

CANCERS OF THE ENDOCRINE ORGANS – ENDOCRINE NEOPLASMS

PREFERRED MODEL OF CARE AND CRITERIA FOR REFERENCE CENTRES

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This section is part of a whole document (KCE Report 219 Addendum) available on the website of the Belgian Health Care Knowledge Centre



PREFERRED MODEL OF CARE AND CRITERIA FOR REFERENCE CENTRES

A. Types of cancer

Rare endocrine neoplasms include

- Adrenocortical Carcinoma (ACC)
- Parathyroid Carcinoma (PCA)
- (Malignant) pheochromocytoma / paraganglioma
- Pituitary tumours (carcinoma and invasive carcinoma)
- Neuroendocrine tumours: Glucagonoma
- Neuroendocrine tumours: Insulinoma
- Familial forms: Multiple Endocrine Neoplasia Type 1 (MEN 1)
- Familial forms: Multiple Endocrine Neoplasia Type 2 (MEN 2), Familial Medullary Thyroid Cancer (FMTC), malignant pheochromocytoma

B. Short description of the cancers

Cancers of endocrine glands are very rare neoplasms. A general characteristic of these cancers is that they usually present with symptoms of excess of the specific hormone secreted by the involved gland and are resistant to radiotherapy and DNA-damaging chemotherapies. For these reasons, early diagnosis and radical surgery are crucial and the prognosis is usually poor in the case of persistent/recurrent disease.

Adrenocortical Carcinoma

The incidence of adrenocortical carcinoma (ACC) in Belgium is approximately 30 cases/year. AAC presentation is rather heterogeneous and the prognosis is usually poor. In approximately 60% of cases, patients present symptoms of adrenal steroid hormone excess and rapidly progressing Cushing's disease, with or without virilization. The remaining 40% are hormonally inactive AAC. Survival is dependent on stage at presentation. Thus, early diagnosis is crucial. The reported 5-year survival rate in stage IV patients is approximately 10%. The management of patients with ACC requires a multidisciplinary approach. After diagnosis, the complete surgical resection is the overriding goal. Adjuvant medical therapy or irradiation should also be considered, to improve the outcome. Systemic therapies for advanced ACC are limited. New targeted treatments are under investigation and a few trials on experimental drugs are in progress.

Parathyroid Carcinoma

The incidence of parathyroid carcinoma (PCA) in Belgium is 3 PCA cases/year. Usually, PCA arises in the normal parathyroid gland locations within the central neck, but it may develop in ectopic glands in other neck or mediastinal locations. The clinical course of PCA is not readily predictable, often quite indolent. PCA may infiltrate locally and/or metastasize distantly, with a specific predilection toward the thyroid and the lungs, but other organs can be involved with metastases. Most patients with PCA present with severe hyperparathyroidism characterized by very high levels of PTH, which ultimately result in severe hypercalcemia. Extensive surgical resection is the treatment of choice in patients with PCA limited to the neck. Recurrence of PCA occurs about 30%–50% of



the time, even after extensive surgical resection. The average time between initial surgery and first recurrence is 3 years, and once it occurs cure is rare. The median survival time following first recurrence is 28 months.

(Malignant) pheochromocytoma / paraganglioma

Both pheochromocytoma (arising from the adrenal medulla) and paragangliomata (arising from sympathetic ganglia) are catecholamine-secreting tumours. Although probably underestimated, annual incidence of pheochromocytoma is estimated at 0.8 per 100 000 person years. Most of these tumours are benign, however 10% of pheochromocytomas are malignant (as defined by the presence of metastases) whereas up to 25% of paragangliomas are malignant.

Malignant properties of the primary tumour cannot be derived from histopathological examination of initially resected tissue and the occurrence of metastases can be delayed for as long as 20 years after initial diagnosis and treatment, therefore, lifelong surveillance is warranted. A diagnosis of malignancy can only be made by identifying tumour deposits in tissues that do not normally contain chromaffin cells.

Actually, in 30-40% of all pheochromocytomas and in an even higher percentage of paragangliomas an underlying genetic mutation can be found. This is of importance, as some genetic mutations give risk to malignant disease.

Prognosis of malignant pheo/paragangliomas is highly variable, with five-year survival rates ranging from 12-84%, depending on primary tumour site and site of metastases.

Pituitary tumours (carcinoma and invasive carcinoma)

Although pituitary adenomas are relatively frequent (prevalence: 1/1 000), prevalence of pituitary carcinomas is rare (0.2% of pituitary symptomatic tumours). According to the World Health Organization classification of pituitary tumours, only those with systemic metastasis must be considered as carcinomas. However, locally invasive and aggressive pituitary tumours (without evident metastases) have bad prognosis.

Eighty per cent of carcinomas are functional, producing ACTH and PRL in most cases (42% and 33% of cases respectively). At diagnosis, tumours are usually more than 1cm, with evident tumour syndrome (headache, chiasma compression, diplopia).

Importantly, pituitary tumours can be observed in the context of Multiple Endocrine Neoplasia type 1.

Neuroendocrine tumours: Glucagonoma

Glucagonomas are tumours arising from pancreatic alpha cells. They are rare and estimated to represent 7% of all pancreatic neuro-endocrine tumours (pNET). Glucagonomas have a propensity to metastasize (mainly to the liver) and are therefore considered malignant. Metastases are often already present at the time of diagnosis.

After diagnosis, complete surgical resection is indicated, since it offers the chance of complete cure. For patients deemed inoperable, external beam radiotherapy might confer symptomatic palliation and slow down local progression. In case of metastatic disease, resection of the primary tumour might still be considered to alleviate symptoms. In addition, treatment with somatostatin analogs often improves symptoms but there is insufficient data to support antitumoural activity of somatostatin analogs on metastatic glucagonoma. Other possible therapies can either be focused on the liver (surgery, chemo-embolization, ablation) or be systemic chemotherapy and targeted therapy. However, although the above mentioned treatments are considered to prolong survival, cure is generally considered rare once the tumour is metastatic. Overall 5-year survival ranges from 36-77%.



Neuroendocrine tumours: Insulinoma

Insulinoma are tumours arising from pancreatic beta cells. They are rare and the annual incidence is estimated at 0.4 per 100 000/year. Excessive and inappropriate secretion of insulin by these tumours leads to hypoglycaemia, causing severe neuroglycopenic symptoms and may occasionally lead to irreversible neurologic damage or death. Insulinoma are mostly unifocal, but can be multifocal or malignant. Multiple insulinoma or metastatic disease may occur in patients with MEN1 syndrome.

After diagnosis and localisation, complete surgical resection is indicated since it offers the chance of complete cure. After successful surgery, the overall survival rate is similar to that of the normal population. However, recurrence rate ranges from 5 to more than 20%, being higher in those patients known with MEN 1, therefore follow-up is warranted.

Multiple Endocrine Neoplasia Type 1 (MEN 1)

MEN1 disease is a rare autosomal dominant hereditary cancer syndrome presenting tumours of the parathyroid glands, endocrine pancreas and anterior pituitary. Other tumour types have also been described (adrenal tumours, thymus or pulmonary carcinoid tumours) and more than 20 various combinations of tumours have already been reported in the literature. This syndrome is characterised by a very high penetrance and an equal sex distribution and occurs in approximately one in 30 000 individuals. It affects people between 8 and 80 years old.

Tumours in MEN1 disease occur as follow: parathyroid (95%), pancreatic islets (30% - 80%) and anterior pituitary tumours (15 - 90%). Other tumours are rare. Hyperparathyroidism is the most common and usually the first clinical manifestation of MEN1 while gastrinoma and carcinoids represent the most frequent causes of mortality.

MEN1 gene is located on chromosome 11q13 and encodes menin, a 610 amino acid nuclear protein that play a crucial role in DNA transcription and replication. Mutations of MEN1 gene lead to a loss of function, suggesting a role as a tumour suppressor gene.

Mortality is mainly the consequence of neuroendocrine tumour of the gastrointestinal tractus and tumour of the thymus. Morbidity results from the consequences of hyperparathyroidism (osteopenia, renal lithiasis, pancreatitis), of pancreatic tumour (insulinoma, glucagonoma) or other gastrointestinal tumour (VIPoma,...). Pituitary tumours in MEN1 are mainly prolactinoma and more resistant to conventional therapies than in sporadic disease.

Multiple endocrine neoplasia type 2 (MEN 2), Familial Medullary Thyroid Cancer (FMTC)

MEN 2 is a genetic syndrome inherited as an autosomal dominant trait, with age-related penetrance. There are two distinct clinical syndromes named MEN 2A and MEN 2B. MEN 2A is characterized by medullary thyroid carcinoma (MTC) (95-100%), pheochromocytoma (50%) and parathyroid hyperplasia or adenoma (25%). Variants of MEN 2A include Familial MTC (FMTC), characterized by the presence of MTC alone in at least four members of affected families, MEN 2A associated with cutaneous lichen amyloidosis and MEN 2A associated with Hirschsprung disease. MEN type 2B consists of MTC, pheochromocytoma, a marfanoid habitus with prominent lips and tongue nodules, mucosal ganglioneuromatosis of the gut, and diffuse neuromegaly. There is significant morbidity and mortality associated with both MTC and an undiagnosed pheochromocytoma. Before the introduction of biochemical and genetic testing, sudden death, probably due to pheochromocytoma occurred in MEN 2 families at a rate almost equivalent or higher to death from MTC.

The susceptibility gene for MEN 2A is the **REarranged during Transfection** (RET) proto-oncogene. A single activating mutation is considered sufficient to induce neoplastic transformation and the presence of a germ-line RET point mutation occurs in more than 90% of MEN 2 patients. At present, RET mutation analysis represents a paradigm in medical genetics for its tremendous diagnostic and therapeutic implications. In fact, genetic screening of patients at risk



gives the opportunity to identify gene carriers, with sensitivity and specificity close to 100%. Once the mutation carrier status has been identified, appropriate clinical interventions can be planned in a prophylactic attempt, prior to neoplastic progression, or at an early pre-symptomatic stage, for optimal cure.

C. Model of care pathway suggested for adult patients with rare endocrine neoplasms

Model of care pathway	Preferred model
1. <u>Model 1: Reference Centres exclusively (from diagnosis to follow-up)</u> . 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
2. <u>Model 2: Shared care between Reference Centres and peripheral hospitals</u> . Part of the care pathway (e.g. diagnosis, MOC, surgical treatment, ..) is performed in the Reference Centre and for another part of the care pathway (e.g. chemotherapy, radiation therapy, follow-up, ..) the patient is referred (back) to the regional hospital	

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

Phase of the Clinical Pathway	Reference Centre	Peripheral centre
MOC	X	
Diagnostic confirmation (AP and/or medical imaging)	X	
Comprehensive AP diagnosis	X	
Genetic counselling for familial forms	X	
Therapeutic modalities	X	
- Surgery	X	
- Radiotherapy	X	
- Chemotherapy/Targeted Therapy	X	
Follow-up	X	



Multidisciplinary Oncological Consult: Reference Centre

1. Adrenocortical Carcinoma

ACC is an aggressive and rare malignancy with limited therapeutic options. The access to advanced imaging techniques, the availability of expert surgeons, the possibility to manage complex chemotherapy protocols and the participation to collaborative international networks, represent the only possibility to offer affected patients adequate therapeutic perspectives.

2. Parathyroid Carcinoma

PCA is a malignancy with limited therapeutic options. In a relevant number of cases the diagnosis is post-surgical, at the time of pathological examination.

3. (Malignant) pheochromocytoma / paraganglioma

The access to advanced imaging techniques, the availability of expert surgeons, the possibility to manage complex chemotherapy protocols and the participation to collaborative international networks, represent the only possibility to offer affected patients adequate therapeutic perspectives.

4. Pituitary tumours (carcinoma and invasive carcinoma)

Management of pituitary tumours requires easy access to advanced nuclear imaging techniques, experienced neurosurgeons, endocrinologists and oncologists. Due to the rarity of the disease, collaborative international network is mandatory as it can give access to adequate therapeutic options.

5. Glucagonoma

The access to advanced imaging techniques, the availability of expert surgeons, the possibility to manage complex chemotherapy protocols and the participation to collaborative international networks, represent the only possibility to offer affected patients adequate therapeutic perspectives.

6. Insulinoma

The access to advanced imaging techniques, the availability of interventional radiologists, expert surgeons, the possibility to manage complex chemotherapy protocols and the participation to collaborative international networks, represent the only possibility to offer affected patients adequate therapeutic perspectives.

7. Multiple Endocrine Neoplasia Type 1 (MEN 1) and type 2 (MEN2).

As MEN diseases affect various organs, they require an extremely complex multidisciplinary approach. The affected patients need genetic counselling and molecular biology tests must be performed in patients and their relatives to adequately identify subjects at risk and to plan appropriate prophylactic treatment.



Diagnostic confirmation: Reference Centre

Complexity and new approaches

- Adrenocortical Carcinoma

A careful endocrine workup and the modern cross sectional imaging techniques are able to identify preoperatively an adrenal mass as ACC. Both size and appearance of an adrenal mass on computerized tomography (CT), magnetic resonance imaging (MRI), and more recently 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) represent useful tools to distinguish between benign and malignant lesions. Imaging is also important for staging. If a surgical approach is not feasible and the diagnosis cannot be otherwise established before starting medical therapy, a biopsy should be performed.

- Parathyroid Carcinoma

Most patients with PCA present with severe hyperparathyroidism characterized by very high levels of PTH, which ultimately result in severe hypercalcemia. Ultrasonography is useful to localize parathyroid tumours, and may help to differentiate PCA from parathyroid adenoma. Technetium-99 (99 Tc)-sestamibi scanning is an unreliable tool for differentiating between adenoma and carcinoma. Generally, biopsy (including fine-needle aspiration cytology) of PCA is unnecessary and should be avoided in resectable cases.

- (Malignant) pheochromocytoma / paraganglioma

Given that malignant pheochromocytomas/paragangliomas might be difficult to localize, diagnostic procedures should be performed in a centre with highly experienced personnel with access to high-resolution computerized tomography (CT), magnetic resonance imaging (MRI), and nuclear imaging (FDG-PET, MIBG-SPECT, somatostatin receptor -PET). Imaging is also important for staging. If a surgical approach is not feasible and the diagnosis cannot be otherwise established before starting medical therapy, a biopsy should only be performed after thorough medical preparation.

- Pituitary tumours (carcinoma and invasive carcinoma)

Pituitary carcinomas mainly produce ACTH and PRL resulting in Cushing syndrome in the first case and in clinical specific symptoms in the latter.

Cushing syndrome is characterized by all manifestations of a cortisol excess. In rare cases, the diagnosis is easy due to the association of evident clinical symptoms (hypertension, hirsutism, diabetes, truncular obesity with muscular amyotrophy, easy bruising, purple stretch marks). More frequently, the diagnosis of Cushing syndrome is difficult and requires repetitive laboratory tests (urinary cortisol and derivatives levels, response to dynamic tests, midnight salivary cortisol levels).

PRL levels can be falsely low because of the so called "hook effect" resulting in misdiagnosis or falsely high by the presence of macroprolactinemia.

Recent studies reported the importance of evaluating genetics in aggressive pituitary disease. AIP and MEN 1 mutation have already been reported.

Diagnosis of pituitary carcinoma relies on the presence of metastases. However, confrontation of imaging, nuclear medicine techniques and histopathological findings can predict bad prognosis in patients with pituitary tumours. In consequence, in absence of evident metastases, diagnosis is based on a multiple approach, requiring experience in all departments concerned.



- Glucagonoma

Given that glucagonomas are often already metastasized at presentation, diagnostic procedures should be performed in a centre with highly experienced personnel with access to high-resolution computerized tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography and nuclear imaging (FDG-PET, somatostatin receptor-PET). Imaging is also important for staging. If a surgical approach is not feasible and the diagnosis cannot be otherwise established before starting medical therapy, a biopsy should be performed.

- Insulinoma

Insulinomas are often difficult to diagnose and localize, multiple diagnostic procedures should be performed. These will include: dedicated clinical laboratory, advanced imaging techniques such as high-resolution computerized tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography, interventional radiology and nuclear imaging (FDG-PET, somatostatin receptor-PET). Imaging is also important for staging. If a surgical approach is not feasible and the diagnosis cannot be otherwise established before starting medical therapy, a biopsy should be performed.

- Multiple Endocrine Neoplasia Type 1 (MEN 1)

MEN1 disease request easy access to physician specialists (endocrinologist, gastroenterologist, surgeon, neurosurgeon), advanced medical imaging technique (MRI, PET scan). Evaluation of gastrointestinal tract tumours require echoendoscopy and experienced gastroenterologist.

- MEN 2, familial medullary Thyroid Cancer (FMTC)

Because of both the high penetrance (>90% of MEN carriers) and its earlier occurrence, MTC is often the first manifestation of both MEN 2A and 2B. At variance with sporadic MTC, which presents as a solitary thyroid nodule, hereditary MTC is more often multicentric and bilateral. The tumour is usually aggressive and more frequently spreads to the regional lymph nodes and subsequently to the liver, lung, bone, and brain.

In MEN 2A, which accounts for 75% of MEN 2 families, pheochromocytoma is the second manifestation in order of frequency (50%). It is more often unilateral at presentation but a contralateral pheochromocytoma may be observed within 10 years. With a lesser frequency, hyperparathyroidism and other neuroendocrine tumours may be associated. In MEN-2B, there are additional extra features. Neuromas may be present.

Concerning MTC, the de novo diagnosis of familial forms can be performed through the same protocol of sporadic MTC.

The clinical suspicion of a pheochromocytoma relies on clinical findings, namely severe hypertension. The suspicion of pheochromocytoma should be confirmed by the measurement of plasma-free or urinary-fractionated metanephrines or both. MIBG scintigraphy, Computed tomography scanning and magnetic resonance imaging are employed for the localization of pheochromocytomas. According to the latest guidelines released by the European Society of Medical Oncology (ESMO), when pheochromocytoma is proven, either Dopa/Dopamine-PET or FDG-PET is necessary.

The possibility of concomitant hyperparathyroidism should be verified by evaluation of Phosphorum/Calcium balance and parathormone measurement. In most cases, it is due to a parathyroid adenoma which should be identified by Ultrasound and parathyroid scintigraphy.

When either MTC or pheochromocytoma are diagnosed in apparently sporadic form, the possibility of a familial form should always be considered. It is now recommended that each patient with apparently sporadic MTC should be tested for germline RET mutations, even though the likelihood to find a RET mutation ranges 1-7% only. Similarly, possible hereditary aetiology (occurring in 5-15% of cases) should also be systematically considered in apparently sporadic pheochromocytomas. In these patients, germline analysis may include succinate dehydrogenase B, D, C SDHB, SDHD, SDHC), von Hippel-Lindau (VHL), VHL and neurofibromin 1 (NF1), in addition to RET gene. At variance with sporadic MTC and pheochromocytoma, RET analysis is not indicated in sporadic hyperparathyroidism, while in the familial form, screening for MEN 1 is considered more appropriate.



Comprehensive AP diagnosis: Reference Laboratory

With regard to histopathological or cytological diagnosis, the methodology developed by the pathology working group within the framework of the KCE project « organisation of care for rare cancers » will be followed.

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 »

Therapeutic modalities: Reference Centre

Complexity

- Adrenocortical Carcinoma
 - Complete tumour removal represents a critical point for initial treatment.
 - Replacement therapy with hydrocortisone will be needed.
 - An adjuvant treatment with mitotane, irradiation of the tumour bed, cytotoxic agents or combinations should be offered.
 - For recurrent AAC, reintervention is recommended, whenever possible.
 - Systemic therapy should be evaluated in patients not qualifying for a localized treatment.
 - Novel approaches should be considered. Trials are ongoing on targeted therapies such as anti-EGF-receptor anti-VEGF-TKI anti-IGF2-receptor etc.
- Parathyroid Carcinoma
 - The recommended initial procedure is en bloc removal of the affected parathyroid including ipsilateral thyroid isthmo-lobectomy, tracheal skeletonization, and excision of any adherent muscle.
 - Radiotherapy has been often considered ineffective for the treatment of PCA.
 - Systemic therapy could be evaluated in recurring patients not qualifying for a localized treatment.
 - Novel approaches should be considered.
- (Malignant) pheochromocytoma / paraganglioma

In case of malignant pheochromocytomas/paragangliomas, surgery should be the first treatment of choice. If metastases are considered not to be completely resectable, surgical debulking therapy should be discussed. After surgery, or if surgery is not feasible, external beam radiotherapy, chemotherapy or peptide receptor radionuclide therapy should be offered.

Novel approaches should be considered. Trials are ongoing on targeted therapies such as thyrosine kinase inhibitors or mTOR-inhibitors.
- Pituitary tumours (carcinoma and invasive carcinoma)
 - Treatment of pituitary carcinoma requires multimodal approach (neurosurgery, medical treatment, chemotherapy, radiotherapy).
 - Experienced neurosurgeon should perform, when possible, total resection of the pituitary cancer. When total resection is not possible, debulking should be performed to avoid consequence of the tumour volume (as optic chiasma compression). Moreover, it can allow to improve medical treatment efficacy.



- o Medical treatment is mainly based on somatostatin analogs and cabergoline, aiming to normalize hormonal levels and to reduce tumour volume.
- o Chemotherapy consists of different combinations of lomustine and 5 fluorouracil in mild cases and of cisplatin and etoposide in severe cases.
- o Advances in radiotherapy (cyberknife, gamma knife) allow a reduction of the total dose delivered, with a reduction of adverse effects frequently associated with conventional radiotherapy (stroke, secondary tumour, panhypopituitarism).
- o Recently, interest was given to temozolomide as this alkylating agent was efficient in controlling pituitary carcinomas..
- Glucagonoma

Pancreatic surgery for glucagonoma should only be performed by an experienced surgeon with the goal to maximize residual pancreatic tissue and the same applies for surgery of liver metastases. Additionally, since surgery for liver metastases should be weighed against other forms of local hepatic treatment (ablation, embolisation, SIRT), the discussion concerning this final decision should be done in a centre with sound experience in these techniques. Enrollment in clinical trials should be possible in the treating centre.
- Insulinoma

Pancreatic surgery for insulinoma should only be performed by an experienced surgeon, with the goal to maximize residual pancreatic tissue. The same applies to surgery of liver metastases. Additionally, since surgery for liver metastases should be weighed against other forms of local hepatic treatment (ablation, embolisation, SIRT), the discussion concerning this final decision should be done in a centre with sound experience in these techniques. Access to clinical trials should be possible in the treating centre.
- Multiple Endocrine Neoplasia Type 1 (MEN 1)

As no preventive surgical approach can be performed, frequent evaluation during follow-up is mandatory. In case of severe hyperparathyroidism, resection of all parathyroid with brachial reimplantation is usually performed.
- MEN 2, familial medullary Thyroid Cancer (FMTC)
 - o The difficulties of sporadic MTC treatment apply also to MTC in the familial settings.
 - o The diagnosis of pheocromocytoma implies surgical treatment. Adrenalectomy should be performed prior to any other surgery, it may be performed by laparoscopic approach in most cases.
 - o Surgical approach for hyperparathyroidism implies the same difficulties as for parathyroid cancer.
 - o A major issue in the management of MEN 2 and FMTC relates to the ascertainment of gene carriers, in order to plan appropriate prophylactic treatment for family members. Because potentially lethal manifestations of the disease, particularly MTC, may occur as early as the age of 6, the identification of the carriers before onset of symptoms is crucial in the management of such families. Thus, genetic counselling represents a main complement to specific treatment option for patients with clinically established disease.



8. Expertise required to perform the treatment

• Adrenocortical Carcinoma

- o Adrenalectomy should be performed by **surgeons experienced in “en bloc resection” of invaded organs and lymphadenectomy**. Laparoscopic adrenalectomy for ACC could be considered only in patients included in adequately designed prospective trials.
- o For recurrent AAC, reintervention should be evaluated only if complete resection is feasible. In this respect, **the experience of the surgical team is crucial for optimal outcome**.
- o The only approved drug for AAC is mitotane, which presents significant systemic toxicity. These effects are mainly gastrointestinal or involve the central nervous system. Mitotane has a narrow therapeutic window, and adverse effects occur frequently and are often dose limiting. Due to the long half-life of mitotane, blood levels and adverse effects usually increase over time, even if the dose remains unchanged. Due to its adrenolytic activity, mitotane treatment induces adrenal insufficiency. Replacement therapy with hydrocortisone will require unusually high doses due to the effect of mitotane on corticosteroids metabolism. Flucortisone may be required. The centre should have access to the monitoring of treatment with the determination of blood mitotane levels.
- o The combination chemotherapy of etoposide, doxorubicin, cisplatin and mitotane (EDP-M) is an alternative.
- o Radiotherapy has been often considered ineffective for the treatment of ACC.
- o Due to the high rate of failure of currently available treatments, the centre should have access to international networks and clinical trials on experimental treatments.

• Parathyroid Carcinoma

Since the extent of tumour resection is critical to minimize the risk of recurrence, and surgery is presently the unique possible approach for recurrent PCA, **the experience of the surgical team is crucial for optimal outcome**.

Due to the high rate of failure of currently available treatments in recurrent PCA, the centre should have access to international networks and clinical trials on experimental treatments.

• (Malignant) pheochromocytoma / paraganglioma

Complete tumour removal should be performed by **surgeons experienced in “en bloc resection” of invaded organs and lymphadenectomy**. Laparoscopic adrenalectomy is the surgical approach of choice. However, metastatic disease is often difficult to remove at laparoscopy. In case of chemotherapy, the treatment centre should have experience with cyclophosphamide, dacarbazine, vincristine, and doxorubicin.

• Pituitary tumours (carcinoma and invasive carcinoma)

Experienced neurosurgeon team. Experienced endocrinologists and oncologists to manage specific medical treatment and explore adverse effects of such therapeutics (pituitary carcinoma and invasive carcinoma)

• Glucagonoma

Complete tumour removal should be performed by **surgeons experienced in “en bloc resection” of invaded organs and lymphadenectomy**. Laparoscopic versus open surgical approach depends on the localization and extent of disease, as well as on the presence of resectable liver metastases. In case of treatment choice for chemotherapy, the treatment centre should have experience with streptozocin and doxorubicin as well as with temozolomide.



- Insulinoma

Pancreatic surgery for insulinoma should only be performed by an **experienced surgeon with the goal to maximize residual pancreatic tissue and the same applies for surgery of liver metastases**. Surgery for liver metastases should be weighed against other forms of local hepatic treatment (ablation, embolisation, SIRT), the discussion concerning this final decision should be done in a centre with sound experience in these techniques. Enrollment in clinical trials should be possible in the treating centre.

- Multiple Endocrine Neoplasia Type 1 (MEN 1)

Experienced abdominal surgeons and endocrine surgeons.

- MEN 2, familial medullary Thyroid Cancer (FMTC)

Concerning neck surgery, the technical complexity of the surgical approach described for MTC and parathyroid carcinoma in sporadic forms applies to the familial settings.

In patients with a single pheochromocytoma, unilateral adrenalectomy is indicated. In patients with bilateral pheochromocytomas, the risk of Addisonian crisis associated with bilateral adrenalectomy is particularly high. For this reason, preoperative and postoperative corticosteroid coverage under close monitoring is necessary. Procedures such as subtotal adrenalectomy, to preserve adrenocortical function, are under investigation in order to reduce substantial morbidity and occasional mortality associated with bilateral adrenalectomy for pheochromocytoma. Due to the low frequency of the disease, such procedures should be performed in multicentric controlled clinical trials.

Follow-up: Reference Centre

Complexity

- Adrenocortical Carcinoma

No international recommendations on follow-up are available, except the ESMO guidelines, which were formulated on the basis of personal experience and consensus among panellists rather than on solid evidence. For patients with complete resection of the tumour, regular follow up will include abdominal CT/MRI, thoracic CT and hormone monitoring. In the case of locally advanced or metastatic disease, closer monitoring is required (8 every 12 weeks or less depending on type of treatment) and time to progression represents a major primary endpoint.

- Parathyroid Carcinoma

Close follow-up is required during the first 2 years from initial surgery, because of the higher rate of recurrence during this period. Recurrence can, however, take place up to 15 years after surgery. Thus, long-term follow-up is recommended.

- (Malignant) pheochromocytoma / paraganglioma

Since hormonal control of persistent disease is crucial for quality of life but also to prevent hypertensive crises, regular biochemical evaluation is key in follow-up of hormonally active tumours. In both hormonally active and non-active tumours, treatment effect should be assessed by both conventional (CT, MRI) as well as functional imaging (MIBG, PET). Follow-up interval obviously depends on progression rate of the disease, ranging from re-evaluation every 2 to 6 months. Treatment effect of external radiotherapy is known to be rather slow and even if successful; regression of the tumoral mass is seldom due to fibrosis.

- Pituitary tumours (carcinoma and invasive carcinoma)



Experience in adverse effects of treatment is mandatory.

- Glucagonoma and insulinoma

Since hormonal control of persistent disease is crucial for quality of life, regular biochemical evaluation is key in follow-up of hormonally active tumours. Follow-up interval of conventional imaging obviously depends on progression rate of the disease, ranging from re-evaluation every 2 to 6 months.

- Multiple Endocrine Neoplasia Type 1 (MEN 1)

Frequent evaluation should be performed (at least 1/year) in each patient with biological tests, MRI, Octreoscan.

- MEN 2, familial medullary Thyroid Cancer (FMTC) malignant pheochromocytoma

Patient follow up relies on the procedures necessary for the various manifestations (MTC, Pheochromocytoma hyperparathyroidism), described in the relative sections of this document.

A major issue in the management of MEN 2 relates to the ascertainment of gene carriers. In this respect, a timely and appropriate diagnosis in the patients presenting with one of the MEN 2 related tumours is extremely important. Because of both the high penetrance (90% of MEN2 carriers) and its earlier occurrence, MTC is often the first manifestation of both MEN 2A and 2B. After genetic analysis has been widely applied, the management of MEN 2 patients has registered a tremendous improvement. In fact, the mortality from hereditary MTC was reduced to less than 5% and the rate of death from cardiovascular events related to pheochromocytoma decreased to even a greater extent.

The risk that offspring of MEN 2 affected subjects will eventually develop clinically relevant disease approximates 35%. Moreover, potentially lethal manifestations of the disease, particularly MTC, may occur as early as the age of 6. For these reasons, the identification of the carriers before onset of symptoms is crucial in the management of such families.

About 90% of children managed in this way exhibit evidence of long-term cure. If no mutations are found after full sequencing, then the risk for a familial case is low because 98% of mutations are identifiable. Most mutation-negative patients are managed on a case-by-case basis because data in this area are evolving.

Continued follow-up of all affected or gene “positive” individuals should include annual screening for both medullary cancer by basal or stimulated calcitonin and pheochromocytoma by standard biochemical and imaging techniques.



E. General and specific criteria for Reference Centres

Human Resources and dedicated team

Due to the heterogeneity of affected organs and the peculiarity of initial manifestations (i.e. the hormone excess syndrome) the presence of an **endocrinology team with specific experience endocrine tumours** is a pre-requisite for timely and correct identification of affected patients. In addition, considering the high prevalence of endocrine complications occurring during treatment, the team should be familiar with the endocrine peri-operative and post-surgical management of such conditions,

- For the medical staff, the following competences are necessary:
 - o Endocrinologist with specific competence in endocrine oncology
 - o Nuclear Medicine Specialist dedicated to radioisotope therapy
 - o Oncologist
 - o Surgeon (ORL-head-neck, thoracic, liver, pancreas, urologist, neurosurgeon)
 - o Chemotherapist
 - o Radiotherapist
 - o Radiologist
 - o Interventional imaging specialist
 - o Neuroradiologist
 - o Pathologist
 - o Care coordinator
 - o Gastroenterologist
 - o Clinical Genetics Specialist
- For the para-medical staff, the following competences are necessary:
 - o Psychologists
 - o Reference nurses
 - o Clinical research unit (nursing and administrative support for patient management in clinical trials)



The MOC of the reference centre should fulfill all the following conditions

1. all required disciplines should be represented by at least one specialist involved in endocrine oncology;
2. the coordinator of the MOC should have a documented experience in endocrine cancer management, demonstrated by the following:
 - o clinical research in endocrine oncology;
 - o hospital-based clinical activity
3. 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 fulfillment of the required conditions should be revised at least every 4 years.

Required facilities and equipment

- Advanced Imaging techniques
 - o Endoscopic ultrasonography
 - o Scintigraphy
 - o SPECT/CT
 - o PET / MIBG / somatostatin receptor scintigraphy
 - o OCTREOSCAN
- Gammaknife, Cyberknife
- Ultrasound-guided Fine Needle Aspiration Cytology
- Clinical Laboratory
- Laboratory for pathology
- Radiology/Interventional
- Radiofrequency
- Radiotherapy
- Medical Oncology unit
- Molecular genetic testing
- For familial forms: A number of techniques have been described to search for RET mutations in the blood or tissue of patients. These include direct DNA sequencing, analysis of restriction sites introduced or deleted by a mutation, and gel shift analysis (single-strand conformation polymorphism analysis or denaturing gradient gel electrophoresis).
- Electronic medical record
- Facilities for videoconference



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

Minimal volume of patients

Due to the rarity of the disease, a minimal number of patients cannot be established. It seems reasonable that the number would be established after a 5 year observation of the actual cases treated in each centre fulfilling all other criteria indicated in the present document.

Quality Assurance

- Capacity to propose quality indicators (structure, process, outcomes)
- Exhaustive and reliable information sent to Cancer Registry. 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 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
- Link with a tumour bank
- Participation to national and international networks
- Case reports publication
- Clinical research in the endocrine oncology 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 scientific congresses