College of Oncology

NATIONAL EXPERT – BASED PRACTICE GUIDELINES

DIFFERENTIATED THYROID CANCER

Guidelines V1.2020

These guidelines have been developed by a national multi-institutional and multidisciplinary expert working party, based on international guidelines.

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INTRODUCTION

This document provides an overview of the clinical practice guidelines for **differentiated thyroid cancer** *(hereafter referred to as **DTC**)* and covers a broad range of topics such as screening, diagnosis, treatment, supportive therapy, follow-up and the role of the GP.

Medullary thyroid cancer will be covered in a separate, upcoming guideline. These guidelines are developed by a panel of experts comprising clinicians of different specialties and designated by their respective scientific societies.

The guidelines are based on the best evidence available at the time they are derived *(2020).*

The aim of these guidelines is to assist all national care providers involved in the care of patients with thyroid cancer and serve as a base and supporting tool for the local institutional guidelines and MOC *(Multidisciplinary Oncological Consult)* discussions in Belgium.

SEARCH FOR EVIDENCE

These guidelines are derived from existing national and international guidelines and have been updated and adapted to the Belgian context by the expert panel.

The expert panel consisted of experts in various settings and representatives of the relevant professional Belgian societies, implicated in the management of Thyroid cancer. The expert panel has been divided in groups, each responsible for one part of the guideline.

This national guideline will be regularly updated as new evidence with practice implications emerges.

EPIDEMIOLOGY

According to the Belgian Cancer Registry, 1.042 new cases of thyroid cancer have been registered in Belgium in 2016. More females (776 cases) than males (266 cases) have been diagnosed with thyroid cancer. The average age at diagnosis was 51.5 years for females and 56.1 for males. [1]

Geographical variations have been reported in several countries, without clear explanations. In Belgium, the global incidence rate is the result of substantial variations between the 3 regions: the highest incidences are reported in the Brussels Capital Region and the Walloon Region and the lowest incidences in the Flemish Region. [1]

Exposure to ionizing radiation, particularly during childhood, is the best-established risk factor associated with thyroid cancer [2]. A significant increased risk for developing thyroid carcinoma following radiation exposure (i.e. radiotherapy, nuclear accidents or atomic bombings) during childhood was observed among people treated with. Ionizing radiation at high doses can cause thyroid cancer also in adults. [4].

Differentiated thyroid cancer *(DTC)* includes papillary *(PTC)* and follicular cancer *(FTC)* that derive from thyrocytes and express the sodium iodine symporter. [2]

DIAGNOSIS

Differentiated thyroid carcinoma usually presents as a solitary thyroid nodule and can have an asymptomatic course for a long time. This typical indolent nature may sometimes lead to late diagnosis of differentiated thyroid carcinoma.

HISTORY AND PHYSICAL EXAM

Diagnosis of thyroid cancer should be considered whenever the following risk factors are present:

- Younger age
- Female sex
- Larger size, solitary nodule, growing nodule [5,6]
- Medical history of neck irradiation
- Family history of thyroid carcinoma
- FDG- avid nodule detected by FDG-PET-CT [7]

DIAGNOSTIC WORK-UP OF THYROID NODULES

- Endocrine assessment with the measurement of TSH.
- Routine measurement of serum thyroglobulin (Tg) for initial evaluation of thyroid nodules is not recommended. Serum Tg can be elevated in most thyroid diseases and is an insensitive and nonspecific test for thyroid cancer.
- Measurement of calcitonin in selected cases. Mild calcitonin elevations are not specific [8].
- Ultrasound assessment: nodule with marked hypoechogenicity, presence of microcalcifications, irregular margins and non-oval shape are considered suspicious [11].
- Fine needle aspiration *(FNA) (see Figure 3)*.
- Thyroid scintigraphy in case of solid nodule(s) > 1cm and TSH < 1 mU/l [10].
- FNA in non-hot thyroid nodules depending on size and ultrasound pattern *(according to the EU-TIRADS classification)* [11].

ULTRASOUND ASSESSMENT

- Thyroid ultrasound should be performed by a dedicated radiologist or endocrinologist.
- Ultrasound must be performed by using high-end ultrasound sonographic machine, equipped with a high frequency linear probe (15 MHz - 18 MHz), an intermediate frequency curvilinear probe (5-7MHz) and/or a linear probe with trapezoidal field of view.
- Report and images should be available for other clinicians (i.e. online tools as PACS-on-web, e-health). A standardized thyroid imaging reporting system must be used for the description of the thyroid nodule and the cervical lymph node [11, 12]. *(Figure 1).*

- Preoperative neck ultrasound for assessing the presence or absence of suspicious lymphadenopathy in the *central and lateral neck* is recommended for all patients undergoing thyroidectomy for malignant or suspicious cytological findings.
- In case of suspicious cervical lymph nodes their exact localization has to be mentioned (including lateralization and level II, III, IV, V, VI), or a drawing can be made [13].

For classification of thyroid nodules depending on ultrasonographic features, three guidelines are in use:

- ATA 2015 classification,
- ACR 2017: ACR-TIRADS classification and
- ETA 2017: EU-TIRADS classification [11, 14, 15].

These systems have unique strengths and limitations. Awaiting an international stratification system with machine learning algorithms, it is recommend to adopt the **ETA 2017: EU TIRADS** classification because it is intuitive and fast, allowing broad adaptation. Moreover validation studies showed a high diagnostic accuracy [16, 17].

It is recommended to include the specific classification used in the conclusion of the report, e.g. EU-TIRADS 4 *(and not TIRADS 4, since EU-TIRADS 4 and ACR-TIRADS 4 differ)*.

Results	Thyroid volume Echogenicity and vascularity of the gland Nodules (above 5 mm unless highly suspect) Location (side, superior, medial, inferior) Size (3 diameters +/– volume) Shape, margins, echogenicity, composition, echogenic foci EU-TIRADS score Numbered and mapped out on the thyroid map Change of size Retrosternal extension Trachea deviation Study of lymph nodes (levels II, III, IV, V, VI) and of the thyroglossal duct

Figure 1: Standardized thyroid imaging reporting system based on EU-TIRADS [11]

Category	US features	Malignancy risk, %
EU-TIRADS 1 : normal	No nodules	None
EU-TIRADS 2 : benign	Pure cyst Entirely spongiform	≅ 0
EU-TIRADS 3 : low risk	Ovoid, smooth isoechoic/hyperechoic No features of high suspicion	2-4
EU-TIRADS 4 : intermediate risk	Ovoid, smooth, mildly hypoechoic No features of high suspicion	6-17
EU-TIRADS 5 : high risk	At least 1 of the following features of high suspicion: • Irregular shape • Irregular margins • Microcalcifications • Marked hypoechogenicity (and solid)	26-87

EU-TIRADS: European Thyroid Imaging Reporting and Data System; US, ultrasound

Figure 2: EU-TIRADS categories and risk of malignancy [11]

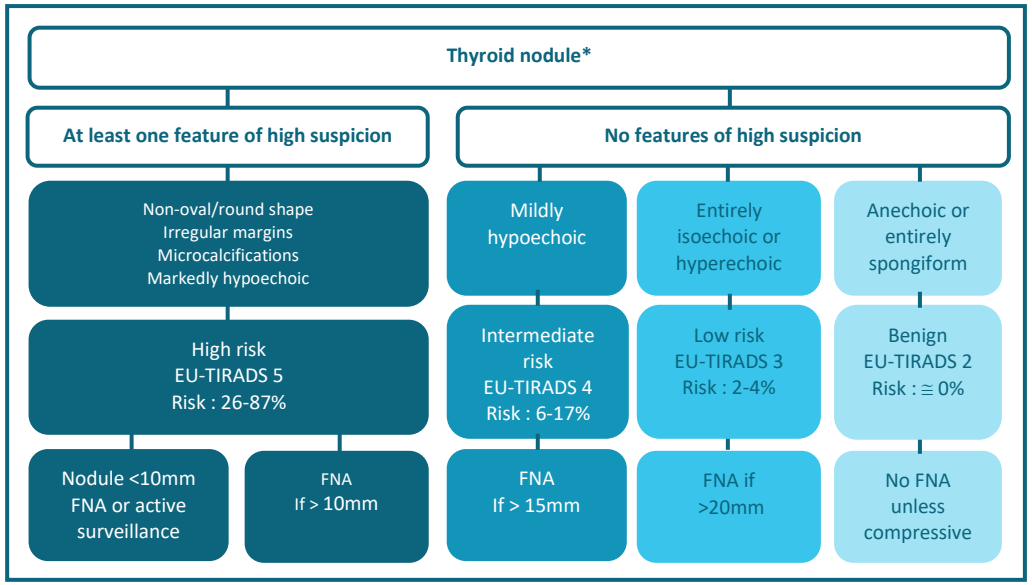

Figure 3: FNA decision-making based on EU-TIRADS [11]

The fundamental features in the EU-TIRADS classification *(Figure 2)* are hypoechogenicity, the presence of microcalcifications, irregular margins and non-oval shape (taller-than-wide and taller-than-long) [11].

Other ultrasound criteria such as vascularity (although its use is controversial) and elastography measured stiffness (with its limitations) might be mentioned, but none of them are part of main sonographic criteria used for EU-TIRADS classification.

The EU-TIRADS category and the size of the nodule guide the indication for FNA *(Figure 3).*

Capsular proximity, the involvement of the capsule or lymph node [11], as well as clinical criteria or the position of the nodule may influence the decision for performing FNA.

FNA can be considered in selected patients with nodules <1 cm, however most of the patients with suspicious subcentimeter nodules could be managed by active surveillance. Nevertheless, suspicious nodules <1 cm located just beneath the capsule where even minor disease progression could be associated with complications *(adjacent to recurrent laryngeal nerve or trachea)* should be considered for FNA [18].

For lesions < 1cm with a FNA diagnosis suspect or diagnostic for DTC and ultrasonographic features suggesting a high risk of aggressiveness are present *(presence of cervical lymph node metastases, extrathyroidal extension, or multiple foci)* a resection will be preferred instead of active surveillance.

Thyroid incidentalomas detected by FDG-PET that are smaller than 1 cm in diameter and have suspicious ultrasound criteria should be considered for FNA in rare cases in which the differential diagnosis between intrathyroid metastases and concomitant DTC affects the treatment of the primary cancer.

FINE NEEDLE ASPIRATION (FNA) OF THYROID NODULES

Purpose of the procedure is to provide clinical management for patient with thyroid nodules.

A FNA procedure is the most accurate and cost- effective method for evaluating thyroid nodules. FNA should be performed using US guidance which leads to a lower rate of non-diagnostic and false-negative cytology [19].

Typically, three of four passes are realized depending of the quantity of material. To be satisfactory for evaluation, at least 6 groups of benign follicular cells are required, each group composed of at least 10 cells. The exception to this are solid nodules with cytologic atypia, solid nodules with inflammation and colloid nodules.

For reporting the results of the FNA cytology, it is recommended to use the most common classification for analysis: the 2017 Bethesda System for Reporting Thyroid Cytopathology which established six categories [21]. Each category is associated with a risk of malignancy *(ROM)* and recommendations about clinical management *(Figure 4)*.

Next Generation Sequencing (NGS) could be used in case of FNA indeterminate cytology [21]. Moreover, recent updates recommend to make molecular testing for AUS/FLUS and FN/SFN [20]. Thus, for these categories (Bethesda III and IV), and the category suspicious for malignancy cytology (Bethesda V), molecular testing, if available, is advised.

Ongoing research into the genetic landscape of thyroid cancer might add additional insights and allow for molecular testing of FNA samples in order to optimize the risk stratification and the need of surgery. [22]. If there is no specific NGS thyroid panel available, BRAF V600E mutation should be considered - it is more specific for papillary carcinoma diagnosis and can be assessed Ongoing research into the genetic landscape of thyroid cancer might add additional insights and allow for molecular testing of FNA samples in order to optimize the risk stratification and the need of surgery. [22]. If there is no specific NGS thyroid panel available, *BRAF* V600E mutation should be considered - it is more specific for papillary carcinoma diagnosis and can be assessed by PCR.

Diagnostic category	*Risk of malignancy if NIFTP ≠ CA (%)*	*Risk of malignancy if NIFTP = CA (%)*	*Usual management*[a]
Nondiagnostic or unsatisfactory	5–10	5–10	Repeat FNA with ultrasound guidance
Benign	0–3	0–3	Clinical and sonographic follow-up
Atypia of undetermined significance or follicular lesion of undetermined significance	6–18	~10–30	Repeat FNA, molecular testing, or lobectomy
Follicular neoplasm or suspicious for a follicular neoplasm	10–40	25–40	Molecular testing, lobectomy
Suspicious for malignancy	45–60	50–75	Near-total thyroidectomy or lobectomy[b,c]
Malignant	94–96	97–99	Near-total thyroidectomy or lobectomy[c]

Adapted with permision from Ali and Cibas (7).
[a]Actual management may depend on other factors (e.g., clinical, sonographic) besides the FNA interpretation.
[b]Some studies have recommended molecular analysis to assess the type of surgical procedure (lobectomy vs. total thyroidectomy).
[c]In the case of "suspicious for metastatic tumor" or a "malignant" interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.
NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; CA, carcinoma; FNA, fine-needle aspiration.

Figure 4: Bethesda system for reporting thyroid cytopathology [21]

SURGICAL TREATMENT

LOBECTOMY VS. TOTAL THYROIDECTOMY

Historically, total thyroidectomy has been the standard surgical therapeutic approach for well-differentiated thyroid cancer.

Lobectomy should be considered in patients with Bethesda III-VI thyroid nodule < 4 cm (Figure 4). Total thyroidectomy should be considered in patients with thyroid nodule > 4 cm, with possible extrathyroidal extension or lymph node involvement and with contralateral nodules [34].

COMPLETION THYROIDECTOMY

Completion thyroidectomy is recommended in patients who have been diagnosed with differentiated thyroid cancer on histopathological evaluation, if their first operation was a conservative approach. Therapeutic central neck lymph node dissection should be included if the lymph nodes are clinically involved.

Thyroid lobectomy alone may be sufficient treatment for low-risk papillary and follicular carcinomas. Completion thyroidectomy may be necessary when the diagnosis of malignancy is made following lobectomy for an indeterminate or non – diagnostic cytology.

In addition, some patients with malignancy may require completion thyroidectomy to provide complete resection of multicentric disease and to allow efficient RAI therapy. However, since intrathyroidal PTC or low-risk FTC can be managed with either lobectomy or total thyroidectomy, a completion thyroidectomy is not always required.

The surgical risks of two-stage thyroidectomy (lobectomy followed by completion thyroidectomy) are similar to those of a near-total or total thyroidectomy in experienced hands. The marginal utility of prophylactic lymph node dissection for cN0 disease argues against its application in re-operations.

PROPHYLACTIC LYMPH NODE DISSECTION

Papillary thyroid cancer (PTC), the most common thyroid malignancy, has a high tendency for regional metastasis to the cervical lymph nodes. The frequency of cervical lymph nodes metastasis is related to tumor size. Cervical lymph node metastasis is present in 20% of 20 mm primary PTC and up to 60% in 40 mm primary PTC.

In case of lymph node involvement (clinically evident or shown by imaging) therapeutic lymph node dissection is necessary. In patients without evidence of lymph node involvement, the optimal management of the neck is an important topic of debate.

Prophylactic central-compartment neck dissection *(*CLND *ipsilateral or bilateral)* has the potential of reducing the risk of recurrence of PTC and should be considered in patients with a measurable risk of recurrence (≥T2 or T3). Clinical and molecular risk stratification strategies may be an important approach to targeting those patients at greatest risk of recurrence. Prophylactic central lymph node dissection should be considered in patients in patients with clinically involved lateral neck nodes (cN1b).

In low risk patients a more conservative approach (total thyroidectomy only) is preferred since second step/revision CLND has been shown to be feasible with acceptable morbidity [29]. Surgical expertise may influence the cut off since it is accompanied by lower complication rates. In the most recent evidence-based workflow algorithms for the management of thyroid nodules, the American Head and Neck Society mentions a minimum of at least 10 cases per year as cut off.

Also, patient preferences and patient characteristics may have an impact on the therapeutic approach. A restrictive use of pCLND is warranted in patients whose profession depends on voice quality and in patients with former bariatric surgery who have a potential risk of treatment refractory hypoparathyroidism [30].

For a high risk upper thyroid pole primary, the first nodal basin is not always the central compartment but often the upper part of the ipsilateral lateral compartment. In that case, not only prophylactic central lymph node dissection, but also ipsilateral lateral lymph node dissection may be warranted [31].

THERAPEUTIC LYMPH NODE DISSECTION

Patients diagnosed with PTC should be assessed preoperatively by ultrasonography of the central and lateral neck. Additional imaging such as CT (with contrast), MRI, laryngoscopy or endoscopy should be obtained in patients presenting with locally advanced disease.

Sensitivity of combined imaging in detecting macroscopic nodal metastasis in both lateral and central neck is high. Preoperatively, a radiographic map utilizing CT and ultrasound should be made to direct PTC surgery. This provides the surgeon an objective baseline upon which to base the extent of nodal surgery [32].

A compartment with definitive proof of nodal metastases should be formally dissected at the time of thyroidectomy [33].

In case central lymph node dissection is performed, the incorporation of both level VI and level VII should be undertaken. Level VII is in direct anatomic continuity with level VI nodes and should be routinely included as part of every central neck dissection [34].

HISTOPATHOLOGIC EXAMINATION

SPECIMEN HANDLING

A standardized protocol for the examination of a thyroid carcinoma resection specimen is recommended.

FROZEN SECTION AT TIME OF SURGERY

Frozen section is the exception. If there is suspicion for lymphoma, which should be diagnosed before surgery in a normal setting, a frozen section is not helpful in the treatment or diagnostic set up of the patient. Whenever a suspected lymph node is found during surgery a frozen section can be performed [35].

HISTOLOGIC SAMPLING

In order to detect capsular or vascular invasion and to exclude presence of true papillae we advise to follow the same criteria for all encapsulated nodules or well-delineated solitary nodules.

There are no set criteria for the number of sections required for adequate histologic evaluation and recommendations vary between different publications.

Following guidance is recommended [36]:

- For tumor measuring less than 6 cm, submit entire tumour
- For tumor measuring 6 cm, submit at least ten blocks with surrounding capsule
- For tumor measuring more than 6 cm, submit one additional block with surrounding capsule per centimetre of tumour.

Multiple pieces can be out in the same cassette [37].

Other present lesions should be checked. For lesions with a FNA diagnosis suspect or diagnostic for papillary thyroid cancer sample *(Bethesda V and VI)* the surrounding thyroid and the margins should also be evaluated.

PATHOLOGY REPORT

The report should include following minimum dataset [35]:

- Type of surgery (total, subtotal or hemi thyroidectomy)
- Localization of tumor
- Classification and subtyping of tumor following WHO 2017 [38]. For follicular carcinoma and EFVPTC (encapsulated follicular variant of papillary thyroid carcinoma) include: minimally invasive, encapsulated angioinvasive, state < 4 (limited vascular invasion) or ≥ 4 vessels (extensive vascular invasion) and widely invasive
- Maximal tumor size, which is the size of largest nodule in case of multifocality
- Extension outside the thyroid [39, 40]

- Status of the section margins
- Pathology outside the tumor: adenoma, hyperplasia, thyroiditis
- Number and aspect of parathyroid glands, if present
- Number and status of lymph nodes per level, report extra-nodal extension when present
- pTNM according the TNM classification of malignant tumors, 8th edition [40].

MOLECULAR TESTING

It is advised to perform molecular testing only if it has implications for treatment [35] and in the case of considering a diagnosis of NIFTP (Non-invasive follicular thyroid neoplasm with papillarylike nuclear features) [41] or invasive encapsulated/well circumscribed follicular variant of papillary carcinoma. Tumours in the spectrum of NIFTP-EFVPTC should be negative for a BRAF V600E mutation [42, 43].

RADIOIODINE REMNANT ABLATION and RADIOIODINE THERAPY

There are three indications for I-131 radioiodine therapy:

- For remnant ablation - to eliminate residual thyroid tissue after total thyroidectomy, whether or not this may represent benign or malignant residual tissue. The aim is to reduce the risk of local recurrence. Moreover serum thyroglobulin (Tg) measurement can be used as an excellent tumor marker and reflects the sum of Tg from normal thyroid tissue and residual or recurrent tumor.
- As adjuvant therapy for residual disease or recurrent tumor.
- As therapy for recurrence or metastatic disease. A comprehensive multidisciplinary discussion is needed for each patient before choosing the appropriate therapy (i.e. surgery, EBRT, intravascular embolization, RAI)

Differentiated thyroid cancer cells express NIS (sodium/iodide symporter) after TSH stimulation, which allows radioactive I- (under the form of sodium iodine) to be taken up by thyroid cells of follicular origin. I-131 radioiodine is hence taken up by these cells and induces cell killing by low-dose rate irradiation.

PATIENT PREPARATION

Normal or neoplastic thyroid cells should be stimulated by TSH at the time of I-131 administration, either by endogen stimulation following withdrawal of L-T4 treatment resulting in hypothyroidism and TSH elevation (at least 30 mU/ml), or by using exogen stimulation with recombinant human TSH (*rh-TSH, ThyrogenTM, Sanofi-Genzyme*).

In addition, patients should be depleted in natural, cold iodine by following a low-iodine diet and by avoiding excessive iodine overload (eg. contrast media, drugs eg. amiodarone).

Patients must be provided with an adequate list of iodine sources to avoid no later than 2 – 4 weeks before administration of radioactive iodine. Urinary iodine may be measured before or at the time of treatment as a way of QA and should ideally be under 30 µg/dL in normally hydrated patients, or < 150 µg/g creatinine.

TREATMENT STRATIFICATION FOR I-131 ABLATION THERAPY

There is currently no consensus on optimal patient selection for I-131 therapy.

- Patients with < 1cm tumors (pT1a) and no additional risk factors should definitively not be treated with radioiodine. There is no consensus on the necessity of radioiodine therapy for patients with low risk tumors such as pT1b and pT2, especially if the Tg is negative (< 0.2 ng/ml in the absence of anti-Tg antibodies) 3 month after the surgery. The results of the ongoing trials on these issues will be available in a few years. Meanwhile, if given, it is recommended to administer 30 mCi (1110 MBq) radioiodine. [59, 60].
- pT3b-pT4 and/or N1b with or without extracapsular invasion and/or M1 patient should receive radioiodine therapy.

DOSAGE AND PATIENT PREPARATION

Currently, most patients may be treated following rh-TSH (ThyrogenTM) stimulation, except patients with metastatic disease, pediatric patients and patients who need repeated treatment.

A limited proportion of patients needs to be treated after L-T4 withdrawal. These patients should be aware of the following side effects: weight gain, fatigue, cold feeling, constipation, aboulia, limited intellectual performance including the ability to drive a car. These sides effects are reversible after reintroduction of L-T4 therapy.

The optimal administrated 131-I dose for treatment, after thyroid hormone withdrawal or administration of rhTSH, should be based on multidisciplinary team management recommendations taking into account the risk of recurrence and disease-specific mortality (staging, histological features, genetically aspects, previous irradiation

extracapsular spread, size of lymph node metastases and the thyroglobulin level measured within a few weeks after thyroidectomy).

PRACTICAL ASPECTS

Following practical aspects should be taken into account

- Radiation protection and hospitalization for 1 – 3 days is needed.
- Radioiodine capsule should be taken on an empty stomach

Radiation protection issues and recommendations are available from the web site of the Superior Health Council (https://www.health.belgium.be/fr/avis-7221-2-radionucleides) or (https://www.health.belgium.be/nl/advies-7221-2-radionucliden).

Whole-body scintigraphy (skull to upper-thighs) preferentially associated with SPECT-CT should be done after radioiodine therapy to rule out metastases. Medical aspects for prevention or alleviation of side effects:

- Local pain can be treated with paracetamol or NSAIDs
- Antiemetic drugs should be prescribed whenever nausea occur, as vomiting should absolutely be avoided.
- Citric acid has been showed to be helpful in reducing the toxicity of I131 treatment on the salivary glands. However the evidence for such preventive treatment remains low.
- Drinking plenty of fluids (1.5L) is recommended for various reasons (to help flush the radioactive iodine out of the body, maintain normal bowel transit, prevent dry mouth).

CONTRACEPTION

Female patients should not be pregnant at the time of the treatment and all necessary efforts shall be taken to ensure this.
Both female and male patients must avoid conception within at least 6 months following the treatment and this can be supported by using a persistent contraceptive measure (preferably oral contraception or IUD).

Men receiving cumulative RAI activities > 400 mCi should be counselled on potential risks of infertility; sperm banking should be considered in this situation.

Systematic sperm banking or ovarian preservation is not recommended in most paediatric or adolescent patients but must be considered in selected cases where high doses may be needed for extensive disease.

Moreover, radioactive iodine should not be given to women who are breastfeeding. Depending on the clinical situation, RAI therapy could be postponed in women who are lactating to prevent the accumulation of radioactive iodine in the breast tissue.

RADIOTHERAPY

IN PATIENTS WITHOUT DISTANT METASTASES

ADJUVANT EXTERNAL RADIOTHERAPY FOLLOWING SURGERY

There is no role for routine adjuvant external radiotherapy of the neck in patients with differentiated thyroid cancer after initial complete surgery. Adjuvant external beam radiotherapy should be considered in following cases:

- Residual tumor that does not concentrate iodine, i.e. radio-active iodine (RAI)-refractory thyroid carcinoma.
- Evidence of macroscopical tumor residue after surgery that cannot be re-excised.

PRIMARY EXTERNAL RADIOTHERAPY

Primary external beam radiotherapy should be recommended in following cases:

- Inoperability or expected morbidity from loco regional surgery that is not compatible with the degree of morbidity which could be accepted by the patient in the primary as well as recurrent setting.
- Refusal of surgery by the patient.

CONTOURING, MODALITIES, DELIVERY AND PLANNED DOSES

Intensity-modulated radiotherapy (IMRT) (or comparable techniques, e.g. VMAT, tomotherapy) is the standard radiotherapy technique in order to sculpt the dose tightly around the target volumes and avoid overdosage to critical organs at risk (OARs), such as submandibular and parotid glands, mucosa of pharynx, larynx and oral cavity, spinal cord, skin and brachial plexus. IMRT can thereby reduce the side effects from external radiotherapy and should be considered a standard [51, 56]. Contouring of OARs should follow contouring guidelines as it has been accepted for most head and neck radiotherapy sites [45].

In case of prophylactic nodal irradiation, consensus guidelines for contouring of the neck nodal levels should be followed [47, 48]. Simultaneous integrated boost techniques are recommended in case of multiple-dose levels, to avoid overdosages outside the boost volumes. Proposed doses [55] in 2 Gy-biologically equivalent doses*:

- 70 Gy: macroscopic disease
- 66 Gy: in regions of positive surgical margins
- 60 Gy: in regions after complete surgery
- 50 Gy: in low-intermediate risk prophylactic regions

** The proposed alpha/beta ratio to calculate the biologically equivalent dose for tumour is 10 Gy.*

Proposed target volumes in case of adjuvant EBRT in follicular or radio-active iodine (RAI)- refractory papillary thyroid carcinoma:

- The thyroid bed
- The direct draining lymph node stations (perithyroidal, upper mediastinal including paratracheal and pretracheal, cervical levels III-IV Additional lymph node levels are addressed on a case by case basis.

There is no evidence that larger prophylactic nodal irradiation results in better regional control. On the other hand, larger elective treatment volumes do result in more treatment induced toxicity such as dysphagia, dysgeusia, erythema, mucositis, hoarseness and xerostomia.
Therefore the prophylactic nodal regions should remain limited to the central thyroid compartment, the involved lymph node regions of the neck containing macroscopic disease and the involved lymph node regions according to the pathological findings after nodal resection.

Remark: Some controversy exists on the use of EBRT in a very short time frame after the administration of I-131. It is not clear in which amount radiation-induced toxicity may be enhanced due to the ionizing radiation from both treatment modalities. As EBRT is only to be envisaged in case of follicular or radio-active iodine-refractory papillary thyroid carcinoma (recurrence after one administration of > 100 mCi I-131 treatment under optimal condition), this point should mostly not be a problem.

PATIENTS WITH DISTANT METASTASES

OLIGOMETASTATIC DISEASE

In case of oligometastatic disease from follicular or radio-active iodine (RAI)-refractory papillary thyroid carcinoma, defined as ≤ 5 lesions, (i.e. regional recurrent lymph nodes with distant metastases), stereotactic body radiotherapy (SBRT) may be envisaged.
Better overall and progression-free survival with equal quality-of-life has been observed in the prospective phase-II trial using stereotactic ablative radiotherapy in case of 1-5 metastases albeit in a mixed group of primary tumours [53]. However, if single metastases can be successfully excised, surgical treatment should be considered first (with the advantage of histological confirmation of the metastatic disease).
The best treatment schemes remain a matter of debate at the moment of writing, but usually cumulative doses from 30-60 Gy are prescribed in 3-8 fractions with generally 48h between fractions. For cranial metastases, radiosurgery can be recommended using single fraction doses.
All stereotactic radiotherapy treatments should be performed in experienced centres and should follow stringent constraints for the dose prescription to the targets and OARs, adequate patient immobilisation and on-line patient position control for each fraction, including all technical aspects that are mandatory to ensure safe and effective use of SBRT (e.g. the report of the AAPM Task Group 101) [44].

PALLIATIVE TREATMENT

PALLIATIVE RADIOTHERAPY

In case of multi-metastases or where no curative intent is proposed, external radiotherapy can offer palliation, e.g. antalgic or anti-haemorrhagic radiotherapy.

- For painful and uncomplicated bone metastases a single fraction of 8 Gy is recommended [46].
- For complicated bone metastases or non-bony metastatic lesions, institutional guidelines for palliative radiotherapy can be followed in the absence of evidence for one vs. another fractionation scheme. A typical example is 5 x 4 Gy over 1 week.
- In case of spinal cord compression by metastases that will not be handled surgically to relive paresis, urgent (<24 hours after onset of symptoms) single or multiple fractionated radiotherapy in combination with high dose glucocorticoids should be preferred over any other palliative therapy [50, 55].

Remark: it is not clear if treatment of spinal metastases located close to the spinal cord and treated by radio-active iodine should be taken into account for retreatment after a certain period of time to the same spinal level. In these cases, it is recommended to balance well the expected benefit of external radiotherapy to the possible damage.

SUPPORTIVE TREATMENT

- A three-step approach of pain drug administration (WHO analgesic ladder) should be followed in patients with pain associated with thyroid cancer.
- Patients with thyroid cancer should be offered specific psychological support from professionals belonging to the multidisciplinary team.

RECURRENT DISEASE

In patients with recurrent disease presenting with metastases, the same principles are applicable as discussed in the section on palliative treatment.

FOLLOW UP

The treatment and follow-up (FU) of DTC is guided by the "TNM classification" *(Table 1)* for predicting mortality, and the "ATA risk of recurrence stratification" *(Table 2)* for predicting recurrence [19].

TABLE 1: TNM classification [19]

T1	≤ 2cm (T1a ≤1 cm, T1b >1 - ≤2 cm)	N0	No node involvement
T2	> 2 - ≤4 cm	N0a	Cyto/histo benign LN
T3a	> 4 cm limited to thyroid	N0b	No RX or clin LN meta
T3b	Gross invasion: strap muscles	N1a	Central (level VI, VII)
T4a	Gross invasion: subcutaneus, larynx, trachea, esophagus, nerves	N1b	Other (level I-V)
T4b	Gross invasion: prevertebral fascia or vessels	M0 M1	No distant meta's distant meta's

TABLE 2: ATA risk of recurrence [19]

ATA low risk	• Papillary thyroid cancer (with all of the following): – No local or distant metastases; – 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 131I is given, there are no RAI-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)a • 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 BRAFV600E mutated (if known)a
ATA intermediate risk	• Microscopic invasion of tumor into the perithyroidal soft tissues • RAI-avid metastatic foci in the neck on the first posttreatment 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 dimensiona • Multifocal papillary microcarcinoma with ETE and BRAFV600E mutated (if known)a
ATA 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 dimensiona • Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)

Tg measurements should always include anti-Tg Ab's measurements to screen for absence of interference. An elevated postoperative Tg 4-6 weeks (> 5 ng/ml after total thyroidectomy, > 30 ng/ml after lobectomy) can give information about the completeness of the surgery and/or the possibility of distant metastases, prompting further examinations before any decision on other therapies [62]. A postoperative Tg (non-stimulated or stimulated on the moment of the RAI) can give important prognostic information.

After I-131 therapy, a post-ablation scan should be performed (usually after 5-7 days).

The level of initial TSH suppression is depending on the ATA risk of recurrence stratification *(Table 3)*.

A stimulated Tg should be planned after 6-12 months, in order to evaluate the response to the therapy. When using a high sensitive Tg assay, a low nonstimulated Tg (< 0.2 ng/ml) can replace (especially in low risk patient's) this stimulated Tg.
A WBS can be useful at the moment of stimulation in the following situations: anti Tg Ab positive patients, I-uptake beyond thyroid bed on post-ablation scan, large remnant on post-ablation scan, ATA high risk patients or selected cases of intermediate risk patients.

If thyroglobulin stimulation or a stimulated diagnostic WBS is needed, Thyrogen® (rhTSH) is the method of choice (Thyrogen® 0.9 mg on day 1 and day 2, eventually diagnostic WBS on day 3, stimulated Tg measurement on day 5) [19].

TABLE 3: ATA risk recurrence [19]	TSH target to be adapted to age and medical conditions
ATA low risk • non-stimulated Tg < 0.2 ng/ml • non-stimulated Tg ≥ 0.2 ng/ml	 TSH 0.5 – 2 mU/l TSH 0.1 – 0.5 mU/l
ATA intermediate risk	TSH 0.1 – 0.5 mU/l
ATA high risk	TSH < 0.1 mU/l

Follow up during the first year has been summarized below. *(Table 4)*

The dynamic risk stratification (DRS) [63] incorporates the monitoring of response to therapy and can change the original risk and prognosis based on TNM and ATA risk of recurrence stratification *(Tables 5 – 7).*

Although the use of DRS is especially useful for the first year of follow up of low risk DTC's, it can also be used for longer FU, and also for most of the intermediate and high risk DTC's.

For the long term FU of DTC, measurement of non-stimulated (and in selected cases stimulated) Tg levels, always in combination with anti Tg Ab's, and repeated ultrasound of the neck, are the most relevant items to follow up.

Table 4: ATA risk of recurrence [19]

	low	intermediate	high
TSH target* *Target to be adapted to age and medical conditions*	TSH 0.5 – 2 mU/l – if non-stimulated Tg < 0.2 ng/ml TSH 0.1 – 0.5 mu/l – if non-stimulated TSH ≥ 0.2 ng/ml	0.1-0.5 mU/l	< 0.1 mU/l
Non stimulated Tg	At 6-8 weeks At 3-6 month At 9-12 month	At 6-8 weeks At 3-6 month At 9-12 month	At 6-8 weeks At 3-6 month At 9-12 month
Neck US	At 6-12 month	At 6-12 month	At 6-12 month
Diagnostic WBS after rhTSH	Mostly not indicated	Mostly indicated	Mostly indicated
MRI or CT	-	-	If Tg elevated or high suspicion
FDG PET	-	-	If Tg > 10 ng/ml

Table 5: DRS After total thyroidectomy + RAI [63]				
Response:	Excellent	Indeterminate	Biochemical incomplete	Structural incomplete
Nonstimulated Tg or stimulated Tg	< 0.2 ng/ml < 1 ng/ml	0.2- 1 ng/ml 1- 10 ng/ml	≥ 1 ng/ml ≥ 10 ng/ml	
Tg trend	AND absent	OR stable / declining	OR rising	
Anti Tg Ab's	AND absent	OR absent / declining	OR persistent / rising	
Imaging	AND negative	OR nonspecific	AND negative	Abnormal
Estimate risk:	**Lower risk**	**Stable risk**	**Higher risk**	**Very high risk**

Table 6: DRS after total thyroidectomy, no RAI [63]				
Response:	Excellent	Indeterminate	Biochemical incomplete	Structural incomplete
nonstimulated Tg or stimulated Tg	< 0.2 ng/ml < 2 ng/ml	0.2- 5 ng/ml 2 - 10 ng/ml	≥ 5 ng/ml ≥ 10 ng/ml	
Tg trend	AND absent	OR stable / declining	OR rising	
anti Tg Ab's	AND absent	OR absent / declining	OR persistent / rising	
imaging	AND negative	OR nonspecific	AND negative	abnormal
Estimate risk:	**Lower risk**	**Stable risk**	**Higher risk**	**Very high risk**

Table 7: DRS after lobectomy [63]				
Response:	Excellent	Indeterminate	Biochemical incomplete	Structural incomplete
Nonstimulated Tg or stimulated Tg	< 30 ng/ml stable		> 30 ng/ml	
Tg trend	AND absent		OR rising	
anti Tg Ab's	AND absent	OR absent / declining	OR persistent / rising	
Imaging	AND negative	OR nonspecific	AND negative	abnormal
Estimate risk:	**Lower risk**	**Stable risk**	**Higher risk**	**Very high risk**

The long term monitoring after the first year is summarized in Table 8.

Additional imaging is only used in selected cases.
Additional diagnostic procedures are required in high risk patients with a low Tg, as the absence of tumor marker may reveal dedifferentiation of the tumor.

Therapy of persistent or recurrent disease should depend on a careful evaluation, and should be done in centers of expertise after multidisciplinary discussion.

In specific at risk patient groups *(e.g. post-menopausal women)*, assessment of the 10-year probability of osteoporotic fragility fracture (FRAX-score) performed by bone densitometry, and treatment should be proposed if indicated. [61]

TABLE 8: Monitoring after the first year

*: target to be adapted to age and medical conditions
**: for high risk DTC: 0.1-0.5 mU/l in the first 5 years, relaxed suppression thereafter (but continued surveillance)

DRS	Excellent response	Indeterminate response	Incomplete biochemical response	Incomplete structural response
TSH target*	0.5-2 mU/l**	0.1-0.5 mU/l	< 0.1 mU/l	< 0.1 mU/l or lower
Serum Tg	Yearly	6-12 month	6 months	3-6 months
Stimulated Tg	-	Consider at 2-3 year interval to establish an excellent response	Consider at 2-3 year interval to establish an excellent response	-
Neck US	3-5 years	1-3 years	Yearly (at least 5 years)	Yearly (at least 5 years)
Diagnostic WBS after rhTSH	-	Consider if Tg is rising	Consider if Tg > 10 ng/ml or rising	Evaluation RAI avidity
MRI or CT	-	Consider if Tg is rising	Consider if Tg > 10 ng/ml or rising	6-12 month: rate of progression
FDG PET	-	Consider if Tg is rising	Consider if Tg > 10 ng/ml or rising	Additional sites?

SYSTEMIC TREATMENT

Systemic treatment is intended for patients with radioidine-refractory DTC. Radioiodine-refractory DTC is classified in patients with appropriate TSH stimulation and iodine preparation in four basic ways:

- The malignant/metastatic tissue did not ever concentrated RAI outside the thyroid bed on the first therapeutic WBS.
- The tumor tissue loses the ability to concentrate RAI after previous evidence of RAI-avid disease, in the absence of iodine contamination.
- RAI is concentrated in some lesions but not in others.
- Metastatic disease progresses despite significant concentration of RAI.

When considering kinase inhibitor therapy for individual patients, several factors should be considered:

- Kinase inhibitor therapy can be associated with improved progression-free survival but is not curative.
- Kinase inhibitor therapy is expected to cause side effects that may have a significant impact on quality of life.
- The natural history of DTC is variable with rates of disease progression ranging from a few months to many years.
- Consider surgical resection and/or radiotherapy or other local therapies of distant metastases if possible before starting kinase inhibitor.

Patients with RAI-refractory metastatic DTC that are asymptomatic, stable or minimally progressive who are not likely to develop rapidly progressive, clinically significant complications can be monitored with serial radiographic imaging every 3-12 months [23, 24]. TSH-suppressive thyroid hormone therapy is usually the standard.

Kinase inhibitor therapy should be considered in RAI-refractory DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to local control by using other approaches. In Belgium both Lenvatinib and Sorafenib are approved. Although no direct comparison is available, Lenvatinib resulted in a response rate of 65% and a prolonged median progression free survival of 14.7 months versus a response rate of <15% and a prolonged progression free survival of 5 months for Sorafenib [25, 26].

Proactive monitoring and optimal management of kinase inhibitor side effects is essential [23, 24].

Denosumab should be considered in case of bone metastases [23, 24]. Calcium and vitamin D supplements should be prescribed concurrently to prevent hypocalcemia. A dental evaluation should take place before initial use.

In case of NTRK gene fusion-positive DTC, Larotrectinib can be considered

[24, 27, 28].
Patients who have disease progression while on initial kinase inhibitor therapy, without prohibitive adverse effects, should be considered for second-line kinase inhibitor therapy, preferably within the context of a clinical trial if available.

Cytotoxic chemotherapy with antracyclines can be considered in RAI-refractory DTC with metastatic rapidly progressive symptomatic and/or imminently threatening disease not otherwise amenable to control through other approaches, including kinase inhibitors [23].

Novel agents, without established efficacy in DTC, should be used primarily only in the context of clinical trials [23]

ROLE OF GENERAL PRACTITIONER

SCREENING AND REFERRALS

- No screening is indicated for the general population.
- All patients with a potential or known diagnosis of thyroid cancer should have access to a multi-disciplinary thyroid cancer team for information and support at every stage of diagnosis, treatment and follow- up.
- The general practitioner (GP) should be aware that investigations in primary care are associated with later referrals to a specialist [57], as communicating the results and organizing the referral may require additional consultations.
- Thyroid function tests might be requested by the GP and attached to the referral letter.

COMMUNICATING THE DIAGNOSIS

- The GP shall be promptly informed about the diagnosis of thyroid cancer, if this has been communicated to the patient. Subsequent alterations in prognosis, management or drug treatment should be also communicated promptly and clearly, preferably in written form.
- Patients will usually undergo thyroidectomy (lobectomy or total thyroidectomy), followed in some cases by an ablative dose of radioiodine (131I). Thereafter, patients will require treatment with levothyroxine and some will need treatment to correct hypocalcaemia.

PREGNANCY AND BREASTFEEDING

Radioiodine (131I) is not given to pregnant patients. Pregnancy must be avoided for 6 months after radioiodine therapy, in treated women and when the male partner is treated. Breastfeeding needs to be stopped at least 3 months before radioiodine ablation or therapy and not be resumed until after a subsequent pregnancy.

LEVOTHYROXINE TREATMENT

The dose of levothyroxine is usually higher than a normal replacement dose and in selected cases it is intended to suppress the level of serum TSH to <0.5 mU/l or even to <0.1 mU/l [19]. For example, if the TSH is in the normal range, the dose of levothyroxine will usually be increased. Suppressive levothyroxine therapy is best supervised by a member of the thyroid cancer MDT, preferably an endocrinologist.

TREATMENT OF HYPOCALCAEMIA

Patients taking calcitriol/alphacalcidol and/or calcium supplements must be monitored closely to ensure that hypercalcemia does not occur. The dose is kept to a minimum required to maintain serum calcium in the (low) normal range and normal calciuria [58].

FOLLOW-UP

- The GP shall ensure that the patient is offered follow-up by the multi-disciplinary thyroid cancer team. This is necessary for the detection of early recurrence and complications and for the appropriate treatment. The GP shall motivate the patient to have a regular follow up with the specialist.
- It is recommended that serial TSH, FT4, Tg and anti-Tg antibodies measurements in thyroid cancer patients are done using the same assay. It is important that neck ultrasound is done by a specialist with experience in thyroid cancer.

TNM CLASSIFICATION FOR THYROID CANCER [19] – PART 1

T Primary Tumour	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the thyroid, ≤ 2 cm or less in greatest dimension
T1a	Tumor ≤ 1 cm in greatest dimension, limited to the thyroid.
T1b	Tumor > 1 cm in greatest dimension, limited to the thyroid.
T2	Tumor > 2 cm but ≤ 4 cm greatest dimension, limited to the thyroid.
T3	Tumor > 4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles.
T3a	Tumor > 4 cm limited to the thyroid.
T3b	Gross extrathyroidal exstenion invading only strap muscles (sternohyoid, sternothyroid, thyrohoid or omohyoid muscles) from a tumor of any size.
T4	Includes gross extrathyroidal extension beyond the strap muscle.
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, espohagus or recurrent laryngeal nerve from a tumor of any size.
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size.

TNM CLASSIFICATION FOR THYROID CANCER [19] – PART 2

N Regional Lymph Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis.
N1	Regional lymph node metastasis
M Distant Metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

STAGING OF DTC

DIFFERENTIATED THYROID CANCER			
AGE AT DIAGNOSIS <55 YEARS			
Stage I	any T	any N	M0
Stage II	any T	any N	M1
AGE AT DIAGNOSIS ≥ 55 YEARS			
Stage I	T1	N0/NX	M0
	T2	N0/NX	M0
Stage II	T1	N1	M0
	T2	N1	M0
	T3a/T3b	any N	M0
Stage III	T4a	any N	M0
Stage IVA	T4b	any N	M0
Stage IVB	any T	any N	M1

EXAMPLE OF MATRIX FOR I131 ACTIVITY 202 [59]

	Nx (cN0)	N0	N1a-b* no ECS [&]	N1a-b ECS [&]
pT1a	(-)	(-)	30 T [°]	100 W
pT1b	30 T May be considered [#]	30 T May be considered [#]	30 T	100 W
pT2	30 T May be considered [#]	30 T May be considered [#]	30 T	100 W
pT3a	30/100 T	30[#]/100 T	100 T	100 W
pT3b-pT4	100 W	100 W	100 W	100 W
M+[&]	100 W	100 W	100 W	100 W

General comment:

This matrix can be used as a guide for treatment.

T = Thyrogen™
W = L-thyroxine withdrawal
30 = 30 mCi (1110 MBq)
100 = 100 mCi (3700 MBq)
ECS = extra capsular spread

Any pT: R1 upstaged to T3; R2 upstaged to T4

[#]: in individual patients, the decision taken will be the responsibility of the multidisciplinary oncology consultation, taking into account specific risk factors (i.e. previous radiation, unfavorable histology, vascular or lymphatic invasion, genetic variants and familial history), the general condition of the patient and factors associated with a favorable prognosis (i.e. undetectable post-operative thyroglobulin and no detectable anti-Tg antibody).
*: if complete lymphadenectomy and < 5 LN < 2mm, to be considered as N0
°: very unlikely situation, pT1a are usually incidental findings during thyroidectomy for other reasons; unless multiple microcarcinomas are found, even with small lymph nodes extension (<3 cm without ECS), low dose radioiodine is sufficient.
[&]: for patients with distant metastases or large (>3 cm) lymph nodes extension, activities up to 150mCi/treatment can be proposed in individual patients.

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