NEUROENDOCRINE TUMOURS (NETS)
PREFERRED MODEL OF CARE AND CRITERIA FOR REFERENCE CENTRES
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PREFERRED MODEL OF CARE AND CRITERIA FOR REFERENCE CENTRES

A. Type of cancer

Neuroendocrine tumours (NETs) consist of a spectrum of malignancies that can arise from neuroendocrine cells throughout the body (1).

Historically, there are large differences in terminology, grading and staging systems of these tumours. Today the International Union Against Cancer (UICC), the American Joint Cancer Committee (AJCC) and the World Health Organization (WHO) substantially endorsed the ENETS proposal. A common language is at the basis of this internationally accepted classification. Its simple rules are:

1. The adjective ‘neuroendocrine’ is defined to specifically connote this neoplastic disease, recognizing the expression of neuroendocrine markers in tumour cells;
2. The word ‘neoplasm’ is defined to embrace the whole family of low-, intermediate- and high-grade tumours (neuroendocrine neoplasm, NEN);
3. The term ‘tumour’ (neuroendocrine tumour, NET) is meant for low- to intermediate-grade neoplasms, as previously defined either ‘carcinoid’ or ‘atypical carcinoid’;
4. The word ‘carcinoma’ (neuroendocrine carcinoma, NEC) is meant only for high-grade neoplasms, as previously defined poorly differentiated carcinomas.

This terminology is adopted by the ENETS 2011 Guidelines (2).

This proposal considers all gastroenteropancreatic neoplasms (GEP-NENs), including goblet cell carcinomas of the addendum and all neuroendocrine tumours of the lung, i.e. low- to intermediate-grade neoplasms: typical and atypical bronchial carcinoids, as well as large cell neuroendocrine carcinoma (‘LCNEC’), but NOT small cell lung carcinoma (SCLC) (3).

This proposal does not consider the following neoplasms: Merkel cell tumours (i.e. neuroendocrine neoplasm of the skin) or endocrine tumours, i.e. tumours that generate steroid hormones (feochromocytoma, adrenal tumours) or thyroid cancer and paraganglioma.

NENs can be a part of genetic syndromes, such as Multiple Endocrine Neoplasia type 1 or 2 and Von Hippel Lindau disease. Therefore this proposal includes a chapter on genetic counselling.

B. Short description of the cancer

Neuroendocrine neoplasms can occur throughout the body. For this reason and because of the different terminologies used in the past, it is difficult to obtain clear epidemiological data. An analysis of the American SEER database in 2008 noted a (29 year limited duration) prevalence of 35/100 000. There was an increase in incidence over time, likely caused by improvements in classification of these tumours. The total number of patients is probably underestimated in the Cancer Registry since only patients with malignant NENs are included. Data on many small, benign appearing tumours are likely excluded from the registries.

Histological evidence of invasion of a basement membrane defines malignant behaviour for most epithelial malignancies. The definition of malignant behaviour for NEN however, is more complex. These tumours are characterized by their ability to produce and secrete (glyco)-peptide hormones and biogenic amines. Therefore, these tumours can cause characteristic hormonal syndromes. The tumours are called neuroendocrine neoplasm because of the marker proteins that they share with the neural cell system. These markers are synaptophysin and neuron-specific enolase. Other markers that also recognise the neuroendocrine phenotype are the chromogranins A, B and C.
Most NENs are more indolent than other epithelial malignancies. Their prognosis largely depends on the site of the primary tumour, the stage of the disease and the grade (Ki67 index or mitotic count, Rindi grade, cfr. Addendum 1). However, NENs can be aggressive and resistant to therapy (1, 2, 4, 5).

C. Model of care pathway suggested for adult patients with neuroendocrine tumours

<table>
<thead>
<tr>
<th>Model of care pathway</th>
<th>Preferred model</th>
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<tbody>
<tr>
<td>1. Model 1: Reference Centres exclusively (from diagnosis to follow-up). Once there is a suspicion of NETs or NET 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.</td>
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<tr>
<td>4. Model 2: Shared care between Reference Centres and peripheral hospitals. Part of the care pathway is performed in the Reference Centre and for another part of the care pathway the patient is referred (back) to the regional hospital</td>
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</table>

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

We propose a model with 3 types of centres or 3 types of care:

- the peripheral centre/hospital with a program in oncology
- the reference centre/network that has certain minimum requirements to fulfil (cfr. E)
- expert centres that possess experience in certain rare indications or treatment techniques (cfr. E). A centre can be an expert centre for transplantation, but not for peptide receptor radionuclide therapy (PRRT) or vice versa. Therefore we cannot propose a structure in 3 layers. Every reference centre however, has to identify the expert centre(s) it collaborates with for each specific kind of expert care, i.e. genetic counselling, peptide receptor radionuclide therapy (PRRT), transplantation, surgery for intra-abdominal recurrence, specific pulmonary surgical interventions (sleeve resections for centrally-located endobronchial carcinoid tumours, complete mediastinal lymph node resection), cardiac surgery.
**Phase of the Clinical Pathway** | **Reference Centre** | **Peripheral centre**
--- | --- | ---
MOC | X (all patients) | X (first discussion)
Diagnostic confirmation (AP and/or medical imaging) | X (both for AP and medical imaging: review in the reference centre is necessary, but additional techniques may be performed in the peripheral centre if it is equipped to do so) | X

**Comprehensive AP diagnosis** | X |

**Therapeutic modalities**
- surgery | X (complex surgery, e.g. pancreatic surgery, planned surgery on patients with hormonal hypersecretion syndromes should be performed in a Reference Centre – liver transplantation, specific pulmonary surgical interventions and surgery for intra-abdominal recurrence should be performed in expert centres) | X
- treatment of hormonal syndromes | X | X
- follow-up and treatment of cardiological complications | X (with cardiac valve surgery in an expert centre) |
- medical treatment | X (discussion of treatment and medical treatment in clinical trials) | X (medical treatment guided by oncologist or gastroenterologist/pulmonologist with a certificate showing specific competence in oncology)
- embolisation and/or PRRT | X ((embolisation in Reference Centres, PRRT in expert centres) |
- diagnosis of a genetic syndrome and counselling | X (identification of patients that need genetic counselling will be performed in Reference Centres; diagnosis and counselling will be performed in expert centres) |

**Follow-up**
- of a lesion before surgery/treatment | X | X
- after treatment | X | X
- Relapse | X | X
Multidisciplinary Oncological Consult (MOC)

Patients will often be identified in a hospital with a program in oncology and thus will be discussed in the local MOC. However, all patients will have to be presented at MOC in the Reference Centre. The use of TELE-MOC would be of particular interest to achieve this goal. Presentation at MOC in Reference Centres is necessary to identify the following situations:

- Patients who might require additional surgery (on the basis of the pathology report or a review of the blocks), e.g. NET of the addendum or rectum
- Patients who might need better/additional imaging
- Patients with functional hypersecretion syndromes that need follow-up by experienced endocrinologists
- Patients at risk for developing carcinoid heart disease that need specific follow-up and possibly early surgical intervention
- Patients with a pancreatic NET, with liver-limited disease or with a specific presentation, e.g. an intra-abdominal recurrence that is eligible for surgery by an experienced surgeon
- Patients in whom treatment with targeted therapy or treatment in clinical trials can be considered, i.e. all metastatic patients who progress on somatostatin-analogue
- Patients who are eligible for treatment with embolisation techniques, Selective internal radiation therapy (SIRT) or peptide receptor radionuclide therapy (PRRT) within or out of clinical trials
- Patients who need genetic counselling

Diagnostic confirmation

Review in the Reference Centre is necessary, but additional techniques may be performed in the peripheral centre if it is equipped to do so

- Complexity and new approaches
  - Pathology review: The pathology of all NENs should be reviewed by a reference pathologist, linked to one of the expert centres for the following reasons: all neuroendocrine neoplasms should be classified according to a standardized approach including a specific TNM staging and grading of the tumour including ki67 index and/or mitotic count (Rindi grade, cfr addendum1). The tumour grade gives very important prognostic information. Depending on the method (eyeballing versus counting) used and the area inspected (random or a hot spot in the tumour), different results may be presented (6). In specific cases, such as a low-, or intermediate-grade NEN of the addendum, additional surgery may be required after appendectomy. This decision is based on size, but also location, extent into the meso-addendum and other criteria that are often underreported in pathology reports (7). Similar arguments hold true for rectal NEN (8).
  - Radiology review: The choice of imaging procedures varies considerably depending on the patient’s tumour status at presentation. For instance, an image during IV contrast enhancement in the late arterial phase is needed in order to diagnose well-vascularised liver metastases. Sometimes, an additional MRI or nuclear medicine procedures may be required (9).
  - Endoscopic ultrasound (EUS), endoscopic bronchial ultrasound (EBUS) and interpretation of cytology: Sometimes a diagnosis is based on the appearance of a lesion at endoscopic ultrasound and cytology acquired through fine needle aspiration.

  - Facilities and equipment required
    - A Reference Centre has to be equipped with a 1.5 tesla MRI at least.
CT scans for follow-up can be performed in peripheral centres, but have to be performed including scanning during IV contrast enhancement in the late arterial phase. Octreoscan and bone scan can also be performed in peripheral centres, but should only be performed in centres equipped with SPECT/CT.

Reference Centres do not require a FDG-PET/CT or $^{68}$Ga-DOTA-Peptide PET/CT on site. However, they need to have easy access to both imaging modalities. FDG-PET/CT centres are limited in Belgium. $^{68}$Ga-DOTA-Peptide PET/CT requires an onsite gallium-68 generator and dedicated expert personnel (e.g. a radiopharmacist). There are advantages of scale if patients are centralized for this indication, such as better use of the generator and better use of a very short-lived product.

- Professional expertise required both to perform the diagnostic procedure and to interpret the results: the initial diagnosis and imaging can be made in the peripheral centre, but specific expertise is necessary to supervise the quality and completeness of diagnostic work-up, especially in specific cases, mentioned under 2a.

   A second reading of the pathology specimen or the radiological images may be needed; therefore a Reference Centre should have at least 2 expert pathologists. The pathologists have to be experienced in reading cytology specimens.

   Additional imaging will sometimes prove to be necessary and depending on what is needed, will be performed in the peripheral centre or in the Reference Centre. A Reference Centre needs a team of radiologists with expertise in MRI (with knowledge on specific imaging issues in NEN and targeted therapies; there are currently no existing specific criteria for subspecialisation in radiology) and a specialist in nuclear medicine (who has easy access on a routine basis to $^{68}$Ga-DOTA-Peptide PET/CT and/or octreoscan SPECT/CT in the Reference Centre – and who has knowledge of the indications for PRRT and easy access to an expert centre for PRRT) who are able to give advice on the necessary further examinations.

   A Reference Centre needs a gastroenterologist that performs endoscopic ultrasound (EUS) with specific expertise (the criteria for this training are under discussion in the training centres for gastroenterology).

   A Reference Centre needs a pulmonologist that performs endobronchial ultrasound (EBUS-TBNA) and invasive endobronchial treatment.

**Comprehensive AP diagnosis**

The working group refers to the structure as proposed by the pathology laboratories (see synthesis).

**Therapeutic modalities**

**Surgery: Hospital with a program in oncology or Reference Centre, depending on the specific type of surgery.**

- Complexity, new therapeutic strategies

**Surgery that has to be performed in Reference Centres**

Patients with a pancreatic NET will need to have a surgery performed by an experienced pancreatic-hepatobiliary surgeon, with expertise in enucleation techniques (10). The criteria for the subspecialisations in surgery are under discussion (see also criteria for Whipple resections in working group on pancreatic cancer).

Specific care is necessary in patients with hormonal hypersecretion syndromes, to provide appropriate treatment and to avoid sometimes life-threatening crises that may occur during manipulation (10). Anaesthesiologists should be aware of these risks and the interventions required.

Patients with liver-limited disease should also be discussed with an experienced hepatobiliary surgeon, working in the reference centre.
Surgery that has to be performed in Expert Centres

Transplantation may be an option in specific cases (11).

Patients that have an intra-abdominal recurrence need care in an Expert Centre by a surgeon with experience in NEN and debulking surgery.

Specific pulmonary interventions (sleeve resections for centrally-located endobronchial carcinoid tumours, complete mediastinal lymph node resection), need to be performed in expert centres (12).

Surgery that can be performed in Peripheral Centres

Surgery for all indications not specified above can be performed in peripheral centres. As for the discussion on additional surgery in appendiceal or rectal NEN (cfr.2a): the surgical procedure that has to be performed does not require specific expertise and therefore can be performed in the peripheral centre.

- Facilities and equipment required: For a Reference Centre, specifically trained surgeons, appropriate intensive care staffing and specialists in interventional radiology (for CT-guided punctures and angiography) are necessary on a 24/7 base.
- Expertise required to perform the treatment: A Reference Centre needs an experienced pancreatic-hepatobiliary surgeon, with expertise in enucleation techniques (10). The criteria for the subspecialisations in surgery are under discussion (see also criteria for Whipple resections in working group on pancreatic cancer). A Reference Centre also needs anaesthesiologists that are aware of risks in patients with hormonal hypersecretion syndromes.
- Paramedical expertise required: psychologists, nurses and dieticians with experience in this field of surgery and this type of tumour.

Treatment of hormonal syndromes: Reference Centre

- Complexity, new therapeutic strategies: in the past, patients frequently died from the untreated effects of the hormone excess state, therefore it is important that this is controlled. It can be accomplished in most cases by using a combination of medical, surgical and radiological approaches. Localisation of the primary tumour can prove to be difficult and sometimes requires selective angiography and embolisation techniques, functional localisation methods, nuclear imaging, endoscopic ultrasound or various intraoperative localization methods (13).

Patients with a carcinoid syndrome that can be treated with somatostatin analogues can receive their treatment in a peripheral centre in close collaboration with the Reference Centre.

- Facilities and equipment required: A Reference Centre has to be equipped with a 1.5 tesla MRI at least. Every Reference Centre has to have easy access to FDG-PET/CT and 68Ga-DOTA-Peptide PET/CT.
- Expertise required to perform the treatment:
  - a team of endocrinologists with specific expertise in hormonal hypersecretion and paraneoplastic syndromes,
  - surgeons that have experience in localizing small tumours in the duodenum and the pancreas,
  - anaesthesiologists who know how to handle a carcinoid crisis,
  - gastroenterologists with experience in EUS (cfr. 2c),
  - a gastroenterologist or pneumologist with a specific competence in oncology or a medical oncologist with experience in GI oncology and a vast experience in NET,
  - radiologists and experts in nuclear medicine (cfr. 2c).
Paramedical expertise required: dieticians and psychologists with knowledge on hormonal hypersecretion syndromes

Follow-up and treatment of cardiological complications: follow-up should be performed in Reference Centres, surgical treatment should be performed in Expert Centres

- Complexity, new therapeutic strategies: Carcinoid heart disease has an important impact on the prognosis of these patients. Early diagnosis and treatment is mandatory in each patient with a carcinoid syndrome (14).

- Expertise required to perform the treatment: Follow-up should be organized by cardiologists in Reference Centres. Personal experience with at least 200 echocardiographies per year is recommended for those evaluating patients with carcinoid heart (14). Surgical valve replacement should be performed in a very limited number of centres that acquire specific expertise (is more difficult than valve replacement in non-carcinoid patients) (15). A Reference Centre needs to have easy access to an Expert Centre that performs surgical valve replacement in this specific situation.

Medical treatment: Reference Centre or Peripheral Centre

All treatment options should be discussed in the Reference Centre at every progression. The medical treatment itself however, can be provided in a hospital with a program in oncology or a Reference Centre.

- Complexity, new therapeutic strategies: All possible treatment options, including surgery, PRRT and medical treatment have to be discussed at every progression (16). Specific radiologic evaluation for response evaluation may be necessary (9). For all these reasons, patients have to be discussed in the Reference Centre upon suspicion of progression.

Patients that are eligible for medical treatment in clinical trials have to be identified. Patients should be encouraged to participate to trials in Reference Centres, whenever appropriate.

Medical treatment outside of clinical trials can be provided in a hospital with a program in oncology, provided the medication is prescribed by an oncologist or a gastroenterologist or pulmonologist who obtained a certificate showing specific expertise in oncology. Medical treatment involves the use of chemotherapy or cytotoxic drugs and also newer molecular targeted agents including those that targeted angiogenesis and the mammalian target of rapamycin (mTOR) pathway (17, 18). Most of these newer agents are oral drugs. There is ample evidence in literature – although mostly in other tumour types - that patient outcome on treatment with tyrosine kinase inhibitors and other oral drugs is largely influenced by patient compliance and handling of side effects (19).

- Paramedical expertise required: Because of the existing evidence in literature that patient outcome on treatment with tyrosine kinase inhibitors and other oral drugs is largely influenced by patient compliance and handling of side effects (19), Reference Centres are encouraged to work within a multidisciplinary team, including nurses and/or pharmacists with knowledge of side-effects, drug-interactions and specific importance of compliance (20). A multidisciplinary team should also include psychologists and dieticians. Being diagnosed with cancer can be very stressful, and even overwhelming, for both the patient and the family. The quality of life (physical, emotional, social and cognitive and role functioning) of both patient and close family is under a lot of strain. This all seems to be even more true for those patients being diagnosed with a rare type of cancer (21). Patients with NET describe long term effects of their treatment, both physically and mentally. The uncertain and chronic nature of the disease, makes coping extra difficult (22, 23). Multidisciplinary cancer clinics focusing on a particular cancer type, will more effectively enlarge knowledge, efficiency and patient outcomes, even on a psychological level (e.g. better coping thanks to better support) (24, 25).
**Embolisation and/or PRRT: Reference Centre and Expert Centre for PRRT**

- Complexity, new therapeutic strategies: The use of embolisation techniques should be evaluated in patients with liver metastases (10). All possible treatment options, including surgery, (chemo-)embolisation (26), selective internal radiation therapy (SIRT) (27), PRRT and medical treatment have to be discussed at every progression (16).
- Facilities and equipment required: easy access to an expert centre for PRRT (28), a unit for interventional radiology.
- Expertise required to perform the treatment: interventional radiologists, specialists in nuclear medicine: follow-up after embolisation or PRRT has to be performed in Reference Centres because of the specific changes that may take place after these interventions (29, 30).

**Diagnosis of a genetic syndrome and counselling: Expert Centre**

Patients that need further work-up for diagnosis of a genetic syndrome and counselling will be identified through discussions at MOC in the Reference Centres. The patients that need to be referred are for instance patients at risk for MEN-1.

Multiple endocrine neoplasia type I (MEN1) is an autosomal dominant cancer syndrome affecting primarily parathyroid, enteropancreatic, endocrine and pituitary tissues. Less commonly associated tumours include carcinoids, lipomatous tumors, angiofibromas, thyroid adenomas and adrenocortical adenomas. Disease-specific mortality in MEN1 is arising largely from the effect of malignant carcinoid and pancreatic islets tumors. MEN1 is caused by germline mutations in MEN1, a tumour suppressor gene encoding a nuclear protein named menin. MEN1 accounts for ~ 10% of patients with parathyroid adenomas occurring before the age of 30 years (or multigland parathyroid disease). In clinical practice, screening for MEN1 should be undertaken in any patient <30 years of age with one MEN1-associated tumours or in any patient with 2 or more tumors.

- Complexity, new therapeutic strategies: In about 70% of MEN1 cases, truncating germline mutations in the MEN1 are found, depending on the range of molecular techniques applied in the analysis. Approximately, 25% are nonsense mutations, approximately 40% are frameshift deletions or insertions, 5% are in-frame deletions or insertions, and 10% are splice site mutations. Techniques relying on PCR amplification, including sequencing, will miss a significant minority of them (deletions and rearrangements that involve the PCR primer binding sites are found in about 10% of the patients). Therefore, the optimal mutation detection strategy should include a combination of the traditional PCR-based methods (like sequencing) and a method to detect large deletions and rearrangements (such as MLPA, multiplex-ligation dependent probe amplification).
- Facilities and equipment required: Genetic counseling of MEN1 patients and their family members should be performed in one of the 8 centres for Human Genetics by a multidisciplinary team including clinical geneticists and psychosocial support. It can occur in several contexts: at the time of diagnosis of MEN1, at the time a MEN1 patient is considering reproductive options, at the time the MEN1 patient is having his or her children to be screened, and at the time that an at-risk person is considering genetic testing. Genetic testing of MEN1 is available in different Centres of Human Genetics in compliance with International Organization for Standardization (ISO) 15189, becoming in 2014 an obligation for assuring laboratory quality. The laboratory offering the molecular test should be equipped to detect point mutations as well as intragenic rearrangements.
- Paramedical expertise required: Psychosocial support in a context of genetic disease.
Follow-up: Reference Centre or Peripheral Centre

Elements for follow-up have been discussed in the previous paragraphs (e.g. 2a, 4: chapter on medical treatment) and depending on the situation will be possible in Peripheral Centres (hospitals with a program in oncology) and/or Reference Centres. Follow-up after embolisation or PRRT has to be performed in Reference Centres because of the specific changes that may take place after these interventions (29, 30).

Relapse: Reference Centre or Expert Centre

Patients with relapse will have to be discussed in Reference Centres, in order to choose the correct imaging modality and/or medical or surgical treatment, as stated in the previous paragraphs. Depending on the site of relapse, treatment can be performed in a hospital with a program in oncology (e.g. as stated in 4: chapter on medical treatment), a Reference Centre (embolisation, pancreatic surgery,...) or an expert centre (intra-abdominal recurrence, transplantation, PRRT,...)

E. General and specific criteria for Reference Centres

Human Resources and dedicated team

A Reference Centre will need:

- At least 2 expert pathologists (with knowledge on cytology, the importance of ki67 staining and molecular technology),
- A team of radiologists with expertise in MRI (with knowledge on specific imaging issues in NEN and targeted therapies; there are currently no existing specific criteria for subspecialisation in radiology),
- An expert in nuclear medicine (who has easy access on a routine basis to 68Ga-DOTA-Peptide PET/CT and/or octreoscan SPECT/CT in the Reference Centre itself – and who has knowledge of the indications for PRRT and easy access to an expert centre for PRRT),
- A dedicated oncologist or a gastroenterologist/pulmonologist who obtained a certificate showing specific expertise in oncology, with experience in NET, targeted therapies,...
- A team of endocrinologists with experience in hormonal hypersecretion and paraneoplastic syndromes,
- An interventional radiologist,
- A gastroenterologist with expertise in EUS (the criteria for this training are under discussion in the training centres for gastroenterology),
- A pulmonologist who performs endobronchial ultrasound (EBUS-TBNA) and invasive endobronchial treatment,
- A dedicated cardiologist with expertise in follow-up of carcinoid heart disease and easy access to an expert centre that performs surgical valve replacement in this specific situation,
- A surgeon with experience in hepatobiliary and liver surgery (the criteria for this expertise are under discussion in other reference groups) and has easy access on a routine basis to a centre for liver transplantation,
- Anaesthesiologists with knowledge on how to handle a carcinoid crisis,
Some elements really need a very specific expertise and are therefore not necessary in Reference Centres. However, **EXPERT centres** that are specialised in these treatments have to be identified:

- Genetic counselling
- PRRT
- Transplantation
- Cardiac surgery
- Specific pulmonary surgical interventions
- Expert surgery for intra-abdominal recurrence

**Required facilities and equipment**

- A pathology lab that is equipped for cytology, ki67 staining and molecular technology,
- A reference centre has to be equipped with a 1.5 tesla MRI at least,
- A department of nuclear medicine with easy access on a routine basis to $^{68}$Ga-DOTA-Peptide PET/CT and/or octreoscan SPECT/CT in the reference centre,
- An unit for interventional radiology that provides 24/7 care,
- An ICU with experience in handling patients after hepatobiliary and liver surgery,
- Peroperative ultrasound.

**Patient centred care**

- Waiting and throughput times: 2 weeks to first visit
- Support services for the patient: oncologic nurse coordinator
- National and international networking with other Reference Centres: Clear links between the Reference Centres and the expert centres have to be defined, communication through tele-MOC or other teleconferences will be necessary

**Minimal volume of patients**

No clear numbers exist in literature. In order to be certified as a Reference Centre for ENETS (European Neuroendocrine Tumor Society), a centre has to have at least 80-100 new patients a year. This figure is deemed too high. In some countries a cut-off of 25-35 patients is cited. It is estimated that there are around 400 new patients per year in Belgium, although we do not have real precise data on the incidence/prevalence of NEN in Belgium (including the ‘more benign’ lesions).

We propose that a minimum number of 30 individual new patients (incidence) has to be discussed and seen in a Reference Centre at an annual basis - and at least half of this number of patients has to be treated in the Reference Centre itself.
Quality Assurance

- Capacity to propose quality indicators: a Reference Centre should be able to provide procedures for specific situations in all types of NEN.
- A Reference Centre has to provide the cancer registry exhaustive and reliable information.
- A Reference Centre has to work in compliance with the existing ENETS guidelines and keep documentation of deviations.
- Involvement in quality initiatives: a Reference Centre should strongly recommend patients to participate in the DNET-registry.
- A Reference Centre should provide a report every 3-5 years ensuring transparency: patient numbers, treatment and outcome data, records of collaboration and continuous education of the medical professionals involved in patient care.

Research and other scientific activities

- Involvement in clinical studies (RCTs, Cohort studies, translational studies), participation rate in clinical trials.
- Publications in peer-reviewed journals, grants, ...
- Possibility of access to a tumour bank and/or blood bank has to be encouraged.
- Development of clinical practice guidelines for diagnosis and care.

Educational activities: Teaching and dissemination

- Involvement in training and continuous education programs has to be reported every 3-5 year.
- Organisation / communication in scientific congresses.

Additional comments

Funding for second opinion by pathologists and radiologists and specialists in nuclear medicine has to be provided.
Funding for tele-MOC is necessary in order to avoid unnecessary trips by multiple health care professionals in Reference and Expert Centres.

References


**Addendum 1**

In addition to the site-specific TNM classifications, a three-tiered grading system of GEP-NENs based on mitotic count and ki67 index and a standardised diagnostic procedure were suggested. This grading system is often referred to as Rindi grade, after the original author.

At pathological examination, one has to count the number of mitoses per 10 high power fields (HPF) (= 2 mm², one has to count at least 40 fields at 40x magnification in the areas of the tumour with highest mitotic density) and/or out of 2000 tumour cells the % of cells that stain for ki67, i.e. a MIB1 antibody (a marker for proliferation). Once again the counting has to be performed in the areas of the tumour with the highest nuclear labelling.

Grade 1 NETs have a mitotic count <2/10 HPF and a ki67 index ≤2. Grade 2 NETs have a mitotic count in between 2 and 20 and a ki67 index in between 3 and 20. Grade 3 NENs have a mitotic count > 2/10 HPF and a ki67 index above 20.