU/L at 4–6 weeks after the surgery in the absence of thyroid therapy replacement
- With a TSH value >40 mIU/L or a significant increment of minimum 100 times comparing the TSH value obtained under thyroid hormone treatment at 4–6 weeks of thyroid hormone withdrawal, in the case of substitutive thyroid hormonal therapy
- After I.M. injection of recombinant TSH in two consecutive days of 0.9 mL solution, if the patient is under hormonal treatment
- Fasting condition
- Avoid any contact with blocking agents, iodine contrast media used for tomographic examination (at least 2-3 months!), attention to some diet restriction

In the case of female patients of childbearing potential, a routine testing for pregnancy within 72 h before the administration of I-131 must be done. When the patient history clearly indicates that pregnancy is excluded, a pregnancy test may be omitted at the discretion of the treating physician. In case of suspicious situation, a serologic analysis of beta HCG (beta human chorionic gonadotropin) may be requested.

Postoperative radioiodine will:
- Ablate the thyroid remnant, which will help in surveillance for recurrent disease.
- Eliminate suspected micrometastases.
- Eliminate known persistent disease.

If preoperative scan is performed or is needed, to avoid or reduce the stunning effect, the

following have been suggested (Anderson 2003; Carril 1992; Gerard 2002)

- The use of I-123 or small (2 or 3 mCi) doses of I-131.
- A shortened interval (of not more than 72 h) between the diagnostic I-131 dose and the therapy dose.

Fixed I-131 Doses

The administration of a fixed dose of I-131 is the simplest and the most widely used method. Most clinics use this method regardless of the percentage uptake of I-131 in the remnant or metastatic lesion. Patients with tumor uptake are routinely treated with large, fixed amounts of I-131. The dose of remnant ablation may be 30–50–70–100 mCi (1.1–1.85–2.59–3.7 GBq), according to the:

- Aggressiveness of histology
- volume of the residual tissue
- the uptake, if is known
- the serum level of the Tg.

Lymph node metastases may be treated with about 100–175 mCi (3.7–6.47 GBq) of I-131. The cancer growing through the thyroid capsule and incompletely resected is treated with 150–200 mCi (5.5–7.4 GBq). Patients with distant metastases are usually treated with 200 mCi (7.4 GBq) of I-131, which typically will not induce radiation sickness or produce serious damage to other structures but may exceed generally accepted safety limits to the blood in the elderly and in those with impaired kidney function.

Diffuse pulmonary metastases that concentrate 50% or more of the diagnostic dose of I-131 (which is very uncommon) are treated with 150 mCi or less of I-131 (5.5 GBq) to avoid lung injury, which may occur when more than 80 mCi remain in the whole body 48 h after the treatment. The administered activity of radioactive iodine (RAI) therapy should be adjusted for pediatric patients.

Quantitative Tumor I131 Dosimetry

A second method is to use quantitative dosimetry methods to estimate the amount of radiation delivered to the lesion per unit of I-131 administered. This approach is attractive because radiation exposure from arbitrarily fixed doses of I-131 can vary substantially. It is necessary to serially measure the radiation activity in the target using a tracer dose and to estimate the tumor size to make these calculations, which is difficult to do and is impossible in the setting of diffuse or microscopic lung metastases (Tuttle 2006; NCCN v1.2016,Schlumberger 2016).

The use of I-123 or I-131 with SPECT/CT or I-124 PET-based dosimetry may facilitate whole-body and lesion dosimetry. The efficacy of RAI therapy is related to the mean radiation dose delivered to neoplastic foci and also to the radiosensitivity of tumor tissue, which is higher in younger patients, with small metastases from well-differentiated papillary or follicular carcinoma and with uptake of RAI, but no or low F18-FDG uptake.

The maximum tolerated radiation absorbed dose (MTRD) is potentially exceeded in a significant number of patients undergoing empiric treatment with various amounts of I-131. Some studies found that an empirically administered I-131 activity of 200 mCi would exceed the MTRD in 8%–15% of patients younger than age 70 and 22%– 38% of patients aged 70 years and older. These estimates imply the need for caution in administering empiric activities higher than 100–150 mCi in certain populations such as elderly patients and patients with renal insufficiency.

Blood I-131 Dosimetry

A third method is to administer a dose calculated to deliver a maximum of 200 cGy to the blood, while keeping the whole-body retention less than 120 mCi (4.4 GBq) at 48 h or less than 80 mCi

(2.96 GBq) in the case of diffuse pulmonary uptake.

The activity of administrated radiopharmaceutical depends on the type of surgery, the thyroglobulin values, and the volume of remnant tissue (ultrasound evaluation).

After the administration, the patient remains in fasting condition for 2 more h, and after that he/she is advised to hydrate himself.

The administration of I-131 for the treatment of DTC is performed in hospitalization conditions, and the discharge of patients is done according to national radioprotection regulation. At this moment, there are countries where the treatment may be done in ambulatory condition even with doses higher than 30 mCi (1.1 GBq) I-131.

All patients have paper and electronic information on each room about the diagnosis, the treatment options, follow-up, side effects, and personal indications about individual medication.

The rooms must have separate facilities and are continuously in surveillance by the staff, on separate cameras. At the discharging time, the patient is advised how to minimize the risk for other persons and for what period of time, depending of the dosimetry measurements at the discharging time (Willegaignon et al. 2011).

Post-Treatment I-131 Imaging

When I-131 therapy is given, whole-body radioiodine imaging should be performed several days later to document I-131 uptake by the tumor. Post-treatment whole-body radioiodine imaging should be done primarily because up to 25% of such imaging shows lesions that may be clinically important, which were not detected by the diagnostic imaging.

It is strongly recommended to respect the indication of surgery and of the extent of surgery, according to the risk classification and the tumor dimensions. A better pre-surgical diagnosis will lead to a limited number of second surgeries for the completion of thyroidectomy; it will also limit the unnecessary total thyroidectomy. The lymphadenectomy will be targeted to all the patients with clinical involvement of the lymph nodes and the central lymph node dissection will be recommended as a routine.

Recommendations:

- Optimizing the schedule of patients for radioiodine treatments at 4–6 weeks postsurgery.
- Avoid hormonal substitution after surgery and before radioiodine, if there is the possibility to have an optimal organization of the waiting list for therapy; use hormonal replacement if the stimulation will be done with rhTSH.
- Do not use CT with contrast media for staging; the cervical ultrasound is the best non-invasive method for correct assessment of the local extension, before the treatment.
- Avoid WBS I-131 before radioiodine treatment, unless distant metastases are suspected and important active thyroid remnant must be removed by surgery.
- Increase TSH more than 30-40 mIU/L.
- Quantitative determination of ablative doses: ultrasound volume determination, 24 h uptake of radioiodine, estimated by using less than 100 μCi I-131 or adequate dose for I-123, and serum Tg and anti-Tg levels.
- Do not use any medication that may influence the uptake of radioiodine.
- Do not use an aggressive wash out of radioiodine by intensive hydration (not more than 2–2.5 L of liquids/day).
- Use WBS after therapy at 2–5 days, for a correct staging of the disease extension.
- The sialadenitis is limited by liberal hydration and by lemon juice given in the first 24–48 h after radioiodine. Our personal experience recommends 500–1,000 mg of vitamin C during the first 5 days of treatment (Cecarelli 1999; Mandel and Mandel 2003; Schlumberger 2004).

- The recommended activity of I-131, range from 1.11 to 5.55 GBq (30–150 mCi).
- Total response and disease free is indicated by:
  - No detectable tumor mass
  - Undetectable Tg in high TSH condition and no anti-Tg

The revised guidelines for the management of thyroid disease in pregnancy include recommendations regarding the interpretation of thyroid function tests in pregnancy, iodine nutrition, thyroid autoantibodies and pregnancy complications, thyroid considerations in infertile women, hypothyroidism in pregnancy, thyrotoxicosis in pregnancy, thyroid nodules and cancer in pregnant women, fetal and neonatal considerations, thyroid disease and lactation, screening for thyroid dysfunction in pregnancy, and directions for future research.

Possible early adverse events following I-131.

- Sialadenitis (lemon juice, candies, chewing gum should be used during the therapy)
- Nausea (can be minimized by prescription of antiemetics)
- Neck discomfort and swelling within a few days of I-131 may occur, especially when a large thyroid remnant is present (simple analgesics and non-steroids anti-inflammatory ointments for neck discomfort are recommended. A short course of corticosteroids is recommended in severe cases).
- Radiation cystitis, radiation gastritis, bleeding and edema in metastases are all extremely rare
- No hair lose radioiodine related

Management of acute side-effects of I-131.

- For patients with known metastatic disease, especially bone and lung metastases, consideration should be given to commencing a short course of corticosteroids to minimize peritumoral edema and an increase in local symptoms. If the patient is to receive rhTSH then starting the corticosteroids prior to the injections is advisable.
- The total cumulative activity should be kept as low as possible.
- Monitoring of lung function for any sign of a restrictive functional deficit is recommended in patients with lung metastases
- Acute symptoms of dyspnea and cough can be reduced with prophylactic corticosteroids

Possible late adverse events following I-131

- Xerostomia and dysgeusia
- Sialadenitis and lacrimal gland dysfunction may occur
- Lifetime incidence of leukaemia and second cancers is low affecting around 0.5% of patients. There are controversial studies regarding the second malignancies after I-131. Some studies showed an increased, but non-significant risk of leukaemia. The risk of leukaemia increases with escalating cumulative activity and with use of additional external beam radiotherapy (BTA, 2014). Patients who have received a high cumulative I-131 activity may also be more likely to develop second solid malignancies (e.g. the bladder, colorectal, breast and salivary glands). The author published the results on 1990 patients treated over a period of 25 years with low and medium doses of I-131 and there was no significant impact on developing second malignancies related to I-131 (Piciu, 2016).
- Radiation fibrosis can occur in patients who have had diffuse pulmonary metastatic disease and have received repeated doses.

Follow-up:

- The serum Tg, rules out the anti-Tg: it must be undetectable after radical treatment; no measurements for 3 months after treatment

- WBS I-131 – 2–3 days after 2–5 mCi I-131 and T4 withdrawal or rhTSH only at the first check-up and till the first negative scan.
- Tg is measured every 6–12 months by immunometric assay in the same laboratory, for all the patients with DTC and radical treatment. Anti-Tg every time in the same determined sample (Schlumberger 2004, 2016).
- Low-risk patients with radical treatment (surgery +/– radioiodine), with negative neck ultrasound and TSH suppression 6 months after the treatment, Tg stimulated after T4 withdrawal or rhTSH at 12 months with undetectable values, are uncertain for subsequent stimulated determinations (Pacini et al. 2006a, Tuttle 2008, ATA 2015).
- Low-risk patients with radical treatment (surgery +/– radioiodine), with negative Tg stimulated after T4 withdrawal or rhTSH, after the first WBS negative, do not need further WBS.
- If the use of human recombinant TSH is not a routine it is recommended to be used at least for the patients with no optimum rising of TSH: Circumstances in which the patient cannot elicit a sustained release of endogenous TSH include hypothalamic or pituitary dysfunction, long term corticosteroid administration, and an unusually slow response, particularly in the elderly (Pacini 2004; Tuttle 2008; Chianelli 2009).
- Perform morphological and functional studies with other radiotracers in case of negative WBS I-131 (see Chapter 11, PET/CT).

It is very important to have a strict follow-up and early detection of the recurrence of the disease and it is mandatory to do our best to have an accurate staging and precision of the extension.

The present studies suggest that previous administration of radioiodine therapy in female patients with well differentiated thyroid cancer does not result in demonstrable adverse effects in subsequent pregnancies (Schlumberger 1996; Ceccarelli 1999; ATA/AACE 2011).

Gonadal tissue is exposed to radiation from RAI in the blood, urine, and feces. Temporary amenorrhea/ oligomenorrhea lasting 4–10 months occurs in 20%–27% of menstruating women after radioiodine therapy for thyroid cancer (ATA, 2015). Although the numbers of patients studied are small, long-term rates of infertility, miscarriage, and fetal malformation do not appear to be elevated in women after RAI therapy (Sawka, 2008). One recent large retrospective cohort study showed that use of RAI was associated with delayed childbearing and decreased birthrate in later years, although it is unclear if this is due to reproductive choice or reproductive health.

In a meta-analysis, no evidence was found that I-131 treatments impaired fertility (ATA, 2011), while in another meta-analysis, radioiodine therapy for thyroid cancer in young men has been associated with transient testicular dysfunction expressed as elevated serum FSH levels for up to 18 months after treatments, and some articles reported low sperm counts exceeding 1-year duration. Limited data indicate that fathering a child within 3 months of radiation exposure is not associated with an increase in congenital anomalies or fetal loss, and there is no evidence of long-term reduced fertility. However, men should be advised to wait at least 3 months.

Special recommendation:

At discharge, the reports and the medical letters consist of all the identity information, diagnosis, laboratory tests, and copies of WBS, administrated activity, calibration data and specific issues about radioprotection (ATA 2011).