UCLouvain

Faculté de médecine et médecine dentaire

Management of pancreatic neuroendocrine neoplasms in “real life” at Cliniques Saint-Luc: analysis based on the Belgian DNET registry

Auteur : Grégoire Brassel

Promoteur : Professeur Ivan Borbath

Lecteurs :

Professeur Abdenor Badaoui

Docteur Astrid De Cuyper

Docteur Timon Vandamme

Année académique 2020 - 2021

Master en médecine à finalité spécialisée

Remerciements

En premier lieu, j'aimerais remercier mon promoteur, le Professeur Ivan Borbath, pour m'avoir donner l'opportunité de réaliser ce travail. Je lui suis reconnaissant pour le temps, la confiance et l'aide précieuse qu'il m'a accordés.

Je voudrais aussi remercier Alexandre Rossez pour son aide et sa flexibilité lors de l'extraction des données du registre DNET.

J'aimerais également remercier Kiswendsida Sawadogo pour ses analyses statistiques précises, ainsi que ses explications claires et accessibles.

Je souhaiterais enfin remercier ma famille et mes amis pour m'avoir soutenu tout au long de ce travail.

Table of contents

1. Abstract

1.1 Abstract in english

Background and Objectives: The management of pancreatic neuroendocrine neoplasms (PNENs) is not well established especially for unresectable metastatic tumors. There is a large choice of medical treatments, but their sequencing is unclear due to the lack of randomized clinical trials comparing them, the rarity of this disease, the heterogeneity of patient populations studied and the variability of response criteria. Our initial objective, which was to clarify this treatment sequencing, had to be revised in view of the small cohort of patients at our disposal. The final objective of this study is therefore to assess the management of patients followed at the Cliniques Universitaires Saint-Luc by evaluating their overall survival, the prognostic factors impacting it and the effectiveness of the two treatments most commonly used in first line, i.e. excision surgery and active surveillance.

Material and Methods: Data from a maximum of patients with PNEN, registered in the Digestive NeuroEndocrine Tumors (DNET) registry and followed up at Cliniques Saint-Luc, were collected between September 2019 and March 2021 to reach a total of 46 patients included in the registry. The data involved were related to the epidemiology, clinic, diagnosis, histology and treatment of PNEN. Some of these were analysed using Kaplan-Meier curves to determine overall survival (OS) for the whole population and progression-free survival (PFS) for patients whose tumor was resected or actively monitored. Overall survival was then compared between WHO grades and between ENETS stages using logrank and Bonferroni tests. Cox proportional hazard model was also used in two uni- and multivariate analysis to identify prognostic factors for OS and PFS.

Results: The median OS of all patients was not reached, and their 5-years overall survival rate was 98% (95% CI, 85.6 to 99.7). Subjects with grade 3 PNENs had significantly shorter OS than those with grade 1 (5-years OS rates 80% vs. 100%; $p = 0.015$). The 5-years OS rates of locally advanced PNENs and stage IV PNENs were estimated to be 100% (95% CI, 100 to 100) and 92% (95% CI, 56.6 to 98.9), respectively. This difference was not significant. A statistically significant difference in OS between stages I and II ($p = 0.045$) and stages III and II ($p = 0.042$) was detected. This is probably due to sampling fluctuation and the small number of subjects in these groups. Independent prognostic factors identified were Ki-67 proliferation index, grade 3 and stages higher than I. The first one has an impact on OS while the others influence PFS. The 5-year PFS rate in the surgery and active surveillance subgroups was 45% (95% CI, 21.7 to 65.9) and 75% (95% CI, 45.9 to 89.9) respectively. The median PFS of patients with resected tumor was 51.8 months (95% CI, 15.7 to not estimable).

Conclusion: Our results suggest that patients with PNENs followed at Cliniques Saint-Luc have good survival. When indicated, surgical resection and active surveillance delay disease progression.

1.2 Résumé en français

Contexte et Objectifs : La prise en charge des néoplasies neuroendocrines du pancréas (PNENs) n'est pas toujours bien établie en particulier pour les tumeurs métastatiques irrésécables. Il existe un vaste choix de traitements médicaux mais leur séquençage est imprécis à cause du manque d'essai clinique randomisé les comparant entre eux, de la rareté de cette maladie, de l'hétérogénéité des populations de patients étudiées et de la variabilité des critères de réponse. Notre objectif initial qui cherchait à préciser cette séquence thérapeutique a dû être révisé face à la faible cohorte de patients dont nous disposions. L'objectif final de cette étude est donc d'apprécier la prise en charge des patients suivis aux Cliniques Universitaires Saint-Luc en évaluant leur survie globale, les facteurs pronostiques impactant celle-ci et l'efficacité des deux traitements les plus utilisés en première intention, à savoir la chirurgie d'exérèse et la surveillance active.

Matériel et Méthodes : Les données d'un maximum de patients atteints d'une PNEN, inscrits dans le registre des Digestive NeuroEndocrine Tumors (DNET) et pris en charge aux Cliniques Saint-Luc, ont été collectées entre septembre 2019 et mars 2021 pour atteindre un total de 46 patients inclus dans le registre. Les données concernées étaient relatives à l'épidémiologie, la clinique, le diagnostic, l'histologie et au traitement de la PNEN. Une partie d'entre elles ont été analysées en utilisant les courbes de Kaplan-Meier afin de déterminer la survie globale (SG) de toute la population et la survie sans progression (SSP) des patients dont la tumeur a été réséquée ou est surveillée activement. La survie globale a été comparée entre les grades OMS et entre les stades ENETS grâce aux tests de logrank et de Bonferroni. La régression de Cox a aussi été utilisée dans deux analyses uni- et multivariées pour identifier les facteurs pronostiques de la SG et de la SSP.

Résultats : La médiane de la SG de l'ensemble des patients n'a pas été atteinte et leur taux de SG à 5 ans s'élevait à 98% (IC à 95%, 85.6 à 99.7). Les sujets avec une PNEN de grade 3 avait une SG significativement plus courte que ceux de grade 1 (taux de SG à 5 ans 80% vs 100% ; $p = 0.015$). Les taux de SG à 5 ans de l'ensemble des stades I à III et du stade IV étaient respectivement estimés à 100% (IC à 95%, 100 à 100) et 92% (IC à 95%, 56.6 à 98.9). Cette différence n'était pas significative. Une différence statistiquement significative de la SG entre les stades I et II ($p = 0.045$) et les stades III et II ($p = 0.042$) a été décelée. Elle résulte probablement d'une fluctuation d'échantillonnage exacerbée par le faible nombre de sujets dans les différents groupes. Les facteurs pronostiques identifiés étaient l'index de prolifération Ki-67, le grade 3 et les stades supérieurs à I. Le premier a un impact sur la SG alors que les autres influencent la SSP. Les taux de SSP à 5 ans dans les sous-groupes chirurgie et surveillance active étaient respectivement de 45% (IC à 95%, 21.7 à 65.9) et 75% (IC à 95%, 45.9 à 89.9). La SSP médiane des patients opérés était de 51.8 mois (IC à 95%, 15.7 à une valeur inestimable).

Conclusion : Nos résultats suggèrent que les patients atteints d'une PNEN et suivis aux Cliniques Saint-Luc ont une bonne survie. La chirurgie d'exérèse et la surveillance active retardent la progression de la maladie, lorsque ces modalités thérapeutiques sont indiqués.

2. List of abbreviations

5-FU	5-fluorouracil
AJCC	American joint committee on cancer
BGDO	Belgian group of digestive oncology
CAPOX	Capecitabine + oxaliplatin
CgA	Chromogranin A
CGH	Comparative genomic hybridization
CT	Computed Tomography
DOTA	1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTANOC	DOTA-(1-Nal^3)-octreotide
DOTATATE	DOTA-(Tyr^3)-octreotate
DOTATOC	DOTA-(Tyr^3)-octreotide
EGFR	Epidermal growth factor receptor
ENETS	European neuroendocrine tumor society
EUS	Endoscopic ultrasonography
FNAB	Fine-needle aspiration and biopsy
FOLFIRI	Folinic acid + fluorouracil + irinotecan
FOLFOX	Folinic acid + fluorouracil + oxaliplatin
HCG	Human chorionic gonadotropin
HPF	High power field
HR	Hazard ratio
IFN-α	Interferon-alpha
IGFR	Insulin-like growth factor receptor
LAR	Long acting release
LT	Liver transplantation
MEN1	Multiple endocrine neoplasia type 1
MiNEN	Mixed neuroendocrine non neuroendocrine neoplasm
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NEC	Neuroendocrine carcinoma
NEN(s)	Neuroendocrine neoplasm(s)
NET(s)	Neuroendocrine tumor(s)
NF-PNET(s)	Non-functional pancreatic endocrine tumor(s)
NSE	Neuron specific enolase
ORR	Objective response rate
OS	Overall survival
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
pEGFR	Phosphorylated epidermal growth factor receptor
PNET(s)	Pancreatic neuroendocrine tumor(s)
PET/CT	Positron emission tomography/computed tomography
PFS	Progression-free survival
PRRT	Peptide receptor radionuclide therapy
PTH-rp	Parathyroid hormon-related protein

RFA	Radiofrequency ablation
SIRT	Selective internal radiation therapy
SRI	Somatostatin-receptor imaging
SSA	Somatostatin analogue
SSTR	Somatostatin receptor
STZ	Streptozocin
TACE	Transcatheter arterial chemo-embolization
TNM	Tumor-lymph node-metastasis
US	Ultrasonography
VEGF	Vascular endothelium growth factor
VEGFR	Vascular endothelium growth factor receptor
vHL	von Hippel-Lindau disease
VIP	Vasoactive intestinal polypeptide
WHO	World health organization

3. Introduction

3.1 Pancreatic neuroendocrine neoplasms

3.1.1 Pathology

3.1.1.1 Definitions

Pancreatic Neuroendocrine Neoplasms (PNENs) are neoplasms emerging from the endocrine cells of the pancreas and characterized by the expression of molecular markers, including neuron specific enolase (NSE), chromogranin A (CgA) or synaptophysin. These proteins define the neuroendocrine origin of the tumor cells. NENs can arise from many organs including gastrointestinal tract, pancreas, thymus, lung, and female reproductive organs. Among NENs, there are two types: the "functional" tumors and the "non-functional" tumors. (1; 2)

The functional tumors have the ability to synthesize, store and secrete a variety of peptides and neuroamines, leading to the development of distinct clinical syndromes, such as the carcinoid syndrome (midgut tumors and rarely PNENs), refractory hypoglycemias (insulinomas), the Zollinger-Ellison syndrome (gastrinomas), diabetes associated with a necrolytic migratory erythema (glucagonomas), large-volume diarrhea (VIPomas), and the clinical syndrome of somatostatinomas. These syndromes are quite rare, furthermore it is even rarer that patients present with all features of each syndrome. (1; 3; 4)

The non-functional NENs do not show clinical symptoms of hormonal hypersecretion although they may exhibit immunohistochemical positivity for hormones and neuropeptides or neurotransmitters. For these reasons, non-functional NENs are also called non-syndromic ones. The majority of PNENs are non-functional, with a proportion of up to 80% (5; 6).

3.1.1.2 Histopathological classification

The 2017 WHO classified GEP-NENs into NETs grade 1 (G1), NETs grade 2 (G2), NETs grade 3 (G3) and NECs grade 3, on the basis of differentiation status, mitotic count and Ki-67 index (Table 1). Mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs) consist of both neuroendocrine neoplasms and non-neuroendocrine neoplasms components, each composing at least 30% of the entire tumor. (7)

Since the introduction of 2010 WHO classification, the term "neuroendocrine carcinoma" has been reserved to poorly differentiated endocrine neoplasms whereas the well-differentiated endocrine tumors have been named "neuroendocrine tumors". Therefore, all neuroendocrine tumors, well- or poorly differentiated, have been designed under the term of "neuroendocrine neoplasms" but they are generally called neuroendocrine tumors by misuse of language. (2; 7; 8)

PNETs G1 have a well-differentiated morphology, a mitotic count < 2/10 high power fields and Ki-67 index < 3%. PNETs G2 have a well-differentiated morphology, a mitotic count 2-20/10 HPFs and/or Ki-67 index 3-20%. Both NETs G3 and NECs G3 have a mitotic count > 20/10 HPF and/or a Ki-67

labelling index > 20%. They are distinguished by their morphology. The first one is well differentiated while the second one has a poorly differentiated morphology. NECs G3 are further divided in small cell and large cell types. (7)

Table 1: 2017 WHO classification of pancreatic neuroendocrine neoplasms (7)

	Differentiation status	Mitotic count	Ki-67 labeling index
NET G1	Well-differentiated	< 2	< 3 %
NET G2	Well-differentiated	2-20	3-20 %
NET G3	Well-differentiated	> 20	> 20 %
NEC G3	Poorly-differentiated • Small cell • Large cell	> 20	> 20 %
Mixed neuroendocrine non neuroendocrine neoplasm (MiNEN)			

3.1.1.3 Genetics

Most NF-PNENs are sporadic but they can be a component of a hereditary tumor syndrome such as MEN1, vHL, neurofibromatosis type 1 or tuberous sclerosis complex. They occur in approximately 80% of individuals with MEN1. (9) This syndrome is inherited via an autosomal-dominant pattern. Sometimes nesidioblastosis-like features are the hallmark of pancreatic involvement in this syndrome. The mutation responsible is located in MEN1 gene, which is placed on the long arm of chromosome 11 region 11q13. (10; 11) This gene encodes for the menin protein, a nuclear protein interacting with several cytoplasmic proteins involved in transcriptional regulation, genome stability and cell division. NF-PNENs and functional PNENs can occur concurrently. (2; 12) Up to 16% NF-PNENs are part of the von Hippel-Lindau syndrome and frequently coexist with pheochromocytomas and hemangioblastomas in the cerebellum and retina. This genetic disease is autosomal dominant and has almost complete penetrance. The chromosome 3 region 3q25 carries the vHL gene that is mutated in all patients. (13; 2; 14)

3.1.2 Epidemiology

PNENs represent about 1-2% of all pancreatic tumors and their incidence is $\leq$ 1 case per 100 000 individuals per year. (15; 16) There is a difference between the prevalence of incidental microadenomas (defined as NF-PNENs with < 0,5 cm in size) and that of clinical relevant NF-PNENs. Indeed, microadenomas rarely come to clinical attention. Their prevalence range from 0,4 to 1,5% according to autopsy studies whereas clinically relevant NF-PNENs have an incidence of 3.5 to 4 per million/year. (17) The incidence of the latter has increased owing to the development of new and more sensitive imaging techniques. NF-PNENs affect equally both sexes with a male to female ratio of 1:1.15. The age at diagnosis stretches from 12 to 79 with a mean age of 50 years. NF-PNENs in patients with MEN1 occur at younger age. (2; 18)

3.1.3 Clinical presentation

As we said before, the clinical presentation of PNENs is divided into 2 broad categories : functional PNENs and NF-PNENs. (1; 2)

Functional PNENs presents with a defined clinical syndrome secondary to hormone hypersecretion. They represent a minority of PNENs. The Whipple triad (hypoglycemias, neuroglycopenic symptoms, and rapid reversal of symptoms with administration of glucose) is characteristic of insulinomas. Gastrinomas lead to symptoms of Zollinger-Ellison syndrome (reflux, refractory peptic ulcer disease, and secretory diarrhea). The symptoms of glucagonoma are a migratory necrolitic erythema, diabetes, depression and deep vein thrombosis. VIPomas are characterized by considerable watery diarrrhea, which may lead to deshydratation and electrolyte abnormalities. Somatostatinomas may present with diabetes mellitus, gallbladder disease, diarrhea, weight loss, and steatorrhea. In exceedingly rare cases, PNENs may manifest as carcinoid syndrome (characterized by diarrhea, flushing, carcinoid heart disease and asthma) secondary to serotonin hypersecretion. (3; 4)

NF-PNENs are characterized by the absence of clinical symptoms related to hormonal hypersecretion. Therefore, these lesions are usually diagnosed late in the course of the disease. The presenting clinical symptoms are usually due to loco-regional effects of the tumor mass with local invasion and/or distant metastases. Incidentally, 80% are present with synchronous liver metastases at the time of diagnostic. The major presenting clinical symptom is abdominal pain, which appear in 35 to 70% of cases. (19) Followed by weight loss (20-35%); anorexia and nausea (45%) are also common presenting features. Finally, intra-abdominal haemorrhage (4-20%) and/or jaundice (17-50%) can be presenting clinical signs in some instances. (2; 19)

3.1.4 Diagnostic Procedures

3.1.4.1 Imaging

Imaging is used either to determine the extent of disease spread in patients with a biopsy proven PNEN or to identify the likely primary site of disease in patients with metastatic disease. Cross-sectional imaging techniques, such as multiphasic computed tomography scan or magnetic resonance imaging, are indicated in these cases. (20) Both techniques are noninvasive and relatively easily available in Belgium. Contrast-enhanced multiphasic CT has a sensitivity of more than 80 %. (21; 22; 23). PNENs and liver metastases enhance during the early arterial phase, with washout during the portal venous imaging phase. (24) This is due to highly vascularized nature of most NENs. CT constitutes also the basic radiological method for surveillance after surgery and for therapy monitoring. Dynamic contrast-enhanced MRI is the gold standard for the evaluation of liver metastases. (25) A study reported a sensitivity of 85% for detecting F-PNENs, (26) and another study showed a greater sensitivity of MRI for liver metastases than either CT or SRI. (27) PNENs are often characterized by low signal intensity on T1-weighted images and by high signal intensity on T2-weighted images. As with CT-scans, early arterial phase imaging is particularly valuable for detection of hypervascular primary tumors and liver

metastases. On MRI, the examination of extended body areas is difficult because of the comparably longer examination procedure.

Endoscopic ultrasonography (EUS) is the most sensitive method to diagnose small, < 1 cm PNENs. (22; 28; 29) It provides high-resolution imaging of pancreas and liver and allows biopsy. EUS requires a highly skilled endoscopist. (20)

Somatostatin-receptor-based imaging (SRI) is recommended for nearly all patients, with the only exception of insulinomas. It can identify an occult primary site and provide information on somatostatin receptor expression, which is predictive of clinical response to therapy with somatostatin analogs and PRRT (30; 20; 31). SRI by ^{68}Ga-DOTATATE PET/CT is preferred over ^{111}In-pentreotide scintigraphy because this tracer offers higher sensitivity. (32) However, SRI for the detection of high-grade tumors may have a lower sensitivity. (33)

NECs have generally low somatostatin receptor expression and higher glucose metabolism than well differentiated PanNENs. In this case, ^{18}FDG PET/CT is better suited than SRI. (25)

3.1.4.2 biochemical testing

The follow-up of patients with PNENs may include tumor markers measurement, such as chromogranin A and pancreatic polypeptide. However, these markers offer suboptimal sensitivity and specificity. For F-PNENs, on the other hand, specific hormones secreted can be measured and correlated with tumor burden and hormonal symptoms. (20)

3.1.4.3 Disease staging

The imaging modalities and histopathological analysis of tissue specimens allow to determine the primary tumor site, its size, its focality, its differentiation, its receptor status, its potential metastases, its proliferation rate (Ki-67 index and mitotic count), and its extension. On basis of these information, we can establish staging of PNEN and predict survival among patients with PNENs. The staging of PNENs is based on the TNM classification and the ENETS staging system is described in Table 2. A large European study displays that the ENETS system provide more equally populated risk groups and more accurate predictive ability than the AJCC manual, an American staging system. (4; 34; 35)

Table 2: European Neuroendocrine tumor society staging system for PNENs (4; 36)

Stage	Tumor	Node	Metastasis	Description
Stage I	T1	N0	M0	Primary tumor only, < 2 cm
Stage IIa	T2	N0	M0	Primary tumor only, 2-4 cm
Stage IIb	T3	N0	M0	Primary tumor only, > 4cm or invading duodenum or bile duct

Stage IIIa	T4	N0	M0	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis, superior mesenteric artery)
Stage IIIb	Any T	N1	M0	Lymph node metastases
Stage IV	Any T	Any N	M1	Distant metastases

3.1.5 Treatment

3.1.5.1 Surgical therapy

Surgery is the only known cure for PNENs to date. Surgery is valuable in reducing symptoms related to hormone overproduction or the mass effect of the tumor, and in preventing malignant transformation or dissemination of the tumor.

The attitude will differ depending on the extent of the disease.

In case of well-differentiated PNEN with no evidence of metastatic disease, patients may benefit from resection with curative intent. Invasion of regional lymph nodes is a poor prognostic factor, but surgical resection is not excluded. (37; 38; 39; 40) In locally advanced PNENs, vascular resection or reconstruction and extensive resection of adjacent organs can be attempted with acceptable mortality and morbidity. (38; 41) On the other hand, surgical resection alone is rarely curative in PNECs without distant metastases. It will be necessary to add chemotherapy and/or radiation therapy and to select patients carefully. (42)

In patients with potentially resectable metastatic disease, we can consider an aggressive surgical approach with resection of the metastatic sites. This management may offer increased long-term survival. (37; 38)

For patients with unresectable metastatic disease, surgery is generally not recommended and systemic medical therapy is preferred. However, debulking surgery can sometimes be performed (see section on debulking surgery below).

The question of resecting the primary tumor in metastatic and unresectable PNENs is debated. A systematic review was conducted on the matter and included 3 small cohort studies. Two of them reported a higher overall survival and 5-year survival rate in the group whose primary tumor was resected. But this benefit could be the result of selection bias. (43) This decision should be individualised according to the presence of compressive symptoms, tumor grade, and metastatic tumor burden.

The extent of resection is determined by the location and size of the primary tumor, any invading lymph nodes and the potential for metastasis, but a maximum amount of the pancreatic mass should be preserved. (44) There is a wide variety of surgical techniques available to treat PNENs. Parenchyma-sparing operations include central pancreatectomy and enucleation. They are used for the management

of small PNENs without lymph node disease. Traditional resections comprise pancreaticoduodenectomy, distal pancreatectomy and total pancreatectomy and are effective for more locally advanced PNENs. (42)

In patients with evidence of tumor recurrence on postoperative surveillance, a new resection should be evaluated. Postoperative surveillance usually involves cross-sectional imaging and monitoring of plasma chromogranin A. (42)

3.1.5.1 Loco-regional Ablative Therapy

The majority of patients with advanced PNEN have liver metastases. For that reason, liver-directed therapies including hepatic surgical resection, radiofrequency or microwave ablation and hepatic arterial embolization are often used to control tumor burden. These locoregional therapies have to be considered in patients with uncontrolled functional tumors with predominant liver disease or as an alternative option to systemic therapy in those with NF-PNET if the disease is limited to the liver.

3.1.5.1.1 Debulking surgery

Resection of neuroendocrine liver metastases could be indicated in patients with uncontrolled functional tumors, especially those with carcinoid syndrome, or in subjects with NF-PNET if there are symptoms related to tumor burden and no disease progression over a 6-month period. (31) For functional tumors, an initial trial of SSA therapy is imperative before debulking surgery is considered. Some retrospective studies support that surgery for liver metastasis provide symptom control and is associated with improved survival. (45; 46; 47; 48) Despite these apparent benefits, high rates of recurrence were also reported and the potential existence of a selection bias in these series is important. Randomized study comparing resection versus systemic therapy have not been performed. (49)

3.1.5.1.2 Ablation

Ablation is most often employed as an adjunct to surgical resection. It can also be envisaged in the therapeutic management of smaller (< 3 cm) neuroendocrine liver metastases because of its limited ablation zone. The ablative techniques available are radiofrequency ablation, the most commonly used, cryoablation and microwave ablation. These different treatment modalities can be performed percutaneously, laparoscopically or at the time of laparotomy. (50) Only retrospective studies with a restricted heterogeneous patient population have evaluated ablation as a primary treatment modality. (51; 52; 53; 54; 55; 56) The combination of surgical resection and ablation was evaluated in a retrospective study in 66 of 339 patients with GEP-NENs who received liver-directed therapy. Fewer subjects who received the combination had a second locoregional therapy. (57)

3.1.5.1.3 Hepatic arterial embolization

This technique is based on the principle that neuroendocrine metastases in the liver obtain their resources from arterial blood, whereas hepatocytes derive their resources from venous blood. (50) The existing forms of embolotherapy are bland embolization, chemoembolization (TACE) and radioembolization

(TARE). Drug-eluting beads chemoembolization (DEB-TACE) was abandoned due to high rates of bilomas and abscesses. (58)

Hepatic arterial embolisation is recommended as an alternative to medical treatment alone or as a palliative procedure for symptomatic patients with unresectable, liver predominant PNENs. (50) No prospective randomised clinical trials have been carried out to compare the effectiveness of the 3 different embolisation methods. (59) Thus, there is no evidence to guide us in selecting the optimal embolisation technique. The choice of embolotherapy will depend on the tumor histology, the comorbidities, the treatment objectives and local expertise. However, in patients with Whipple's procedure, portal vein occlusion or ampulla of Vater stent, ^{90}Yttrium-TARE is preferred to reduce the risk of infection. (59; 60; 61) This recommendation is justified by the mode of action of ^{90}Y-TARE which is not, *per* se, an embolisation technique, thus prevents ischemia and necrosis of bile ducts that are fed exclusively by arteries.

3.1.5.1.4 Liver transplantation

Liver transplantation may be a therapeutic option in highly selected, young patients with functional syndromes and early resistance to systemic and locoregional therapies. (31) One of the largest series undertaken involved 213 patients who received liver transplants throughout Europe between 1982 and 2009. Overall survival at one, three and five years were 81, 65 and 52% respectively and progression-free survival at the same time intervals was 65, 40 and 30%. (62) A retrospective cohort study compared long-term outcomes between patients who received transplantation or not according to the Milan-NET criteria. All patients were eligible for transplantation. After matching between groups made on multiple Cox models adjusted for propensity score, adjusted transplant-related survival benefit was 6.82 months at 5 years and 38.43 months at 10 years. Both results were significant. This shows that liver transplantation for metastatic NETs under restrictive criteria provides excellent long-term outcome. (63)

3.1.5.2 Active surveillance

The "watch and wait" approach which involves active surveillance of PNEN without giving any treatment, appears to be a safe and effective management for small and asymptomatic grade 1 PNENs. A meta-analysis was made by pooling data from 5 studies to reach 327 patients with a "watch and wait" approach for small and asymptomatic PNETs. (64) Tumor growth could be measured in 0-51% of cases after a median follow-up period of 28 to 45 months. There were no disease-related deaths and only 14% of 327 subjects benefited from tumor resection. The main reason was an increase in tumor size (19 of 46 resected PNENs).

However, there is debate about the size below which this attitude is recommended. The ENETS guidelines suggest active surveillance for PNETs < 2 cm, whereas the NCCN does so for those < 1 cm. (65; 66; 42) In these circumstances, the decision to actively observe before surgical resection must be individualized by weighing the risks and benefits of both approaches, i.e. surgery and active surveillance. At least 3 prospective trials are currently assessing the value of this strategy.

3.1.5.3 Systemic therapy

Medical therapy is required for the majority of patients who are not suitable for surgery or who have residual disease after surgery. Among the options, we will discuss the roles of somatostatin analogues (SSA), novel targeted drugs, systemic chemotherapy and peptide receptor radionuclide therapy (PRRT).

3.1.5.3.1 Somatostatin analogues

Somatostatin is a peptide that inhibits the secretion of a broad range of hormones in vivo. Octreotide and lanreotide are the most effective somatostatin analogs and bind with similar affinity to somatostatin receptor subtypes 2 and 5 which are expressed on the majority of NETs. (67; 59)

The control tumor growth by somatostatin analogs may results from direct and indirect antiproliferative effects. The direct antiproliferative effects could include cell cycle inhibition and pro-apoptotic effects while the indirect antiproliferative effects could involve inhibition of tumor angiogenesis and the release of trophic growth hormones. (68; 69)

SSA, octreotide and lanreotide, are considered as a first-line therapy in unresectable, somatostatin-receptor-positive, advanced, well-differentiated PNEN. There is no established Ki-67 threshold, but they should be used if Ki-67 is ≤ 10%. Based on the CLARINET study, the level of evidence for the use of lanreotide autogel in PNET is higher than octreotide, while the antiproliferative efficacy of both SSA is considered a drug class effect. (31; 70). For asymptomatic patients with small-volume disease, an initial observation alone is suggested rather than early administration of a somatostatin analog. We initiate somatostatin analog therapy if there is evidence of clinically meaningful tumor progression. (69)

SSA have an antisecretory effect and can palliate hormonal syndromes such as gastrinoma, glucagonoma, and VIPoma syndrome. In series that include patients with only PNENs or combined series of patients with functioning gastroenteropancreatic NETs, SSA provide symptoms control in over 60%. (71; 72; 73; 74; 75; 76; 77; 78; 79)

In addition to controlling symptoms associated with hormone hypersecretion, SSA have also shown antiproliferative activity. This antitumor activity was established in the phase III CLARINET trial. In this trial, 204 patients with SSTR receptor-positive advanced enteropancreatic NETs with Ki-67 proliferation indices ≤ 10% were randomized to receive lanreotide 120 mg every 4 weeks versus placebo. (70) There was a highly significant advantage in PFS with the use of lanreotide. Estimated rates of two years PFS were 65% with lanreotide compared with 33% with placebo.In NF-PNENs the aim of somatostatin analogue is to stabilize tumor growth. Indeed, objective tumor regression is very limited and several studies demonstrated that occurs in < 10%. (49; 80; 81; 82; 83)

SSA are well-tolerated, safe drugs, with mild adverse effects even after sustained usage. During first weeks of therapy, almost one-third of patients may have mild nausea, abdominal discomfort, bloating, loose stools, and fat malabsorption. Symptoms associated with pancreatic insufficiency can be ameliorate by use of pancreatic enzyme supplements. A transient inhibition of insulin secretion can cause mild glucose intolerance. Up to 25 percent of patients develop asymptomatic gallstones or sludge

within the first 18 months of therapy. (84; 69) The favorable toxicity profile of SSAs is one of the reasons for their use as first-line therapy in patients with SSTR-positive PNENs.

After disease progression on a long-acting somatostatin analog, an option is dose escalation but the benefits of the use of SSAs beyond progression are not well established. (68; 69) But recently, a preliminary report of the CLARINET FORTE study was presented at the 18th annual ENETs conference. This prospective cohort study evaluated the efficacy and safety of doubling the dose frequency of lanreotide autogel in patients with progressive PNENs or midgut NETs. The median PFS was estimated to be 8 months (95% CI, 5.6 to 8.3) in the PNENs group with a Ki-67 index <10% with no loss of quality of life. A lower median PFS was reported for PNENs with a Ki-67 index > 10%. (85)

The role of continuation of SSAs beyond first line either concurrently with everolimus or after PRRT treatment remains controversial in patients with NF-PNENs. (59)

3.1.5.3.4 Targeted therapies

The better understanding of the molecular biology of PNENs has revealed involvement of several growth factors, their receptors (especially VEGF and VEGFR) and the mammalian target of rapamycin (mTOR) in tumorigenesis. VEGF receptors function as tyrosine kinase and can be target of small molecule TK inhibitors (e.g. sunitinib, sorafenib, pazopanib, etc.). (86; 87; 88; 69)

Targeted therapies are recommended for patients with advanced, unresectable, progressive, well-differentiated PNENs whose disease has progressed on SSA and who are not symptomatic from tumor bulk that would benefit from cytoreduction or chemotherapy. Although targeted drugs may be the first therapy choice in PNEN, there is consensus that targeted drugs should not be broadly used as first-line therapy for their potential toxicity. They can be considered as a first-line therapy, especially if SSA is not an option (e.g. SSTR-negative PNEN), and if systemic chemotherapy is not clinically required, not feasible or not tolerated. Given similar outcomes of phase III studies, the selection of the targeted drug is based on the medical history of the patient, the patient comorbidities, the side effect profile of the drug and availability of the treatment. In the absence of a comparative study of targeted drugs with SSA compared to the targeted drug alone, this combination therapy is not recommended. (31)

Small molecule TK inhibitors

Sunitinib is a multi-target tyrosine kinase receptor inhibitor targeting VEGFR among other receptors (CD117, PDGFR, etc.). VEGFR is a key driver of angiogenesis, which is essential for tumor growth and for process of metastasis. (89; 31)

Sunitinib 37,5 mg daily was compared with placebo in a randomized phase III study of 171 patients with progressive low- and intermediate-grade PNENs. Median PFS improved significantly from 5,5 months on placebo to 11,4 months with sunitinib. The ORR was 9%. (90)

Side effects like hypertension, proteinuria, other forms of renal toxicity, arterial thromboembolism, left ventricular dysfunction, clinical heart failure, thyroid dysfunction, bleeding, myelosuppression, hand-

foot skin reaction, delayed wound healing, hepatotoxicity, and muscle wasting may occur in patients receiving sunitinib. (69)

In a recent phase III study in China of 172 patients with advanced, well-differentiated PNEN who had progressed on previous systemic therapy, surufatinib showed a significant improvement in PFS. (91) The median PFS was 10.9 months in the surufatinib group and only 3.7 months in the placebo group.This drug has an acceptable safety profile and could be a therapeutic option in this patient population. The worse treatment-related adverse events observed in this study were hypertension, proteinuria and hypertriglyceridaemia.

Other TK inhibitors exist including sorafenib, pazopanib, cabozantinib and Lenvatinib, but there is not sufficient data to recommend their use in PNEN. They have demonstrated activity in PNEN in a few prospective studies. (92; 93; 94; 95)

mTOR inhibitors

Everolimus is the most studied mTOR inhibitor. Its use is approved for the same indication than sunitinib, but it is of particular value in patients with functioning insulinomas and refractory hypoglycemia because of the hyperglycemia it can cause. (96)

In the RADIANT-3 trial, 410 patients with advanced progressing PNEN were randomly assigned to receive everolimus monotherapy versus best supportive care alone. (97) Everolimus was associated with a significant prolongation in median PFS (11 versus 4,6 months). The ORR was 5% in patients receiving everolimus versus 2% in placebo group. Overall survival analysis demonstrated a modest trend toward improved OS with median 37.7 months on placebo versus 44.0 months on everolimus.

In analysis of data from the RADIANT-3 trial, reported drug-related adverse events included stomatitis, rash, diarrhea, fatigue, infections (predominantly of the upper respiratory tract, anemia, hyperglycemia (more frequent in those with preexisting diabetes mellitus or baseline hyperglycemia). (97)

3.1.5.3.5 Systemic chemotherapy

Systemic chemotherapy is indicated as first-line therapy in patients who are highly symptomatic from tumor bulk, who have rapidly enlarging metastases or who suffer from G3 NEN because of its higher objective response rate (cytostatic agents such as SSA, sunitinib and everolimus have ORR < 10%). If there is a chance of achieving a response to allow for surgery, chemotherapy is favoured too. (59; 98; 69)

Combination of capecitabine and temozolomide (CAPTEM)

Capecitabine with temozolomide (CAPTEM) is considered as a reasonable initial treatment choice for patients with large volume or symptomatic, metastatic NF-PNENs. There are not comparative trials between CAPTEM and streptozocin-containing regimen. The choice of chemotherapy should be

individualized, taking into account the route of administration, the performance status, and the anticipated side effect profile of both combinations. (69; 59)

Reported objective response rates from prospective studies achieved with temozolomide combined with targeted therapy range between 24 and 45%. (99; 100)

Promising activity with CAPTEM in patients with PNEN has been reported in a retrospective study and preliminary reports of a randomized phase II trial. In a retrospective series of 143 patients who were treated with CAPTEM, the objective response rate was 54%. This study demonstrated also a median PFS of 17 months, and median OS of 73,2 months. (101) The randomized phase II Eastern Cooperative Oncology Group 2211 trial compared temozolomide monotherapy with capecitabine and temozolomide in 144 patients with progressive low and intermediate-grade PNENs. (98) In a preliminary report communicated at ASCO 2018, median progression-free survival was significantly better with combined therapy (22,7 versus 14,4 months) . Median OS was 38 months with temozolomide and not reached with the combination. The objective response rates were similar, and the disease control rate was higher for combined therapy (82 versus 68%).

In this last study, adverse effects of CAPTEM included neutropenia and thrombocytopenia.

Few studies indicate that there is a correlation between expression of methylguanine DNA methyltransferase (2) (2) and temozolomide responsiveness in advanced NET. (102; 103) Alkylating agents (including temozolomide, dacarbazine and streptozocin-based regimens) induce DNA damages, and MGMT is an enzyme that is responsible for DNA repair. MGMT cannot be recommended routinely at this time to guide decisions on the use of capecitabine/temozolomide in PNENs. (31)

Streptozocin combination

Streptozocin-based therapy has been approved for use in PNENs for more than forty decades, although early trials did not use modern response criteria. Temozolomide-based chemotherapy has replaced its use due to its cumbersome administration schedule coupled with its relatively unfavorable toxicity profile (including myelosuppression, nausea, hair loss, and renal dysfunction). (59; 104; 69)

Streptozocin can be used in combination with either 5-fluorouracil or doxorubicin.

Several studies support the antitumor activity of streptozocin-based therapy. In an early randomized trial, streptozocin plus doxorubicin had a rate of tumor regression of 69% and a median survival of 2,2 years. These results was significantly superior to streptozocin plus fluorouracil. (105) A retrospective study of streptozocin, doxorubicin, and 5-fluorouracil demonstrated a response rate of 39% and median PFS of 18 months. (106) In another retrospective analysis of 96 patients with PNENs treated with streptozocin plus 5-FU, objective response rate was 43%, and an additional 41% of patients showed stable disease as the best response. (107)

The use of doxorubicin is limited by a cumulative dose of 500 mg/m^2 (due to the risk of cardiotoxicity). (31)

Platinum-based chemotherapy

Cisplatin- or Carboplatin-based chemotherapy is recommended as a first-line therapy in poorly differentiated PNENs. (31)

The NORDIC-NEC study reported higher response to cisplatin or carboplatin in combination with etoposide in tumors with higher Ki-67 proliferation indices. Patients with a Ki-67 index ≥ 55% had a significantly higher response rate (42% vs 15%) than did patients with Ki-67 index < 55%, but they had a lower survival (10 vs 14 months). (108) In the same way, in a retrospective analysis of 45 patients with G3 PNENs, the ORR to platinum agents was 10% of G3 NETs and 37% of patients with NECs. (109)

FOLFOX and FOLFIRI can be considered as second-line systemic therapy in G3 NECs although there are insufficient data to support any particular second-line systemic therapy option. (31)

A combined analysis of two separate prospective phase II studies examined effectiveness of bevacizumab plus FOLFOX or CAPOX in advanced NETs. (110) From the two patients with poorly differentiated NEC and treated with FOLFOX-bevacizumab, the ORR was 50% after 12 cycles. The contribution of bevacizumab to these results is unclear. The ORR in PNENs (12 patients) at 12 cycles was 41,7%. Another retrospective analysis of patients treated with second-line chemotherapy for poorly differentiated NEC from various anatomic sites reported a short PFS of only 2,3 months and no second-line regimen showed a statistically significant superiority. (111)

3.1.5.3.6 Peptide receptor radionuclide therapy

PRRT is recommended in G1 or G2 NET that expresses somatostatin receptors and after failure of medical therapy including SSA, chemotherapy or novel targeted drugs. (31) The most frequently used radionuclides for targeted radiotherapy include yttrium-90 (90Y) and lutetium-177 (177Lu).

177Lu-DOTATATE may surpass 90Y-DOTATOC according to some data. A registry-based series of 450 patients with progressive low- or intermediate grade neuroendocrine neoplasms assessed effectiveness of 177Lu-DOTATATE alone, 90Y-DOTATOC alone and the combined therapy. (112) The median PFS for the 177Lu-DOTATATE group, the 90Y-DOTATOC group and the combined therapy group was respectively 40 months, 27 months and 50 months. It was significantly inferior in patients treated with 90Y-DOTATOC. However, given the non-randomized design of this series, clear conclusions can't be drawn about the relative efficacy of these treatments.

Efficacy results with 177Lu-DOTATATE alone are available from the phase III randomized controlled trial NETTER-1. (113) In this study, 229 patients who had well-differentiated, metastatic midgut neuroendocrine tumors were randomly assigned to receive 177Lu-DOTATATE and octreotide or octreotide alone. This study reported a significantly better ORR of 18% versus 3% for the control arm and an estimated PFS of 65.2% at 20 months in the 177Lu-DOTATATE group versus 10.8% in the control group. Nevertheless, this trial was only conducted in patients with midgut neuroendocrine tumors. In a prospective phase II trial of 60 patients with progressive PNENs and treated with up to 5

cycles of 177Lu-DOTATATE, the disease control rate, defined as the sum of complete response, partial response and stable disease, was 81.7%. The median PFS was 28.7 months. In another prospective study, 49 patients with metastasized PNEN were treated with 177Lu-DOTATATE. (114) The partial response rate achieved was 42.9% and stable disease was obtained in 49% of patients. Long-term adverse effects reported by the NETTER-1 trial include loss of renal function, pancytopenia, and myelodysplastic syndrome. (112) As in the NETTER-1 trial, it is advisable to continue therapy with a somatostatin analog in patients undergoing PRRT, particularly if the tumor is functional. (112; 115).

3.1.6 Prognosis

Most NF-PNENs are well-differentiated endocrine tumors at diagnosis, which is a good prognosis factor. The prognosis is related to stage of the disease, tumor differentiation, patient age and possibility of surgery. A study performed in 324 patients with PNENs demonstrated the following independent prognostic factors (with their HR): surgery (3,3), poorly differentiated carcinoma (12,3), primary referral (1,9), stage IV (7,9), age > 60 (2,9). (36) In another study of 425 patients with PNENs treated between 1999 and 2010, 5-years survival rates for ENETS classification stages I, II, III and IV were 100%, 88%, 85% and 57% respectively. (116) Ki-67 value is an important prognostic factor with a cut-off level of 3%. WHO classification and TNM stages are other prognostic factors, as recently shown in a very large cohort study from the ENETS registry. (117)

4. Objectives

The sequencing of medical treatment of PNENs is unclear, especially for patients with extensive disease and ineligible for locoregional therapies. Different reasons can be highlighted: the lack of randomized clinical trials directly comparing active treatments, the variability of response criteria, the sometimes questionable efficacy of some control groups (such as interferon) and the variability of the patient populations studied which is notably related to the scarcity of PNENs and the variability of the inclusion criteria. The initial objective of this work was thus to determine in "real life" which are the treatments prescribed by Belgian physicians, which is the sequencing implemented by Belgian physicians, and which is the sequencing preferred according to WHO grade and Ki-67 proliferation index of the PNENs? However, during the data collection phase, which was longer and more tedious than expected, we realized that the number of patients would be insufficient to answer the questions we raised above. The objective of our study therefore evolved and consisted of evaluating the survival of patients managed at Saint-Luc Hospital, the factors that predict their survival, as well as the effectiveness of the two most commonly used treatments in the first instance, surgical resection and active surveillance, by measuring the progression-free survival that they offer.

5. Patients and methods

5.1 Patients

Between September 2019 and March 2021, 46 patients suffering from PNENs and followed at the Cliniques Universitaires Saint-Luc, in Brussels, Belgium, were recorded in the DNET registry. The registry is an electronic database created by the BGDO (www.bgdo.org/DNET), whose aim is to gather epidemiological and medical data of patients with digestive neuroendocrine tumors.

The patients included in this database are > 18 years of age at diagnosis. They suffer from histologically confirmed PNET and are under the care of Professor Ivan Borbath, gastroenterologist and digestive oncologist at Saint-Luc Hospital. All patients provided signed, informed consent. After the *Commission d'Ethique Biomedicale Hospitalo-Facultaire* had given its approval, data collection could begin.

5.2 Treatments and evaluation of tumor response

All patients were discussed during the multidisciplinary oncology consultation and received the most effective available treatment depending on the spread of the disease, its grade and the latest scientific knowledge. Follow-up were planned every 3-6 months after initiation of each treatment. Follow-up frequency was decreased in case of stable disease for several years.

The evaluation comprised a complete physical examination and tumor measurement by CT, MRI or US. FDG PET scan, bone scan and SRI were obtained as needed. Each treatment was continued until disease progression, unacceptable toxicity, or patient intolerance. Dose adjustments were sometimes done due to toxicity or intolerance.

A lot of patient were taken care in first line by "watch and wait" approach, which is defined as the regular follow-up of patients without giving any treatment until disease progression.

5.3 Methods

Patients were included according to their date of diagnosis. The most recently diagnosed patients were the first to be entered into the DNET registry. By including patients with an increasingly older date of diagnosis, we reached a total of 46 patients, which represents about half of the patients with PNENs followed up at the Saint-Luc hospital.

The objectives of DNET registry are broader than those of this thesis, as a large amount of data is collected in the registry. For each patient, the following details are captured in the registry: common demographic data (sex, date of birth, and eventually cause and date of death), comorbidities, clinical, radiological, biological and histological information accumulated at diagnosis, the initially chosen management, the evolution of these same clinical and paraclinical parameters at each follow-up, and the treatment changes. Among all these data, we extracted the following thanks to Alexandre Rossez' computer skills: date of diagnosis, date of death, stage at diagnosis, Ki-67 index at diagnosis, WHO grade at diagnosis, treatments provided and starting date, and the date of disease progression. To

simplify the statistical analysis and the interpretation of the results, the names of systemic therapies were replaced by their drug class. As an example, lanreotide autogel was substituted by SSA and doxorubicin by chemotherapy. These data allowed us to determine progression free survival and overall survival in all patients.

5.4 Statistical analysis

The primary objective was to assess PFS and OS. The PFS was defined as the time between start of treatment and the first date of documented recurrence, progression or death due to any cause. Patients who did not have progressive disease at the date of treatment change or at their last follow-up date were censored on these two dates. The OS was defined as the time between diagnosis and the date of death due to any cause. Surviving patients were censored on their last follow-up date. The same thing happened with patients who withdrew from the study for reasons other than progression or death. Both PFS and OS were estimated by the Kaplan-Meier method. The statistical differences in OS between the WHO grades of tumors or the ENETS stages of tumors were estimated by the log-rank test. The comparisons for OS according to WHO classification or to ENETS staging were also assessed by the Bonferroni test. Differences were considered statistically significant when the P value was less than 0.05. Univariate analysis of OS and PFS for all patients was performed for WHO grade, ENETS stage, Ki-67 index and sex. Then, all variables with a p-value < 0.20 were selected for multivariate analysis. For this, a Cox proportional hazard model was used to identify independent prognostic factors of OS and PFS. All statistical analyses were carried out by Kiswendsida Sawadogo.

6. Results

6.1 Characteristics of the patient population

A total of 46 patients were enrolled, including 22 men and 24 women (Table 3). The median age at the time of diagnosis was 56 years (range, 19 to 82 years).

Slightly less than half the subjects (21 patients, 46%) were treated by only one line of treatment.

The majority of patients (89%) had PNET with a Ki-67 index of less than 20% at the time of diagnosis by histological examination of a fine-needle aspiration and biopsy or surgical resection specimen. These tumors therefore belonged to grades 1 or 2 of the WHO classification.

Conversely, few tumors were metastatic at the time of diagnosis (13 subjects, 28%), i.e. ENETS stage IV. The remaining patients had locally advanced PNET including 20 stage I, which represents 43%.

As a result of the data collection method, most patients (78%) were diagnosed after 2010 and a large proportion (23 subjects or 50%) between 1 January 2010 and 31 December 2014. Small, asymptomatic lesions were offered a “watch and wait” approach. Patients with more advanced disease were treated by

surgery. These 2 represent the high majority of managements. As small subset of patients, usually with stage 4 disease at diagnosis, received as first line, somatostatin analogs or sunitinib.

Table 3: Baseline characteristics of the patient population

Characteristic	**No. (%)**
No. of subjects	46
Age at diagnosis, years	
• Median	56
• Range	19-82
Sex	
• Male	22 (48)
• Female	24 (52)
In first intention, no. of subjects treated by	
• surgery	20 (43)
• “watch and wait” approach	19 (41)
• Somatostatin analog	5 (11)
• Sunitinib	2 (4)
Tumor grade according to WHO classification	
• NET G1	20 (43)
• NET G2	21 (46)
• NET G3 and NEC	5 (11)
Tumor ENETS stage	
• Stage I	20 (43)
• Stage II	9 (20)
• Stage III	4 (9)
• Stage IV	13 (28)
Number of subjects diagnosticated between	
• 2000 and 2004	4 (9)
• 2005 and 2009	6 (13)
• 2010 and 2014	23 (50)
• 2015 and 2020	13 (28)
Number of lines of treatment	
• One line of treatment	21 (46)
• Two lines	9 (20)
• Three lines	1 (2)
• Four lines	2 (4)

• At least five lines	13 (28)

From the population analysis, 3 groups of interest could be identified: the overall population, patients who had undergone surgery in the first instance and those for whom the "watch and wait" attitude was adopted in the first line. Each group was analyzed separately, and results are presented below.

6.2 The overall population

For the whole group, OS at 1 year was 100% (95% CI, 100 to 100; Table 4; Fig. 1) and, at 3 and 5 years, it was 98% (95% CI, 85.6 to 99.7). The median OS could not be estimated by the Kaplan-Meier method because of the insufficient number of events.

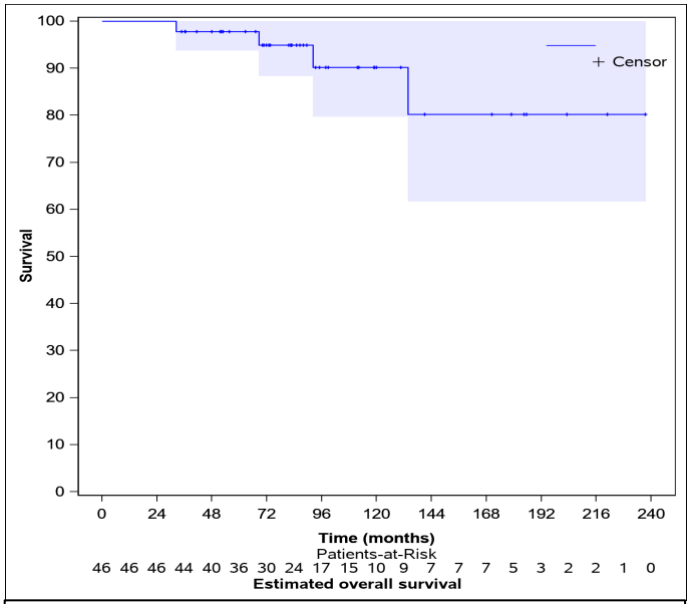

Fig. 1. Overall survival for all patients

Table 4: Overall survival for all patients

Overall survival rate	Patients alive	42 (91.3%)
	Deceased patients	4 (8.7%)
Estimated 1-year overall survival rate	Rate	100%
	CI95	100% - 100%
Estimated 3-years overall survival rate	Rate	98%
	CI95	85.6% - 99.7%
Estimated 5-years overall survival rate	Rate	98%
	CI95	85.6% - 99.7%
Kaplan-Meier estimate of overall survival (months)	Median	NE
	CI95	133,9 – NE
	Minimum	32.4
	Maximum	237.7

Abbreviation: NE = not estimable.

Looking at overall survival according to WHO classification (Table 5; Fig. 2), we notice that the 5-year overall survival rate is lower in the group with WHO grade 3 PNETs (80%; 95% CI, 20.4 to 96.9) compared to grade 1 and 2, in which there were no deaths at 5 years from diagnosis. The overall differences in OS among the WHO grade groups are highly significant ($p < 0.001$). By post-hoc analysis with Bonferroni correction, we determined that the PNET grade 3 group had a significantly lower OS than the PNET grade 1 group ($p = 0.015$). There was no statistically significant difference between grade 1 and 2. The only median overall survival that could be calculated was for the grade 3 PNET group, which was evaluated at 92.3 months (95% CI, 32.4 to not estimable).

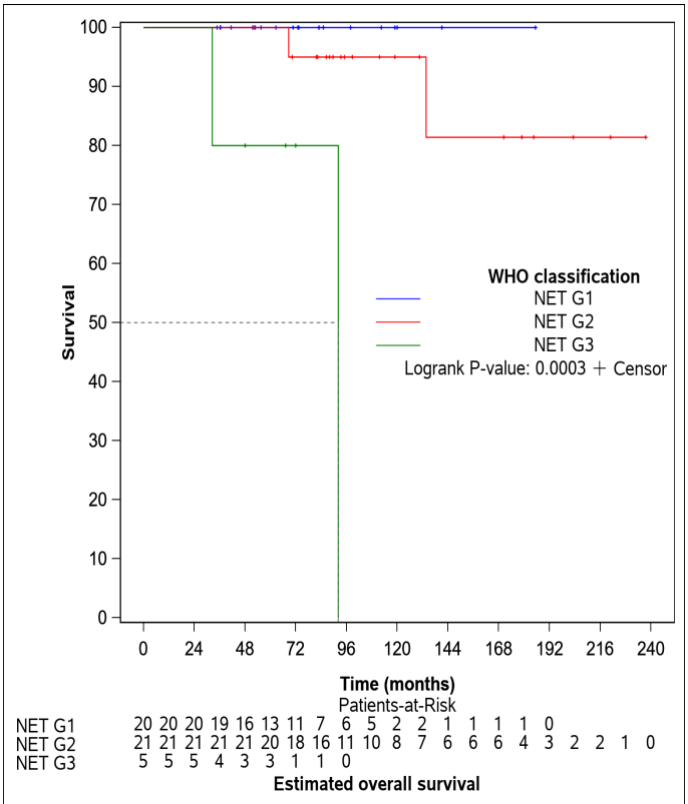

Fig. 2. Overall survival according to WHO classification grade

Table 5: Overall survival according to WHO classification grade

		NET G1 N=20	NET G2 N=21	NET G3 N=5	Total N=46
Overall survival rate	Patients alive	20 (100.0%)	19 (90.5%)	3 (60.0%)	42 (91.3%)
	Deceased patients	0 (0.0%)	2 (9.5%)	2 (40.0%)	4 (8.7%)
Estimated 1-year overall survival rate	Rate	100%	100%	100%	100%
	CI95	100% - 100%	100% - 100%	100% - 100%	100% - 100%
Estimated 3-years overall survival rate	Rate	100%	100%	80%	98%
	CI95	100% - 100%	100% - 100%	20.4% - 96.9%	85.6% - 99.7%
Estimated 5-years overall survival rate	Rate	100%	100%	80%	98%
	CI95	100% - 100%	100% - 100%	20.4% - 96.9%	85.6% - 99.7%
Kaplan-Meier estimate of overall survival (months)	Median	NE	NE	92.3	NE
	CI95	NE - NE	133.9 – NE	32.4 – NE	133.9 – NE
	Minimum	34.7	52.2	32.4	32.4
	Maximum	185.7	237.7	92.3	237.7
Comparison between groups	Logrank				< 0.001

Abbreviation: NE = not estimable, G = grade

We also examined overall survival according to ENETS staging (Table 6; Fig. 3). We found that the 5-year overall survival of locally advanced tumors, whatever their stage, reached 100% (95% CI, 100 to 100). Stage IV PNETs in contrast had an overall survival at 1 year of 100% (95% CI, 100 to 100), at 3 years of 92% (95% CI, 56.6 to 98.9) and at 5 years of 92% (95% CI, 56.6 to 98.9). The comparison between the groups demonstrated a significant difference (p = 0.017) using the logrank test. The Bonferroni post-hoc test provided statistical evidence that this difference in OS existed between stage I and II (p = 0.045) and between stage II and III (p = 0.042). This can be explained by the high 20% Ki-67 index for two of the deceased stage II patients, by the refusal of systemic medical treatment at the time of relapse for the third deceased stage II patient and by the censoring of the other patients due to the short duration of their follow-up.

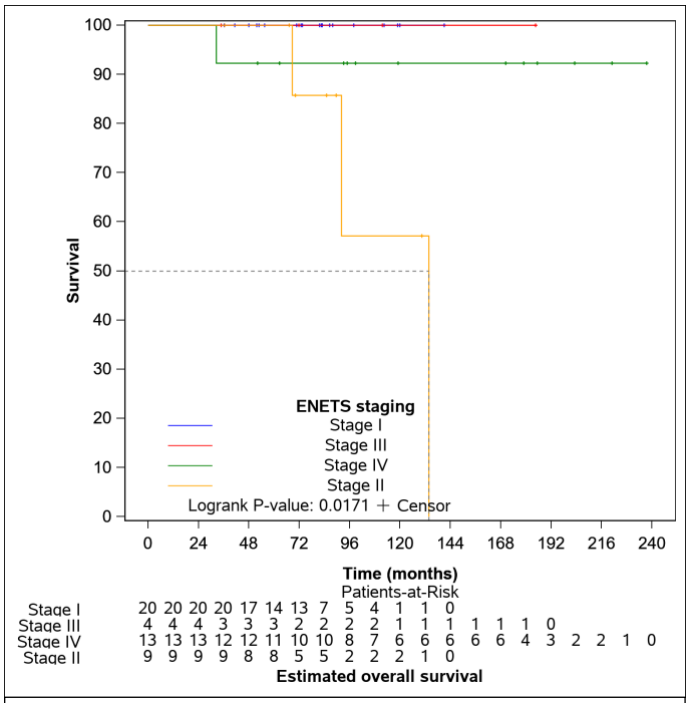

Fig. 3. Overall survival according to ENETS staging

Table 6: Overall survival according to ENETS staging

		Stage I N=20	Stage II N=9	Stage III N=4	Stage IV N=13	Total N=46
Overall survival rate	Patients alive	20 (100.0%)	6 (66.7%)	4 (100.0%)	12 (92.3%)	42 (91.3%)
	Deceased patients	0 (0.0%)	3 (33.3%)	0 (0.0%)	1 (7.7%)	4 (8.7%)
Estimated 1-year overall survival rate	Rate	100%	100%	100%	100%	100%
	CI95	100% - 100%	100% - 100%	100% - 100%	100% - 100%	100% - 100%
Estimated 3-years overall survival rate	Rate	100%	100%	100%	92%	98%
	CI95	100% - 100%	100% - 100%	100% - 100%	56.6% - 98.9%	85.6% - 99.7%
Estimated 5-years overall survival rate	Rate	100%	100%	100%	92%	98%
	CI95	100% - 100%	100% - 100%	100% - 100%	56.6% - 98.9%	85.6% - 99.7%
Kaplan-Meier estimate of overall survival (months)	Median	NE	133.9	NE	NE	NE
	CI95	NE - NE	68.7 – NE	NE - NE	NE - NE	133.9 – NE
	Minimum	36.2	36.5	34.7	32.4	32.4
	Maximum	141.3	133.9	184.7	237.7	237.7
Comparison between groups	Logrank					0.017

Abbreviation: NE = not estimable.

6.3 Univariate and multivariate survival analysis

Table 7 highlights the results of both univariate and multivariate analysis on overall survival in whole group of patients. The multivariate analysis was performed using the Cox proportional hazards model. The Ki-67 index was found to be a negative predictor of survival (p = 0.016; HR = 1.37; 95% CI, 1.052 to 1.623). ENETS stage, gender and WHO classification did not significantly influence OS in the univariate analysis. Their p-value had to be less than 0.20 to be included in the multivariate analysis.

Table 7: Uni- and multivariate regression analysis on overall survival for all patients

		Univariate			Multivariate		
Factor	Value	p-value	Hazard-Ratio	HR 95% CI	p-value	Hazard-Ratio	HR 95% CI
ENETS stage	Stage II	0.997	1.0361E8	(0.000 - NE)			
	Stage III	0.999	0.31	(0.000 - NE)			
	Stage IV	0.997	12461644	(0.000 - NE)			
Gender	Man	0.835	1.23	(0.173 - 8.776)			
Ki-67 index		0.016	1.31	(1.052 - 1.623)	0.016	1.31	(1.052 - 1.623)
WHO classification	Grade 2	0.997	19750423	(0.000 - NE)			
	Grade 3	0.997	3.3672E8	(0.000 - NE)			

References are follows: Gender “woman”, WHO classification “grade 1”, ENETS stage “stage I”. Abbreviation: NE = not estimable.

In order to assess which variables might be individually associated with PFS for all patients whatever their first line of treatment, we carried out another multivariate Cox proportional hazards analysis (Table 8). Independent prognostic factors of disease-free survival were tumor stage and grade 3 (p = 0.017; HR = 1.37; 95% CI, 1.404 to 29.59). Hazard of disease progression of stage II, III and IV PNENs relative to stage I were respectively 47.09 (95% CI, 4.853 to 456.9; p < 0.001), 29.59 (95% CI, 2.565 to 341.4; p = 0.007) and 163.96 (95% CI, 16.45 to 1634; p < 0.001). Gender and Ki-67 index were not variables independently associated with PFS. The same upper p-value threshold as in the previous multivariate analysis was applied here.

Table 8: Uni- and multivariate regression analysis on progression-free survival for all patients

		Univariate			Multivariate		
Factor	Value	p-value	Hazard-Ratio	HR 95% CI	p-value	Hazard-Ratio	HR 95% CI
ENETS stage	Stage II	0.003	25.34	(2.991 - 214.7)	< 0.001	47.09	(4.853 - 456.9)
	Stage III	0.009	20.06	(2.081 - 193.4)	0.007	29.59	(2.565 - 341.4)
	Stage IV	< 0.001	53.19	(6.787 - 416.9)	< 0.001	163.96	(16.45 - 1634)
Gender	Man	0.832	0.91	(0.380 - 2.179)			
Ki-67 index		< 0.001	1.07	(1.028 - 1.109)			

WHO	Grade 2	0.038	3.02	(1.062 - 8.579)			
classification	Grade 3	0.001	9.27	(2.382 - 36.06)	0.017	6.45	(1.404 - 29.59)

References are follows: Gender “woman”, WHO classification “grade 1”, ENETS stage “stage I”. Abbreviation: NE = not estimable.

6.4 Surgery in first-line treatment

Twenty patients were managed surgically first, they were equally divided between men and women. Their median age at diagnosis was 54 years (Table 9). The majority had WHO grade 2 (65%) and locally advanced (70%) PNET, with 6 metastatic PNETs (30%), of which 50% had resection of the metastatic lesions in addition to resection of the primary lesion.

Table 9: Characteristics of subjects treated by surgery in first line

Characteristic	**No. (%)**
No. of subjects	20
Age at diagnosis, years	
• Median	54
• Range	19-76
Sex	
• Male	10 (50)
• Female	10 (50)
Tumor grade according to WHO classification	
• NET G1	3 (15)
• NET G2	13 (65)
• NET G3 and NEC	4 (20)
Tumor ENETS stage	
• Stage I	5 (25)
• Stage II	6 (30)
• Stage III	3 (15)
• Stage IV	6 (30)
Metastatic PNETs: strategy in first intention	6 (30)
• Surgery of primary lesion	3 (15)
• Surgery of primary and metastatic lesions	3 (15)

The median PFS was 51.8 months (95% CI, 15.7 to not estimable; Fig. 4). At one year, the PFS was 80% (95% CI, 54.5 to 91.9), at three years 63% (95% CI, 37.4 to 80.4) and at five years 45% (95% CI, 21.7 to 65.9). An analysis of overall survival was not performed in this subgroup as there were only 3 deaths, more than 5 years from diagnosis.

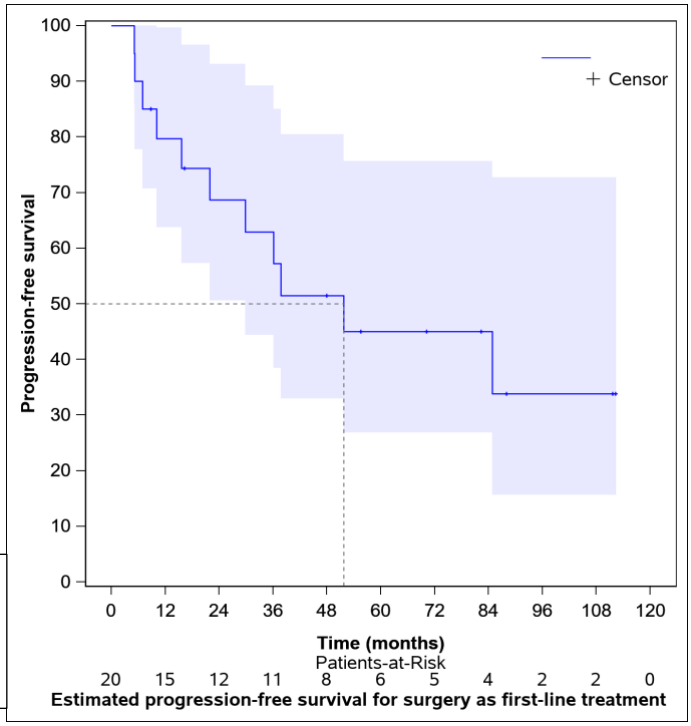

Fig. 4. Progression-free survival for patients with surgery in first-line treatment

6.5 “Watch and wait” approach as first-line treatment

The subgroup of 19 patients followed regularly without receiving any treatment consisted of 10 men (53%) and 9 women (47%). The median age of these subjects was 59 years at diagnosis (Table 10). They were grade 1 in 84% of them, with 3 grade 2: 2 of them had a low Ki-67 index (5 and 6%). In contrast, the histological examination of the third patient revealed a Ki-67 index of 15%, analyzed on the surgical specimen. This subject actually has multiple endocrine neoplasia type 1 and was operated on because one of the lesions was growing in size. The subgroup was almost entirely composed of locally advanced PNETs (15 stage I and 3 stage II), only one patient had metastatic PNETs. His PFS was only 9 months with the "watch and wait" attitude. He then received systemic medical therapy with somatostatin analogues until the progression of his disease 50 months later. Treatment with sunitinib was then initiated before the patient was lost to follow-up 5 months later.

Table 10: Characteristics of subjects treated by “watch and wait” approach in first line

Characteristic	**No. (%)**
No. of subjects	19
Age at diagnosis, years	
• Median	59
• Range	30-70
Sex	
• Male	10 (53)
• Female	9 (47)
Tumor grade according to WHO classification	
• NET G1	16 (84)
• NET G2	3 (16)
○ Ki-67 index $\geq$ 3% and $<$ 10%	2 (11)
○ Ki-67 index $\geq$ 10% and $<$ 20%	1 (3)
• NET G3 and NEC	0 (0)
Tumor ENETS stage	
• Stage I	15 (79)
• Stage II	3 (16)
• Stage III	0 (0)
• Stage IV	1 (3)

The median PFS (Fig. 5) was not estimable due to the insufficient number of disease progression events (only 4). The PFS at 1, 3 and 5 years was estimated to be 94% (95% CI, 66.6 to 99.2), 89% (95% CI, 61.4 to 97.0) and 75% (95% CI, 45.9 to 89.9) respectively. No death was recorded in this subgroup. Therefore, it was not possible to conduct an overall survival analysis.

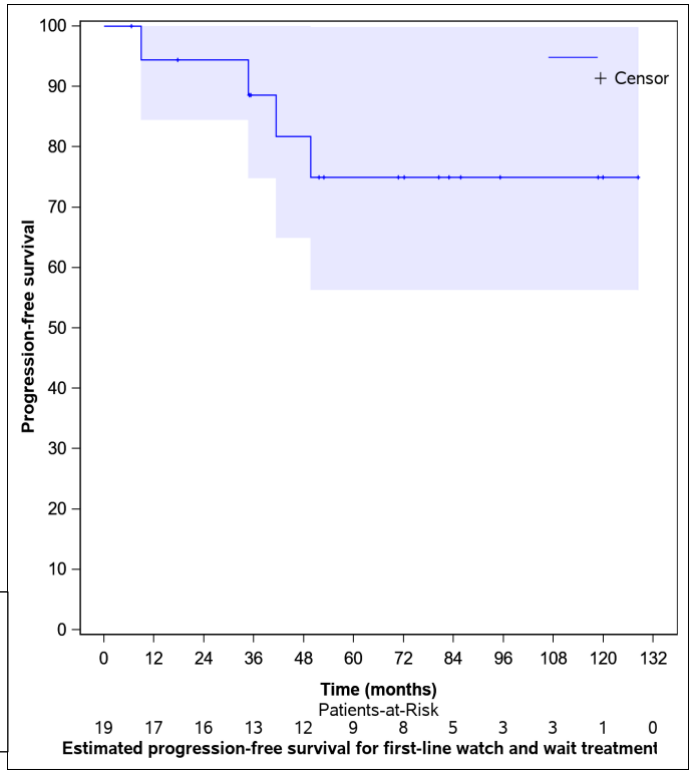

Fig. 5. Estimated progression-free survival for patients with "watch and wait" approach in first-line treatment

7. Discussion

In this thesis, we have shown that the overall survival of patients with PNENs followed at Cliniques Saint-Luc is very long: 98% OS at 5 years, median OS not reached. Subjects with WHO grade 3 PNEN had a significantly shorter OS than those with grade 1. Their overall survival at 5 years is estimated at 80% and their median overall survival is estimated at 92.3 months. We also found that the 5-year overall survival of locally advanced tumors (stage I-III) was close to 100%. In contrast, the 5-year overall survival of ENETS stage IV PNENs was estimated to be between 56.6 and 98.9%, but this difference in survival with other stages was not significant. This study was also able to show the role of the Ki-67 index value as a negative prognostic factor for survival. Similarly, it has been proven that grade 3 and stages higher than I are significant prognostic factors of poorer progression-free survival.

First-line surgery for PNENs appears to offer an estimated median PFS of 51.8 months and a presumed 5-year PFS of 45%.

For subjects actively monitored ("watch-and-wait") in first-line treatment, 75% had no disease progression at 5 years and the true value of this 5-year PFS lies between 45.9 and 89.9%.

When we compare the results, we have just described with the data in the scientific literature (See review in Appendix), we find that there are few data are in line with ours, with OS on this work being generally much better. There are several reasons for this: firstly, it should be remembered that many outcomes could not be estimated because of the low occurrence of the events of interest. Second, our patient sample is mainly early stage pNENS, with only 28% of stage IV, compared to many other studies.

The median overall survival could not be estimated in our sample, but the lower limit of its confidence interval was determined (133.9 months). The ENETS registry (118) analyzed data from more than 10,000 patients across Europe and reported a median overall survival of 178 months for all NET types combined. This value seems to be coherent with our data, but this is not the case for the 5-year overall survival rate which is 74% in the same study. In the subpopulation with PNENs from this study, OS at 1, 3 and 5 years were 93%, 82% and 74% respectively (data not published). These PNENs were Stage IV in 48% of the cases. The overall survival medians of two other studies (119; 120) are both below 133.9 months. These two retrospective studies involving more than 60,000 patients with NETs for one and more than 30,000 for the other, both retrieved from the US SEER database, obtained the very close median OS of 3.6 years and 42 months respectively.

Looking at metastatic PNENs, the 3-year overall survival rate was assessed to be between 56.6 and 98.9%. This range includes the 3-year overall survival rate calculated in the study by Li G. et al. (121). Indeed, the 3-year OS in the population of 624 metastatic PNENs was 61% in this retrospective study. In contrast, Li G. and his colleagues give a 5-year overall survival rate of 48.7%, which is inconsistent with our own.

For patients treated with first-line surgical resection, the median recurrence-free survival in the Kim et al. study (122) appears similar to ours. In this study, half of the 542 subjects who underwent surgical resection for PNEN had not progressed until 19 months. However, the 5-year recurrence-free survival rate is discordant with 3 studies (122; 123; 124), including Kim et al. These latter authors described a 5-years disease-free survival of 86.4% but this parameter takes into account the progression of the recurrent disease and not its simple recurrence. The other two studies reported at least 80% PFS at 5 years. The 5-year overall survival rate in this subgroup is debated. Three studies reported a conflicting value, (38; 124; 123) but two others reached a similar value (125; 126). The three conflicting studies showed 5-year OS rates ranging from 74 to 91% while the other two studies with similar results found 5-year OS rates of 100% and 95.5%. The primary outcome of the study by Andreasi et al. was not to estimate survival after surgery but to assess the postoperative development of diabetes mellitus and/or exocrine pancreatic insufficiency. (123) A selection bias could therefore be present. As for the other two conflicting studies, apart from their relative age, we do not note any major difference in their population. (38; 124)

For subjects who received initial observation before any treatment, the median progression-free survival in two studies is both below the lower limit of the confidence interval in our cohort. (64; 127) However, the study by Partelli and colleagues did not actually measure PFS but the time from diagnosis to surgery, which has a median of 30-41 months. Many patients chose to undergo surgery without progression of the disease. In their retrospective study, Gao and colleagues only selected patients with metastatic PNEN and their median PFS was only 10 months. The 5-year overall survival rate in this same group is similar in two studies, (64; 128) but is contested by another study. (126) In the latter, the observation subgroup

was significantly older, and its 5-year OS rate was 85%. Partelli and colleagues as well as Sadot and colleagues, on the other hand, reached a value of 5-year OS rate equal to or extremely close to 100%.
Uni- and multivariate analyses allowed us to isolate the independent prognostic factors influencing overall survival and progression-free survival for the entire study population. It was found that overall survival was influenced by the Ki-67 proliferation index value and that grade 3 and stage II to IV were prognostic factors for progression-free survival. Numerous studies have highlighted these same factors but also many others such as age at diagnosis, Charlson-Deyo comorbidity score, tumor location, surgical resection, race, time period at diagnosis, differentiation status, sex, being unmarried. (126; 118; 119; 120; 121; 125) The study conducted by Yao and colleagues in over 35,000 patients with NETs pointed to gender as a prognostic factor, unlike us. (120)

The divergence of results between the literature and our thesis forces us to question the validity of our results. The main weakness of our study is the small number of subjects included. This results in a high risk of error β, insufficient events (death and disease progression) and a large sampling fluctuation giving very wide confidence intervals and a not very accurate estimation of the parameters of interest. Some biases are also to be deplored. Regarding patient selection, the inclusion of patients based on their date of diagnosis reduces their follow-up time and in default of an event leads to the censoring of a large number of patients in the survival analysis. Sampling subjects from patients followed up in an expert centre such as ours may increase the proportion of rare forms of PNENs. There may have been some errors in classification because, at the time of data collection, we did not use the RECIST criteria to determine stable or progressive disease status but only the radiology protocol. Moreover, it is not only radiological criteria that play a role in the determination of disease progression. Progression-free survival was therefore sometimes underestimated. Finally, although the histological type of the tumor and possible genetic diseases were collected in the DNET registry, this information was not extracted for the analyses in this thesis. As some histological types are more indolent than others (e.g. insulinomas), this neglect could constitute a confounding bias.
Despite the weaknesses discussed above, we must acknowledge that this study has some advantages. Firstly, the management of the patients is homogeneous since only one physician, Professor Borbath, followed them up in one centre. The large number of patients who benefited from active surveillance in the first intention is a highlight because few studies have been conducted on this approach. Finally, this study provides very good survival parameters. These do not always agree with the data in the literature, but they are very often better (see table in the appendix).

8. Conclusion and perspectives

Based on this analysis, we show that patients with PNENs followed-up and treated at the Cliniques Saint-Luc have a good survival, as 5 years OS is between 85.6 and 99.7%. A high initial value of their

Ki-67 index (and therefore of their WHO grade) is a poor prognostic factor of survival, while grade 3 and stage higher than I are significant predictors of worse disease-free survival. Patients for whom surgical resection of their tumor is recommended have an estimated median progression-free survival of 51.8 months. Those for whom active surveillance is indicated in the first instance will only exhibit disease progression at 5 years in 10.1-54.1% of them.

As things stand, the contribution of this study to the management of PNENs is limited. The objective now would be either to include the data collected in another larger database in order to increase the scope of the future analysis of this database by multicentric collaboration, and/or to continue to enrich the DNET registry in such a manner that all Belgian patients with PNENs are added and analysed.

9. Appendix

		Results of this thesis (95% CI)	Comparable results in other studies											
Author; year			**Kim; 2019**	**Partelli; 2017[2]**	**Assi; 2020**	**Sadot; 2016[5]**	**Borbath; 2018[6]**	**Dasari; 2017**	**Yao; 2008**	**Li; 2020**	**Tao; 2017**	**Birnbaum; 2014**	**Gao; 2020**	**Andreasi; 2019**	**Ricci; 2017**
5-years OS rate		98% (85.6 to 99.7)					74.5%								
Median OS		NE months (133,9 to NE)					178 months	3.6 years	42 months[8]						
3-years OS rate in stage IV PNENs		92% (56.6 to 98.9)								61%					
5-years OS rate in stage IV PNENs		92% (56.6 to 98.9)								48.7%					
PNENs treated by surgery in first-line	**5-years PFS rate**	45% (21.7 to 65.9)	86.4%[1]											80%	97.8% and 82.3%[13]
	Median PFS	51.8 months (15.7 to NE)	19 months												
	5-years OS rate	100% (100 to 100)			100%[4]						95.5%	74%		91%	85.8% and 69.4%[14]
PNENs with active surveillance first	**Median PFS**	NE months (49.8 to NE)		30 to 41 months[3]									10 months[12]		
	5-years OS rate	100% (100 to 100)		100%	85%[4]	99% (95% CI, 97–100)									

Independent prognostic factor of survival identified in surgical subgroup	Independent prognostic factor of PFS identified	Independent prognostic factor of survival identified
/	WHO grade and ENETS stage	Ki-67 index
Grade 3, lymph node metastasis, lymphovascular invasion, perineural invasion and resection margin		
		age at diagnosis, Charlson-Deyo comorbidity score, stage, tumor location, and surgical resection.
		grade (Ki-67 index) and stage.
		Race, age at diagnosis, stage, grade, time period at diagnosis, and primary tumor site.[7]
		Differentiation status, disease stage, primary tumor site, histologic grade, sex, race, age, and year of diagnosis.[9]
		age at diagnosis of ≥ 80 years, year of diagnosis, histological grade, and primary site surgery.[10]
		Not receiving surgery, being unmarried and N1 stage.[11]
synchronous liver metastases and portal vein resection		

Independent prognostic factor of PFS identified in surgical subgroup												the largest axis of the liver metastasis > 5 mm, non-resection of the primary tumor, and T3-4 stage.[11]		

Abbreviation: NE = not estimable.

In green, the results that are in accordance with the results of this thesis.

1. It is not the 5-years recurrence-free survival rate but the 5-years disease-free survival rate which is defined as the duration between primary resection and the first documented progression of recurrent disease on CT or positron-emission tomography (PET) during regular follow-up.
2. Systematic review including five retrospective studies about asymptomatic, sporadic, small NF-PNENs.
3. It is not the median PFS but the median time from diagnosis to surgery.
4. Among patients with tumor size <1 cm. The observation subgroup was significantly older than the surgical subgroup.
5. A matched case–control study including incidentally discovered, sporadic, small (< 3 cm), stage I–II PNEN diagnosed between 1993 and 2013.
6. Poster collecting global 36uropean epidemiological data on neuroendocrine neoplasia. Data from 10,102 patients with various NETs were compiled.
7. From the multivariate analysis performed with the data of the 64 971 NETs cases collected from 1973 to 2012.
8. For grade 1 and grade 2 PNETs diagnosed from 1973 to 2004.
9. From the multivariate analysis performed with the data of the 35 618 NETs cases collected from 1973 to 2004.
10. From the multivariate analysis performed with the date of the 624 patients with distant metastatic PNET diagnosed between 1973 and 2015.
11. From the multivariate analysis performed with the data of 191 patients diagnosed with PNET with liver metastases.
12. For 76 patients with liver metastatic NF-PNENs.
13. Of 45 PNENs < 20 mm and of 96 PNENs > 20 mm, respectively.
14. Of 281 PNENs < 20 mm and of 1160 PNENs > 20 mm, respectively

.

10. References

1. **Modlin I.M., Öberg K., Chung D.C., Jensen R.T., de Herder W.W., Thakker R.V., Caplin M., Delle Fave G., Kaltsas G.A., Kidd M., Krenning E.P., Moss S.F., Nilsson O., Rindi G., Salazar R., Ruszniewski P. & Sundin A.** The Current Status of Gastroenteropancreatic Neuroendocrine Tumors. [book auth.] I.M. Modlin K.Öberg. *A Century of Advances in Neuroendocrine Tumor Biology and Treatment.* s.l. : Felsenstein C.C.C.P., 2007.

2. **Öberg K., Modlin I.M.** Non-functioning Pancreatic Endocrine Tumors. [book auth.] K.Öberg I.M. Modlin. *A Century of Advances in Neuroendocrine Tumor Biology and Treatment.* s.l. : Felsenstein C.C.C.P., 2007.

3. **Kvols, L.** Symptom Control in Malignant Carcinoid Syndrome and Pancreatic Neuroendocrine Tumors. [book auth.] I. M. Modlin and K. Öberg. *A Century of Advances in Neuroendocrine Tumor Biology and Treatment* . s.l. : Felsenstein C.C.C.P., 2007, pp. 354-363.

4. **Amin, S. and Kim, M. K.** Islet Cell Tumors of the Pancreas. *Gastroenterol Clin N Am.* 83-100, 2016, 45.

5. **Couvelard, A, et al.** Microvascular density and hypoxia-inducible factor pathway in pancreatic endocrine tumours: negative correlation of microvascular density and VEGF expression with tumour progression. *Br J Cancer.* 2005, Vol. 92, 1, pp. 94-101.

6. **Pape, UF, et al.** Survival and clinical outcome of patients with neuroendocrine tumors of the gastroenteropancreatic tract in a german referral center. *Ann N Y Acad Sci.* 2004, Vol. 1014, pp. 222-33.

7. **Scoazec, J.-Y., Couvelard, A. and TENpath, Réseau.** Classification of pancreatic neuroendocrine tumours: Changes made in the 2017 WHO classification of tumours of endocrine organs and perspectives for the future. *Annales de pathologie.* 445-446, 2017, 37.

8. **Kim, J.Y., Hong, S.-M. and Ro, J.Y.** Recent updates on grading and classification of neuroendocrine tumors. *Annals of Diagnostic Pathology.* 11-16, 2017, 29.

9. **Skogseid, B, et al.** Limited tumor involvement found at multiple endocrine neoplasia type I pancreatic exploration: can it be predicted by preoperative tumor localization? *World J Surg.* 1998, Vol. 22, 7, pp. 673-7.

10. **Agarwal, SK, et al.** Menin molecular interactions: insights into normal functions and tumorigenesis. *Horm Metab Res.* 2005, Vol. 37, 6, pp. 369-374.

11. **Hessman, O, et al.** Mutation of the multiple endocrine neoplasia type 1 gene in nonfamilial, malignant tumors of the endocrine pancreas. *Cancer Res.* 1998, Vol. 58, 3, pp. 377-9.

12. **Agarwal, S.K., et al.** Multiple Endocrine Neoplasias. [book auth.] I.M. Modlin and K. Öberg. *A Century of Advances in Neuroendocrine Tumor Biology and Treatment.* s.l. : Felsenstein C.C.C.P., 2007.

13. **Curley, SA, et al.** Surgical decision-making affected by clinical and genetic screening of a novel kindred with von Hippel-Lindau disease and pancreatic islet cell tumors. *Ann Surg.* 1998, Vol. 227, 2, pp. 229-35.
14. **Binkovitz, LA, Johnson, CD and Stephens, DH.** Islet cell tumors in von Hippel-Lindau disease: increased prevalence and relationship to the multiple endocrine neoplasias. *AJR Am J Roentgenol.* 1990, Vol. 155, 3, pp. 501-5.
15. **Klimstra, DS.** Nonductal neoplasms of the pancreas. *Mod Pathol.* 2007, Vol. 20 Suppl 1, p. S94.
16. **Hallet, J, et al.** Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer.* 2015, 121, p. 589.
17. **Barakat, MT, Meeran, K and Bloom, SR.** Neuroendocrine tumours. *Endocr Relat Cancer.* 2004, Vol. 11, 1, pp. 1-18.
18. **Klimstra, D., et al.** Non-functioning tumors and microadenomas. *IARC Press* . 2004.
19. **Madura, J.A., et al.** Nonfunctioning islet cell tumors of the pancreas a difficult diagnosis but one worth the effort. *Am Surg.* 1997, Vol. 63, pp. 573-577.
20. **Strosberg, JR.** Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms. *UpToDate.* 2020.
21. **Legmann, P, et al.** Pancreatic tumors: comparison of dual-phase helical CT and endoscopic sonography. *AJR Am J Roentgenol.* 1990, 170, p. 1315.
22. **Khashab, MA, et al.** EUS is still superior to multidetector computerized tomography for detection of pancreatic neuroendocrine tumors. *Gastrointest Endosc.* 2011, Vol. 73, p. 691.
23. **Dromain, C, et al.** MR imaging of hepatic metastases caused by neuroendocrine tumors: comparing four techniques. *AJR Am J Roentgenol* . 2003, 180, p. 121.
24. **Paulson, EK, et al.** Carcinoid metastases to the liver: role of triple-phase helical CT. *Radiology.* 1998, 206, p. 143.
25. **Sundin, A, et al.** ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Radiological, Nuclear Medicine and Hybrid Imaging. *Neuroendocrinology.* 2017, 105, pp. 212–244.
26. **Thoeni, RF, et al.** Detection of small, functional islet cell tumors in the pancreas: selection of MR imaging sequences for optimal sensitivity. *Radiology.* 2000, 214, p. 483.
27. **Dromain, C, et al.** Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. *J Clin Oncol.* 2005, 23, p. 70.
28. **James, PD, et al.** Incremental benefit of preoperative EUS for the detection of pancreatic neuroendocrine tumors: a meta-analysis. *Gastrointest Endosc.* 2015, 81, p. 848.
29. **Hellman, P, et al.** Endoscopic ultrasonography for evaluation of pancreatic tumours in multiple endocrine neoplasia type 1. *Br J Surg.* 2005, Vol. 92, p. 1508.

30. **Toumpanakis, C, et al.** Combination of Cross-Sectional and Molecular Imaging Studies in the Localization of Gastroenteropancreatic Neuroendocrine Tumors. *Neuroendocrinology.* 2014, Vol. 99, pp. 63-74.
31. **Pavel, M., et al.** ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. *Neuroendocrinology.* 2016, 103, pp. 172-185.
32. **Sadowski, SM, et al.** Prospective Study of 68Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero- Pancreatic Neuroendocrine Tumors and Unknown Primary Sites. *J Clin Oncol.* 2016, 34, p. 588.
33. **Fjällskog, ML, et al.** Expression of somatostatin receptor subtypes 1 to 5 in tumor tissue and intratumoral vessels in malignant endocrine pancreatic tumors. *Med Oncol.* 2003, 20, p. 59.
34. **Parbhu, S.K. and Adler, D.G.** Pancreatic neuroendocrine tumors: contemporary diagnosis and management. *Hospital Practice.* 2016, Vol. 44, 109-119.
35. **Rindi, G, et al.** TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. *J Natl Cancer Inst.* 2012, Vol. 104, 10, pp. 764–77.
36. **Rindi, G., et al.** TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch Int J Pathol.* 2006, Vol. 449, 4, pp. 395-401.
37. **Kazanjian, KK, Reber, HA and Hines, OJ.** Resection of pancreatic neuroendocrine tumors: results of 70 cases. *Arch Surg.* 2006, Vol. 141, p. 765 .
38. **Birnbaum, DJ, et al.** Pancreatic neuroendocrine tumor: A multivariate analysis of factors influencing survival. *the Journal of Cancer Surgery.* 2014, Vol. 40, pp. 1564-1571.
39. **Bahra, M, et al.** Surgical strategies and predictors of outcome for malignant neuroendocrine tumors of the pancreas. *J Gastroenterol Hepatol.* 2007, Vol. 22, p. 930.
40. **Bonney, GK, et al.** Results following surgical resection for malignant pancreatic neuroendocrine tumours. A single institutional experience. *JOP.* 2008, Vol. 9, p. 19.
41. **Norton, JA, et al.** Pancreatic endocrine tumors with major vascular abutment, involvement, or encasement and indication for resection. *Arch Surg.* 2011, Vol. 146, p. 724.
42. **Lee, J, Allendorf, J and Chabot, J.** Surgical resection of sporadic pancreatic neuroendocrine tumors. *UpToDate.* 2020.
43. **Capurso, G, et al.** Role of Resection of the Primary Pancreatic Neuroendocrine Tumour Only in Patients with Unresectable Metastatic Liver Disease: A Systematic Review. *Neuroendocrinology.* 2011, Vol. 93, pp. 223–229.
44. **Gomez-Rivera, F, et al.** Surgical treatment of pancreatic endocrine neoplasms. *Am J Surg.* 2007, Vol. 193, p. 460.
45. **Franko, J, et al.** Non-functional neuroendocrine carcinoma of the pancreas: incidence, tumor biology, and outcomes in 2,158 patients. *J Gastrointest Surg.* 2010, Vol. 14, pp. 541–548.

46. **Yuan, CH, et al.** Meta-analysis of liver resection versus nonsurgical treatments for pancreatic neuro- endocrine tumors with liver metastases. *Ann Surg Oncol.* 2016, Vol. 23, pp. 244–249.
47. **Watzka, FM, et al.** Surgical therapy of neuroendocrine neoplasm with hepatic metastasis: patient selection and prognosis. *Langenbecks Arch Surg.* 2015, Vol. 400, pp. 349–358.
48. **Mayo, SC, et al.** Emerging approaches in the management of patients with neuroendocrine liver metastasis: role of liver-directed and systemic therapies. *J Am Coll Surg.* 2013, Vol. 216, pp. 123–134.
49. **Pavel, M, et al.** ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology.* 2012, Vol. 95, p. 157.
50. **Ang Chan, J, Kulke, M and Clancy, TE.** Metastatic gastroenteropancreatic neuroendocrine tumors: Local options to control tumor growth and symptoms of hormone hypersecretion. *UpToDate.* 2020.
51. **Gillams, A., et al.** Radiofrequency ablation of neuroendocrine liver metastases: the Middlesex experience. *Abdominal Imaging.* 2005, Vol. 30, pp. 435-441.
52. **Wessels, FJ and Schell, SR.** Radiofrequency ablation treatment of refractory carcinoid hepatic metastases. *J Surg Res.* 2001, Vol. 95, p. 8.
53. **Hellman, P, et al.** Radiofrequency tissue ablation using cooled tip for liver metastases of endocrine tumors. *World J Surg.* 2002, Vol. 26, p. 1052.
54. **Berber, E, Flesher, N and Siperstein, AE.** Laparoscopic radiofrequency ablation of neuroendocrine liver metastases. *World J Surg.* 2002, Vol. 26, p. 985.
55. **Mazzaglia, PJ, et al.** Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10-year experience evaluating predictors of survival. *Surgery.* 2007, Vol. 142, p. 10.
56. **Mazzaglia, PJ, Berber, E and Siperstein, AE.** Radiofrequency thermal ablation of metastatic neuroendocrine tumors in the liver. *Curr Treat Options Oncol.* 2007, Vol. 8, p. 322.
57. **Mayo, SC, et al.** Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. *Ann Surg Oncol.* 2010, Vol. 17, p. 3129.
58. **Guiu, B, et al.** Liver/biliary injuries following chemoembolisation of endocrine tumours and hepatocellular carcinoma: lipiodol vs. drug-eluting beads. *J Hepatol.* 2012, Vol. 56, pp. 609–617.
59. **Hafdanarson, TR, et al.** The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Pancreatic Neuroendocrine Tumors. *Pancreas.* 2020, Vol. 49, pp. 863-881.
60. **Cholapranee, A, et al.** Risk of liver abscess formation in patients with prior biliary intervention following yttrium-90 radioembolization. *Cardiovasc Intervent Radiol.* 2015, Vol. 38, pp. 397–400.
61. **Devulapalli, KK, et al.** 90Y Radioembolization for hepatic malignancy in patients with previous biliary intervention: multicenter analysis of hepatobiliary infections. *Radiology.* 2018, Vol. 288, pp. 774–781.

62. **Le Treut, YP, et al.** Liver transplantation for neuroendocrine tumors in Europe-results and trends in patient selection: a 213-case European liver transplant registry study. *Ann Surg.* 2013, Vol. 257, p. 807.
63. **Mazzaferro, V., et al.** The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors. *American Journal of Transplantation.* 2016, Vol. 16, pp. 2892-2902.
64. **Partelli, S, et al.** Systematic review of active surveillance versus surgical management of asymptomatic small non-functioning pancreatic neuroendocrine neoplasms. *BJS.* 2017, 104, pp. 34-41.
65. **Falconi, M, et al.** ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. *Neuroendocrinology.* 2012, Vol. 95, p. 120.
66. **(NCCN), National Comprehensive Cancer Network.** NCCN clinical practice guidelines in oncology. *NCCN.* October 14, 2020.
67. **Modlin, IM, et al.** Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. *Aliment Pharmacol Ther.* 2010, Vol. 31, pp. 169-188.
68. **Susini, C and Buscail, L.** Rationale for the use of somatostatin analogs as antitumor agents. *Ann Oncol.* 2006, Vol. 17, p. 1733.
69. **Ang Chan, J, Kulke, M and Clancy, TE.** Metastatic well-differentiated pancreatic neuroendocrine tumors: Systemic therapy options to control tumor growth and symptoms of hormone hypersecretion. *UpToDate.* 2020.
70. **Caplin, M.E., et al.** Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *The New England Journal of Medecine.* 2014, Vol. 371, pp. 224-233.
71. **Kvols, LK, et al.** Treatment of metastatic islet cell carcinoma with a somatostatin analogue (SMS 201-995). *Ann Intern Med.* 1987, Vol. 107, p. 162.
72. **Saltz L, Trochanowski B, Buckley M, et al.** Octreotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors. *Cancer.* 1993, Vol. 72, p. 244.
73. **Arnold, R, et al.** Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. *Gut.* 1996, Vol. 38, p. 430.
74. **di Bartolomeo, M, et al.** Clinical efficacy of octreotide in the treatment of metastatic neuroendocrine tumors. A study by the Italian Trials in Medical Oncology Group. *Cancer.* 1996, Vol. 77, p. 402.
75. **Eriksson, B, et al.** High-dose treatment with lanreotide of patients with advanced neuroendocrine gastrointestinal tumors: clinical and biological effects. *Ann Oncol.* 1997, Vol. 8, p. 1041.
76. **Tomassetti, P, Migliori, M and Gullo, L.** Slow-release lanreotide treatment in endocrine gastrointestinal tumors. *Am J Gastroenterol.* 1998, Vol. 93, p. 1468.
77. **Toumpanakis, C and Caplin, ME.** Update on the role of somatostatin analogs for the treatment of patients with gastroenteropancreatic neuroendocrine tumors. *Semin Oncol.* 2013, Vol. 40, p. 56.

78. **Modlin, IM, et al.** Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. *Aliment Pharmacol Ther.* 2010, Vol. 31, p. 169.
79. **Panzuto, F, et al.** Long-term clinical outcome of somatostatin analogues for treatment of progressive, metastatic, well-differentiated entero-pancreatic endocrine carcinoma. *Ann Oncol.* 2006, Vol. 17, 3, pp. 461-6.
80. **Aparicio, T, et al.** Antitumour activity of somatostatin analogues in progressive metastatic neuroendocrine tumours. *Eur J Cancer.* 2001 May;37(8):1014-9., Vol. 37, 8, pp. 1014-9.
81. **Sidéris, L, Dubé, P and Rinke, A.** Antitumor effects of somatostatin analogs in neuroendocrine tumors. *Oncologist.* 2012, Vol. 17, p. 747.
82. **Strosberg, J and Kvols, L.** Antiproliferative effect of somatostatin analogs in gastroenteropancreatic neuroendocrine tumors. *World J Gastroenterol 2010; 16:2963.* 2010, Vol. 16, p. 2963.
83. **Verslype, C, et al.** The antiproliferative effect of somatostatin analogs: clinical relevance in patients with neuroendocrine gastro-entero-pancreatic tumours. *Acta Gastroenterol Belg.* 2009, Vol. 72, p. 54.
84. **Newman, CB, et al.** Safety and efficacy of long-term octreotide therapy of acromegaly: results of a multicenter trial in 103 patients--a clinical research center study. *J Clin Endocrinol Metab.* 1995, Vol. 80, p. 2768.
85. **Pavel, M, et al.** Efficacy, Safety and Quality of Life (QoL) with Lanreotide Autogel (LAN) 120 mg Every 14 Days in Progressive Pancreatic or Midgut Neuroendocrine Tumours (NETs): CLARINET FORTE Study Results. *ENETS 2021 VIRTUAL – 18th Annual ENETS Conference.* February 25 – 27, 2021.
86. **Oberg, K, et al.** Molecular pathogenesis of neuroendocrine tumors: implications for current and future therapeutic approaches. *Clin Cancer Res.* 2013, Vol. 19, p. 2842.
87. **Missiaglia, E, et al.** Pancreatic endocrine tumors: expression profiling evidences a role for AKT-mTOR pathway. *J Clin Oncol.* 2010, Vol. 28, p. 245.
88. **Zhang, J, et al.** Current understanding of the molecular biology of pancreatic neuroendocrine tumors. *J Natl Cancer Inst.* 2013, Vol. 105, p. 1005.
89. **Yao, J.C. and Xie, K.** Development of Novel therapeutic Agents for Neuroendocrine Tumors. [book auth.] I. M. I. M. Modlin and K. Öberg. *A Century of Advances in Neuroendocrine Tumor Biology and Treatment.* s.l. : Felsenstein C.C.C.P., 2007.
90. **Raymond, E., et al.** Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med.* 2011, Vol. 364, pp. 501–513.
91. **Xu, J, et al.** Surufatinib in advanced pancreatic neuroendocrine tumours (SANET-p): a randomised, double-blind, placebo-controlled, phase 3 study. *The Lancet Oncology.* 2020, Vol. 21, 11, pp. 1489-1499.

92. **Raymond, E, et al.** Therapy innovations: tyrosine kinase inhibitors for the treatment of pancreatic neuroendocrine tumors. *Cancer Metastasis Rev.* 2011, Vol. 30 Suppl 1, p. 19.
93. **Phan, AT, et al.** Pazopanib and depot octreotide in advanced, well- differentiated neuroendocrine tumours: a multicentre, single-group, phase 2 study. *Lancet Oncol.* 2015, Vol. 16, p. 695.
94. **Chan, JA, et al.** Phase II trial of cabozantinib in patients with carcinoi d and pancreaetic neuroenddocrine tumors (abstract). *J Clin Oncol.* 2017, Vol. 353, p. 228.
95. **Capdevilo, J, et al.** Final results of the TALENT trial (GETNE1509): a prospective multicohort phase II study of lenvatinib in ptients with G1/G2 advanced pa ncreatic and gastrointestinal neuroendocrine tumors. *J Clin Oncol.* 2019, Vol. 37, p. 106.
96. **Kulke, MH, Bergsland, EK and Yao, JC.** Glycemic control in patients with insulinoma treated with everolimus. *N Engl J Med.* 2009, Vol. 360, p. 195.
97. **Yao, JC, et al.** Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011, Vol. 364, p. 514.
98. **Kunz, PL, et al.** A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: a trial of the ECOG-ACRIN Cancer Research Group (E2211). *J Clin Oncol.* 2018, Vol. 15, 36.
99. **Kulke, MH, et al.** Phase II study of temo- zolomide and thalidomide in patients with metastatic neuroendocrine tumors. *J Clin Oncol.* 2006, Vol. 24, pp. 401-406.
100. **Chan, JA, et al.** Prospective study of bevacizumab plus temozolomide in patients with advanced neuroendocrine tumors. *J Clin Oncol.* 2012, Vol. 30, pp. 2963-2968.
101. **Cives, M, et al.** Analysis of potential response predictors to capecitabine/temozolomide in metastatic pancreatic neuroendocrine tumors. *Endocr Relat Cancer.* 2016, Vol. 23, pp. 759-767.
102. **Kulke, MH, et al.** O6-methylguanine DNA methyltransferase deficiency and response to temozolomide-based therapy in patients with neuroendocrine tumors. *Clin Cancer Res.* 2009, Vol. 15, p. 338.
103. **Walter, T, et al.** O6-Methylguanine-DNA methyltransferase status in neuroendocrine tumours: prognostic relevance and association with response to alkylating agents. *Br J Cancer.* 2015, Vol. 112, p. 523.
104. **Krug, S, et al.** Streptozocin-Based Chemotherapy in Patients with Advanced Neuroendocrine Neoplasms--Predictive and Prognostic Markers for Treatment Stratification. *PLoS One* . 2015, Vol. 10, e0143822.
105. **Moertel, CG, et al.** Streptozocin-doxorubicin, streptozocin- fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med.* 1992, Vol. 326, 519.
106. **Kouvaraki, MA, et al.** Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol.* 2004, Vol. 22, 4762.

107. **Dilz, LM, et al.** Streptozocin/5-fluorouracil chemotherapy is associated with durable response in patients with advanced pancreatic neuroendocrine tumours. *Eur J Cancer.* 2015, Vol. 51, 1253.
108. **Sorbye, H, et al.** Predictive and prog- nostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol.* 2013, Vol. 24, pp. 152–160.
109. **Raj, N, et al.** Treatment response and outcomes of grade 3 pancreatic neuroendocrine neoplasms based on morphology: well differentiated versus poorly differentiated. *Pancreas.* 2017, Vol. 46, pp. 296–301.
110. **Kunz, PL, et al.** Oxaliplatin-Fluoropyrimidine Chemotherapy Plus Bevacizumab in Advanced Neuroendocrine Tumors: An Analysis of 2 Phase II Trials. *Pancreas.* 2016, Vol. 45, 1394.
111. **McGarrah, PW, et al.** Efficacy of second-line chemotherapy in extrapulmonary neuroendocrine carcinoma. *Pancreas.* 2020, Vol. 49, pp. 529–533.
112. **Hörsch, D, et al.** Effectiveness and side-effects of peptide receptor radionuclide therapy for neuroendocrine neoplasms in Germany: A multi-institutional registry study with prospective follow-up. *Eur J Cancer.* 2016, Vol. 58, 41.
113. **Strosberg, J, et al.** Phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med.* 2017, Vol. 376, pp. 125–135.
114. **Garske-Román, U, et al.** Prospective observational study of 177Lu-DOTA-octreotate therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and impact of a dosimetry-guided study protocol on outcome and toxicity. *Eur J Nucl Med Mol Imaging.* 2018, Vol. 45, pp. 970–988.
115. **Yordanova, A, et al.** The Role of Adding Somatostatin Analogues to Peptide Receptor Radionuclide Therapy as a Combination and Maintenance Therapy. *Clin Cancer Res.* 2018, Vol. 24, 4672.
116. **Strosberg, JR, et al.** Prognostic validity of a novel American Joint Committee on Cancer Staging Classification for pancreatic neuroendocrine tumors. *J Clin Oncol.* 2011, Vol. 29, 3044.
117. **Borbath, Ivan, et al.** Assessing prognosis of neuroendocrine neoplasms: Results of a collaborative multinational effort including over 10.000 european patients—The ENETS registry. *Journal of Clinical Oncology.* 2018, Vol. 36, 15, pp. 4095-4095.
118. **Borbath, I, et al.** #4095: Assessing prognosis of neuroendocrine neoplasms: Results of a collabora;ve mul;na;onal effort including over 10.000 European pa;ents - The ENETS registry. 2018.
119. **Dasari, A, et al.** Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncology.* April 27, 2017, pp. E1-E8.
120. **Yao, JC, et al.** One Hundred Years After "Carcinoid": Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States. *JOURNAL OF CLINICAL ONCOLOGY.* 2008, Vol. 26, 18, pp. 3063-3072.

121. **Li, G, et al.** Nomograms predict survival outcomes for distant metastatic pancreatic neuroendocrine tumor. *Medicine.* 2020, Vol. 99, 13, pp. 1-8.
122. **Kim, H, et al.** Time-trend and recurrence analysis of pancreatic neuroendocrine tumors. *Endocrine Connections.* 2019, Vol. 8, 7, pp. 1052-1060.
123. **Andreasi, V, et al.** Long-Term Pancreatic Functional Impairment after Surgery for Neuroendocrine Neoplasms. *Journal of Clinical Medicine.* 2019, Vol. 8, 1611, pp. 1-14.
124. **Ricci, C, et al.** Sporadic Small (£20 mm) Nonfunctioning Pancreatic Neuroendocrine Neoplasm: is the Risk of Malignancy Negligible When Adopting a More Conservative Strategy? A Systematic Review and Meta-analysis . *Ann Surg Oncol.* 2017.
125. **Tao, L, et al.** Surgical resection of primary tumor improves survival of pancreatic neuroendocrine tumor with liver metastases. *Oncotarget.* 2017, Vol. 8, 45, pp. 79785-79792.
126. **Assi, HA, et al.** Surgery Versus Surveillance for Well-Differentiated, Nonfunctional Pancreatic Neuroendocrine Tumors: An 11-Year Analysis of the National Cancer Database. *The Oncologist.* 2020, 25, pp. e276–e283.
127. **Gao, H-L, et al.** Active surveillance in metastatic pancreatic neuroendocrine tumors: A 20-year single-institutional experience. *World J Clin Cases.* 2020, Vol. 8, 17, pp. 3751-3762.
128. **Sadot, E, et al.** Observation versus Resection for Small Asymptomatic Pancreatic Neuroencrine Tumors: A Matched Case–Control Study. *Ann Surg Oncol.* 2016, Vol. 23, 4, pp. 1361–1370.
129. **Panzuto, F., Capurso, G. and Delle Fave, G.** Medical Treatment of Gastro-Entero-Pancreatic Endocrine Tumors. [book auth.] Modlin I. M. and Öberg K. *A Century of Advances in Neuroendocrine Tumor Biology and Treatment.* s.l. : Felsenstein C.C.C.P., 2007.
130. **Lombard-Bohas, C.** Traitement médical antitumoral des tumeurs endocrines pancréatiques. [book auth.] P. Ruszniewski P. Lévy and A. Sauvanet. Paris : Flammarion Médecine-Sciences, 2005.
131. **Sundin, A.** Radiological and nuclear medicine imaging of gastroenteropancreatic neuroendocrine tumours. *Best Pract Res Clin Gastroenterol.* 803–18, 2012, Vol. 6, 26.
132. **Treglia, G., et al.** Diagnostic performance of Gallium-68 somatostatin receptor PET and PET/CT in patients with thoracic and gastroenteropancreatic neuroendocrine tumours: a meta-analysis. *Endocrine.* 80–87, 2012, Vol. 42.
133. **Bonaccorsi-Riani, E., et al.** Liver transplantation and neuroendocrine tumors: lessons from a single centre experience and from the literature review. *Transplant International.* 2010, Vol. 23, pp. 668–678.
134. **Mignon, M., Cadiot, G. and Aparicio, T.** Diagnostic clinique et biologique des tumeurs endocrines pancréatiques. [book auth.] P. Lévy, P. Ruszniewski and A. Sauvanet. *Traité de pancréatologie clinique.* Paris : Flammarion Médecine-Sciences, 2005.
135. **Rinke, A., et al.** Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic

Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group. *Journal of Clinical Oncology.* 2009, Vol. 27, pp. 4656-4663.
136. **Perren, A., et al.** ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pathology: Diagnosis and Prognostic Stratification. *Neuroendocrinology.* 2017.
137. **Lloyd, R.V.** Practical markers used in the diagnosis of neuroendocrine tumors. *Endocrine pathology.* 2003, Vol. 14, pp. 293-301.
138. **Bussolati, G., Volante, M. and Papotti, M.** Classic and recent special stains used in differential diagnosis of endocrine tumors. *Endocrine pathology.* 2001, Vol. 12, pp. 379-387.
139. **Paik, WH, et al.** Clinical usefulness of plasma chromogranin a in pancreatic neuroendocrine neoplasm. *J Korean Med Sci.* 2013, Vol. 28, 5, pp. 750–754.
140. **Qiao, X-W, et al.** Chromogranin A is a reliable serum diagnostic biomarker for pancreatic neuroendocrine tumors but not for insulinomas. *BMC Endocr Disord.* 2014, Vol. 14, p. 64.
141. **Evans, D.B., et al.** Nonfunctioning islet cell carcinoma of the pancreas. *Surgery.* 1993, Vol. 114, pp. 1175-1181.
142. **Solorzano, C.C., et al.** Nonfunctioning islet cell carcinoma of the pancreas :survival results in a contemporary series of 163 patients. *Surgery.* 2001, Vol. 130, pp. 1078-85.
143. **Thompson, G.B., et al.** Islet cell carcinomas of the pancreas: a twenty-year experience. 1988, Vol. 104, pp. 1011-1017.
144. **Chamberlain, R.S., et al.** Hepatic neuroendocrine metastases: does intervention alter outcomes? *J Am Coll Surg.* 2000, Vol. 190, pp. 432-45.
145. **Chen, H., et al.** Isolated liver metastases from neuroendocrine tumors: does resection prolong survival? *J Am Coll Surg.* Vol. 187, pp. 88-92.
146. **House, M.G., et al.** Differences in survival for patients with resectable versus unresectable metastases from pancreatic islet cell cancer. *J. Gastrointest Surg.* 2006, Vol. 10, pp. 138-45.
147. **Coppa, JC, et al.** Resection versus transplantation for liver metastases from neuroendocrine tumors. *Transplant Proc.* Vol. 33, pp. 1537-1539.
148. **Kulke, M.H., et al.** Telotristat etiprate is effective in treating patients with carcinoid syndrome that is inadequately controlled by somatostatin analog therapy (the phase 3 TELESTAR clinical trial) . *Eur J Cancer.* 2015, Vol. 51, p. 728.
149. **Arnold, R., et al.** Octreotide versus octreotide plus interferon-alpha in endocrine gastroenteropancreatic tumors: a randomized trial. *Clin Gastroenterol Hepatol.* 2005, Vol. 3, pp. 761-771.
150. **Eriksson, B., et al.** Treatment of malignant endocrine pancreatic tumours with human leucocyte interferon. *Lancet.* 1986, Vol. 2, pp. 1307-1309.
151. **Yao, J.C., et al.** RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group: Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011, Vol. 364, pp. 514-523.

152. **Turner, N.C., et al.** Chemotherapy with 5-fluoro- uracil, cisplatin and streptozocin for neuroendocrine tumours. *Br J Cancer.* 2010, Vol. 102, pp. 1106-1112.
153. **de Baere, T, et al.** GEP-NETS update: interventional radiology: role in the treatment of liver metastases from GEP- NETs. *Eur J Endocrinol.* 2015, Vol. 172, pp. 151-166.
154. **Hellman, P., et al.** Surgical strategy for large or malignant endocrine pancreatic tumors. *World J Surg.* 2000, Vol. 24, 11, pp. 1353-60.
155. **Perry, L.J., et al.** Hepatic arterial chemoembolization for metastatic neuroendocrine tumors. *Surgery.* 1994, Vol. 116, pp. 1111-1116.
156. **Dominguez, S, et al.** Hepatic arterial chemoembolization with streptozotocin in patients with metastatic digestive endocrine tumours. *Eur J Gastroenterol Hepatol.* 2000, Vol. 12, 2, pp. 151-7.
157. **Eriksson, BK, et al.** Liver embolizations of patients with malignant neuroendocrine gastrointestinal tumors. *Cancer.* 1998, Vol. 83, 11, pp. 2293-301.
158. **Falconi, M, et al.** Role of chemoembolization in synchronous liver metastases from pancreatic endocrine tumours. *Dig Surg.* 1999, Vol. 16, 1, pp. 32-8.
159. **Gupta, S., et al.** Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rates and survival. *Cancer.* 2005, Vol. 104, pp. 1590-1602.
160. **Chung, JW, et al.** Hepatic tumors: predisposing factors for complications of transcatheter oily chemoembolization. *Radiology.* 1996, Vol. 198, 1, pp. 33-40.
161. **Panzuto, F, et al.** Unlabelled somatostatin analogues in treatment of digestive endocrine tumours. *Dig Liver Dis.* 2004, Vol. 36, 1, pp. 42-7.
162. **Trendle, MC, Moertel, CG and Kvols, LK.** Incidence and morbidity of cholelithiasis in patients receiving chronic octreotide for metastatic carcinoid and malignant islet cell tumors. *Cancer.* 1997, Vol. 79, 4, pp. 830-4.
163. **Kamp, K, et al.** Safety and efficacy of everolimus in gastrointestinal and pancreatic neuroendocrine tumors after (177)Lu-octreotate. *Endocr Relat Cancer.* 2013, Vol. 20, pp. 825-831.
164. **Konno, H, et al.** Antitumor effect of a neutralizing antibody to vascular endothelial growth factor on liver metastasis of endocrine neoplasm. *Jpn J Cancer Res.* 1998, Vol. 89, 9, pp. 933-9.
165. **Choi, IS, et al.** Hypomethylation of LINE-1 and Alu in well-differentiated neuroendocrine tumors (pancreatic endocrine tumors and carcinoid tumors). *Mod Pathol.* 2007, Vol. 20, 7, pp. 802-10.
166. **Moore, AM, et al.** Gefitinib in patients with chemo-sensitive and chemo-refractory relapsed small cell cancers: a Hoosier Oncology Group phase II trial. *Lung Cancer.* 2006, Vol. 52, 1, pp. 93-7.
167. **Druker, BJ, et al.** Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med.* 2001, Vol. 344, 14, pp. 1031-7.
168. **Makowka, L, et al.** Transplantation of the liver for metastatic endocrine tumors of the intestine and pancreas. *Surg Gynecol Obstet.* 1989, Vol. 168, 2, pp. 107-11.

169. **Yao, JC, et al.** Clinical and in vitro studies of imatinib in advanced carcinoid tumors. *Clin Cancer Res.* 2007, Vol. 13, 1, pp. 234-40.
170. **Kouvaraki, MA, et al.** Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol.* 2004, Vol. 22, 23, pp. 4762-71.
171. **Strosberg, JR, et al.** First-line chemotherapy with capecitabine and temo- zolomide in patients with metastatic pancre- atic endocrine carcinomas. *Cancer.* 2011, Vol. 117, pp. 268-275.
172. **Kwekkeboom, DJ, et al.** Treatment of patients with gastro-entero-pancreatic (GEP) tumours with the novel radiolabelled somatostatin analogue [177Lu-DOTA(0),Tyr3]octreotate. *Eur J Nucl Med Mol Imaging.* 2003, Vol. 30, 3, pp. 417-22.
173. **Kwekkeboom, DJ, et al.** Overview of results of peptide receptor radionuclide therapy with 3 radiolabeled somatostatin analogs. *J Nucl Med.* 2005, Vol. 46, 1.
174. **Chu, QD, et al.** Predictive factors associated with long-term survival in patients with neuroendocrine tumors of the pancreas. *Ann Surg Oncol.* 2002, Vol. 9, 9, pp. 855-62.
175. **Que, FG, Sarmiento, JM and Nagorney, DM.** Hepatic surgery for metastatic gastrointestinal neuroendocrine tumors. *Adv Exp Med Biol.* 2006, Vol. 574, pp. 43-56.
176. **Stivanello, M, et al.** Circulating chromogranin A in the assessment of patients with neuroendocrine tumours. A single institution experience. *Ann Oncol.* 2001, Vol. 12.
177. **Detjen, KM, et al.** Molecular mechanism of interferon alfa- mediated growth inhibition in human neuroendocrine tumor cells. *Gastroenterology.* 2000, Vol. 118, p. 735.
178. **Rosewicz, S, et al.** Interferon-alpha: regulatory effects on cell cycle and angiogenesis. *Neuroendocrinology.* 2004, Vol. 80, p. 85.
179. **Faiss S, Pape UF, Böhmig M, et al.** Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors--the International Lanreotide and Interferon Alfa Study. *J Clin Oncol* . 2003, Vol. 21, p. 2689.
180. **Arnold, R, et al.** Octreotide versus octreotide plus interferon-alpha in endocrine gastroenteropancreatic tumors: a randomized trial. *Clin Gastroenterol Hepatol.* 2005, Vol. 3, p. 761.
181. **Yao, J, et al.** SWOG S0518: phase III prospective randomized comparison of depot octreotide plus interferon alpha-2b versus depot octreotide plus bevacizumab in advanced, poor prognosis carcinoid patients. *J Clin Oncol.* 2015, Vol. 33, p. 4004.
182. **Ang Chan, J and Kulke, M.** Metastatic well-differentiated gastrointestinal neuroendocrine (carcinoid) tumors: Systemic therapy options to control tumor growth. *UpToDate.* 2020.
183. **Välimäki, M, et al.** Is the treatment of metastatic carcinoid tumor with interferon not as successful as suggested? *Cancer 1991; 67:547.* 1991, Vol. 67, p. 547.
184. **Panzuto, F, et al.** Real-world study of everolimus in advanced progressive neuroen- docrine tumors. *Oncologist.* 2014, Vol. 19, pp. 966-974.

185. **Kamp, K, et al.** Safety and efficacy of everolimus in gastrointestinal and pancreatic neuroendocrine tumors after (177)Lu-octreotate. *Endocr Relat Cancer.* 2013, Vol. 20, pp. 825-831.
186. **Kulke MH, Niedzwiecki D, Foster NR, et al.** Randomized phase II study of everolimus vers us everolimus plus bevacizumab in patients with locally advanced or metastatic pancreatic neuroendocrine tumros (pNET),CALGB 80701 (Alliance). *J Clin Oncol.* 2015, Vol. 33, p. 4005.
187. **Hobday, TJ, et al.** Multicenter Phase II Trial of Temsirolimus and Bevacizumab in Pancreatic Neuroendocrine Tumors. *J Clin Oncol.* 2015, Vol. 33, p. 1551.
188. **Imhof, A, et al.** Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. *J Clin Oncol.* 2011, Vol. 29, 2416.
189. **Nwosu, AC, et al.** Assessment of the efficacy and toxicity of (131)I- metaiodobenzylguanidine therapy for metastatic neuroendocrine tumours. *Br J Cancer.* 2008, Vol. 98, 1053.
190. **Nguyen, C, et al.** Long-term efficacy of radionuclide therapy in patients with disseminated neuroendocrine tumors uncontrolled by conventional therapy. *J Nucl Med.* 2004, Vol. 45, 1660.
191. **Khashab, MA, et al.** EUS is still superior to multidetector computerized tomography for detection of pancreatic neuroendocrine tumors. *Gastrointest Endosc.* 2011, 73, p. 691.
192. **Gibril, F, et al.** Somatostatin receptor scintigraphy: its sensitivity compared with that of other imaging methods in detecting primary and metastatic gastrinomas. A prospective study. *Ann Intern Med.* 1996, 125, p. 26.
193. **Pisegna, JR, et al.** Prospective comparative study of ability of MR imaging and other imaging modalities to localize tumors in patients with Zollinger-Ellison syndrome. *Dig Dis Sci.* 1993, 38, p. 1318.
194. **Rösch, T, et al.** Localization of pancreatic endocrine tumors by endoscopic ultrasonography. *N Engl J Med.* 1992, 326, p. 1721.
195. **Anderson, MA, et al.** Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. *Am J Gastroenterol.* 2000, 95, p. 2271.

UNIVERSITÉ CATHOLIQUE DE LOUVAIN
Faculté de médecine et médecine dentaire
Avenue Mounier, 50 bte B1.50.04, 1200 Woluwe-Saint-Lambert, Belgique | **www.uclouvain.be/mede**