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Consensus

Radioactive iodine therapy, molecular imaging and serum biomarkers for differentiated thyroid cancer: 2017 guidelines of the French Societies of Nuclear Medicine, Endocrinology, Pathology, Biology, Endocrine Surgery and Head and Neck Surgery☆

Traitement par iode 131, imagerie moléculaire et biomarqueurs sériques des cancers thyroïdiens différenciés : recommandations 2017 des Sociétés françaises SFMN/SFE/SFP/SFBC/AFCE/SFORL

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The following guidelines update the treatment and follow-up of thyroid cancer of follicular origin. They were drawn up by the Endocrinology Work Group of the French Society of Nuclear Medicine (SFMN: authors SZ, ALG, SL, JC, SB, IK, MET, EH, DT) and experts appointed by five other scientific societies: French Society of Endocrinology (SFE: LL, CB, LG), French Society of Pathology (SFP: AAG), French Society of Clinical Biology (SFBC: PJL), French-speaking Association of Endocrine Surgery (AFCE: FS, EM), and French Society of Otorhinolaryngology and Head and Neck Surgery (SFORL: RG).

The experts were chosen by the respective societies. Guidelines were first drawn up by two writing groups working on two subtopics: (1) radioactive iodine (RAI) therapy using iodine-131 (^{131}I) after initial surgery, treatment of persistent/recurrent locoregional disease and treatment of distant metastases,

☆ These guidelines were read and commented by an external panel of experts in thyroid cancer. Their names are listed in the Acknowledgments section.

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radioprotection issues and ^{131}I-induced side-effects (coordinator: SZ); (2) imaging and biomarkers, including ^{131}I scintigraphy, fluorodeoxyglucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT), serum thyroglobulin (Tg) and anti-Tg antibodies (coordinator: ALG). Literature search used the PubMed database and covered guidelines, meta-analyses, randomized studies and other prospective and retrospective studies. Articles were selected by the experts. Guidelines were graded according to the American College of Physicians Guideline Grading System (GRADE) [1].

Retrieved texts underwent full commentary by the Work Group as a whole, with telephone conferences and formal meetings of both groups, singly and together. Drawing up of guidelines began in November 2014. The work is presented here in the Annals of Endocrinology in its summary form; the full version of the 2017 guidelines will be published in French in Médecine Nucléaire-Imagerie Fonctionnelle et Métabolique.

1. Epidemiology

Incidence of thyroid cancer of follicular origin is increasing throughout the world, currently approximating 4/100,000 males and 13.5/100,000 females. Mortality is stable, at around 0.5/100,000 [2]. Rising incidence is mainly related to subcentimeter papillary carcinoma, accounting for about 40% of cases. The strong increase over recent decades raises the issue of overdiagnosis of small indolent forms, often discovered incidentally after thyroidectomy performed for other indications [3], and calls for changes in our criteria for delivering adjuvant iodine-131 therapy. The capability to detect minimal residual disease by new thyroglobulin (Tg) assays and the role of molecular imaging modalities should also be taken into account in the decision-making process.

2. Iodine-131 therapy following primary surgery

2.1. Objectives

Radioactive iodine (RAI) therapy using iodine-131 (^{131}I) is a targeted therapy against thyroid cancer of follicular origin [4]. Treatment modalities are stratified according to risk factors for disease persistence/recurrence or poor outcome, in order to improve outcome, limit cumulative radiation dose exposure and preserve quality of life [5]. Besides its impact on disease-free survival, the role of adjuvant ^{131}I therapy in dynamic restratification of patients has also been taken into consideration.

The administered activity of ^{131}I can be low, typically at 20–30 mCi (740–1110 MBq), 30 mCi being more widely used, or high, typically at 100 mCi (3.7 GBq) or more. Preparation can use endogenous TSH stimulation (following thyroid hormone withdrawal) or exogenous TSH (after injection of recombinant human TSH [rhTSH]) [6–8]. Informations regarding the mode of patient preparation (e.g., TSH stimulation protocols, iodine-deprivation diet and avoidance of iodine-containing drugs and contrast agents) are detailed in the 2008 EANM guidelines [9].

Postoperative RAI therapy has 3 objectives:

- ablation: ablation is intended to destroy postoperative physiological thyroid remnants so as to achieve an undetectable serum Tg level, facilitating follow-up and early detection of relapse.

  It also enables high-sensitivity whole-body imaging, to diagnose and locate any residual disease; this post-ablation scintigraphy may also be used as a prognosticator via the so-called "dynamic reclassification" method, enabling more personalized subsequent follow-up;
- adjuvant: ^{131}I therapy enables irradiation and destruction of occult infra-radiologic residual disease in the neck or other occult micrometastases, improving recurrence-free survival;
- therapeutic: in patients with known residual or metastatic disease, ^{131}I therapy aims to treat iodine-avid metastases in order to achieve cure or remission, reduce persistent or recurrent disease, and improve overall prognosis.

2.2. Clinical/anatomic classification

There are several classification systems: the 2010 (7th edition) [10] and 2017 (8th edition) [11] versions of the pTNM classification and the derived AJCC staging system (Tables 1 and 2) assess risk of mortality. The other systems focus on risk of relapse. Patient classification is based on 3-level risk stratification for persistence/recurrence, currently stratified as low, intermediate or high [9,12,13]. The 2015 American Thyroid Association guidelines [14] made some significant changes compared to the 2009 version [15]: some intermediate or even high-risk tumors were transferred to the low-risk group. Table 3 presents the 2015 ATA classification.

More recently, the new TNM classification [11] has also made significant changes.

Firstly, the definition of pT3 has been revised as follows: T3a now refers to tumor greater than 4 cm in the greatest dimension, and T3b to tumor of any size with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid). In this edition, minor extrathyroidal extension, involving perithyroidal adipose tissue, strap muscles, nerves or small vascular structures, identifiable only by microscopy, is no longer considered as a risk factor for staging, and is thus counted as pT1, pT2 or pT3a. Secondly, nodal extension in the upper mediastinum (level VII) is now considered as central neck involvement (N1a). Thirdly, in the AJCC prognostic grouping, the age threshold for poor prognosis has changed from 45 to 55 years. Finally, some categories have been moved to lower risk groups (Table 2).

The present guidelines have integrated the TNM 2017 [11]. However, beyond these latest changes, we have also taken into account the presence/absence of minor extrathyroidal extension [16,17] and the degree of nodal extension (compartment, size and number of invaded lymph nodes, presence of extracapsular extension) [18–20].

2.3. Indications

The present guidelines distinguish, as detailed below, between patients at low, intermediate and high risk of recurrent/

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Table 1
TNM Classification for thyroid cancer TNM UICC/AJCC 7th (2010) [10] vs 8th edition (2017) [11].

		TNM 2010	TNM 2017
T	Tx	Primary tumor cannot be assessed	Primary tumor cannot be assessed
	T0	No evidence of primary tumor	No evidence of primary tumor
	T1a	Tumor ≤ 1 cm, limited to the thyroid	T ≤ 1 cm[a]
	T1b	Tumor > 1 cm but ≤ 2 cm in greatest dimension, limited to the thyroid	T > 1 cm and ≤ 2 cm[a]
	T2	Tumor size > 2 cm but ≤ 4 cm, limited to the thyroid	T > 2 cm and ≤ 4 cm[a]
	T3	Tumor size > 4 cm, limited to the thyroid or any tumor with macroscopic or microscopic minimal extrathyroidal extension (e.g., extension to strap muscles or perithyroidal adipose tissue	T3a: tumor more than 4 cm in greatest dimension, limited to the thyroid T3b: tumor of any size with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles)
	T4a	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve	Tumor extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, esophagus, recurrent laryngeal nerve
	T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessel	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
N	Nx	Regional lymph nodes cannot be assessed[b]	Regional lymph nodes cannot be assessed[b]
	N0	No regional lymph node metastasis	No regional lymph node metastasis
	N1a	Metastasis in level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)	Metastases in level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes) or upper/superior mediastinum (level VII)
	N1b	Metastasis to unilateral, bilateral, or contralateral cervical (levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (level VII)	Metastasis in other unilateral, bilateral or contralateral cervical lymph nodes (levels I, II, III, IV or V) or retropharyngeal
M	M0	No distant metastasis is found	No distant metastasis is found
	M1	Distant metastasis is present	Distant metastasis is present

[a] In this edition, minor extrathyroidal extension that involves perithyroidal adipose tissue, strap muscles, nerves, or small vascular structures, identified only by microscopy but not clinically appreciated (no gross invasion), is no longer used as a risk factor for staging.
[b] pN0: histological examination of a selective neck dissection specimen will ordinarily include 6 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0. In the last TNM edition, even a single examined negative node would classify the patient in the category pN0.

Table 2
AJCC prognostic grouping for thyroid cancer TNM UICC/AJCC 7th (2010) [10] vs 8th edition (2017) [11].

	AJCC 7th edition (2010)		AJCC 8th edition (2017)	
	Stage < 45 years old	Stage > 45 years old	Stage < 55 years old	Stage ≥ 55 years old
Stage I	Any T, any N, M0	T1, N0, M0	Any T, any N, M0	T1/T2, N0, M0
Stage II	Any T, any N, M1	T2, N0, M0	Any T, any N, M1	T3a/T3b, N0, M0 T1/T2/T3, N1, M0
Stage III	–	T3, N0, M0	–	T4a, any N, M0
Stage IVA	–	T1/T2/T3, N1a, M0 T4a, N1b, M0	–	T4b, any N, M0
Stage IVB	–	T4b, any N, M0	–	Any T, any N, M1
Stage IVC	–	Any T, any N, M1	–	–

persistent disease: LR, IR and HR, respectively. In these French guidelines, the at-risk groups do not correspond exactly to those of the 2015 ATA classification [14].

Apart from tumor size, the following factors are associated with poorer prognosis:

- unfavorable histological aspects (e.g., tall cell, hobnail variant, columnar cell papillary thyroid carcinoma, oxyphilic-Hürthle cell variant of follicular thyroid, presence of a poorly differentiated component);
- lymph-node involvement, classified as limited, intermediate, large or severe (detailed below);
- extrathyroidal extension (ETE), classified as minor/microscopic (mETE) or gross;
- vascular invasion or tumor emboli, emboli leading to lymphatic spread (mostly in papillary carcinoma) or to hematogenous spread and distant metastasis;
- incomplete tumor resection;
- advanced age (adopting the new cut-off of > 55 years), and male gender;
- presence of BRAF and/or TERT gene mutation, especially when combined.

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Table 3
ATA 2015 Risk Stratification System [14].

Low risk	Papillary thyroid cancer (with all of the following) No local or distant metastases All macroscopic tumor has been resected No tumor invasion of locoregional tissues or structures The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) If ^{131}I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first post treatment whole-body RAI scan No vascular invasion Clinical N0 or ≤ 5 pathologic N1 micrometastases (< 0.2 cm in largest dimension) Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer Intrathyroidal, well-differentiated follicular thyroid cancer with capsular invasion and no or minimal (< 4 foci) vascular invasion Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAF-V600E mutated (if known)
Intermediate risk	Microscopic invasion of tumor into the perithyroidal soft tissues RAI-avid metastatic foci in the neck on the first post-treatment whole-body RAI scan Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) Papillary thyroid cancer with vascular invasion Clinical N1 or > 5 pathologic N1 with all involved lymph nodes < 3 cm in largest dimension Multifocal papillary microcarcinoma with ETE and BRAFV600E mutated (if known)
High risk	Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE) Incomplete tumor resection Distant metastases Postoperative serum thyroglobulin suggestive of distant metastases Pathologic N1 with any metastatic lymph node ≥ 3 cm in largest dimension Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)

The present guidelines, rather than opposing 30 versus 100 mCi, broaden the range of possibilities of administered ^{131}I activity, simply distinguishing low versus high activity. Activities used in children should be adapted according to specific guidelines [21].

2.3.1. Patients at low risk of relapse

Characteristics of patients at low risk of relapse (LR):

- complete tumor resection;
- and no unfavorable histological aspect;
- and no vascular invasion;
- and pT1a/pT1b/pT2, without extrathyroidal extension, N0/Nx;
- or pT1a/pT1b, without extrathyroidal extension, N1a with minimal central compartment lymph-node involvement: ≤ 5 metastatic nodes and size of metastases < 2 mm;
- or well-differentiated follicular carcinoma (pT1, pT2, pT3a) without capsular or vascular invasion;
- or well-differentiated follicular carcinoma (pT1, pT2, pT3a) without extrathyroidal extension, without vascular invasion or with minimal vascular invasion (< 4 emboli);
- and in case of RAI administration: absence of extra-thyroid bed extension on post-therapy scintigraphy.
- N.B.: large NIFTPs (non-invasive follicular thyroid neoplasm with papillary-like nuclear features) (> 4 cm) are included in this low-risk category, awaiting publication of the new pathologic classification of thyroid tumor.

Recommendation 1 (R1)

Radioactive iodine therapy is not recommended in patients with unifocal pT1a tumor, or multifocal pT1a with total lesion size ≤ 1 cm, without extrathyroidal extension, N0/NX: strong recommendation, moderate-quality evidence.

Recommendation 2 (R2)

In multifocal pT1a with total lesion size > 1 cm or pT1b, without extrathyroidal extension, N0/Nx, in pT1a with minor extrathyroidal extension (mEET), N0/Nx and in follicular carcinoma without vascular invasion, the use of radioactive iodine is optional.

If ^{131}I therapy is administered, low activity is to be preferred and rhTSH is to be preferred to thyroid hormone withdrawal [22,23]: Strong recommendation, moderate-quality evidence.

Recommendation 3 (R3)

In other patients with low risk of relapse (apart from R1 and R2), including pT1bNx/N0 with minor extrathyroidal extension, radioactive iodine treatment is recommended: weak recommendation, low-quality evidence.

Recommendation 4 (R4)

In these patients (R3), low ^{131}I activity is to be preferred and rhTSH is to be preferred to thyroid hormone withdrawal [22,23]: strong recommendation, high-quality evidence.

Indications for RAI therapy and optimal administered activity are still controversial, especially regarding impact on tumor

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relapse. Thyroid cancers generally exhibit a slow growth pattern, necessitating long-term follow-up. In the published retrospective studies, long-term follow-up data for patients treated with low ^{131}I activity or abstention remain sparse [5,24,25] and, most critically, there are no prospective studies. The French multicenter Estimabl 2 study and the British IoN study include low-risk patients, but are still ongoing and results are expected around 2020.

In indicating RAI therapy, several parameters should be taken into consideration, such as the potential impact on tumor relapse and on Tg monitoring, which can be simplified by RAI remnant ablation, and the patient's wishes.

Special case of NIFTP: diagnosing the new entity NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features, previously termed non-invasive follicular variant of papillary thyroid carcinoma [FVPTC]) requires exhaustive analysis of the nodule capsule [26,27], which can be difficult in large tumors and is not always included in current histological analysis. In case of tumor exceeding 4 cm and/or of doubt as to the exhaustiveness of nodule capsule analysis, the tumor should be assimilated to low-risk cancer and the use of ^{131}I is then optional (R2).

2.3.2. *Patients at intermediate risk of relapse*

Characteristics of patients at intermediate risk of relapse (IR) [18,19,28–32]. These patients have at least one of the following:

- pT2, N0/Nx, with minor extrathyroidal extension; pT3a (tumor size > 4 cm, other than NIFTP), N0/Nx, with or without minor extrathyroidal extension;
- pT2/pT3a N1a with limited lymph-node involvement: ≤ 5 metastatic nodes and size < 2 mm;
- pT1a/pT1b/pT2/pT3a, N1 (N1a or N1b) with intermediate to large lymph-node involvement, the largest metastatic node being < 3 cm;
- clinical N1 disease at diagnosis (cN1) (e.g., metastatic neck lymph node confirmed by ultrasound-guided fine-needle aspiration biopsy);
- unfavorable histological aspect (e.g., tall cell, hobnail variant, columnar cell carcinoma, oxyphilic-Hürthle cell variant of follicular thyroid);
- papillary thyroid carcinoma with limited vascular invasion (< 4 emboli);
- or, in case of RAI administration, positive cervical lymph nodes on post-therapy scan.

Recommendation 5 (R5)

Radioactive iodine is recommended in IR patients. Either rhTSH or thyroid hormone withdrawal can be used [33]. Strong recommendation, moderate-quality evidence.

The administered ^{131}I activity depends on tumor type, stage, presence of one or several extranodal IR criteria (age > 55 years, unfavorable histological aspect, presence of vascular invasion) and on the degree of lymph-node involvement as outlined below.

In the absence of nodal involvement or with only limited lymph-node involvement (≤ 5 metastatic nodes, with size < 2 mm).

Recommendation 6-a (R6a)

In case of a single extra-nodal IR criterion, low to high ^{131}I activity can be used. Strong recommendation, moderate-quality evidence.

Recommendation 6-b (R6b)

In case of multiple IR criteria or additional factors of poor prognosis (advanced age, aggressive histotype and/or presence of lateral lymph-node involvement [pN1b]), high ^{131}I activity may be considered. Strong recommendation, moderate-quality evidence.

In the presence of intermediate lymph-node involvement (cN0, ≤ 5 metastatic nodes, with size 2–10 mm and no extracapsular lymph-node extension).

Recommendation 7 (R7)

Radioactive iodine therapy is systematically indicated. High ^{131}I activity can be considered. Strong recommendation, moderate-quality evidence.

Either thyroid hormone withdrawal or rhTSH can be used for patient preparation. Weak recommendation, low-quality evidence.

In large lymph-node involvement (cN1 and/or nodes ≥ 10 mm) and ≤ 30 mm and/or extracapsular lymph-node extension and/or > 5 metastatic nodes (by definition, such patients are not pT4 or M1 and show < 4 vascular emboli).

Recommendation 8 (R8)

High ^{131}I activity is recommended. Strong recommendation, moderate-quality evidence.

Either thyroid hormone withdrawal or rhTSH can be used for patient preparation. Weak recommendation, low-quality evidence.

2.3.3. *Patients at high risk of relapse*

Characteristics of patients at high risk of relapse (HR) [33–35]. HR patients have any of the following features:

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- incomplete resection;
- pT3b, any N (pT3b in the TNM 2017 staging system, corresponding to gross extrathyroidal extension invading strap muscles: sternohyoid, sternothyroid, thyrohyoid or omohyoid);
- pT4, any N;
- N1 with severe lymph-node involvement (one or more metastatic lymph node > 30 mm);
- carcinoma with vascular invasion with > 4 emboli in follicular or papillary carcinoma;
- M1;
- presence of a poorly differentiated component;
- or highly elevated postoperative serum Tg, suggestive of distant metastasis.

Recommendation 9 (R9)

Radioactive iodine therapy is systematically indicated in HR patients. Strong recommendation, moderate-quality evidence.

Recommendation 9b (R9b)

The recommended schedule includes high-administered ^{131}I activity and thyroid hormone withdrawal. Strong recommendation, moderate-quality evidence.

Further studies are needed before implementing rhTSH as a preparation method in the treatment of distant metastasis. However, where comorbidity precludes hypothyroidism (medical or psychiatric comorbidities), rhTSH may be considered. Strong recommendation, low-quality evidence.

Table 4 presents a summary of indications for ^{131}I therapy.

3. Iodine-131 treatment for persistent or recurrent locoregional disease

Indications for RAI therapy in persistent or recurrent locoregional disease vary according to the clinical situation [9,12–15].

Recommendation 10 (R10)

In case of biochemical evidence of disease [36,37] without structural abnormality on anatomic imaging, a second ^{131}I treatment can be recommended for diagnostic and therapeutic purposes in presence of the following criteria:

- stimulated Tg level > 10 ng/mL after thyroid hormone withdrawal or 5 ng/mL after rhTSH;
- Progression of basal (unsuppresed) Tg and/or basal Tg > 1 ng/mL, using the same assay technique;
- appearance or progressive elevation (> 50%) of Tg antibodies (TgAb), using the same assay technique.

In these situations, ^{131}I is delivered at an empiric activity of 100 mCi (3.7 GBq), preferably after thyroid hormone withdrawal, although rhTSH stimulation may be applied in case of contraindications due to comorbidities.

Strong recommendation, low-quality evidence.

It should be underlined that diagnostic scintigraphy is less sensitive than post-therapy scintigraphy. However, its sensitivity can vary depending on radionuclide imaging techniques and TSH stimulation method [38,39].

Recommendation 11 (R11)

In case of biochemical evidence of disease with abnormalities on functional (^{18}F-FDG PET/CT) or anatomic imaging [40,41], ^{131}I administration may be considered for diagnostic purposes, in order to determine whether the lesions are iodine-avid or not, and for therapeutic purposes, especially for subcentimeter metastatic lymph nodes or distant metastases. Strong recommendation, low-quality evidence.

Post-treatment ^{131}I scan and intraoperative detection can be used to guide and optimize reoperative surgery.

Recommendation 12 (R12)

At least one additional ^{131}I treatment is recommended, at 100 mCi, preferably after thyroid hormone withdrawal, in presence of biochemical evidence of disease (with or without structural disease) after a targeted therapeutic approach (e.g., surgery, external radiotherapy) [42]. Strong recommendation, low-quality evidence. ^{131}I treatment may be repeated, depending on tumor response.

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Table 4
Indications for ^{131}I therapy after total thyroidectomy, with levels of evidence.

Tumor stage and characteristics	Indication for ^{131}I with strength of recommendation and level of evidence	^{131}I activity, type of preparation and strength of recommendation and level of evidence	Corresponding present guideline
Low risk (LR) of recurrence			
Unifocal pT1a	No ^{131}I therapy		R1
Multifocal pT1a with total lesion size ≤ 1 cm without extrathyroidal extension, N0/NX	Strong recommendation		
NIFTP ≤ 4 cm ascertained by total capsule examination	Moderate-quality evidence		
Multifocal PT1aN0/Nx (with total lesion size > 1 cm)	^{131}I therapy is optional	Activity: low ^{131}I activity preferable	R2
pT1aN0/Nx, with minor extrathyroidal extension		Preparation: rhTSH	
pT1bN0/Nx, without extrathyroidal extension		Strong recommendation	
Follicular carcinoma pT2/pT3a, N0/Nx without vascular emboli, without extrathyroidal extension		Moderate-quality evidence	
NIFTP > 4 cm or doubt on the completeness of capsular examination			
Papillary pT2 N0/Nx without extrathyroidal extension	^{131}I therapy is recommended	Activity: low ^{131}I activity preferable	R3 and R4
Well-differentiated follicular pT2/pT3a N0/Nx with minimal vessel invasion (< 4 emboli) without extrathyroidal extension	Weak recommendation	Preparation: rhTSH	
pT1a/pT1b, N0/Nx/N1 (with minimal central compartment lymph-node involvement) and/or with minor extrathyroidal extension (seen only by microscopy)	Low-quality evidence	Strong recommendation High-quality evidence	
Intermediate risk (IR) of recurrence			
pT2, N0/Nx, with minor extrathyroidal extension	^{131}I therapy is recommended	Preparation	R5
pT3a (tumor size > 4 cm), N0/Nx, with or without minor extrathyroidal extension	Strong recommendation	rhTSH	
pT2/pT3aN1 with minimal central compartment lymph-node involvement: ≤ 5 metastatic nodes and size < 2 mm	Moderate-quality evidence	Or hypothyroidism Activity: according to	
pT1a/pT1b/pT2/pT3a, N1 (N1a or N1b) with intermediate or large lymph-node involvement with largest metastatic node < 3 cm		Extranodal IR criteria Degree of lymph-node involvement cf. below	
Clinical lymph node disease (cN1)			
Unfavorable histologic aspect			
Papillary thyroid carcinoma with limited vascular invasion (< 4 emboli)			
Limited lymph-node involvement (≤ 5 N1, < 2 mm) or pT3N0/Nx			
One extranodal IR criteria	^{131}I therapy is recommended	Low or high ^{131}I activity	R6
	Strong recommendation	Strong recommendation	
	Moderate-quality evidence	Moderate-quality evidence	
Multiple extranodal IR criteria	Recommended	High ^{131}I activity can be considered	R6b
	Strong recommendation	Strong recommendation	
	Moderate-quality evidence	Moderate-quality evidence	
Intermediate lymph-node involvement (≤ 5 N1, 2–10 mm)			
Regardless of number of extranodal IR criteria	Recommended	High ^{131}I activity can be considered	R7
	Strong recommendation	Strong recommendation	
	Moderate-quality evidence	Moderate-quality evidence	
Large lymph-node involvement: cN1 and/or nodes ≥ 10 ≤ 30 mm and/or extracapsular lymph-node extension and/or > 5 nodes			
Regardless of number of extranodal IR criteria	Recommended	High ^{131}I activity is recommended	R8
	Strong recommendation	Strong recommendation	
	Moderate-quality evidence	Moderate-quality evidence	
High risk (HR) of recurrence			
Incomplete resection	^{131}I therapy recommended	Preparation: thyroid hormone withdrawal	R9 and R9b
pT3b (gross extrathyroidal extension invading strap muscles), all N	Strong recommendation	Activity of ^{131}I: high	
pT4, all N	Moderate-quality evidence	Strong recommendation	
N1 severe lymph-node involvement (any metastatic lymph nodes > 30 mm)		Moderate-quality evidence	
Carcinoma with vascular invasion with > 4 emboli in follicular or papillary carcinoma			
M1			
Presence of a poorly differentiated component			

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Recommendation 13 (R13)

In non-resectable locoregional disease [5,40], at least one RAI treatment is recommended, at an empiric activity level of 100 mCi, preferably after thyroid hormone withdrawal. Treatment may be repeated, depending on tumor response. Strong recommendation, low-quality evidence.

4. Iodine-131 treatment for distant metastases

Seventy years after it was first introduced, ^{131}I remains the main treatment for distant metastases of thyroid cancer, which has an incidence of 5–10% of patients. They may be present at diagnosis or occur during follow-up. The most frequent locations are lung and bone. Early detection and eradication of occult distant metastases are the main rationales for postoperative adjuvant ^{131}I therapy. About two-thirds of M1 patients exhibit iodine-avid metastases, and about 40% of these patients can achieve complete remission, after a cumulative dose of less than 600 mCi (22.2 GBq). Complete remission is especially observed in patients with early-detected, small, well-differentiated metastases with high RAI avidity [43,44]. Conversely, elderly patients with poorly differentiated carcinoma, large metastases and high ^{18}F-FDG avidity exhibit poorer response to RAI [45–47].

The treatment relies on the use of high RAI activity, with empiric activities of 100 mCi to 200 mCi (3.7 to 7.4 GBq) according to metastatic disease and patient-related parameters. ^{131}I administration based on dosimetry protocols (based on estimation of lesion dosimetry or blood/bone-marrow absorbed dose) [48–50] are not widely used in France. Dosimetry can be discussed for treatment of metastatic pediatric thyroid cancer and in older patients (> 75 years).

Recommendation 14 (R14)

Metastatic disease should be treated under thyroid hormone withdrawal [51–54]. Strong recommendation, moderate-quality evidence. In case of risk of poor tolerance of hypothyroidism or hypopituitarism, rhTSH may be used (off-label, after validation by multidisciplinary team meeting).

Recommendation 15 (R15)

In case of diffuse or isolated lung micrometastases, curative RAI therapy is indicated, with several cycles of therapy until disappearance of metastatic foci on post-therapy CT scan. The recommended schedule is a 6-monthly treatment regimen for the 1–2 years following initial therapy then yearly or at longer intervals depending on treatment response and tolerance [55,56]. The personalized schedule is validated in a local multidisciplinary team meeting, or at regional or national level for difficult cases. Treatment is performed after thyroid hormone withdrawal; if this is contraindicated, off-label rhTSH may be proposed, and preferably validated in a multidisciplinary team meeting. Strong recommendation, moderate-quality evidence.

Recommendation 16 (R16)

In case of pulmonary macro-metastases (supracentimeter tumor), iterative ^{131}I therapy, at 100–200 mCi (3.7–7.4 GBq) under thyroid hormone withdrawal is indicated for as long as uptake persists on post-therapy ^{131}I scan and if there is clear clinical, scintigraphic, morphologic or biochemical response [55]. Treatment is performed after thyroid hormone withdrawal. If thyroid hormone withdrawal is contraindicated, off-label rhTSH may be proposed, and preferably validated in a multidisciplinary team meeting. Weak recommendation, low-quality evidence.

Thermoablation may also be considered in addition to ^{131}I treatment for pulmonary macronodules few in number and measuring < 3 cm.

Recommendation 17 (R17)

In case of bone metastases, RAI therapy is indicated for as long as uptake persists on post-therapy ^{131}I scan and if there is clinical, scintigraphic, morphologic or biochemical response, and should be systematically accompanied by precise radiological evaluation and neurologic risk-pain-stability assessment for each location. Local consolidation treatment or surgical resection may be necessary prior to iodine-131 therapy [57,58]. Strong recommendation, moderate-quality evidence.

Recommendation 18 (R18)

In case of bone metastases, iterative ^{131}I therapy, at 100–200 mCi (3.7–7.4 GBq) per cycle is performed under thyroid hormone withdrawal. Weak recommendation, low-quality evidence.

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If thyroid hormone withdrawal is contraindicated, off-label rhTSH may be proposed, and preferably validated in a multidisciplinary team meeting.

Corticosteroid cover may be considered, depending on location, to prevent the risk of neurologic aggravation induced by thyroid hormone withdrawal or rhTSH administration.

Treatment is repeated for as long as there is therapeutic response. In large tumors, tumor mass reduction should be considered prior to ^{131}I therapy. The optimal schedule is to be validated in a local multidisciplinary team meeting, or at regional or national level for difficult cases.

Recommendation 19 (R19)

In case of brain metastases, local treatment (surgery and/or external radiation therapy) should be firstly considered. ^{131}I therapy, if indicated, should be associated to corticosteroid therapy [59]. The TSH stimulation method should be considered individually and validated in a multidisciplinary team meeting. Weak recommendation, low-quality evidence.

5. Refractory thyroid cancer

Progression toward refractory thyroid cancer implies lack or loss of efficacy for ^{131}I therapy, which should be therefore discontinued. The criteria for ^{131}I refractory disease are as follows [60,61]:

- no or only a few lesions show RAI uptake, after administration of a therapeutic ^{131}I activity during optimal TSH stimulation and after excluding causes of false negative findings;
- tumor progression according to RECIST criteria during an interval of 12 to 14 months, despite significant ^{131}I uptake and well-conducted ^{131}I treatment.

RAI-refractory disease is rare, at 4–5 cases per million per year. Tyrosine kinase inhibitors (TKI) have been implemented in the therapeutic arsenal for this disease. Two phase-III studies have shown improvement in progression-free survival compared to placebo [62,63]. Impact on overall survival remains to be established. Given their side effects, the timing of initiation of these treatments needs to be carefully considered.

More recently, a novel way to achieve disease control with limited toxicity has been described, using targeted agents which selectively inhibit MEK 1/2 in the MAPK pathway and re-induce RAI uptake [64,65]. Results from prospective studies are needed prior to implementation in routine practice.

6. Radioprotection

Hospitalization in special rooms designed as controlled-radiation zones reduces exposure of the general public and allows collection of radioactive effluent, mostly in urine.

From the legal standpoint, there are no official rules in France as to the level of administered activity beyond which patients should be kept in an isolation room. The conventional threshold actually used in France is 740 MBq. Nor do regulations specify duration of hospital stay. In France, the dose limit at 1 meter, below which patients may leave the isolation room, is usually set at 20 μSv/h. In practice, hospital stay is mainly determined by the administered activity, TSH stimulation method (hypothyroidism or rhTSH) and the volume of iodine-avid disease. For patients treated under hypothyroidism with activity $\geq$ 100 mCi (3.7 GBq), hospital stay should preferably be $\geq$ 48 hours, and $\geq$ 24 hours for patients treated after rhTSH premedication with activity usually ranging from 30 to 100 mCi (1.1 to 3.7 GBq).

Special cases:

- for women of child-bearing age, it is mandatory to rule out an pregnancy and a negative pregnancy test is required prior to ^{131}I therapy;
- for breast-feeding women, an interval of $\geq$ 3 months should be left between cessation of breast-feeding and initiation of therapy to protect breast tissue from ^{131}I uptake;
- an interval of > 6 months should be left between ^{131}I therapy and pregnancy;
- for patients with distant metastases, large residual tumor and/or lesions with prolonged effective ^{131}I half-life, hospital stay may have to be longer;
- patients under dialysis are often treated with low ^{131}I activities, but require 48 hours hospital stay; staff in direct patient contact should receive specific prior information and carry an operational dosimeter.

Radioprotection of the patient, friends and relatives and the public is mainly based on hygiene guidelines and common sense. The guidelines are set out in a written document given to the patient before admission to the isolation room, so that he or she can take whatever measures are necessary. They aim to maintain good radiopharmaceutic elimination (good hydration, good transit) and limit exposure and contamination of others: reinforced hygiene (frequent washing, especially of the hands; not sharing bedclothes), and limited prolonged close contact with family and friends and especially with pregnant women and young children.

7. Adverse effects

Radioactive iodine can lead to early adverse effects (acute sialadenitis, nausea, radiation-induced thyroiditis, especially with large residual tumor) or delayed adverse effects (chronic sialadenitis, xerophthalmia, impact on fertility). Incidence is dose-dependent, and such complications are almost always absent in low-activity treatment regimens.

Recommendation 20 (R20)

Salivary damage is the most frequent side effect of radioactive iodine. Preventive salivary stimulation cannot be recommended, as evidence

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is sparse and contradictory. When performed, it should not be too early, leaving an interval of 24 hours after ^{131}I therapy. Weak recommendation, low-quality evidence.

Recommendation 21 (R21)
Young male patients at high risk of persistent disease, requiring repeated ^{131}I administration, should be offered sperm cryopreservation. Weak recommendation, low-quality evidence.

In thyroid cancer, the risk of ^{131}I-related malignancy is controversial. The risk of leukemia, however, is significantly increased with cumulative doses > 600 mCi (22 GBq). In general, ^{131}I treatment should only be used when expected benefit outweighs risk.

Recommendation 22 (R22)
Patients receiving high cumulative activity (> 600 mCi) should have long-term clinical and hematologic follow-up. Intermediate recommendation, low-quality evidence.

8. ^{131}I-scintigraphy

Recommendation 23 (R23)
After ^{131}I therapy for ablative and therapeutic purposes, a whole-body scintigraphy scan should be performed between days 2 and 7 post-treatment, associated, either systematically or in doubtful situations, to a cervicothoracic SPECT/CT acquisition. An additional SPECT/CT scan may be necessary to explore foci located outside of the cervicothoracic region. Strong recommendation, moderate-quality evidence.

When SPECT/CT is not available, static acquisitions centered over specific areas may be contributive.

The aim of post-treatment scintigraphy is to early detect any persistent locoregional or distant metastases [43,44].

SPECT/CT provides precise location of iodine-avid lesions, improving diagnostic accuracy. The rate of inconclusive examinations is 29% for whole-body scintigraphy and decreases to 7% when SPECT/CT is associated [66].

Recommendation 24 (R24)
Preablation diagnostic scintigraphy is less sensitive than post-therapy scintigraphy in detecting residual disease, even with the contribution of SPECT/CT, and cannot be used to decide whether ^{131}I therapy is needed. Strong recommendation, moderate-quality evidence.

Thanks to technological progress, preablation diagnostic scintigraphy with SPECT/CT can, even so, detect cervical lymph-node invasion and/or distant metastasis or serve for choosing the optimal activity regimen [67,68]. Some authors combine histopathologic risk factors, diagnostic scintigraphy and stimulated Tg level obtained at the time of scintigraphy for personalizing ^{131}I administrated activity [67,68]. Thus, although preablation diagnostic scintigraphy with ^{131}I or ^{123}I SPECT/CT is not widely used in France, further research in this area, as well as investigation of the capabilities of new imaging techniques, such as ^{124}I PET/CT are encouraged.

Recommendation 25 (R25)
Diagnostic ^{131}I scintigraphy is not recommended for routine use in the 9–12 month follow-up control. Strong recommendation, moderate-quality evidence.

It may be indicated:

- in case of persistent serum TgAbs at stable or increasing levels;
- to determine the nature of indeterminate lesions on initial post-therapy scan, especially in high-risk patients;
- in case of large thyroid remnant on initial post-therapy scan hindering image interpretation of the cervicothoracic region.

9. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT

Tumoral dedifferentiation leads to reduced iodine uptake and usually increased ^{18}F-FDG uptake (notably via increased expression of the GLUT1 transporter), displaying the so-called "flip-flop" phenomenon [69]. By contrast, apart from a few histologic subtypes, most well-differentiated thyroid carcinomas exhibit low ^{18}F-FDG uptake.

Recommendation 26 (R26)
^{18}F-FDG PET/CT may be indicated for evaluation of thyroid carcinoma with unfavorable histologic aspect and/or thyroid carcinoma with advanced locoregional extension. Strong recommendation, moderate-quality evidence.

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Recommendation 27 (R27)

^{18}F-FDG PET/CT is indicated to locate persistent/recurrent disease in patients with biochemical evidence of disease and no uptake on post-therapy scan or in cases with high pretest positivity (i.e., high serum Tg level value or serum Tg progression on TSH suppression, high risk of tumor recurrence, and unfavorable histologic subtypes) [70,71]. Strong recommendation, moderate-quality evidence.

The sensitivity of ^{18}F-FDG PET/CT correlates with serum Tg value and even more so with serum Tg doubling time. Sensitivity is greater for aggressive histological subtypes: poorly differentiated, tall cell or Hürthle cell [72].

Recommendation 28 (R28)

^{18}F-FDG PET/CT is indicated in metastatic disease, regardless of the pathological subtype, to refine prognosis and perform personalized treatment strategies. Strong recommendation, moderate-quality evidence.

TSH stimulation premedication is not required for ^{18}F-FDG PET/CT.

Several studies have demonstrated the role of PET/CT as a prognosticator in metastatic thyroid cancer [73]. Patients with ^{18}F-FDG-negative ^{131}I-positive metastases have good life expectancy close to that of non-metastatic patients, whereas tumor uptake of ^{18}F-FDG is associated with poorer outcome.

10. Thyroglobulin (Tg) and thyroglobulin antibodies (TgAb)

Tg is a biomarker of disease after total thyroidectomy. TgAbs are found in about 15–25% of differentiated thyroid cancers at diagnosis and are the main cause of interference with Tg assay.

Recommendation 29 (R29)

Serum Tg measurements should:

- use assays with functional sensitivity < 1 ng/mL;
- use assays calibrated according to the international Tg standard CRM-457;
- use the same assay and if possible in the same laboratory throughout follow-up;
- be systematically associated to assessment of TgAb and TSH.

Strong recommendation, moderate-quality evidence in all 4 cases.

Recommendation 30 (R30)

There is no reliable postoperative serum Tg threshold (under levothyroxine [LT4] or during TSH stimulation) for indicating RAI therapy, and the decision for RAI therapy cannot rely on postoperative Tg level alone [74,75]. Strong recommendation, moderate-quality evidence.

Recommendation 31 (R31)

Initial follow-up includes measurement of serum Tg, TgAb and TSH under LT4, at 3 months following RAI therapy. Strong recommendation, moderate-quality evidence.

The first rhTSH stimulation test at 9–12 months post-RAI can be maintained in intermediate to high-risk patients, and discussed on a case by case basis in low-risk patients, in the light of serum Tg values on LT4 using second-generation (2G) Tg assays. Strong recommendation, low-quality evidence.

Subsequent follow-up controls include measurement of serum Tg on LT4 every 12–24 months or more frequently in high-risk patients or those with detectable Tg values, in order to assess serum Tg kinetics. Strong recommendation, low-quality evidence.

rhTSH stimulation tests should not be repeated in case of excellent response to RAI (Table 5), but their repetition may be considered on a case-by-case basis in high-risk patients. Weak recommendation, low-quality evidence.

Baseline serum Tg level < 0.2 ng/mL under LT4 or rhTSH-stimulated Tg level < 1 ng/mL show > 95% negative predictive value for persistent/recurrent disease [76].

Table 5
Definitions of treatment response after total thyroidectomy and RAI therapy according notably to second-generation Tg and TgAb assay [14].

Complete remission (excellent response)	Negative imaging And Tg under LT4 < 0.2 ng/mL Or stimulated Tg < 1 ng/mL TgAb negatives or stable
Indeterminate response	Non-specific imaging 0.2 ≤ Tg under LT4 < 1 ng/mL Or 1 ≤ stimulated Tg < 10 ng/mL Or TgAb stable or decreasing
Biological residual disease	Negative imaging And Tg under LT4 ≥ 1 ng/mL Or stimulated Tg ≥ 10 ng/mL Or TgAb increasing
Morphologic residual disease	Abnormal imaging suggesting residual disease regardless of Tg and TgAb levels

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Recommendation 32 (R32)

Measurement of serum TgAb should be systematically performed in parallel to Tg determination, in order to detect any interference. There is no consensus on a TgAb threshold beyond which interference occurs; interference may occur at low TgAb levels, but it is widely accepted that there is a dose-response relationship between TgAb and interference [77]. TgAb-related interference varies from patient to patient and according to Tg assay [78].

TgAb should be measured using the same assay throughout follow-up in order to estimate TgAb kinetics.

Increase in or appearance of TgAbs during follow-up suggests persistent or recurrent disease, requiring further evaluation.

Strong recommendation, moderate-quality evidence for all 3 points.

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