CANCERS OF THE ENDOCRINE ORGANS – RARE THYROID CANCERS

PREFERRED MODEL OF CARE AND CRITERIA FOR REFERENCE CENTRES

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- **The coordinators of the working groups and all the authors listed by chapter have worked autonomously under the supervision of the KCE team. The KCE experts are not co-authors of these proposals and did not necessarily validate their content.**
- **Hospitals with which coordinators and authors of these proposals are affiliated are not de facto considered Reference Centres. Similarly, Belgian hospitals that are not represented in these proposals are not de facto considered Peripheral Centres.**
- **These proposals were not submitted to the external validators.**
- **This addendum only exists in English. No French or Dutch translation was done.**
- **Finally, the report to which this addendum refers has been approved by common assent by the Executive Board.**

PREFERRED MODEL OF CARE AND CRITERIA FOR REFERENCE CENTRES

A. Type of cancer

Rare forms of thyroid cancers (intermediate or high risk differentiated thyroid cancers, anaplastic thyroid cancer, medullary thyroid carcinoma)

B. Short description of the cancers

They may arise from follicular or parafollicular cells. Thyroid cancers of follicular origin are Differentiated Thyroid cancers (DTC) and Anaplastic Thyroid Cancer (ATC). Medullary Thyroid Carcinoma (MTC) derives from parafollicular cells. DTC comprises papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC). PTC is far more common than FTC.

Thyroid cancers represent the most rapidly growing category of cancer in both sexes. The present incidence in Belgium is approximately 700 cases/year.

As mortality rates from DTC are very low, the 2006 European Thyroid Association Consensus and the 2009 American Thyroid Association guidelines for the management of DTC proposed to classify DTCs according to the probability of recurrence: high, intermediate, or low on the basis of pTNM parameters plus other types of information that are generally available shortly after the initial surgery.

Low risk DTC (classical variant of Papillary Thyroid Cancer T1-3N0M0, "minimally invasive" follicular thyroid carcinoma)

Approximately 70-80% of DTCs are small (≤10mm), localized, asymptomatic low risk forms. A relevant proportion is discovered incidentally in patients sent to surgery for other thyroid disease, in the absence of preoperative suspicion of malignancy or during a neck imaging procedure performed for other reasons. Low risk DTCs include: classical variant of PTC T1-3N0M0, the so-called "minimally invasive" follicular thyroid carcinoma (FTC) and FTC without vascular invasion.

Intermediate risk Differentiated Thyroid Cancer (DTC)

A considerable proportion (15-25%) of DTC carries an intermediate risk of recurrence. Although the mortality rate is relatively low (less than 3%), recurrence occurs in more than 20 % of this class of tumours, with a strong impact in terms of quality of life and cost of required treatment.

Intermediate risk DTC is defined as follows: T1-3N1M0 classical PTCs, all T1-3N0-1M0 aggressive variants of PTC (insular, tall cell, trabecular, Hurtle cell, diffuse sclerosing), T1-3N0-1M0 follicular thyroid carcinoma, Hurtle cell carcinoma.

High risk Differentiated Thyroid Cancer (DTC)

Five to ten per cent of DTCs carry a high risk (approximately 70%) of recurrence.

DTCs are defined at high risk when one of the following conditions would apply: presence of distant metastases, incomplete tumour resection, macroscopic invasion of perithyroidal soft tissues, serum Thyroglobulin out of proportion as compared to post-treatment scan. Distant metastases occur at presentation in less than 5% of DTC patients. Recurrent disease occurs in 10–15%. When distant metastases occur, radioactive iodine treatment is effective in approximately 1/3 of cases. Approximately 1/3 of patients with distant metastases do not respond to this treatment because the tumour has lost the ability of iodine uptake. Another 25-35 % of cases are defined radioactive iodine "resistant" (i.e. the iodine uptake is conserved, but the administration of therapeutic doses is ineffective with respect to tumour progression). In these 2 latter instances, the mortality rate is 58-75% at 10 years. Persistent/recurrent disease has a strong impact on the quality of life of affected patients.

Anaplastic Thyroid Cancer (ATC)

Anaplastic thyroid carcinoma (ATC) is one of the most aggressive cancers in humans. It represents 2% of all thyroid carcinomas and is associated with a rapidly lethal clinical course, accounting for 14–39% of all thyroid carcinoma deaths. ATCs are often observed in patients with longstanding goitre or incompletely treated DTCs (both papillary and follicular). Due to the rarity of ATC and its aggressive nature, the prognosis is poor and it is difficult to predict patient outcome and to adequately assess the response to therapeutic approaches. In ATC patients, invasion of surrounding tissues and distant metastases rapidly occur. The median survival is usually less than 6 months and the 1 year survival rate is less than 20%. Poor prognostic factors are male sex, age >60 years, and the presence of extra-thyroidal extension.

The best chance of improved survival and long-term control is dependent on complete surgical resection. This is possible only in few cases, while most patients have unresectable cancer at presentation.

In a relevant number of ATC patients, death is related to local invasion and mainly occurs from upper airway respiratory failure. For this reason, if the patient can tolerate it, aggressive local therapy is recommended. If safely achievable, surgical treatment should always be considered. Surgery is not to be considered only when distant metastases of the ATC, determining life-threatening conditions, are present.

Since ATCs do not concentrate radioiodine, external beam radiotherapy represents a mainstay for control of local invasion and may also be used as neoadjuvant treatment for disease control prior to surgery. Systemic chemotherapy can be administered as adjuvant treatment. Nevertheless, most ATCs are resistant to chemotherapy and radiotherapy.

Medullary Thyroid Cancer (MTC)

Medullary thyroid carcinoma (MTC) derives from parafollicular or C cells, producing calcitonin (CT) and accounts for 5–10% of all thyroid cancers. Its incidence in Belgium is approximately 40 cases/year. It is a rather aggressive cancer, with an average 10 year mortality rate of 40. Distant metastases are the main cause of MTC-related death. They are often multiple and occur simultaneously in several organs (liver, lungs and bones). After the discovery of distant metastases, the 5 year survival is <30%. MTC prognosis is influenced by several factors, including male gender, age at diagnosis, tumour size, extra-thyroid and vascular invasion and the initial disease extent, including lymph node and distant metastases.

MTC may occur in sporadic (75% of cases) or hereditary (25% of cases) form. In the familial form, some genotypes are associated with increased aggressiveness.

Sporadic MTC can occur at any age, with a peak between the fourth and sixth decades of life. Lymph node metastases are initially present in approximately 50% patients and distant metastases at presentation occur in about 20% of cases. Approximately 5% of apparently sporadic MTC have a germline mutation of the RET proto-oncogene and are, therefore, familial forms.

The diagnosis of MTC has a number of important implications: a careful evaluation of disease extent should be performed, the possible association of other tumours, particularly parathyroid adenoma and/or pheochromocytoma should be screened and a direct genetic analysis of the RET proto-oncogene is also required, to ascertain whether MTC is sporadic or hereditary.

C. Model of care pathway suggested for adult patients with rare forms of thyroid cancer

Model of care pathway	Preferred model
1. Model 1: Reference Centres exclusively (from diagnosis to follow-up). Once there is a suspicion of the cancer type described in A or the cancer type described in A has been diagnosed, the patient should be referred to a Reference Centre. A network with other Reference centres or with specific experts working in other centres is encouraged.	X (high risk DTC, ATC, MTC)
2. Model 2: Shared care between Reference Centres and peripheral hospitals. The patients can have initial treatment and be followed up in the Peripheral Centres. The second opinion on histopathology should be performed in the Reference Centre. The decision to administer radioactive ablation therapy should be agreed between the Peripheral MOC and the MOC in the Reference Centre. Recurrence or relapse should be addressed to Reference centre.	X (low risk DTC)
3. Model 3: Alternative model proposed by the working group. Ideally, a network between several Peripheral Centres and a Reference Centre should aggregate in a two level structure, with more sophisticated procedures and pathological examination performed at the Reference Centre. The decision concerning both the administration of radioactive ablation therapy and the dose to be administered should be made within the MOC in the Reference Centre. The follow up is performed in Reference Centres for the first 3 years, The patients that do not present evidence of persistence/relapse can be readdressed to Peripheral Centres for further follow up.	X (intermediate risk DTC)

D. Phase(s) of the clinical pathway for which Reference Centres are required

Phase of the Clinical Pathway	Reference Centre	Peripheral centre
Low risk DTC		
• MOC		X
• Diagnostic confirmation		X
• AP: second reading of AP slices may be necessary	X	
• Surgery		X
• Radioactive iodine ablation therapy		X
• Follow-up		X
• Recurrence	X	
Intermediate risk DTC		
• MOC	X	
• 1st Surgery		X
• 1st Surgery in case of cN1 or T3	X	
• Reintervention	X	
• Radioactive iodine ablation therapy		X
• Further Radioactive iodine treatment	X	
• Initial follow-up	X	
• Long term: follow up in absence of disease		X
High risk DTC, ATC, MTC		
• MOC	X	
• Diagnostic confirmation	X	
• 1st Surgery	X	
• High risk DTC, Radioactive iodine treatment	X	
• Radiotherapy	X	
• ATC, Medical oncology treatment	X	
• Medical Oncology standard treatments and experimental treatments	X	
• Follow-up	X	

Multidisciplinary Oncological Consult: Reference Centre for intermediate or high risk DTC, ATC, MTC

Diagnostic confirmation: Reference Centre for intermediate or high risk DTC, ATC, MTC

1. Complexity and new approaches Differentiated Thyroid Cancer (DTC)

   Most patients with DTC present with thyroid nodular disease and are usually managed pre-operatively by endocrinologists or surgeons. Ultrasonography by a dedicated radiologist is indicated to localize and correctly describe suspicious nodules. Radioactive scanning is an unreliable tool for differentiating between adenoma and carcinoma, but may be of use to exclude benign autonomous nodules. Fine-needle aspiration cytology is the most reliable tool for preoperative diagnosis of thyroid cancer. The use of preoperative US guided FNA should be encouraged. Approximately 15-20% of thyroid nodules present with “indeterminate” cytology (i.e. follicular lesion). In such instance, molecular diagnostic testing could be of help but is not yet routinely used. Only post-operative histology provides the conclusive diagnosis. It is, therefore, advised that intraoperative histopathology should be performed in such cases. Furthermore, due to the critical role of radical surgery and pathological evaluation for risk assignment, and for adequate definition of further treatment and follow up it is recommended that peripheral hospitals would interact with reference centres.

- Low risk DTC

  Classical PTC (stages T1-T3N0M0) and “minimally invasive” FTC do not mandatorily require a reference centre for management. A second reading of AP slices may be necessary to confirm “minimally invasive” FTC and in selected PTC cases, to exclude more aggressive variants of PTC.

- Intermediate risk DTC

  Diagnosis and initial treatment of intermediate risk DTC patients do not necessarily require reference centres.

  Due to the critical role of surgical pathology for risk assignment, all aggressive variants of PTC (insular, tall cell, trabecular, Hurtle cell, diffuse sclerosing) follicular thyroid carcinoma, Hurtle cell carcinoma should undergo second reading of slices at the reference center. Post-surgical management of intermediate risk patients requires a multidisciplinary approach which includes ultrasonography, thyroglobulin measurement, scintigraphy and in some instances SPECT/CT and/or PET imaging. Disease persistence/relapse in the neck should be confirmed by fine needle aspiration biopsy for cytological and/or biochemical confirmation (i.e. Thyroglobulin measurement in the wash out fluid and/or molecular biology procedures). A second reading of AP slices may be necessary for selected PTC cases, to exclude more aggressive variants of PTC and for FTC confirmation.

- High risk DTC

  The assignment to the high risk group of DTC patients requires the appropriate consideration of elements provided by the pathological examination at the first surgery or by imaging/biochemical findings at initial treatment or subsequent follow up. Therefore, it is possible that patients who received initial treatment in peripheral centres will be belong to the high risk category. It is crucial, at this stage, to perform all procedures necessary to determine the exact extent of the disease and to identify the optimal therapeutic approach.

  Presently, the achievement of these goals requires a multidisciplinary effort which includes ultrasonography, thyroglobulin measurement, scintigraphy and in some instances SPECT/CT and/or PET imaging. Disease persistence/relapse in the neck should be confirmed by fine needle aspiration biopsy for cytological and biochemical confirmation (i.e. Thyroglobulin measurement in the wash out fluid and/or molecular biology procedure).

- Anaplastic Thyroid Cancer (ATC)

  ATC usually present as a rapidly growing thyroid mass. Ultrasonography is useful to localize suspicious nodules and tumour extension, but most often other conventional imaging (CT, MRI) is needed due to extrathyroidal extension. Generally, fine-needle aspiration cytology (FNA) is the most reliable tool

for preoperative diagnosis of ATC. Depending on the morphologic pattern, the differential diagnosis may be difficult and in several instances the material obtained at FNA may not be adequate for diagnosis. In such instances, the need for core biopsy or open biopsy should be evaluated. Intraoperative pathology consultation should be performed in those patients in whom the diagnosis could not be anticipated preoperatively.

- Medullary Thyroid Cancer (MTC)

  MTC usually presents as a palpable thyroid nodule. Ultrasonography and scintigraphy may help in selecting suspicious nodules. Unlikely with DTC, for which fine-needle aspiration cytology is the most reliable tool for preoperative diagnosis, this technique is less sensitive (<50%) for MTC diagnosis.

  Virtually all MTC patients have elevated basal circulating calcitonin (CT) levels and plasma CT is a very sensitive marker of C cell disease. Unfortunately, when CT is employed for universal screening of thyroid nodules, the specificity of increased basal CT levels is rather low and further stimulation testing (pentagastrin, i.v. calcium) are necessary to confirm MTC diagnosis. No clear-cut threshold values for basal and stimulated CT levels are presently available.

  CT measurement in the wash out fluid of fine-needle aspiration is an important complement to cytology for both pre-surgical diagnosis and detection of local recurrence of MTC.

  Carcinogenic antigen (CEA) presents a high specificity for MTC diagnosis and follow-up and can be used as a complement to CT for MTC diagnosis and follow up.

  Although the great majority of MTCs are sporadic, the possibility of a familial form should always be considered. Thus, all newly diagnosed cases should be tested for germline RET mutations. When a RET mutation is identified, the patient should be referred for genetic counselling in a Reference Centre for the management of familial endocrine tumours.

Comprehensive AP diagnosis: for low, intermediate or high risk DTC, ATC, MTC

1. Complexity and new approaches:

   The second opinion (with ancillary techniques) will be organized as proposed by the methodology developed by the pathology working group within the framework of the KCE project « organization of care for rare cancers ».

2. Facilities and equipment required:

   Immunohistochemistry, molecular biology

Therapeutic modalities: Reference Centre for intermediate or high risk DTC, ATC, MTC

1. Complexity of treatment:

   The treatment of most DTC patients is based on surgery, radioactive iodine and thyroid hormone therapy.

- Low risk DTC
  - In both T1N0M0 classical PTC and “minimally invasive” FTC patients, thyroidectomy is considered curative and no further treatment options need to be considered in addition to surgery. The surgery can be performed in a peripheral center.
  - Thyroid hormone doses at non suppressive TSH levels is adequate.
  - Radioiodine ablation should be evaluated for PTCs T1b-T3 patients on an individual basis. Following a MOC decision agreed with the reference centre, a few patients with “minimally” invasive FTC can also be considered for radioiodine ablation. Since both the indication whether to refer for

ablation and the optimal activity to be administered are not conclusively been established, **it is** advised that this treatment option should be discussed in the peripheral MOC and submitted for advice to the MOC of a Reference centre.

- Recurrence occurs in approximately 3% of cases and carries virtually no risk for mortality.
- In case of recurrent disease, the model 3 proposed for intermediate risk patients should be considered and it is recommended that re-intervention should be performed in reference centres.

- Intermediate risk DTC

  For patients initially diagnosed in peripheral centres, the preferred treatment should be evaluated on an individual basis and agreed between the MOC of both the peripheral and Reference centres.

  For cN1-T3 PTC patients, it is recommended that the surgical treatment should be performed in the Reference centre.

  Thyroid hormone doses at suppressive TSH levels should be considered. Radioiodine ablation should be evaluated.

  All patients with persistence/relapse or rare histological variants should be initially addressed to Reference Centres.

- High risk
  - Patients with preoperatively already evidence for high risk disease as defined by gross extrathyroidal extension or multiple lymph node involvement should undergo surgery in the reference centre, by definition need postoperative I131 ablation, and should be treated with levothyroxine at thyrotropin (TSH)-suppressive doses. Selected patients might also need external beam radiation therapy postsurgically.
  - Patients with recurrent or persistent disease may require additional surgery, radioiodine, and in some cases external beam radiation therapy. In case external beam RT is indicated, IMRT should be used. Complete remission in such patients may be observed in approximately 2/3 of cases.
  - Distant metastases should be treated with administration of high activities of radioiodine if uptake is present, as needed.
  - Among the patients for whom the radioiodine treatment may be considered, a complete remission may occur in only one-third of cases. Importantly, approximately 1/3 patients, who present radioiodine uptake in their metastases do not respond to this treatment and further administration is useless. In some instances, other local treatment modalities for the distant metastases (surgery, external beam radiation therapy, radiofrequency, cement injection, or embolization) should be considered.
  - In recent years, new targeted therapies with multikinase inhibitors have become available and need to be considered in case of clearly progressive disease. Trials are ongoing on targeted therapies.
- Anaplastic Thyroid Cancer (ATC)
  - Optimal preoperative imaging studies should be performed to determine resectability. Thyroidectomy represents the initial treatment of ATC and current guidelines recommend surgery to be always performed unless surgical inrresectability or life threatening conditions due to distant metastases are present. Total or near-total thyroidectomy with dissection of the central and lateral neck lymph node compartments should be the preferred approach in resectable ATCs. In patients with diffuse metastatic disease, resection of the primary tumour for palliation to prevent airway or esophageal obstruction should be evaluated.
  - In patients with extrathyroidal invasion, the aim of surgery is to achieve grossly negative margins (R1 resection).
  - In some patients, isthmectomy or debulking of the pretracheal tumor may be necessary prior to perform tracheostomy.

- High dose radiotherapy should be administered.
- Interventional radiological approaches may be required.
- Radio-sensitizing and adjuvant chemotherapy, in addition to surgery and radiotherapy may allow improved ATC outcome.
- Chemotherapy with cisplatin and taxane based chemotherapy may give some benefit to patients.
- Concerning the optimal sequence of radiation and systemic therapy, no definitive data are presently available.
- The combination of radiotherapy and cytotoxic chemotherapy should be considered in good performance status patients. However, often a purely supportive treatment is the best therapeutic choice.

- Medullary Thyroid Cancer (MTC)
  - Surgery is the cornerstone of treatment of MTC and should always be performed in a reference centre. Thyroidectomy represents the initial treatment of MTC and current guidelines recommend prophylactic central neck dissection in case of cN0 disease. Therapeutic neck dissection should be extended to the lateral compartment in the presence of suspect lymph nodes. In patients with locally invasive MTC involving the trachea and/or the esophagus, more extensive surgery may be necessary (debulking, laryngectomy, esophagectomy, laryngopharyngectomy). Of importance, biochemical cure is obtained only in 75–90% of patients without lymph node involvement. The rate of cure in patients with lymph node metastases or large primary tumours is definitely low (20–30%) and virtually null (4%) in patients with more than 10 metastatic lymph nodes. External radiation therapy may be selectively used as adjuvant treatment after surgery, especially in case of suboptimal resection.
  - External radiation therapy to the neck and mediastinum should be considered in inoperable patients or in patients with persistent disease and might be of benefit for the treatment of symptomatic distant metastases, particularly for bone metastasis.
  - Bone surgery may be required in patients with orthopaedic or neurological complications. Surgical treatment may also be useful in some instance for brain, lung or liver of metastases.
  - Embolization could be the treatment of choice in some patients with bone or liver metastases.
  - Traditional chemotherapy with several different approaches has been used with disappointing results.
  - In recent years the multikinase inhibitors have provided promising results and should nowadays be considered in case clearly progressive disease. A novel approach using octreotide-targeted isotope administration has provided promising results.

2. Expertise required to perform the treatment:

- Intermediate risk and High risk DTC

  Re-intervention to remove tumour recurrence in the neck requires a **high surgical expertise** and it is advised that it should be performed in Reference centres. In some instances, it could be useful to perform surgery after radioiodine administration, under guidance of a probe for radioactive iodine, which facilitates the identification of metastatic foci.

- Anaplastic Thyroid Cancer (ATC)

  Surgery for anaplastic thyroid cancer is extremely complex and carries high risk of complication/ death. Thus, **high expertise in head and neck surgery** is necessary. Post-operative management demand access to intensive care and palliation therapy units. The decisions concerning radiotherapy and chemotherapy required highly qualified specialists.

- Medullary Thyroid Cancer (MTC)

  The rate and extent of persistent disease is strongly influenced by the **experience of the surgical team**. Moreover, the rate of surgical complications (laryngeal nerve palsy, and hypoparathyroidism) increases with the wider extent of neck dissection.

Follow-up: Reference Centre for intermediate or high risk DTC, ATC, MTC

1. Low risk DTC

   The follow up relies on neck ultrasonography and laboratory monitoring of serum Thyroglobulin and thyroid function tests. In a limited number of patients (e.g. in case of Tg antibodies), Whole Body Scintigraphy with diagnostic dose of radioiodine may be required. **The follow up can be performed in hospitals with a program in oncology.**

2. Intermediate risk DTC

   The follow up is mainly aimed at the identification of persistence/relapse and to the choice of appropriate treatment.

   It relies on neck ultrasonography, laboratory monitoring of serum Thyroglobulin under suppression therapy and stimulated by either thyroid hormone withdrawal or exogenous TSH administration and in selected cases Whole body Scintigraphy either with diagnostic or therapeutic radioactive iodine doses, according to the individual patient's needs, as defined at the MOC session of the reference centre. **The patients should be examined at least once a year in the Reference centre for the first three years. The patients will undergo evaluation for delayed risk assessment after this period of follow up. All those patients that after three years of follow up do not present evidence of persistence/recurrence can be reclassified as low risk and have further follow- up in the peripheral centre.**

   The identification of persistence/relapse requires further treatment, which could be either reiteration of surgery or additional radioiodine therapy. In such instance, the patients will be treated as high risk DTC patients for whom treatment and further follow up will be performed in Reference centres only, according to the proposed Model 1.

3. High risk DTC
   - The follow up is mainly aimed at monitoring the effectiveness of treatment on persistence/relapse and/or distant metastases. It relies on neck ultrasonography, laboratory monitoring of serum Thyroglobulin under suppression therapy and stimulated by either thyroid hormone withdrawal or exogenous TSH administration and in selected cases Whole body Scintigraphy either with diagnostic or therapeutic radioactive iodine doses. In addition, Contrast-enhanced computed tomography may help to detect lesions in the brain, neck, chest, and abdomen (triple-phase scanning is required for liver studies). Magnetic resonance imaging is more appropriate for the detection of brain, liver, and bone lesions. Bone scintigraphy may be useful in case of skeletal lesions.
   - 18FDG–PET is indicated for the identification of occult metastases in patients with elevated Tg levels and negative wholebody
   - scans. It is also of pivotal importance to identify patients unlikely to respond to RAI therapy or patients with distant metastases at a highest risk for cancer-related mortality.
   - The responses to systemic or local treatment should be carefully documented in order to timely address the patient to innovative treatment options.

4. Anaplastic Thyroid Cancer (ATC)
   - ATC is a very aggressive rapidly life- threatening cancer. The emergency relates to both the threat to the airway and oesophagus and the risk of metastatic spread. The survival of patients with metastatic ATC is very short, with negligible cure prospects.
   - Patients with ATC require close monitoring of the airway during radiation therapy.
   - Maintenance of nutrition by PEG/feeding tube can be required in patients with oesophageal invasion. Enteral nutrition may also be necessary prior to chemotherapy and radiation therapy.
   - An extremely important issue relates to the potential toxicity of chemotherapy, namely neutropenia with consequent complicating infection. This risk is heightened by the concomitant use of chemotherapy and radiation.
   - In case of rapid progression under chemo/radiotherapy, a timely decision to supportive treatment is crucial.
5. Medullary Thyroid Cancer (MTC)
   - Patients should receive thyroxine replacement therapy without need for TSH suppression.
   - Appropriate follow up requires an accurate definition of the individual patient risk, which relies on postoperative staging according to the updated (2002) American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging system and on other prognostic factors such as age and the postoperative CT and CEA levels. Of importance, the CT and CEA doubling time have been shown reliable predictors of survival. Persistently elevated CT levels indicate the need for identifying the site of residual disease. Tumour localization can be pursued by ultrasonography, CT or MRI of the neck, chest and liver, and bone scintigraphy. FDG-PET has provided disappointing results, but the recent implementation of somatostatin receptor-PEThas provided improvement of disease detection.
   - When possible, surgery is the optimal treatment for local and regional recurrences. The extent of surgery should take into account the type of previous surgical procedures, the site and the nature of the recurrence. When tumour markers remain elevated and distant metastases cannot be identified, external radiation therapy to the neck and mediastinum may be indicated after surgery.
   - The management of metastatic disease should first be aimed to both removal of the metastatic mass and symptoms relief. Palliative surgical procedures should be evaluated on an individual basis.
   - In case of symptomatic progressive disease, multikinase inhibitors and other innovative therapies should be considered.
   - Innovative treatments using octreotide-targeted isotopes are also under investigation.

E. General and specific criteria for Reference Centres

The MOC of the reference centre

Because there is a rather wide grey zone where no clear cut indication for optimal approach is provided in the existing guidelines, it is recommended that each Reference centre should previously establish criteria concerning the preferred treatment modalities according to the various clinical, staging and grading conditions. These criteria should be revised on a 3 year basis, taking into account the progress in current practice international guidelines.

The MOC of the reference centre should fulfil all these conditions:

1. At least the following disciplines should be represented: Endocrinology, Nuclear Medicine, Radiology, Surgery (ORL-head-neck, thoracic), Medical Oncology, Radiotherapy, Pathology; a Care coordinator should also be included;
2. It is recommended that all specialists participating to the MOC are specifically involved in the management of thyroid cancer patient;
3. The coordinator of the MOC should have a documented experience in thyroid cancer management and members of the MOC should have documented research activity in this field;
4. The pathologist should have an accomplished experience for revision of histopathological or cytological diagnosis, according to the criteria established by the pathology working group, within the framework of the KCE project « organization of care for rare cancers ».

The list of specialists included in the MOC and the fulfilment of the required conditions should be revised at least every 4 years.

Human Resources and dedicated team

1. Medical expertise

- Endocrinologist experienced in thyroid cancer management
- Nuclear Medicine Specialist with experience in radioisotope therapy
- Radiologist with experience in head-neck sonography
- FNA sampling expert
- Surgeon (ORL-head-neck, thoracic, bone, liver)
- Medical oncology specialist
- Radiation oncologist with experience in highly conformal external beam radiotherapy
- Pathologist
- Gastroenterologist (for ATC)

2. Paramedical expertise required:

- Care coordinator
- Psychologists
- Reference nurses

- Speech therapist
- Clinical research unit (nursing and administrative support for patient management in clinical trials)

Required facilities and equipment

- Electronic medical record
- Facilities for videoconference
- Advanced Imaging techniques
  - Ultrasonography
  - Scintigraphy
  - SPECT/CT
  - PET
- Isolation room for radioactive Iodine treatment (for DTCs requiring radioiodine ablation therapy)
- Pathology lab for Fine Needle Aspiration Cytology and histology
- Clinical Laboratory
- Radiology/Interventional Radiofrequency
- Radiotherapy-oncology equipped to perform IMRT
- Palliative care unit (for ATC)

Patient centred care

- Waiting time with regard to first outpatients' visit, admission, and tests should not exceed 15 working days
- Continuity of care for critical patients should be covered 24 h a day 7 days a week by specialised staff,
- Support should be provided through a the Oncology care program
- The centre should be able to offer support services (identification of a care coordinator, support for patient's information, link with patient's associations, specific website for patients / professionals, information on accessibility to clinical trials) to patients requiring complex or innovative treatments,
- The centre should be involved in National and international networking (Belgian Cancer Register, EORTC, European Thyroid Association Cancer Research Network, etc.)
- The centre should have access to clinical trials

Minimal volume of patients

1. surgery :

- Initial
  - Low risk DTC: 12/year
  - Intermediate risk DTC: 4 patients/year
  - High risk DTC : 2 patients/year
  - Medullary Thyroid Cancer (MTC): 2 patients/year
  - Anaplastic thyroid cancer: Due to the rarity of the disease, it cannot be provided a yearly based volume of patients
- **complex surgical interventions:** 10 or more /year for thyroid cancers;
  - **medical management**: 25 or more complex (i.e. metastatic disease, persistence/recurrence) thyroid cancer patients;
  - **radioiosotopic treatment procedures:** 40 or more/year.
  - The minimal number of cases/year will be re-evaluated according to the actual distribution of observed cases countrywide over a 4 year period.

Quality Assurance

- Capacity to propose quality indicators (structure, process, outcomes)
- Exhaustive and reliable information sent to Cancer Registry and the MOC decisions should be recorded according to the standard requirements of the oncology care programme.
- Compliance with existing guidelines should be ensured. For all those conditions for which sharp indications on the international guidelines are not available, it is recommended that each Reference centre , by preference in consensus with other Reference centres, should previously establish a policy concerning the preferred treatment modalities according to the various clinical, staging and grading conditions. This policy should be revised on a regular basis (3-5 years). If the Reference centre is recognized as a network, the policy must be agreed between the different units, approved by their Institutional Ethical Committees and published on the Institutional website.
- Involvement in quality initiatives (e.g. benchmarking)
- Annual activity should be reported and the data published on the Institutional website (e.g. number of new patients / type of cancer; diagnostic, treatment and outcome data; specific protocols for reporting and recording complications...)

Research and other scientific activities

- Access to clinical trials for experimental drugs.
- Link with a tumour bank
- Participation to national and international networks (European Thyroid Association Cancer Research Network, IAES)
- Case reports publication
- Clinical and basic research in the Thyroid field

Educational activities: Teaching and dissemination

- Involvement in training and continuous education programs (annual or multi-annual training / educational programme for physicians, nurses, supportive disciplines)
- Organisation / communication in international and national (Belgian Thyroid Club) scientific congresses