Multiple Endocrine Neoplasia Type 1 (MEN1) and the Pancreas

Diagnosis and Treatment of Functioning and Non-Functioning Pancreatic and Duodenal Neuroendocrine Neoplasia within the MEN1 Syndrome – An International Consensus Statement

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This consensus statement is dedicated in honor of the Austrian pathologist **Jakob Erdheim** and the (Austrian-)American internist **Paul Wermer**.

Jakob Erdheim was born on May 24, 1874 in Boryslav, Galicia and died on April 18, 1937 in Vienna. He was born into a Jewish family and was an Austrian pathologist. In 1901, he received his medical degree from the University of Vienna, later working as an assistant at the Institute of Pathological Anatomy in Vienna. In 1913, he became assistant professor of pathological anatomy, and in 1916 was named director of the Pathological-Anatomical Institute at Vienna City Hospital. From 1924 onward, he was associated with the "Krankenhaus der Stadt Wien-Lainz". He distinguished himself in research on hyperparathyroidism, acromegaly, Paget's disease and pituitary gland abnormalities. His name is associated with "Erdheim's syndrome", a condition that is also known as "Scaglietti-Dagnini syndrome" (cervical spondylosis secondary to acromegaly), Erdheim disease (a synonym for cystic medial necrosis) and Erdheim tumor (a synonym for craniopharyngioma).

Paul Wermer was born on February 2, 1898 in Austria and died on November 18, 1975 in New York. He earned his medical degree from the Medical School of the University of Vienna in 1922 and emigrated to New York City, USA on December 5, 1939. He participated in research projects in many hospitals, including the Vanderbilt Clinic, Delafield Hospital, Bellevue Hospital, and worked in the Department of Medicine, Columbia University, Presbyterian Hospital. His most important scientific contribution was a description of the genetic aspects of adenomatosis of the endocrine glands. In this publication, he described the MEN1 syndrome.

Abstract

The better understanding of the biological behavior of MEN1 organ manifestations and the increase in clinical experience warrant a revision of previously published guidelines.

DP-NENs are still the second most common manifestation in MEN1 and, besides NENs of the thymus, remain a leading cause of death. DP-NENs are thus of main interest in the effort to re-evaluate recommendations for their diagnosis and treatment. Especially over the last two years, more clinical experience has documented the follow-up of treated and untreated (natural-course) DP-NENs.

It was the aim of the international consortium of experts in endocrinology, genetics, radiology, surgery, gastroenterology and oncology to systematically review the literature and to present a consensus statement based on the highest levels of evidence. Reviewing the literature published over the past decade, the focus was on the diagnosis of F- and NF-DP-NENs within the MEN1 syndrome in an effort to further standardize and improve treatment and follow-up, as well as to establish a "logbook" for the diagnosis and treatment of DP-NENs. This shall help further reduce complications and improve long-term treatment results in these rare tumors.

The following international consensus statement builds upon the previously published guidelines of 2001 and 2012 and attempts to supplement the recommendations issued by various national and international societies.

Introduction

Bruno Niederle and Andreas Selberherr

Historical Background

One hundred and seventeen years ago, the Viennese pathologist Jakob Erdheim described a patient with multiple endocrine tumors [1]. His necropsy report documented pituitary adenoma with acromegaly and three enlarged parathyroid glands. Without knowing the background, this was the first coincidental report of a patient with multiple endocrine tumors. In 1953, Underdahl et al. reported eight patients with a syndrome of pituitary, parathyroid and pancreatic islet tumors [2].

One year thereafter, Paul Wermer established that the syndrome was transmitted as a dominant trait [3]. The same year, Moldawer and coworkers published some more experience with respect to the concomitance of multiple parathyroid adenomas, pancreatic and pituitary tumors [4]. Analyzing the literature available at that time (24 patients) and adding four more new cases, these authors emphasized the theory of a "syndrome with familial incidence".

The term "multiple endocrine neoplasia" was introduced by Steiner et al. in 1968 to summarize disorders affecting a combination of endocrine tumors [5]. The authors proposed to rename Wermer's syndrome "MEN1", while indicating that these diseases and syndromes are very rare and therefore very complicated to diagnose and treat [5].

Genetics

MEN1 (OMIM 131100) is caused by inactivating germline mutations in the MEN1 gene on the long arm of chromosome 11 (11q13). MEN1 is a tumor suppressor gene and consists of 10 exons that encode a 610-amino acid protein called menin [6]. Menin is predominantly a nuclear protein that has roles in transcriptional regulation, genome stability, cell division and proliferation [7, 8].

Germinal inactivating heterozygote mutations have been identified to be responsible for the development of the syndrome, mostly through the loss of the second wild-type copy of the gene at the somatic level of specifically predisposed neuroendocrine tissues. Over 1500 different germinal and somatic mutations – encompassing the entire coding region (exons 2-10) and splicing sites of MEN1 – have been described, none of them being associated with a specific clinical phenotype and/or disease penetrance [9, 10].

Since the first case reports and the detection of the genetic background of the complex disease, **major progress has been made to improve its diagnosis and treatment.** However, a direct genotype-phenotype correlation is still lacking, while the clinical course of the disease and tumor localization cannot be precisely foreseen in attempts to develop personalized diagnostic screening or treatment plans.

Clinical Manifestations

MEN1 is an autosomal dominant, rare, hereditary endocrine tumor syndrome with an estimated prevalence of 1 to 10/100,000. MEN1 develops neoplastic lesions, mostly in the parathyroid glands (up to 100%), pancreas and duodenum (30-90%), and the anterior pituitary (30-40%) [11]. Tumors of the adrenal glands are documented in approx. 20-40% of patients. Less frequently, MEN1-associated NENs are diagnosed in the thymus or in the bronchopulmonary tract in 3-10% of cases. Multiple non-endocrine skin lesions are also frequent (i.e. collagenomas, angiofibromas, fibromas, angiomas and lipomas). They are often clinically manifest before the diagnosis of a MEN1 NEN. In young subjects, multiple lipomas may lead to an early diagnosis of MEN1.

As shown recently [12], breast cancer appears to be a new MEN1-related manifestation, and female patients with MEN1 appear to be at an increased risk for breast cancer, independent of other known breast cancer risk factors or familial cancer history [13]. Breast cancer is identified in approx. 7% of female patients with MEN1 [14].

Definition of MEN1

MEN1 may be diagnosed by clinical, familial or genetic characteristics:

- Clinical: A patient shows two or more MEN1-associated endocrine tumors (i.e. parathyroid adenoma, entero-pancreatic tumor and pituitary adenoma);
- Familial: A patient shows one MEN1-associated tumor and has a first-degree relative with MEN1;
- Genetic: A patient who has one of the various MEN1 mutations but does not have clinical (or biochemical) manifestations of MEN1 (asymptomatic gene carrier) [10, 11, 15-17].

Reasonable suspicion of MEN1 is justified in patients who are young at onset (< 30 years) and in the presence of one or multiple clinically or biochemically diagnosed MEN1-related lesions in a single organ or in two distinct organs [18]. Genetic testing is justified in these cases. MEN1 mutational analysis

facilitates clinical management and provides benefits for affected patients and families with MEN1 [16]. Due to a time lag between the diagnosis of a given index case and other members of the same family, a clinically relevant delay is associated with an increased morbidity and mortality risk [13].

Genetic testing is not available everywhere. Systematic use of a specific query for a personal or family history of MEN1 with a simple six-question panel may help to diagnose MEN1 at an early stage. Especially young males with primary hyperparathyroidism – the first biochemical or clinical manifestation of the disease in most affected patients – and positive panel results should be further evaluated for MEN1 (Table 1) [19].

Table 1. Specific query for a personal and family history of MEN1 with six standardized questions

Do you have a personal or family history of MEN1?	**Yes**	**No**
Do you have any blood relatives with …		
Neck surgery?	Yes	No
Kidney stones?	Yes	No
Brain tumors?	Yes	No
Ulcers?	Yes	No
High calcium levels?	Yes	No
Pancreatic tumors?	Yes	No

Neuroendocrine Pancreatic Cells and NENs

Apart from primary hyperparathyroidism, ***DP-NENs are the second most common manifestation in MEN1***. They arise from proliferating neuroendocrine cells (islets cells) which are part of the diffuse neuroendocrine system. In general, gut endocrine cells are recognized by the expression of several "general" markers, including the large dense-core vesicle marker CgA and the synaptic-like microvesicle marker synaptophysin. The expression of different hormones identifies specific cell types. A single cell may produce and secrete one or more biologically active peptides [20].

Alpha cells (producing glucagon), beta cells (producing insulin), delta cells (producing somatostatin; physiological paracrine production for the internal regulation of alpha and beta cell secretion), and PP cells (gamma cells or F cells; producing PP) are found predominantly in the pancreas and are arranged in well vascularized clusters throughout the (exocrine) organ. In turn, gastrin cells (producing gastrin) are localized in the duodenum (and stomach). Gastrin cells are found slightly ectopically in the pancreas [21].

Pipeleers-Marichal et al. [22] were the first investigators to describe the majority of gastrinomas in MEN1-ZES patients in the duodenum. A recent pathological study of DP specimens has shown that ***patients with MEN1-ZES always have duodenal gastrinomas and almost never pancreatic gastrinomas*** (GR: 4, LE: 2b). It has also been demonstrated that proliferative gastrin cells are the precursors of duodenal gastrinomas (LE: 2b) [23, 24].

F- and NF-NENs

From a pathophysiological point of view, and to simplify the complexity of NENs of the pancreas in MEN1, DP-NENs are summarized as one entity in this international consensus statement. ***Patients with MEN1 may develop F-NENs and NF-NENs of the duodenum and pancreas.*** F-NENs produce and secrete elevated levels of a specific GI hormone (i.e. gastrin or insulin), resulting in clinical syndromes due to hormone excess (Table 2).

F-DP-NENs include gastrinomas (releasing gastrin with ZES), insulinomas, VIPomas (secreting VIP and resulting in Verner-Morrison syndrome), glucagonomas and somatostatinomas. F-NENs are defined on the basis of clinical symptoms due to inappropriate hormone secretion rather than IHC findings. In the majority of functioning tumors, the hormone causing the syndrome can be detected by IHC. However, staining intensity and the number of positive cells are not related to the severity of symptoms (Table 2).

Table 2. F-DP-NEN syndromes and laboratory tests

Tumor type	**Hormone**	**Clinical symptoms**	**Diagnostic laboratory tests**	**Characteristics**
Gastrinoma	Gastrin	ZES (gastric ulcers)	Gastrin > 1000, pH < 2 (If available: secretin stimulation test)	Location in the duodenal wall (multiple lesions) Malignant behavior
Insulinoma	Insulin	Hypoglycemia	Insulin C-peptide 72h fasting test	Location in the pancreas Benign behavior
Glucagonoma	Glucagon	Diabetes, necrolytic migratory erythema	Glucagon, hyperglycemia	Location in the pancreas Malignant behavior
VIPoma	VIP	WDHA syndrome	VIP	Location in the pancreas Malignant behavior (40%)
Somatostatinoma	Somatostatin	Diabetes, gallstones, inability to digest fats	Somatostatin	Location in the pancreas Malignant behavior (75%)
ACTHoma	ACTH	Cushing syndrome, weight gain, depression, easy bruising, increased risk of infection and darkened skin		

Very few patients with gastrin-producing NENs but without ZES have been described [25].

NF-DP-NENs (inactive, clinically silent, non-syndromic) do not secrete the typical GI hormones and therefore cause no endocrine syndromes (asymptomatic DP-NENs). However, they may secrete several different peptides, e.g., CgA, PP and glucagon, and rarely neuron-specific enolase, human chorionic gonadotrophin subunits, calcitonin and neurotensin. Increasingly, they are incidentally detected on imaging tests. Tumors with a diameter of less than 5 mm, the minimum size required for gross detection, are defined as microadenomas and are, as a rule, non-functioning. Non-functioning tumors may become clinically apparent due to their larger size and malignant regional invasion of adjacent tissue with local clinical symptoms, or may show distant spread [26].

Although NENs in all locations including the pancreas are potentially malignant tumors, they differ in their metastasizing capacity (i.e. their biological behavior), depending on several features and criteria, such as histological differentiation, size, angioinvasion, Ki-67 index and hormonal syndrome [25].

Comparing hereditary and sporadic DP-NENs, there seem to be no differences in the biological behavior of a single neuroendocrine pancreatic tumor. However, due to the genetic background of the disease, every single neuroendocrine cell of the duodenum and pancreas is a potential NEN progenitor. Therefore, MEN1 patients generally present with multifocal and variously large DP-NENs at an earlier age. F-NENs and NF-NENs may develop in coexistence. In terms of clinical presentation, natural history and long-term follow-up, there are indeed significant differences between sporadic and DP-NENs in MEN1 patients. **These MEN1-specific characteristics raise the important question as to whether diagnostic and treatment concepts developed for sporadic P-NENs can be applied without modification to patients with hereditary disease.**

Many pancreatic lesions are "viewable" and definitively diagnosed by transgastric EUS with biopsy and/or cross-sectional and/or functional imaging. ***While F-DP-NENs must be treated to reduce or cure hormonal excess, the strategies addressing the treatment of NF-DP-NENs, which are distributed throughout the entire pancreas, remain a matter of controversial discussion*** [27].

Although overall knowledge of the pathophysiology, diagnosis and treatment of DP-NENs within MEN1 has improved since the first guidelines were published in 2001 and 2012 [11, 15], the primary life-threatening manifestations of MEN1 continue to persist along with the malignant nature of DP-NENs, but more recently with malignant thymic NENs [28-30].

Aim of the International Consortium

It was the aim of the international consortium of experts to systematically review the literature and to present a consensus statement based on the best scientific evidence available. However, the majority of minimal consensus statements and recommendations were not based on prospective studies,

the studies were not performed in a randomized fashion, and they generally involved only a small number of consecutively collected patients in one or multiple national and international centers and are thus based on LE 3 or 4. Large prospective observational studies or RCTs comparing different diagnostic and therapeutic strategies could overcome the overall ***low LEs and GRs***, but they are unrealistic owing to the rarity of the disease. Meta-analyses combining the results of multiple scientific studies were included, whenever possible.

Reviewing the literature published over the past decade, the focus was on the diagnosis of F-DP-NENs and NF-DP-NENs within the MEN1 syndrome to further standardize and improve treatment and follow-up. Earlier publications were included ***to enhance the understanding of the disease and ongoing controversies, as well as to establish a "logbook" for the diagnosis and treatment of DP-NENs. This shall help to further reduce complications and improve long-term treatment results in these rare tumors.***

The present "Supplement" reviews the available English literature in more detail, including additional background information regarding DP disease within MEN1, presents expert advice on the diagnosis and management of DP-NENs and technical details of surgery, and documents more extensively the discussion of controversies.

Management decisions to treat F-and NF-DP-NENs in MEN1 have to be made in a multidisciplinary team and the patients should be followed individually by experts. The following reassembled consensus statement confirms or modifies former recommendations published previously for the diagnosis and treatment of MEN1 [11, 15], while attempting to supplement the recommendations issued by various national and international societies [16, 27, 31-33].

Methods

At the beginning of the consensus process, all experts discussed the topics in detail and divided them into subtopics. All participants accepted their subtopics, as well as their responsibility to review the current literature and to prepare their contributions for a combined consensus manuscript (see Addendum 1). All participants agreed to perform literature reviews using PubMed, MEDLINE and Embase (time period: 2000-06/2020); and key publications prior to 2000). The following search terms were used:

- "Multiple endocrine neoplasia type 1" in combination with "gastrinoma",
- "Zollinger-Ellison syndrome",
- "Insulinoma",
- "VIPoma",
- "Glucagonoma",

- "Somatostatinoma",
- "Neuroendocrine pancreatic neoplasia and tumor",
- "Surgical and medical treatment", and
- "Prognosis, natural course, follow-up".

Based on titles and abstracts, all relevant papers were identified. In addition, reference tracking was carried out in an attempt to identify further publications. Accordingly, and following careful reviews of the current literature, each participant agreed to prepare a draft manuscript summarizing the specific subtopic. It was decided that the first final draft should be reviewed by external experts not involved in the initial literature search and in the preparation of the draft manuscript (see Addendum 1). After discussing the comments, the final manuscript was to be set up and submitted for publication.

Methodological quality was assessed using the Oxford CEBM LEs and GRs (March 2009; Addendum 2). The Delphi method was applied and a questionnaire circulated among all authors in order to harmonize controversial topics (e.g., when to start screening, methods of diagnosing ZES, indication for surgery, surgical strategies, long-term follow-up). The Delphi questionnaire was adapted for use in the authors' face-to-face meetings. The preliminary draft of the manuscript was then prepared and sent to the external reviewers.

The external reviewers of all specialties – endocrinology, genetics, radiology, surgery, gastroenterology and oncology – and the ENETS and ESES representatives submitted their expert opinions twice (see Addendum 1). Their recommendations and comments were included in the final manuscript.

Epidemiology – Diagnosis – Indications for Treatment

Epidemiology, Penetrance, Incidence and Frequency

Thorvardur R. Halfdanarson and Maria L. Brandi

Who Should Be Screened Genetically?

A diagnosis of MEN1 should be considered for any patient with either a family history of endocrine tumors of the pancreas, pituitary or parathyroid glands, or a family history of another endocrinopathy [8]. ***Genetic testing is recommended in all patients with clinical suspicion of MEN1 to confirm the diagnosis and in all first-degree relatives of MEN1 gene carriers*** [15, 34, 35]. Suspicion should also be raised in patients who are diagnosed with a typical MEN1 manifestation (e.g., primary hyperparathyroidism, ZES) at a young age (< 30 years), who show multiple DP-NENs, or DP-NENs associated with hypercalcemia or another endocrinopathy at any age.

In most but not all patients, MEN1 presents clinically after the age of 21 [36]. ***The MEN1 genetic test helps the specific diagnosis of MEN1 and allows the early identification of asymptomatic carriers***, strongly contributing, together with progressions in tumor diagnostic techniques and in pharmacological and surgical therapeutic approaches, to the reduction of morbidity and mortality associated with the syndrome [37]. Gene mutation carriers and even negative-tested patients with a high clinical suspicion for MEN1 should be kept under "individualized" surveillance running "standardized screening programs" [11, 15].

The responsible physicians should have detailed knowledge about the syndrome, the varying phenotypes and its treatment options. Surveillance with a consecutive timely and individualized intervention reduces the morbidity and mortality of F- and NF-DP-NENs [38, 39].

When Should Genetic and Biochemical Screening for DP-NENs Start in MEN1?

The current guidelines [11] recommend genetic testing to start at the age of 5 years for MEN1 and annual biochemical (and imaging) screening in affected individuals. ***The aim of "screening programs" for inherited tumor syndromes should be effectiveness with regard to diagnostic yield documenting clinically relevant manifestations, costs and psychological burden and distress of the positively screened but clinically asymptomatic individuals and their families.*** The expert recommendations [11, 15] are based on the fact that severe organ manifestations (e.g., insulinoma, gastrinoma, high-grade

thymic or bronchopulomary NENs, adrenal lesions) can occur in children early on but that they are very rare [40-43].

Up to now, there are two prospective databases retrospectively analyzing the incidence of typical MEN1 lesions in children [41, 43] and reviewing the current guidelines [11, 15]. Twenty of 166 (12%) MEN1 patients under the age of 19 years and 8 (4.8%) of 166 patients younger than 16 years revealed at least one MEN1 organ manifestation. Only five (25%) of the 20 patients < 19 years and 166 (3%) of the whole cohort had symptomatic or clinically significant manifestations before the age of 16 years, including four symptomatic insulinomas and one bronchial NEN. The authors concluded that symptomatic or severe manifestations in MEN1 patients rarely occur before the age of 16 years [43].

In the second study [41], at least one organ manifestation was reported before the age of 21 years in 160 (17%) and before the age of 16 years in 76 (8.2%) of 924 MEN1 patients. Four (5.2%) of the patients below 16 years had symptomatic and malignant lesions (one gastrinoma with liver metastases, two 70 mm adrenal carcinomas, and one metastatic carcinoma of the thymus). These authors concluded that MEN1 lesions may occur during the first two decades of life. As insulinomas implicate a potential life-threatening risk and PHPT is the most prevalent manifestation, the authors suggested that regarding these tumors, young MEN1 patients should be already screened at the age of five years. According to the GTE study, screening of further MEN1 lesions should be postponed until the age of 10 years.

The penetrance of MEN1-related P-NENs in patients between 12 and 20 years of age was reviewed in 19/113 subjects (16.8%) [44]. The overall penetrance of P-NENs during the second decade of life was 42% (8 of 19). Eight patients had NF-P-NENs, and half of those tumors were multicentric. Insulinoma was detected in 2/19 (11%) at the initial screening. Gastrinoma was not present in any case. At least one large tumor > 20 mm was documented in 4/19 (21%). Distal pancreatectomy and the nodule enucleation of pancreatic head tumors were conducted on three patients with large tumors (> 20 mm; T2N0M0) that were classified as grade 1 NENs (Ki-67 < 2%)[44].

Herath et al. [45] reviewed 180 MEN1 patients for whom clinical records, imaging and pathology results were available at the age of less than 22 years. In 12 (26.7%) of the 45 patients at a mean age of 17.0 ± 2.6 years and having undergone abdominal imaging, seven patients had pancreatic lesions < 10 mm in diameter, three of which were symptomatic insulinomas that were successfully treated surgically (two patients were diagnosed at 14 years of age, while the third was diagnosed at 18 years of age). Three patients had benign P-NENs between 11 mm and 20 mm in diameter that were non-secretory and managed surgically, and two patients had pancreatic lesions > 20 mm diameter, one of which was resected and found to have perineural invasion. No cases of gastrinoma were diagnosed in this patient group. The authors reported that children identified as MEN1-positive through cascade screening typically commence regular biochemical screening at the age of 10.

Results from a recent study [46] analyzing the time of penetrance of MEN1-related manifestations in three generations and ranking patients from the oldest to the youngest generation showed a decreased age at detection of MEN1 manifestations in successive generations, thus suggesting the presence of genetic anticipation. In all MEN1-related manifestations, the median age at detection was the highest in the first generation and the lowest in the last (third and fourth) generations. The results might add to future, more personalized screening protocols and earlier screening for future generations of MEN1 patients.

Therefore, it is a matter of ongoing discussion whether genetic testing should be postponed until the second decade of life [43, 44] and whether annual routine biochemical tests and radiological imaging should be extended up to 2- or 3-year intervals if no clinically relevant organ manifestations were detected at the initial screening visit and in the family, since rapid progression of organ manifestations is rarely observed [47, 48].

The arguments for shifting genetic examinations and, if positive, for biochemical screening to the age of 16 and for prolonging the follow-up and screening intervals are that the majority of manifestations start around that age and that there is no role for prophylactic medical treatment or surgery in asymptomatic individuals. This more restricted screening strategy prohibits unnecessary examinations without missing serious manifestations [49].

Characteristics of DP-NENs

MEN1 shows a high degree of penetrance. Clinical and biochemical manifestations of the disorder will have developed in 80% and in more than 98% of MEN1 patients, respectively,[11, 15].

DP-NENs usually develop before the age of 50 years and are diagnosed at an earlier stage due to periodic screening (LE: 4) [26, 29, 30, 50-52]. Both insulinomas and gastrinomas occur earlier in MEN1 patients than in those with sporadic pancreatic endocrine tumors. A detailed study in gastrinomas showed a difference of one decade (43.5 vs. 33.2 years) [26].

In a recently published study of DP-NENs in MEN1-affected (MEN1 [+]) and MEN1-non-affected (MEN1 [-]) patients, DP-NENs were more often seen to be multicentric compared to MEN1 [-] DP-NENs. The frequency of liver and lymph node metastatic spread was higher in MEN1 [-] compared to MEN1 [+] DP-NENs. It was concluded that stage disease and prognosis could be positively influenced by early diagnosis and screening in index patients' first-degree relatives [53].

Prevalence

NENs in the pancreas and/or duodenum are seen in 30 to 75%, and even up to 100% of patients with MEN1 in recent studies. Determining the prevalence of DP-NENs in patients with MEN1 is difficult, as the published studies are very heterogeneous in terms of definitions of F-DP-NENs and NF-DP-NENs, differences between P-NENs and D-NENs, and applied detection methods.

The prevalence of NF-DP-NENs is probably equal to that of DP-NENs in general, since NF-DP-NENs are found in nearly all patients undergoing surgery for functional tumors [54-56] and increase with age [11, 36, 37, 54, 57-67]. Prior to 2010, representative studies mostly reported F-DP-NENs, with a prevalence ranging from 36 to 74% and with gastrinomas and insulinomas comprising most of the NENs [35, 36, 60-62, 66, 68-71]. The characteristics of MEN-associated DP-NENs are listed in Table 3 (see: [72]).

Table 3. Characteristics of sporadic and MEN-associated DP-NENs

Tumor type	**Annual incidence (cases per million)**	**Age (years)**	**Percent malignant (potential to metastasize)**	**Percent located in the pancreas**	**Percent associated with MEN1**
Insulinoma	0.7-4.0	30-60	5-10	> 95	4-8
Gastrinoma	0.5-4.0	20-60	40-90	25-40	15-30
VIPoma	0.1-0.6	20-80	> 50	75-90	6-11
Glucagonoma	$\leq$ 0.1	40-60	> 50	> 80	5-20
Somatostatinoma	< 0.1	30-80	> 60	40-70	2-7
Other hormones	Very rare	-	-	-	unknown
Non-functioning	3-12 0.1-10% autopsy and surgery series	40-70	> 80	100	0-21

F-DP-NENs

The diagnosis of MEN1 should be considered in all patients with so-called sporadic DP-NENs, especially in those with gastrinomas or insulinomas, because MEN1 is found in 10 to 54% (mean: 25%) of all patients with gastrinomas and in 4% of those with insulinomas [26, 31, 35, 43, 55, 65, 73-75]. On the other hand, gastrinomas occur in 54% (range: 20-61%) of MEN1 patients, whereas insulinomas

occur in 18% (range: 7-31%); other F-P-NENs are much less common (< 5%) [26, 30, 50]. Among 580 patients with MEN1, DP involvement was present in 307 (52.9%). Five (1.6%) had a glucagonoma, three (0.98%) a VIPoma and two (0.65%) a somatostatinoma. A clinical syndrome was present in one patient with glucagonoma, in the three with VIPomas and in one with somatostatinoma [59].

From genetic considerations and observational studies, the distribution of typical MEN1 lesions has been assumed to be almost equal in men and women [11]. However, some recent studies have shown gender-dependent prevalence of some MEN1-asscociated organ manifestations [28, 52, 64, 76]. Bartsch et al. provided detailed information on a cohort of patients with MEN1 and found a higher prevalence of DP-NENs in male patients compared to women (100 vs. 88%, $p = 0.042$). Goudet et al. [64] analyzed the impact of gender on the prevalence of MEN1 lesions. DP-NENs were found to be more prevalent among men than women, but the differences were explained by a higher prevalence of gastrinomas in men. This study showed the prevalence of NF-NENs to be 13.9% and 16.5% among men and women, respectively. However, the prevalence of gastrinomas was 36.5% in men and 24.3% in women ($p < 0.001$), respectively. Gastrinomas were the most commonly observed F-NENs, followed by NF-NENs and insulinomas (52%, 27% and 19%, respectively).

However, as shown recently, and apart from some minor differences between males and females, gender-adapted diagnostic and therapeutic approaches cannot be recommended [77].

NF-DP-NENs

NF-DP-NENs were infrequently reported in earlier studies and likely went undetected in many cases. More recent studies, some relying on more sensitive imaging modalities, have suggested that NF-NENs are the most commonly encountered NENs in patients with MEN1, followed by gastrinomas and insulinomas [30, 55, 64, 78-82]. Some of the more recent studies are briefly discussed below.

Kouvaraki et al. reported their single-center experience with 98 MEN1 patients in the United States [78]. Fifty-six percent of the patients had DP-NENs and of those, 64% were functioning and most often gastrinomas. The median age of the patients was 37 years. NF-DP-NENs comprised 36% of the patients with pancreatic tumors and were diagnosed at an older age than the functioning tumors. A study of 82 MEN1 patients from Northern Finland reported four types of NENs – NF-DP-NENs, gastrinomas, other hormonally active DP-NENs, and GI tract NENs [81]. NENs were found in 73% of the patients and the median age was 46.8 years. NF-DP-NENs comprised 68.3% of all NENs detected in this cohort of patients and several subjects had more than one type. Another study of 74 Dutch MEN1 patients found DP-NENs in 46%, and of those, 24% were non-functioning [65]. Using a large European dataset, Triponez et al. investigated the penetrance and clinical course of NF-P-NENs [30]. Of 579 patients with MEN1, 108 (18.7%) were diagnosed with NF-DP-NENs.

In recent studies, the most common DP-NENs in MEN1 have been non-functioning (80 to 100%) [37]. Applying more sensitive imaging modalities, such as upper EUS, has resulted in a higher detection rate than previously reported. As an example [47], this imaging modality detected DP-NENs in 11 of 13 asymptomatic MEN1 patients in one study. A prospective observational study evaluated 82 asymptomatic tumors < 15 mm detected by EUS in 20 patients with MEN1-disease over a period of 20 +/- 12 months (33.8 patient years, 106.7 tumor years) by EUS. Only a minority of the tumors were visualized on CT (5%) and MRI 10%) [82]. Another investigation reported a 55% prevalence of NF-DP-NENs among MEN1 patients [11, 56]. A longitudinal follow-up revealed both an increase in the number and size of pancreatic lesions in this cohort of patients [80].

DP-NENs are characteristically diagnosed between the ages of 30 and 50 years. However, the age range is wide, varying from 5 to 15 years for the youngest with the different DP-NENs to 68 to 80 years for the oldest [26]. The penetrance of NENs rises with age. DP-NENs in MEN1 are found in 9% at the age of 20, in 53% at the age of 50, increasing to 84% at the age of 80, with the penetrance of NF-P-NENs of 34% and 53% at the age of 50 years and 80 years, respectively [41, 62, 83]. Most MEN1 patients who develop DP-NENs are older than 20 years of age, but both F-DP-NENs and NF-DP-NENs have been reported to occur before the age of 21 [41]. The earliest reported age of onset was between 5 and 12 years [41].

According to one large national study, 50% patients of MEN1 patients developed DP-NENs, 59% were non-functioning and in 19%, DP-NENs were the first manifestation of MEN1 [55]. The prevalence of DP-NENs in MEN1 is between 20% and 75% clinically and between 80% and more than 90% after consequent imaging [15, 26, 28, 29] and in postmortem studies. The most common tumors in MEN1 are NF-DP-NENs (80% to more than 90%). In most patients, however, they are microadenomas, with only 12 to 15% causing symptoms [26].

Regional Differences

Reviewing the literature, regional differences appear possible. NF-DP-NENs were also found to be common in a study by members of the Japanese MEN Consortium [84]. Five hundred sixty patients were analyzed and GEP NENs were seen in 58.6%. The prevalence of insulinomas was higher than seen in Western countries (22% vs. 10%). The prevalence of gastrinomas and NF-NENs was identical (29%). Patients with insulinomas were younger than those with gastrinomas or NF-NENs [84].

Diagnosis and Follow Up

Biochemical Diagnosis

Tetsuhide Ito and Robert T. Jensen

Although prospective randomized data are lacking, current clinical expert guidelines recommend various laboratory screening and imaging modalities (LE: 3) to detect and localize neuroendocrine manifestations in the MEN1 pancreas as early as possible. ***Based on biochemical screening results and imaging, the goal is timely intervention to improve quality of life and to increase life expectancy by preventing the development of life-threatening hormonal syndromes and/or metastatic disease*** [11, 15].

F-DP-NENs

In all newly diagnosed MEN1 patients, biochemical screening for DP-NENs aims to primarily assess the presence of F-DP-NENs (LE: 3) [11, 15, 35, 74, 75, 85, 86]. ***The particularly produced and hypersecreted hormones prevail as the specific tumor marker of the specific F-DP-NEN*** [86]. A biochemical evaluation of various fasting GI tract hormones including gastrin, insulin with an associated glucose level, glucagon and VIP is recommended (LE: 3) [11, 15].

DP lesions occur frequently before the age of 21, but mainly after the age of 10 years [41] [44]. Concerning the age at which screening should be initiated, it has been shown recently that symptomatic or severe manifestations in MEN1 patients rarely occur before the age of 16 years [43]. MEN1 screening is determined by local resources and clinicians' expertise. Screening is a life-long program respecting patients' preferences [87, 88]. With regard to psychological burden and cost effectiveness, ***routine screening may be postponed until the age of 16 years or later but has to be applied at the least when clinical symptoms become manifest, regardless of age*** [89]. This updated recommendation is in contrast to the current clinical practice guidelines [Brandi, Gagel et al. 2001, Thakker, Newey et al. 2012], proposing the application of a series of biochemical tests annually even in all asymptomatic MEN1 mutation carriers starting with the age of 10 for insulinoma (fasting glucose; insulin) and age of 20 for gastrinoma (fasting gastrin levels).

Annual Screening or Extended Screening Intervals?

Although the frequency of screening for DP-NENs in MEN1 is advised to be yearly (LE: 3) [11, 15]. This, too, has not been systemically studied, while one group has even proposed that it should be

extended to every three years [48]. If a careful history for symptoms of an F-DP-NEN is performed and proves negative, it has not even been established whether the specific determination of a fasting GI hormone value in a screening manner is likely to uncover additional F-DP-NENs.

One of the problems in determining the value of systematic regular screening of fasting GI hormone levels in detecting F-DF-NENs in MEN1 patients is that it is also not clear at what rate new F-DP-NENs *de novo* appear in MEN1 patients.

A number of studies in MEN1 patients have shown the diagnosis of F-DP-NENs to often be delayed [13, 90-95], which is frequently postponed by as much as 9.6 years in the case of ZES (LE: 2b) [91, 92, 95]. Similar results have recently been reported with insulinomas in MEN1 patients with a 3.3-year delay in diagnosis (LE: 3) [95]. For two reasons, this does not necessarily imply that these DP-NENs were newly arising. First, the proper initial history to suspect the F-DP-NENs was not taken in many of these cases. Second, the appropriate biochemical tests were not done to establish that a *de novo* F-DP-NEN subsequently developed which was not initially present. In almost all of these cases, this delay was thus due to missed diagnoses. In one prospective study extending over 72 months [48], by far the majority of functioning abnormalities and non-functioning abnormalities in 48 MEN1 patients were detected at the initial evaluation, and only one new case of a gastrinoma arose during follow-up. This led the authors to conclude that a longer follow-up period of three years was more appropriate.

History has taught us that undiagnosed F-DP-NENs in MEN1 patients, particularly ZES, can be a major cause of morbidity and mortality [13, 29, 96-98]. With the development of effective medical therapies for F-NENs including ZES [99-103], as well as the need to alter follow-up protocols for MEN1-ZES [26, 89, 103-106], it is essential that these be systematically sought for in all new MEN1 patients. A missed diagnosis of ZES can be particularly devastating for MEN1 patients [26, 29, 103]: On account of the marked oversecretion of a gastric acid secondary to the ectopic tumoral secretion of gastrin, MEN1-ZES carries a high level of morbidity and mortality if untreated. The result is an increased acid secretory capacity due to the trophic effect of gastrin on the gastric mucosa / gastric parietal cell mass and the potentiating effects of hypercalcemia to hyperparathyroidism on gastrin release [26, 29, 103, 107-109].

To establish the diagnosis of an F-DP-NEN, first, a careful history related to the common symptoms of each of the F-DP-NENs should be carefully sought. It is uncommon to find a true F-DP-NEN in MEN1 patients that is asymptomatic, especially with gastrinomas and VIPomas [59, 91], and in most studies, 90 to 100% of MEN1 patients with insulinomas and MEN1 are symptomatic [110]. However, in one recent study (LE: 3) [79] of patients with insulinomas with MEN1, hypoglycemic symptoms were present in 60%, whereas the other 40% were primarily found on screening. Particularly important, especially in suspecting gastrinomas, is a past or current history of using gastric antisecretory agents, particularly PPIs, which can elevate FSG in 100% of patients as well as plasma CgA levels [97, 111-113].

The presence of F-DP-NENs in MEN1 is demonstrated by evidence of the effects of hormonal hypersecretion (clinical, laboratory) with the appropriate elevated plasma hormone levels [11, 114].

Gastrinomas and ZES

Patients with ZES may experience abdominal pain (severe ulceration in the stomach, duodenum and small bowel, failing to respond to initial treatment) and chronic diarrhea, including steatorrhea. ***The diagnosis of ZES is strongly supported by demonstrating elevated FSG <u>with</u> gastric pH < 2. It is unequivocally established if FSG > 10 x normal with pH < 2.***

Unfortunately, elevated FSG alone can give a false-positive suggestion of ZES, as it may be elevated in patients with physiological hypergastrinemia (due to hypoachlorhydria secondary to any cause, such as atrophic gastritis, pernicious anemia, PPIs)[97, 111, 112]. Furthermore, antral G-cell hyperfunction has been reported in MEN1, which can false-positively elevate FSG levels. For these reasons, an assessment of gastric pH is required at the time of repeat FSG determination to make sure the increased FSG is inappropriate [97, 111, 112, 114]. pH assessment of gastric fluid is being increasingly carried out at the time of endoscopy [115] rather than using the (older) methods with nasogastric tubes.

The presence of a gastrinoma causing ZES is established in MEN1 patients in a fashion similar to that in patients with sporadic (non-MEN1) ZES [86, 92, 97, 102, 105, 111, 112, 114]. The initial screening test is almost invariably a determination of FSG, which is elevated in 99 to 100% of patients with MEN1-ZES (LE: 2b) [91, 97, 107, 111]. The well documented situations in which FSG may be normal in the presence of ZES are after effective parathyroidectomy in MEN1 patients [116, 117] or rarely and temporarily following enucleation of a gastrinoma [106, 118].

The diagnosis of ZES has become more difficult [97, 102, 111, 112, 119-121] ***because of the increasing unreliability of commercial gastrin assays*** (both over- and underestimating it) [122, 123], ***the lack of availability of secretin used to perform secretin provocative tests*** [124, 125], and the ***widespread use of PPIs which cause rapid development of fasting hypergastrinemia*** in most non-ZES patients [97, 111, 120, 126]. As shown by Endall et al. [127] H. pylori exposure was associated with increased prevalence and severity of hypergastrinemia in MEN1 patients. Past H. pylori-related hypergastrinemia may contribute to the pathogenesis of ongoing gastrin hypersecretion by neuroendocrine tissues. ***These findings reinforced the recommendation that, after identifying elevated FSG raising the possibility of ZES in a MEN1 patient, the patient should be referred to a group well versed in this area to establish the diagnosis.***

For a long time, gastric secretory tests were recommended routinely for patients with < 10-fold increased FSG and gastric pH >2 [92, 97, 105, 111, 112, 114], but they are rarely available now and therefore infrequently applied. Multiple gastrin-provocative tests were reported to be helpful in distinguishing ZES from other causes of hypergastrinemia associated with hyperchlorhydria [102, 107,

111, 128]. At present, if available, only the "secretin test" is recommended [107, 111, 129] [107, 111, 112, 114, 129] as an important confirmatory tool to establish ZES in patients with FSG elevated < 10-fold and gastric pH < 2. [92, 97, 105, 111, 112, 114]. This is because a number of other conditions (antral G-cell hyperfunction, H. pylori infection, etc.) can be associated with hyperchlorhydria/hypergastrinemia in this range and the secretin test will distinguish them [97, 105, 107, 111, 112, 114, 129]. Numerous studies have demonstrated that the test is highly sensitive and specific for ZES under the proper conditions (acidic pH, preferably pH < 2) [107, 124, 129], except in the occasional MEN1-ZES patient with corrected hyperparathyroidism [116, 117, 130].

Two IUs of secretin/kg body weight are applied intravenously within 30 seconds and basalblood samples are taken 15 minutes before stimulation, at stimulation and 2, 5, 10, 15 and 30 minutes after stimulation. The best criterion is an increase in FSG with secretin provocation [107] of 120 pg/ml, which has a sensitivity of 94% for ZES and a specificity of 100%. As pointed out in a recent editorial [121], the secretin test is highly accurate when performed properly, yet it is not without problems in many settings.

Until recently, the diagnosis of ZES was hindered by a period in which synthetic secretin was not available in all centers. It is now available again as ChiRhoStim® (16 μg/vial) (NDC 67066-0005-01) in the United States, but is still rarely available (as Secrelux®) in most European countries. Secretin is expensive and, most importantly, it can give misleading results if the patient is achlorhydric or hypochlorhydric [97, 105, 111, 120, 124, 131].

PPIs are widely used for many conditions and make the diagnosis of ZES more difficult because they can cause hypergastrinemia in normals and non-ZES patients and also delay the diagnosis of ZES by masking clinical symptoms of ZES. PPIs have to be withdrawn for 5 to 7 days to distinguish appropriate from inappropriate hypergastrinemia in patients with suspected ZES. This is important to restore normal levels of gastric acid production, allowing proper measurements of gastrin and pH concomitantly.

The reduction and stopping of PPIs can lead to adverse outcomes in patients with ZES with a sudden and dramatic increase in gastric acid production [132]. Therefore, this is a potentially dangerous intervention that needs to be performed carefully with clear instructions to the patient. An alternative method of acid suppression has to be used during this wean. To prevent the extreme risk of developing severe rebound hypersecretion and peptic ulcer disease with possible complications, histamine H_2-receptor antagonists are recommended to have a shorter duration of action than PPIs. They should be started at sufficient doses to control acid hypersecretion as soon as the PPIs are reduced and stopped (e.g., ranitidine, an oral histamine H_2-receptor antagonist; depending on body habitus, degree of hypergastrinemia and level of suspicion for ZES: 450 to 750 mg every 6 hours).

This shift to H_2-receptor antagonists reduces the period of time during which the patient is at risk from rebound hypersecretion. However, before final diagnosis starts, H_2-receptor antagonists have

also to be stopped for at least 24 hours to exclude antisecretory drug effects from impacting on the determination of the type of hypergastrinemia that is present. During the last 24 to 30 hours of the PPI wean, patients may use antacids *ad libitum* until midnight on the night before the measurements of serum gastrin and acid secretory measurement, e.g., gastric acid pH [97].

Insulinomas and Organic Hyperinsulinism

The clinical manifestations of hyperinsulinemic hypoglycemia vary by age and hypoglycemic severity. In general, most signs and symptoms can be attributed to, first, the effects on the brain of insufficient glucose (neuroglycopenia) or, second, to the adrenergic response of the autonomic nervous system to hypoglycemia. In most cases, all effects are reversed when normal glucose levels are restored.

In the case of clinically suspected insulinoma, this is usually screened for by fasting insulin and blood glucose levels, and thereafter, when definitively suspected, a formal assessment with 72-hour fast with insulin, glucose, proinsulin, C-peptide, and excluding the presence of oral hypoglycemic agents [31, 74, 114, 133]. The exact criteria for the diagnosis of insulinoma are the findings of symptoms, signs or both during a fast of up to 72 hours with plasma concentrations of glucose less than 55 mg/dl (3.0 mmol/l), insulin of at least 3.0 μU/ml (18 pmol/l), C-peptide of at least 0.6 ng/ml (0.2 nmol/l), and proinsulin of at least 5.0 pmol/l. β-hydroxybutyrate levels of 2.7 mmol/l or less and an increase in plasma glucose of at least 25 mg/dl (1.4 mmol/l) after i.v. glucagon indicates mediation of the hypoglycemia by insulin [133].

The use of an insulin cut-off value of ≥ 3 instead of ≥ 5 μU/ml is supported by a recent study showing that 9% of all patients with insulinoma would remain undetected with the older recommended value of ≥ 5 μU/ml [134]. Another study [135] demonstrated that some patients with insulinoma (23%) can have plasma β-hydroxybutyrate levels of > 2.7 mmol/l, especially if they have previously undergone partial pancreatectomy and are being evaluated for recurrence.

Glucagonomas and Glucagonoma Syndrome

In the case of glucagonomas, the diagnosis requires the demonstration of an elevated plasma glucagon level with evidence of glucagon hypersecretion clinically (diabetes; necrolytic migratory erythema; normochromic, normocytic anemia etc.) [74, 114, 136].

VIPomas and WDHA Syndrome

VIPomas demonstrate elevated plasma VIP levels. They cause a specific syndrome – WDHA syndrome. The massive amounts of VIP cause profound and chronic (secretory) watery diarrhea, which characteristically exceeds 800 ml/day [74, 114, 136, 137] (PC syndrome), resulting in dehydration,

hypokalemia, achlorhydria, acidosis, flushing and hypotension (from vasodilation), hypercalcemia and hyperglycemia.

Somatostatinomas

Lastly, in most papers in the literature, the presence of somatostatinomas has been reported from IHC findings. This has led to much confusion, because in most cases, there was no evidence of clinical somatostatinoma syndrome or of elevated plasma somatostatin levels [74, 114, 136]. Therefore, it has been suggested the term somatostatinoma syndrome be used when clinical features are present [74, 114, 136]. This diagnosis requires the clinical features of somatostatinoma syndrome (diabetes, cholelithiasis, steatorrhea, etc.) and elevated plasma somatostatin levels [74, 114, 136]. Many histological somatostatinomas, especially those in the duodenum, are only rarely associated with elevated somatostatin levels in the plasma or the existence of clinical somatostatinoma syndrome. For this reason, its existence as a specific clinical syndrome has been recently called into question [138].

NF-DP-NENs

The majority of NF-DP-NENs secrete different regulated secretory proteins not causing a functional syndrome. CgA and PP are frequently secreted and glucagon, neuron-specific enolase, human chorionic gonadotrophin subunits, calcitonin and neurotensin infrequently [114]. These neuroendocrine markers may serve to early suspect NF-DP-NENs [11, 15].

A high penetrance of NF-DP-NENs in MEN1 patients is documented between the age of 15 and 20 years. If NEN markers are applied, screening may start at this age. However, no recommendations for biochemical screening are based on prospective and/or randomized studies.

PP and CgA to Improve the Early Diagnosis of F- and NF-DP-NENs?

There exist controversies regarding the value of several biochemical diagnostic tests including CgA, PP and glucagon. In the case of F-DP-NEN diagnosis, some studies have shown that the combination of fasting plasma PP and CgA leads to increased diagnostic sensitivity [139]. In contrast, other studies have demonstrated that both have low sensitivity in identifying either F- or NF-DP-NENs in MEN1 patients [85, 93, 140]. No study has established the added utility of fasting plasma PP or CgA determination over the specific fasting hormone level for each F-DP-NEN subtype (gastrin for gastrinoma, insulin for insulinoma, etc.) [119, 141, 142]. Even their utility for the early diagnosis of NF-DP-NENs has recently been called into question [143-145].

Specifically, in a recent prospective study by de Laat (LE: 2b) [85] of 274 MEN1 patients, the diagnostic accuracy of CgA, PP and glucagon in detecting DP-NENs was compared to results from pathology and imaging. The sensitivity of each of these three tumor markers was < 45%, with specificities of 73 to 74%, backing the conclusion that imaging is required to detect most NF-DP-NENs. These results are supported by other studies in MEN1 patients, in which the sensitivity of CgA and PP for DP-NENs was lower in MEN1 than reported in non-MEN1 patients and was inferior to imaging results [144, 145]. Recent studies have called attention to the numerous flaws in using CgA as a tumor marker for GEP-NENs [146]. Based on a systematic review [93], one may conclude that the currently applied neuroendocrine biomarkers may no longer play a role in the diagnostic process for NF-DP-NENs, as accuracies to diagnose or follow NF-DP-NENs are too low.

While increased attention is being paid to the value of using circulating tumor DNA, RNA or microRNA as GEP-NEN tumor markers [147-149], specific data is lacking for their value in the diagnosis of GEP-NENs in MEN1 patients.

NETest

Recently [93], the ability of a blood transcription profiling test, the NETest, to identify patients with sporadic NENs was evaluated (20% DP-NENs, 60% ileal NENs) and compared to CgA. The NETest [93] had low specificity and it was concluded that it was not a useful screening test for GEP-NENs. However, its sensitivity was greater than that of CgA, suggesting it might be useful for follow-up in sporadic GEP-NEN patients. At present, similar studies have not been performed in MEN1 patients and thus the potential value of the NETest in MEN1 patients is not known.

Cross-Sectional and Functional Imaging

Samira M. Sadowski

Various imaging techniques, e.g., CT, MRI or EUS, are available and have been suggested for diagnosing, localizing and the follow-up of DP-NENs in MEN1 [150]. ***There is currently a lack of evidence from controlled clinical trials to evaluate the best single or combined methods.*** The majority of retrospective studies in the literature compare cross-sectional imaging (CT or MRI) to EUS and/or to functional imaging (SRS using various radiolabeled peptides with and without PET technology).

HRCT

HRCT is the most widely used imaging modality applied to localize P-NENs. The predominantly small, multiple and slow-growing tumors typically enhance in the arterial phase [30, 80].

A recent retrospective, single-center cohort study with 217 DP-NEN patients [151] showed that the sensitivity of CT for the detection of DP-NENs has significantly increased with the improvement in multidetector CT technology from 1984 to 2009 (p = 0.02), and that CT was likely to miss lesions smaller than 20 mm and insulinomas. Another study has shown multidetector CT to have a high level of sensitivity (94%) in the detection of DP-NENs [152].

In a study by Khashab and coworkers [151] in 56 patients who had both CT and EUS, the sensitivity of EUS was greater than that of CT (91.7% vs. 63.3%, p = 0.0002), and EUS detected CT-negative tumors in 90.9% (20/22). The sequential combination of EUS and CT scan was thus concluded to possibly detect most DP-NENs (LE: 3) [151].

Specifically for patients with MEN1, a well designed, retrospective, single-center study assessing the preoperative management of DP-NENs in 52 patients with MEN1 compared preoperative findings from CT, EUS and ^{111}In-pentetreotide scintigraphy (SRS) to pathologic results, the gold standard [153]. Their results showed that EUS had the highest preoperative sensitivity and PPV, of 100%, as compared to CT with 81% and 97% and SRS with 84% and 96%, respectively. The study was retrospective, the radiologists non-blinded and follow-up consisted of a median of 4.3 years. However, the findings were all matched with surgical pathology. ***The authors concluded that preoperative imaging for patients with MEN1 should consist of EUS, more so than CT and SRS,*** both of which may show false-negative and false-positive results (LE: 3) [153].

Further, a prospective, observational, single-center study in 22 patients with MEN1 compared CT to EUS and SRS between 1997 and 2003 to determine their diagnostic value in DP-NEN detection [154].

The median follow-up was 35 months (2 to 230 months). Subgroup analyses were performed for patients who had undergone surgery and for another group with asymptomatic DP-NENs. Again, EUS showed to be the most sensitive imaging technique to detect tumors smaller than 10 mm in patients with MEN1 when compared to CT (LE: 2b) [154].

MRI

MRI identifies more than 50% of DP-NENs larger than 30 mm in diameter, but only 5% if the tumors are smaller than 10 mm [155, 156]. One of the typical imaging features of P-NENs is the hypervascular enhancement. ***MRI can yield a very high level of sensitivity compared to CT in identifying DP-NENs***, especially when fat-saturated T1-weighted and delayed enhanced T1-weighted MRI are used [157, 158]. Typically, those tumors have a lower signal on T1-weighted sequences and high signal intensity on T2-weighted sequences.

A recent prospective multicenter study, including 90 patients with MEN1 having undergone both EUS and MRI (blinded gastroenterologists and radiologists), showed complementary results with EUS and MRI combined [159]. Performed in nine French centers between 2005 and 2008, EUS detected more tumors, especially small-size tumors, but both examinations failed to identify a high percentage of lesions larger than 10 mm, in 18.9% and 36.8%, respectively (LE: 3). This study did not assess progression over time.

As mentioned previously, EUS and MRI should be used complementarily for the work-up of patients with MEN1. Kann [160] performed a systematic analysis of the literature on sensitivities of EUS and MRI in insulinomas and DP-NENs in MEN1 (all were case series, no prospective study was included). Eighteen publications on insulinomas (782 cases) were analyzed and resulted in a mean correct detection/localization rate (sensitivity) for EUS of 80%, MRI 66%, CT 63%, angiography 52%, SRS 42%, and US 23%; and arterial calcium stimulation with hepatic venous sampling regionalized correctly in 80%. No study in patients with MEN1 fulfilled the inclusion criteria. Overall, EUS seemed more sensitive than MRI in localizing P-NENs. The author concluded that if a specialized endosonographist was available, EUS was the preferable imaging procedure, and that otherwise, MRI represented a suitable alternative [160]. However, MRI performs well compared to EUS for the detection and subsequent surveillance of MEN1-related DP-NENs larger than 10 mm and seems to be cost-effective. Both modalities, MRI and EUS, could be used at initial assessment and MRI alone could be utilized thereafter in patient surveillance. EUS retains its value in surgical planning and the detection of small, mostly functional DP-NENs [161].

MRI has the advantage of providing homogeneous performance throughout the pancreas. On the other hand, a significant proportion of clinically relevant NF-P-NENs > 20 mm was missed by EUS as

well. The authors concluded that to ensure maximum sensitivity, both modalities MRI and EUS can be used alternately to detect lesions, should be used as early as possible, and that if combined, could reduce the burden of invasive EUS [93].

There is no risk of radiation with MRI when compared to other cross-sectional imaging modalities such as CT or PET/CT, this being a major advantage of MRI (LE: 3) [89]. ***HRCT and MRI are non-invasive localization techniques and therefore the most often applied tools.It is to mention that the radiation exposure of CT has to be taken into consideration, especially as MEN1 patients undergo regular surveillance.*** In a retrospective study, Casey et al. analyzed the cumulative radiation exposure of MEN1 patients due to screening and calculated an estimated mean lifetime risk of secondary cancer of 0.49% [38]. Thus, these authors and several other groups [73, 86, 89] (LE: 3) have preferred the use of MRI over CT for the screening/imaging of DP-NENs in patients with MEN1.

SRI

NENs express SSTRs in tumor cells. There are five different SSTR subtypes; more than 70% of NENs of both the duodenum and pancreas express multiple subtypes, with a predominance of SSTR2 and SSTR5 [162, 163].

Functional Imaging with SRS

SRS with ^{111}In-pentetreotide is a useful modality to investigate occult tumors of the duodenum and pancreas and metastases. ***Studies in the past have shown SRS to be more sensitive than CT and MRI to detect liver disease and metastatic lymph nodes*** (LE: 2b) [164-166]. Two of those investigations were prospective single-center studies comparing SRS to cross-sectional imaging modalities in patients with NENs: In a large prospective cohort study with 80 consecutive patients with ZES, including 17 patients with MEN1, SRS with SPECT showed the highest sensitivities to detect primary or metastatic liver lesions in patients with ZES [166]. Further, in a prospective study in 29 patients with MEN1, Yim et al. [165] showed that SRS was useful in identifying occult tumors compared to CT and pathology results.

Another observational retrospective cohort study in 127 patients with MEN1 and gastrinoma from the French GTE showed an increasing use of SRS and EUS after 1991, with positive detection of metastasis and tumors in 81.3% and 92.3%, respectively [167].

More recent studies in patients with MEN1 have compared SRS to cross-sectional imaging and EUS. A retrospective study showed SRS to have a sensitivity of 84% and a PPV of 96% when compared to final pathology, CT 81% and 97% and EUS 100% for both, respectively, and to be able to detect small lesions (3 mm) [153]. Langer et al. [154] demonstrated SRS to be useful in detecting metastases in

patients with MEN1, although only two patients of a total of 22 presented with metastasis and recurrence.

Functional Imaging with PET

Recent studies have suggested that functional imaging with PET-CT and more recently PET-MRI is the preferable method to diagnose, localize and stage DP-NENs whenever available and should be considered as the first-line diagnostic imaging method for staging in patients replacing ^{111}In-pentetreotide [168]. However, its routine use in MEN1 patients is not yet defined exactly and it is not recommended as a screening tool in asymptomatic patients.

The expression of SSTRs enables new imaging techniques using PET/CT with radioactively labeled SAs such as ^{68}Ga-DOTATATE (octreotate) [169]. Recent studies showed that ***imaging with ^{68}Ga-labeled SAs with PET/CT is more sensitive and highly specific and therefore recommended it be performed to evaluate and stage the extent of disease*** [170, 171].

PET using different SAs may have several advantages over octreotide scintigraphy: a shorter procedure (as scintigraphy results are available only within 24 to 48 hours), lower costs [172], lower radiation doses and better diagnostic accuracy due to the higher affinity of ^{68}Ga analogs for SSTR2, as well as higher spatial resolution with PET [173-175].

18-FDG-PET scans have been reported to be helpful for localizing and possibly for distinguishing malignant from benign NENs [176]. A recent retrospective study considered 18-FDG-PET to be useful in screening for aggressive or metastatic NENs in patients with MEN1, finding increased Ki-67 in 18-FDG-avid lesions [177]. However, ***18-FDG-PET scans have limited use in well differentiated NENs due to the low expression of glucose transporters and low proliferative activity in these tumors*** [178].

The localization of primary tumors and detection of metastases are crucial for optimizing treatment strategies. Slow-growing DP-NENs are best treated by complete surgical removal, but in the presence of metastases or non-resectable disease, unnecessary surgery could be spared. Furthermore, ***PET with ^{68}Ga-labeled somatostatin ligands has been used as a tool in localizing unknown primary tumors in metastatic NENs*** [179] ***and has shown to be superior to SRS and conventional imaging*** [180]. According to Hofman et al. [181], ^{68}Ga-PET is superior to SRS and conventional imaging (CT, MRI, bone scintigraphy) in identifying additional sites of disease, with bone and local lymph nodes being the most frequent sites. Furthermore, PET with ^{68}Ga-labeled somatostatin has been suggested to be superior to FDG-PET and F-DOPA-PET in the detection of additional tumors [169, 182, 183]. The ENETS recommended it as a diagnostic modality in 2012 [184], providing staging by assessing metastases that can lead to changes in both medical and surgical management strategies (LE: 2b) [181, 185, 186].

The lifelong predisposition to DP-NENs in patients with MEN1 makes decisions about the timing and extent of surgery a very important and difficult matter [29]. Several recent studies have evaluated the use of ^{68}Ga-PET in patients with GEP NENs. In a retrospective single-center analysis, Versari et al. [187] compared ^{68}Ga-DOTATOC PET/CT to multidetector CT and EUS in 19 consecutive patients for the diagnosis of DP-NENs, seven of whom were diagnosed with MEN1. The findings were confirmed by EUS-FNA and/or surgery. They found correct identification in 100% of the patients by EUS, in 92% by PET/CT, and in 91% by CT. Unfortunately, CT was performed only in 16 patients and failed to identify multifocal lesions in a patient with MEN1, which were detected by EUS and PET/CT. On a per-lesion analysis, EUS, PET/CT and CT correctly identified 96%, 87% and 72% of the lesions, respectively. Further, EUS, PET/CT and CT detected 91%, 91% and 50% of lesions, respectively, with a diameter smaller than 20 mm (p = 0.06, EUS and PET/CT vs. CT).

Another retrospective study investigated ^{68}Ga-DOTATOC PET/CT in 21 patients with NENs, of whom 19 presented with MEN1 [188]. They found a sensitivity and specificity for detecting NENs by ^{68}Ga-DOTATOC PET/CT in 91.7% and 93.5%, respectively, with an impact on management in 47.6% of the patients (LE: 3). Similarly, a study with 33 MEN patients (9 with MEN1) using DOTANOC showed high diagnostic accuracy for both primary and metastatic NENs (LE: 3) [189]. Recent studies have been specifically performed in patients with MEN1 using ^{68}Ga-DOTATATE PET/CT in comparison to conventional imaging: In 26 patients with MEN1, Sadowski et al. [190] showed prospectively that ^{68}Ga-DOTATATE PET/CT was more sensitive for detecting NENs and led to a change in management in 31% of patients as a result of findings not seen on SRS or CT scan (LE: 3). Sharma et al. [191] examined 18 patients and found no significant difference in sensitivity compared with axial imaging for the pancreas, pituitary and adrenal glands. However, the progression of pancreatic lesions was significantly associated with an SUVmax < 12.3. All these results have been summarized in a recent review [86], which concludes that ^{68}Ga-DOTA PET/CT has higher sensitivity than axial imaging for the detection of DP-NENs and other MEN1-associated NENs. Additionally, prospective studies have suggested that PET/CT will be helpful in the workup and staging of MEN1-related lesions, as its use changes management in up to 30% of patients (LE: 3) [86]. However, further studies are needed to determine at what age PET/CT should initially be used and what its place is in the follow-up of patients with MEN1. Also, certain groups have questioned its utility in the screening of patients with MEN1, their findings showing useful additional information only in subjects with suspected or known metastatic disease [73].

Controversies exist in using ^{68}Ga-DOTA PET/CT for the detection of insulinomas because of the low/absent SSTR expression on insulinomas. Antwi et al. [192] investigated GLP-1R PET/CT using ^{68}Ga-DOTA-exendin-4 in 52 consecutive adult patients for the localization of insulinomas, comparing to ^{111}In-DOTA-exendin-4 SPECT/CT, standardized MRI and previously performed external CT and/or MRI (LE: 2b). GLP-1R is known to have higher expression on insulinomas than SSTR2 [193]. An accuracy for

PET/CT, SPECT/CT, study MRI and prior external CT/MRI of 93.9% (87.8–97.5%), 67.5% (58.1–76.0%), 67.6% (58.0–76.1%) and 40.0% (23.9–57.9%), respectively, was identified. Most interestingly, they found an impact on clinical management in 42.3%, 32.7% and 33.3% for PET/CT, SPECT/CT and study MRI, respectively, defined as successful image-guided surgery in the presence of previous (before recruitment) negative or ambiguous imaging findings or negative invasive procedures. The authors concluded that ^{68}Ga-DOTA-exendin-4 PET/CT performed significantly better than ^{111}In-DOTA-exendin-4 SPECT/CT and MRI in the localization of benign insulinomas and should be considered in patients in whom localization fails with CT/MRI. Furthermore, PET/CT is also more convenient than SPECT/CT, with a lower radiation burden and a shorter investigation time [194].

Antwi and coworkers [194] recently reported the results of a multicenter study distinguishing insulinoma from other (NF-DP) pancreatic lesions in the context of six patients with MEN1 and biochemically verified organic hyperinsulinism using GLP-1R imaging (^{68}Ga-DOTA-exendin-4 PET/with low-dose contrast medium CT) as well as morphological cross-sectional imaging (MRI). GLP-1R allows the (functioning) imaging of insulinoma and because of low-dose contrast medium CT imprecisely the size of the lesions. MRI can document tumor size (and the anatomical neighborhood of the lesion) but cannot discriminate between NF- and F-DP-NENs (=insulinoma). Fourteen lesions were detected by MRI. Twenty-two lesions were not detected by MRI. Finally, 11 insulinomas were revealed immunohistochemically after various surgical procedures. GLP-1R imaging was "true-positive" in 10 NENs (all insulinomas), "false-negative" in one insulinoma (1 mm), "false-positive" in one NF-NEN (21 mm) and "true-negative" in 25 NF-DP-NENs, respectively. All six patients presented with normalized postoperative blood sugar levels. The authors concluded that ***combining GLP-1R imaging with morphological cross-sectional imaging is a helpful tool in differentiating insulinomas from other pancreatic islet tumors present in MEN1 patients and that GLP-1R imaging may guide successful surgical intervention.***

Selective Arterial Calcium Stimulation and Venous Sampling

(also see Surgical Strategies for DP-NENs: Insulinoma)

Calcium is essential for many physiological processes such as stimulus-secretion coupling and in the second-messenger process. Therefore, calcium stimulation tests are able to stimulate the hormone secretion of various endocrine tumors (e.g., gastrinoma, insulinoma).

Arterial calcium stimulation with hepatic vein catheterization [Doppman, Miller et al. 1991] can be used when functional tumors such as insulinomas or (in selected cases) gastrinomas are not detected on cross-sectional imaging. It uses intravenous calcium for the release of insulin (SACI) or gastrin (SASI) from the F-DP-NEN [195-197].

The selective use of secretin to establish gastrin gradients or portal venous sampling to localize gastrinomas is an alternative [198-200]. This is because they stimulate the release of gastrin from the

gastrinoma when injected into the appropriate feeder artery [195-197]. The hepatic, gastroduodenal, superior mesenteric and splenic arteries are selectively catheterized and subsequently injected with calcium gluconate (0.025 mEq calcium/kg body weight). The second catheter is placed in the right or left hepatic vein via the inferior vena cava. Blood samples for insulin (proinsulin and C-peptide) or gastrin are obtained before and 20, 40 and 60 seconds after calcium injection.

A ≥ 2-fold increase in insulin (gastrin) concentration from baseline regionalizes the tumor within the anatomic region perfused by the injected artery. A response after calcium infusion into the gastroduodenal or superior mesenteric arteries assigns the lesion to the head and neck, whereas a response after splenic artery injection localizes in the body and tail of the pancreas. A response following a hepatic artery injection suggests the presence of liver metastases [195-197].

In a retrospective study of 45 patients at the NIH, arterial calcium stimulation with angiography showed to be superior to abdominal US, CT or MRI as a preoperative localizing tool for insulinomas when then compared to surgical results [197].

Some authors have recommended SASI angiography [201] to regionalize the source of gastrin hypersecretion after selective calcium injection in the rare situation of (multiple) gastrinoma detection in the pancreas [11, 202, 203]. However, others do not recommend SASI angiography in the situation of MEN1-ZES [89], as it is now shown that > 95% of gastrinomas are located in the duodenum and that concomitant DP-NENs in the pancreas are likely non-functioning [23].

Similar to the selective use of secretin to establish gastrin gradients or portal venous sampling to localize gastrinomas [198-200], venous hormonal sampling for gradients after SACIs are used to localize insulinomas or glucagonomas in patients with and without MEN1. This is because they stimulate the release of insulin/glucagon from the insulinoma/glucagonoma when injected into the appropriate feeder artery [195-197].

Follow-up by Imaging

In terms of follow-up regimens, surveillance programs should focus on identifying the course of disease in patients with DP-NENs and MEN1. The frequency of screening should be adapted for the growth rate in an individual. According to the systematic review by van Treijen et al. [93], the authors recommended starting with repeated measurements every year after detection of NF-P-NENs by EUS or MRI in order to observe growth tendencies. After confirmation of tumor stability, surveillance could be extended to every one to two years over the course of time. In growing tumors, imaging should be repeated at least every year, and ^{68}Ga-DOTA PET-CT could be added to the surveillance when tumors > 10 mm are present and/or are growing to identify metastasis in a timely fashion [93]. However, future prospective studies will be needed to validate these surveillance programs in patients with DP-

NENs and MEN1, with regards to modality and interval (also see Natural Course of Untreated NF-DP-NENs).

Endosonography / FNAB / CNB

Alberto Larghi

Compared with CT showing a sensitivity of 81% and a PPV of 97% for P-NENs, ***EUS was seen to have 100% sensitivity and PPV*** [93], with a close correlation between the largest lesion on EUS and pathology [48].

Studies comparing CT to EUS have very early suggested that ***EUS is superior for the diagnosis and localization of DP-NENs, particularly those smaller than 20 mm*** [204]. In a screening program of 19 patients between 15 and 20 years of age, DP-NENs were observed in a high frequency by EUS and/or MRI/CT (8/16; 50%), and an even higher frequency was found in those investigated solely by EUS (6/11;54%) [44].

This has led to propose EUS as the first choice among techniques to investigate and follow DP-NENs ***in patients with MEN1. EUS was superior to CT/MRI and SRS for pancreatic lesion detection, being able to detect multiple lesions of various sizes*** [145]. However, also many small NF-P-NENs without therapeutic consequences are detected, with the necessity of follow-up.

Several relatively small studies in patients with MEN1 previously suggested that EUS is a very sensitive method for the early imaging of P-NENs [47, 80, 153, 154, 205]. EUS has been recommended as the first-choice pancreas imaging technique in patients with MEN1 as it is the most sensitive imaging modality for NF-P-NENs, detecting lesions even as small as 2 mm [93]. However, ***EUS is limited by availability, is invasive, time-consuming and operator-dependent, especially in patients with MEN1, in whom complete pancreatic examination is necessary*** [47]***. EUS has a decreased sensitivity in the pancreatic tail.***

A recent publication by the Dutch MEN1 Study Group in 41 patients with MEN1 investigated which imaging study is to be performed to diagnose P-NENs. In a prospective head-to-head study fashion, EUS and 11C-5-HTP PET were compared with standardized conventional screening imaging, i.e. CT and/or MRI and SRS [145]. All EUS and 11C-5-HTP PET examinations were performed in one center (Groningen), with EUS done by one single operator who used a linear echoendoscope and had the option to perform qualitative assessments of the elasticity and rigidity of the detected lesions using elastography. CT or MRI detected pancreatic lesions with a diameter ≥ 10 mm in 14 patients (34.1%), SRS in 12 patients (29.3%), and CT or MRI + SRS in 18 patients (43.9%). In total, 32 pancreatic lesions were detected with CT and/or MRI (24 lesions) and SRS (13 lesions). Among 22 patients with elevated tumor markers (CgA, gastrin, PP and glucagon), pancreatic lesions were found in 10 (45.5%) by CT and/or MRI and/or SRS. EUS detected 101 pancreatic lesions in 34 patients (82.9%), with a mean size

of 9.1 ± 7.5 mm. Most lesions were homogeneous, hypoechoic and isoelastic, and 42% were hypervascular. Interestingly, 15 lesions were cystic and found to have thickened walls and hypervascularity in nine and five cases, respectively. As compared with CT and/or MRI + SRS, EUS confirmed the presence of pancreatic lesions in 18 patients, but 31 additional lesions were detected in 11 subjects (61.1%). In the 23 patients without pancreatic lesions on CT and/or MRI + SRS, EUS was positive in 16 patients (69.6%) and revealed 43 lesions.

Overall, 35 of the 41 patients (85.4%) had pancreatic lesions detected by at least one of the imaging techniques utilized. At a patient-based level, EUS showed pancreatic lesions in a significantly higher number of patients compared with CT, SRS and CT and/or MRI + SRS (all $p < 0.001$). In total, 107 pancreatic lesions were detected; 48 were located in the pancreatic head and 59 in the pancreatic body and/or tail region. Compared with CT and/or MRI, SRS and CT and/or MRI + SRS, EUS was able to find the largest amount of lesions (all $p < 0.001$). This was also the case for lesions > 10 mm (all $p < 0.01$). 11C-5-HTP PET performed similarly to CT/MRI and CT/MRI + SRS but found more lesions compared with SRS only ($p < 0.05$). At a patient-based and lesion-based level (also lesions > 10 mm), EUS performed better than 11C-5-HTP PET ($p < 0.01$). Of the 35 patients with pancreatic lesions, 18 (51.4%) had elevated tumor marker levels, among whom eight had < two-fold elevations of tumor markers, four between two-fold and three-fold, and six had > three-fold elevations. Of the six patients without visualized pancreatic lesions, four (66.7%) also had elevated tumor marker levels, all with < two-fold elevations [145].

The experience of the Dutch group [145] was confirmed by others (see review [89]). In addition, several relatively small studies in patients with MEN1 previously suggested that EUS is a very sensitive method for the early imaging of P-NENs [47, 80, 153, 154, 205]. However, ***EUS frequently overestimates the size of MEN1-DP-NENs, especially those with a size < 20 mm.*** This should be considered when indicating surgery in MEN1 patients with small NF-DP-NENs at other imaging modalities [206].

A multicenter prospective study [159] designed to evaluate the concordance between EUS and MRI for the detection of P-NENs ≥ 10 mm among 90 patients enrolled in nine French centers arrived at slightly different conclusions. Overall, EUS served to identify 75 (83.3%) patients with at least one certain P-NEN, with a total of 268 lesions detected. Among them, 48 (53.3%) had at least one certain tumor ≥ 10 mm and 13 (14.4%) had at least one tumor ≥ 20 mm. Sixty-one (67.8%) patients had multiple lesions. MRI identified 67 (74.4%) patients with at least one certain P-NEN, with a total of 158 lesions detected. Among them, 46 (51.1%) had at least one certain tumor ≥ 10 mm and 17 (18.9%) had at least one tumor ≥ 20 mm. Forty-two (46.7%) patients had multiple lesions. When considering EUS and MRI together, 57 patients with lesions ≥ 10 mm were detected. Concordance between the two techniques for the identification of patients with tumors ≥ 10 mm was moderate (Kappa coefficient = 0.55 [95% CI 0.38-0.73]). The authors concluded that although EUS was able to visualize more lesions,

both examinations failed to identify a high percentage of significant lesions (≥ 10 mm) (18.9% EUS and 36.8% MRI) and that the techniques should be viewed as complementary for the detection of P-NENs ≥ 10 mm.

The discrepancy between the results of this study and the Dutch study might be due to different factors: First, in the French study, EUS examinations were performed by at least nine endosonographers versus one dedicated operator in the Dutch study. In the latter, videos from all cases were independently reviewed by a well established endosonographer from another academic center (P. Fockens) who confirmed all the detected lesions. Moreover, in the Dutch study, only a linear echoendoscope was used with high-quality devices that perform equally well in both the pancreatic head and body/tail region. In turn, most of the examinations in the French study were done using a radial echoendoscope, which is known to have some limited ability to detect lesions in the pancreatic tail where P-NENs are more frequent [207].

In the previosly mentioned evidence-based review of the literature [93], 17 out of a total of 5083 studies were found to be of sufficient quality to be included for risk of bias assessment. EUS showed the highest sensitivity for the detection of NF-P-NENs. This has even been demonstrated in the preoperative setting [153]. However, due to the small size of these tumors, the detection rate of EUS is suboptimal, despite that the use of linear EUS echoendoscopes has become favored over radial EUS. Moreover, a strategy of EUS in combination with MRI was considered to be more useful, while ^{68}Ga octreotate-DOTA PET-CT could be added to identify lymph nodes and liver metastases [93].

Because of the limited ability to detect metastastic disease, EUS should always be coupled with SRS, which is the most reliable method for detecting metastases [80, 154].

EUS and FNAB

No precise recommendations regarding whether and when to perform EUS-FNAB to confirm the suspicious diagnosis of P-NENs in patients with MEN1 are available in the literature. Meta-analyses of the performance of EUS-FNAB for all pancreatic solid lesions have reported a pooled sensitivity close to 90%, a specificity of 96%, a positive likelihood ratio of EUS between 15.2 and 16.88, and a negative likelihood ratio between 0.13 and 0.17 [208, 209].

However, no subgroup analyses focused on P-NENs have been performed. Several retrospective studies including very few patients with MEN1 have shown the sensitivity and accuracy of EUS-FNAB for DP-NENs to range from 80 to 90% [210-212]. Importantly, not only can EUS-FNAB confirm the neuroendocrine nature of pancreatic lesions, but can also give prognostic information by predicting the five-year survival probability of affected patients [210, 213] and by establishing the grading of such neoplasias with the Ki-67 proliferation index [213-217]. Still, ***Ki-67 index obtained from EUS-FNAB***

bears the risk of undergrading compared to the analysis of the resected tumors [218] due to heterogeneity of proliferation [215-217].

EUS and CNB

Theoretically, the possibility of obtaining tissue CNB for histologic examination may circumvent this problem. Only one study in the literature has addressed this issue in 30 patients with NF-P-NENs, not including subjects with MEN1 [219]. Histologic core biopsy was obtained in 28 of the 30 patients evaluated, with the Ki-67 performed in 26 of the 28 subjects with available tissue. Twelve patients underwent surgery, and the concordance rate of Ki-67-based tumor grading between the EUS biopsy and histology of the surgical specimen was 83% when a cut-off of 2% was used to distinguish G1 and G2 tumors. However, a cut-off of 5% appeared to be more useful than the 2% value to stratify the prognosis of patients with P-NENs within the same disease stage [220]. Applying this cut-off to distinguish between G1 and G2 tumors, a 100% concordance was found [219].

Results from studies ***applying novel 22-gauge needles*** specifically developed for FNB ***to gather tissue for histological examination*** [221, 222] ***have demonstrated a diagnostic yield for histology in about 95%.***

Indication for EUS with Biopsy?

EUS-FNAB is not recommended routinely and should be reserved for firm indications such as for borderline tumors (approx. 20 mm in diameter; undefined classification in imaging) or for those with uncertain biological behavior (growth habit, proliferation index).

The decision whether or not to perform EUS-FNAB/FNB should be based on the impact of its results on the clinical decision-making process. For unresectable tumors, EUS-FNAB/FNB should be performed to reach a definitive diagnosis necessary to choose the most appropriate therapeutic option and to exclude other rare forms of pancreatic tumors in these patients, i.e. adenocarcinoma [223].

On the other hand, in patients with an indication for surgical resection and multiple pancreatic lesions, the pretest probability of EUS-FNAB/FNB for P-NENs is so high that sampling procedures might not be justified. Finally, in patients with a single lesion between 10 and 20 mm, EUS-FNAB may be indicated to rule out other conditions mimicking P-NENs, such as accessory spleen [224], which would change clinical management.

EUS and Follow-Up

Regarding how to follow patients with MEN1 and NF-P-NENs, expert opinion based on very few prospective studies seems to favor EUS as the most accurate imaging modality to monitor such patients [225].

In a study authored by Thomas-Marques et al. [80], 16 of the 26 patients found to have P-NENs underwent EUS monitoring over a median of 50 months. In 10 patients (62.5%), the number and diameter of the lesions remained stable, while in the remaining six patients, an increase in the number (four patients) and in the diameter of the lesions (two patients) was observed. In another study published by Kann et al. [47], a total of 82 asymptomatic tumors < 15 mm in 20 patients were followed by linear EUS performed every six months. An increase was identified in the largest tumor diameter of 1.3 ± 3.2% per month with an incidence rate of 0.62 new tumors per patient per year [47]. This is in line with recent data showing that the majority of small NF-P-NENs remain stable during follow-up [226, 227]. However, in the the study by D'Souza and colleagues [226], concern was raised about a faster growth rate of new tumors discovered during follow-up as compared to those diagnosed at the initial EUS.

Interventional EUS

The proximity of the EUS transducer to the pancreas and the possibility to place needles or other accessories into a target located adjacent to the wall of the GI tract have encouraged researchers to develop various EUS-guided local treatments directed also towards P-NENs. The use of preoperative EUS-guided tattooing or fiducial marker placement to facilitate intraoperative tumor localization has proven effective in reducing operative time of laparoscopic surgeries. EUS-guided locoregional treatments such as ethanol and and radiofrequency ablation have been proposed and the results are hitherto promising (also see Surgical Strategies for F- and NF-DP-NENs: Insulinoma)

The feasibility and the preliminary results of application of interventional EUS in some individual MEN1 cases (in the majority with insulinoma) were summarized recently reviewing the current literature [228]. ***EUS-RFA of pancreatic NENs is safe but has a relatively high complication rate,*** which can be decreased by improved prophylaxis for the procedure [229]. These alternative tretaments should be applied in specialized centers only.

Indications for Surgery

Is Size the Issue?

Samira M. Sadowski and Frédéric Triponez

Size and F-DP-NENs

Gastrinoma

In a prospective long-term investigation, ***there was a highly significant correlation of primary tumor size and the occurrence of liver metastases in patients with gastrinoma***. Only 4% of patients with a primary tumor ≤ 10 mm had metastases to the liver, whereas these were detected in 28% of the patients whose primary gastrinoma measured between 11 and 29 mm and in 61% of patients with primary tumors > 30 mm [230] (Table 4).

Table 4. Comparison of size of gastrinoma with presence or absence of metastatic disease to lymph nodes or liver [230].

Size (mm)	*n*	Metastasis			
		No	Lymph nodes	Liver	Lymph nodes or liver
		n (%)	*n* (%)	*n* (%)	*n* (%)
≤ 10	45	23 (51)	20 (44) [a]	2 (4) [b]	20 (44)
11-29	32	13 (41)	10 (31) [a]	9 (28) [b]	16 (50)
≥ 30	41	2 (5)	16 (41) [a]	25 (61) [b]	39 (90)

Note: Data are for 118 patients in whom primary tumors were localized and size of the primary tumor was assessed.

[a]: $p = 0.7$ for the correlation of primary tumor size to frequency of lymph node metastases

[b]: $p < 0.00001$ for the correlation of primary tumor size to frequency of liver metastases

Insulinoma and Other F-DP-NENs

Insulinoma are in the majority around 10 mm in diameter and show a benign biological behavior rarely resulting in regional and distal metastasis. Although showing characteristic clinical symptoms

of their hormone excess, the diagnosis of glucagonomas and vipomas (and somatostatinoma) is surprisingly late. ***At the time of diagnosis, the majority of these rare F-DP-NENs is 30 mm in diameter or larger with local and distant metastasis***.

Glucagonoma

The development of clinical manifestations and malignancy are related to size. A tumor less than 20 mm in diameter has a low incidence of symptoms and malignancy, but when tumor size is more than 50 mm in diameter, two thirds of glucagonomas are symptomatic and malignant (LE: 4) [231].

VIPoma

The ***majority of VIPomas are larger than 30 mm in diameter, malignant and associated with synchronous or metachronous liver metastases*** (LE: 4) [110].

Somatostatinoma

Somatostatinomas localized in the duodenum or the jejunum have small dimensions (around 0.5 to 1 mm) and are often multiple. ***Pancreatic somatostatinomas have large dimensions*** (30 to 50 mm), ***are frequently multiple and may metastasize early to peripancreatic lymph nodes and to the liver*** (LE: 4) [59, 138]. Because of large tumor size and the high rate of metastasis, the prognosis of glucagonomas, VIPomas and somatostatinomas is poor [59].

Size and NF-DP-NENs

The natural history of NF-DP-NENs in patients with MEN1 is not well established. However, also ***their biological behavior and therefore the risk of progression seem to be linked to size*** (LE: 4).

In their retrospective analysis of the French GTE database, Triponez et al. [83] showed that the risk to develop lymph nodes and/or distant metastases correlates with the size of the primary tumor and that the risk of death was low for patients with MEN1 and small (< 20 mm) NF-DP-NENs (Table 5).

Table 5. Correlation between the size of NF-P-NENs and the likelihood of synchronous or metachronous hepatic metastases [83]

Size (mm)	*n*	Metastasis		
		No	Synchronous	Metachronous
		n (%)	*n* (%)	*n* (%)
≤ 10	25	24 (96)	1/25 (4)	0
11-20	40	34 (85)	4 (10)	2 (5)
21-30	11	8 (73)	2 (18)	1 (9)
> 30	21	10 (48)	9 (43)	2 (9)
	97	76 (78)	16 (17)	5)

In this study, only 5 (7.7%) of 65 patients with NF-DP-NENs < 20 mm had synchronous lymph nodes or distant metastases and 2 (3.1%) of those who underwent surgery died of the disease. Moreover, the overall survival rate of patients with MEN1 and NF-DP-NENs < 20 mm was similar to the survival rate of patients with MEN1 who had no DP involvement (LE: 3) [83]. The average follow-up time after NF-DP-NEN diagnosis was 6.7 years in the surgery group and 3.3 years in the non-surgery group. Because of these follow-up results, those authors proposed a conservative attitude for patients with MEN1 and NF-DP-NENs < 20 mm in the absence of other aggressive features. Further, in the largest reported series on MEN1-associated NF-DP-NENs (*n* = 108), they showed that distant metastases were seen in 19% of the patients and the disease-specific survival rate to be 91% after a mean follow-up of four years (LE: 3) [232]. Compared to other series [55, 68], distant metastases were reported in about 6 to 22%.

Criticized for their relatively short follow-up time, the same group performed a 10-year prospective follow-up study within the same cohort: In 46 patients with NF-DP-NENs < 20 mm without surgical treatment, only one patient had died of the disease and 16 showed significant disease progression (indicated by an increase in the size or number of tumors, development of hypersecretion syndrome or need for surgery). However, these patients were then treated accordingly (seven underwent surgery, the others were followed), with none presenting metastases at the end of the 10.7 years of follow-up (LE: 2b) [233].

To date, ***the recommendation for surgical resection in NF-DP-NENs has been based on tumor size, as a higher rate of metastases was found in patients with larger tumors*** [83, 232, 234]. One study reported the presence of synchronous metastases in 43% of patients with NF-DP-NENs > 30 mm, in 18% of those with tumors between 21 and 30 mm, and in only 4% of patients with tumors < 10 mm

[232]. In the series published by Oleinikov et al.[235], tumor size also correlated with the risks of metastasis and death. The metastatic rate according to the dominant P-NEN lesion reached 100%, 62% and 6% for tumors sized > 40 mm, 21-40 mm, and 10-20 mm, respectively.

A study by the GTE [96] assessed the distant metastatic potential of DP-NENs in 603 patients with MEN1 (347 surgeries), with a follow-up of 6.9 years and using a multistate Markov piecewise constant intensities model (metastasis / metastasis-free death / death after metastasis). The investigators found that ZES-related tumors (regardless of tumor size), large tumors > 20 mm, and age over 40 years were independently associated with an increased risk of metastasis. The authors concluded that DP-NENs > 20 mm should be removed to prevent metastasis and increase survival, regardless of their associated secretion (LE: 2b).

On the other hand, there are studies that have not confirmed the association between primary tumor size and presence of metastasis [68, 236]. Bartsch et al. [68] showed no correlation between tumor size and metastatic potential in a retrospective single-center analysis of 26 patients with MEN1 and DP surgery performed between 1981 and 2004 and a median follow-up of 83 (5 to 241) months. This was shown for patients with ZES (*n* = 17) and with NF-DP-NENs (*n* = 9) (LE: 3).

Along with former observations [237], the GTE has advocated conservative management of NF-DP-NENs smaller than 20 mm if there are no signs of aggressiveness, such as rapid progression on imaging studies [83, 233]. Conservative management for NF-DP-NENs smaller than 20 mm has been reinforced by the results of a recent retrospective, multicenter European study in 27 patients with MEN1 [238]. Initial surgery was compared with conservative treatment and progression-free survival was found to be similar after a median follow-up of 126 months. Those authors concluded that NF-DP-NENs < 20 mm are indolent neoplasias and that their surgical treatment at initial diagnosis is rarely justified (LE: 3). This was further shown in a large Dutch MEN1 cohort that included 152 patients with NF-DP-NENs, in which 53 underwent surgery (median follow-up: 4.5 years) and 99 were managed by watchful waiting (median follow-up: 7.2 years) [239]. Metastasis-free survival was not found to be lower or higher in patients who had undergone surgery compared to watchful waiting (HR: 0.73 [0.25-2.11]). After stratification for tumor size, no significant differences in metastasis-free survival were seen between the two groups. However, for NF-DP-NENs > 30 mm, five out of the six patients managed by watchful waiting developed liver metastases or died compared to the six out of 16 patients who had been given surgery. The authors concluded that MEN1 patients with NF-DP-NENs < 20 mm can be managed conservatively and advised against watchful waiting for NF-DP-NENs > 30 mm (LE: 2b).

Is Tissue the Issue?

Aurel Perren

While macroscopically, an average of five DP-NENs [55] has been described in patients undergoing surgery, the number of microscopically detectable tumors is much higher because of the multifocality of the disease [240]. The entire pancreas involves multiple microadenomas and monohormonal cell clusters, as well as islets, interstitially and in ducts [241]. These lesions have been referred to as dysplastic islets [242] but have been shown to be true neoplasias due to the very frequent loss of the second MEN1 allele by FISH [241]. Such multifocality explains the high frequency of local recurrences [55], which therefore are frequently additional neoplasias rather than true recurrences. Apart from such neoplastic lesions, hyperplastic changes of islets have also been observed: These could represent preneoplastic changes or be an effect of MEN1 haploinsufficiency without direct relations with the neoplasias [241]. A similar situation has been observed in the duodenum with multiple primary gastrinomas (and fewer somatostatin-producing tumors), as well as hyperplasia of G-cells [240, 243].

These data suggest that ***most MEN1-associated DP-NENs remain stable in the state of microadenomas and only very few tumors arrive at the state of clinical detectability and possibly even less at the state of clinical relevance.*** It is unclear what mechanisms lead to progression in a subset of DP-NENs. Such progression involves secondary mutations such as DAXX/ATRX mutations in a subset of tumors [244]. In the setting of MEN1 disease, these mutations have been shown to occur exclusively in rare MEN1-associated DP-NENs > 30 mm [244].

TNM staging and grading is performed according to the WHO classification [245] (Tables 6 and 7).

P-NENs larger than 20 mm have more chromosomal aberrations than small P-NENs. The number of chromosomal alterations has been seen to correlate with loss of DAXX/ATRX in sporadic P-NENs [246], together with induction of the (telomerase-independent) ALT phenotype [246]. The mechanisms involved are still unknown but could include epigenetic changes. Such ***P-NENs with DAXX/ATRX mutations and ALT have a higher risk of relapse.***

The second known important factor for relapse prediction in P-NENs ***is tumor grade measured by proliferation*** (> 3% Ki-67 index or > 2 mitosis / 2 mm^2) [247]. This risk factor is independent of stage and plays a role in MEN1-associated DP-NENs [244]. In a recent study, an increased risk of metastasis was described in DP-NENs > 20 mm that are G2 by MI, however not by Ki-67 [248]. Unfortunately, no large series of MEN1-associated P-NENs has been carried out in this respect.

The evaluation of 60 DP-NENs harvested from six MEN1 pancreatic glands adds additional information regarding the importance of size (pT) in combination with proliferation (G) [249]. In this series,

significantly more tumors ≥ 20 mm were classified as G2 (Ki-67 index: > 2-20%), thus indirectly yielding a higher capacity of malignancy.

When tumors reach the cut-off (20 mm; leading tumors), it may be recommended to obtain tissue specimens of those tumors to select patients at risk of highly proliferating neoplasias and who may require early surgical intervention to prevent invasive growth, regional and distant metastasis. DP-NENs with Ki-67-positive cells > 2% should probably be given early-stage surgery, regardless of their size [249].

As shown recently [250], ***NF-DP-NENs G2 should be considered high risk.***

Since 2006, there has been a gradual development of the classification of NENs of the DP-NENs, in parallel and finally together, by the AJCC/UICC and ENETS [251, 252]. The recently published rules for the classification of NENs as modified by the WHO in 2019 are summarized in Table 6 [253]. The term "neuroendocrine neoplasm" was used synonymously with "neuroendocrine tumors" in many older and more recent publications. In 2018, the WHO published a uniform classification framework for all NENs. The key feature of the new classification is a distinction between "well differentiated" neuroendocrine tumors (NETs) and "poorly differentiated" neuroendocrine carcinomas (NECs), as they both share a common expression of neuroendocrine markers. This dichotomous morphological subdivision into NETs and NECs is supported by genetic evidence at specific anatomic sites as well as clinical, epidemiologic, histologic and prognostic differences. Also located in the duodenum and pancreas, NENs may be graded as NET G1 (low grade), NET G2 (intermediate grade), or NET G3 (high grade) based on mitotic count and/or Ki-67 labeling index, and/or the presence of necrosis. NECs are considered "high-grade" by definition and should be classified according to the criteria for ductal carcinomas at the pancreas [253] (Tables 7-10).

Regarding DP-NENs G3 in the setting of MEN1, poorly differentiated NECs G3 are exceedingly rare and therefore expected even less frequently than NETs G3 due to the underlying MEN1 mutation. However, no literature is available regarding this topic in MEN1 patients.

Table 6. Classification and grading criteria for NENs of the GI tract and hepatopancreatobiliary organs according to WHO 2019 [253]

Terminology		Differentiation	Grade	MI rate	Ki-67 (%)
(NEN G1) NET G1		Well differentiated	Low	< 2	< 3
(NEN G2) NET G2			Intermediate	2-20	3-20
(NEN G3) NET G3			High	> 20	> 20
NEC	Small-cell type (SCNEC)	Poorly differentiated	High	> 20	> 20
	Large-cell type (LCNEC)				
MINEN		Well or poorly differentiated	Variable	Variable	Variable

LCNEC: large-cell neuroendocrine carcinoma; MI: mitotic index; MINEN: mixed neuroendocrine-non-neuroendocrine neoplasia; NEC: neuroendocrine carcinoma; NEN: neuroendocrine neoplasia; NEN: Neurondocrine neoplasia NET: neuroendocrine tumor; SCNEC: small-cell neuroendocrine carcinoma

Mitotic rates are to be expressed as the number of mitosis / 2 mm^2 (equaling 10 high-power fields at 40x magnification and an ocular field diameter of 0.5 mm) as determined by counting in 50 fields of 0.2 mm^2 (i.e. in a total of 10 mm^2). The Ki-67 proliferation index value is determined by counting at least 500 cells in the region of highest labelling. The final grade is based on whichever of the two proliferation indexes places the neoplasia in the higher grade category. Poorly differentiated NECs are not formally graded but are considered high-grade by definition.

In most MINENs, both the neuroendocrine and non-neuroendocrine components are poorly differentiated and the neuroendocrine component has proliferation indexes in the same range as other NECs. However, this conceptual category allows for the possibility that one or both components may be well differentiated. When feasible, each component should therefore be graded separately.

Table 7. TNM classification of P-NENs (NET G1 and NET G2) according to WHO 2019 [253]

T – Primary tumor (G1 + G2) *	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor

T1	Tumor limited to the pancreas**, less than 20 mm in greatest dimension
T2	Tumor limited to the pancreas**, 20 mm or more but less than 40 mm in greatest dimension
T3	Tumor limited to pancreas**, more than 40 mm in greatest dimension or tumor invading duodenum or bile duct.
T4	Tumor invades adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (coeliac axis or the superior mesenteric artery)
N – Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M – Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Hepatic metastasis only
M1b	Extrahepatic metastasis only
M1c	Hepatic and extrahepatic metastasis

*For any T, add (m) for multiple tumors.

**Invasion of adjacent peripancreatic adipose tissue is accepted, but invasion of adjacent organs is excluded.

Table 8. Staging of P-NENs (NET G1 and NET G2) according to WHO 2019 [253]

Stage	**T**	**N**	**M**
I	T1	N0	M0
II	T2,3	N0	M0
III	T4	N0	M0
	Any T	N1	M0
IV	Any T	Any N	M1a-c

Table 9. TNM classification of NENs of the duodenum/ampulla according to WHO 2019 [253]

T – Primary tumor (G1 + G2) *	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Duodenal: Tumor invades mucosa or submucosa and 10 mm or less in greatest dimension Ampullary: Tumor 10 mm or less in greatest dimension and confined within the sphincter of Oddi
T2	Tumor invades muscularis propria or size > 10 mm
T3	Tumor invades pancreas or peripancteatie adipose tissue
T4	Tumor perforates visceral peritonoum (serosa) or invades other organs
N – Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M – Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Hepatic metastasis only
M1b	Extrahepatic metastasis only
M1c	Hepatic and extrahepatic metastasis

*For any T, add (m) for multiple tumors

Table 10. Staging of well differentiated NENs of the GI tract (NET G1 and NET G2): D-NENs/ampullary NENs [251]

Stage	**T ***	**N**	**M**
I	T1	N0	M0
II	T2,3	N0	M0
III	T4	N0	M0
	Any T	N1	M0
IV	Any T	Any N	M1a-c

*For any T, add (m) for multiple tumors

Is Genetics the Issue?

Pierre Goudet

For this critical analysis answering the raised question, care was taken to only consider publications with correct methodology: large series, using time-dependent procedures, avoiding multiple statistical tests without any correction, and considering, if possible, intrafamilial correlations.

Only one recent publication has established a genotype-phenotype correlation in MEN1 disease. An increased prevalence of DP-NENs was found in a series with 188 MEN1 patients when a mutation in exon 2 was present (LE: 2b) [254].

Other large cohorts of more than 100 patients using time-dependent procedures were negative. These series comprised 258 and 806 patients, respectively (LE: 2b) [52]; (LE: 2b) [255]. Three series with 109, 145 and 170 patients, respectively, yielded the same results without using time-dependent procedures (LE: 4) [256]; (LE: 4) [37]; (LE: 4) [257]. Although a possible association between ABO blood type and the development of P-NENs has been raised, the two largest studies on this topic arrived at contradictory conclusions. An NIH study with 104 patients found a significant association between blood type O and NENs (including DP-NENs), whereas a Dutch investigation with 200 patients did not confirm this result (LE: 2b) [258]; (LE: 2b) [239].

By contrast, two studies tended to show that the tumor aggressiveness of P-NENs may be related to the loss of menin interaction with functional partners (LE: 2b) [255]; (LE: 3) [76]. On the one hand, mutations affecting the JunD-interacting domain seemed to be associated with a higher risk of death secondary to a MEN1 tumor in a cohort study with 806 patients related to 262 families (LE: 2b) [255]. On the other hand, a higher risk of aggressive P-NENs in patients with MEN1 mutations affecting the CHES1-interacting menin domain was established in a 67-patient series affecting 56 families (LE: 3) [76]. Moreover, the study published by Christakis and coworkers, which showed a genotype-phenotype correlation, also described a two-fold increased risk of metastasis among patients between 20 and 40 years of age when a mutation in exon 2 was found, knowing that the JunD domain is partially included in exon 2 (LE: 2b) [254]. These investigators advised to decrease the size recommendation for DP-NEN resection to ≥ 15 mm for exon 2-mutated patients, yet they also suggested that confirmation be obtained from other independent studies. Finally, the Dutch MEN1 Study Group investigated the long-term course of 115 small NF-DP-NENs. This study aimed at quantifying the growth rate of such tumors, the size of which was initially 10 ± 4 mm. Missense mutations were significantly associated with accelerated growth. The authors were very careful in their conclusions, as missense mutations are not truncating mutations, usually considered as aggressive mutations. In addition, this study ad-

dressed the question of small tumors which are usually not aggressive at their initial stage of development (LE: 2b) [259]. By contrast, aggressive phenotypes with a high penetrance of malignant P-NENs within particular families have been described (LE: 4) [260]; (LE: 4) [261]. Both of these families carried germline mutations that completely abolished menin function. Belonging to this type of family is a reasonable additional factor that may help surgeons make the final decision for pancreatic surgical resection when the indication is questionable.

Therefore, further international cooperative studies are required before recommendations on this topic can be established, even though the indications for a possible genotype-phenotype correlation are promising.

Surgical Treatment

Surgical Strategies

Prerequisite

Hyperparathyroidism: Gastrinoma and Insulinoma

MEN1 patients with F-DP-NENs have one important aspect regarding the effect of hyperparathyroidism on the hypersecretory state. Studies have demonstrated that the presence of hyperparathyroidism and hypercalcemia generally lead to a stimulation of hypersecretion and also a relative resistance to antisecretory therapy. This has been well documented in MEN1-ZES patients who, after having undergone effective parathyroidectomy (usually 3.5-gland or 4-gland removal and an implant), experienced a decrease in FSG levels and in basal acid output. Secretin tests may revert to negative and an increased sensitivity may develop to antisecretory drugs (LE: 2b) [116, 117, 130].

Evidence suggests that a similar phenomenon occurs with insulinomas in MEN1 patients. In a patient with MEN1 and diabetes mellitus [262] who had developed hyperparathyroidism, the insulin dose required to control blood sugar decreased by 50% after parathyroidectomy.

Hyperparathyroidism-related hypercalcemia may increase the hormone output. Therefore, before treating MEN1-ZES [116] and hyperinsulinism, it is recommended to treat hyperparathyroidism

Various Strategies for the Surgical Treatment of F- and NF-DP-NENs

Limited Procedures

Enucleation refers to the selective surgical removal of a tumor mass without cutting into or dissecting the lesion.

(Middle) segmental pancreatic resections [263] / pancreatic tail resections [264] are appropriate procedures for selected patients with lesions in the mid-portion (body) or the tails of the pancreas. These procedures preserve pancreatic parenchyma and function. However, this technique is associated with a two-fold risk to develop pancreatic fistulas.

In **PPTD**, the duodenum is separated from the head of the pancreas by cutting the branches of the DP arcade vessels and leaving all parts of the pancreas behind [265]. Imamura M et al. [202] presented the outcome of this novel surgical technique for the treatment of MEN1-ZES patients with good results in a small set of subjects.

Extended Procedures

The **Thompson procedure** involves distal pancreatic resection (left pancreatic) up to the superior mesenteric vein with/without spleen preservation and enucleation of lesions larger than 20 mm in the pancreatic head in the case of biochemically proven organic hyperinsulinism [266]. In patients with biochemically verified gastrinoma, duodenotomy and local excision of gastrinoma is mandatory to remove solitary or multiple gastrin-producing tumors [267, 268].

PPD (Whipple procedure [269] with PPPD [270] or without pylorus preservation is the gold standard operation for resection of the pancreatic head. It is most commonly performed for large pancreatic NENs which cannot be enucleated. It is discussed in MEN1 patients with biochemically verified gastrinomas, the majority of which are multiple. PPPD leaves postpyloric duodenal mucosa behind which may theoretically be the basis for recurrent gastrinoma.

TP [271] is defined as the removal of the entire pancreas, the duodenum, the gall bladder, part of the bile duct and occasionally the stomach. Most experts agree that TP as an initial procedure should be an exception, given the relatively long natural course of MEN1 DP-NENs, even in the presence of malignancy. It results in insulin-dependent diabetes mellitus and exocrine pancreatic insufficiency, both causing significant morbidity and quality of life restrictions in the mostly young MEN1 patients.

Gastrinoma (MEN1-ZES)

Detlef K. Bartsch

MEN1 gastrinoma causing ZES is the most frequent F-DP-NEN *(30%)****. Gastrinomas are duodenal in origin and not in the pancreas*** (LE: 2b) [22, 23, 272, 273].

Indication for Surgery

At least 70 to 80% of MEN1 gastrinomas have been demonstrated to be malignant at the time of diagnosis and to show lymph node and/or liver metastasis, although the primary tumor(s) may be microgastrinomas as small as 1 to 2 mm in size (LE: 2b) [23, 26, 266, 272, 274].

Whereas lymph node metastases may not adversely affect survival, the presence or development of liver metastases is the major life-threatening determinant in MEN1-ZES, (LE: 2b) [230, 275, 276]. Therefore, the management of MEN1 gastrinoma, be it medical treatment with PPIs or surgery, is a highly controversial issue [277]. Recent expert guidelines have suggested medical management using PPIs for most patients (weak recommendation, low-quality evidence), since the course of disease is rather mild and MEN1-ZES is considered a surgically non-curable disease based on the published literature [11].

It has been shown that patients with MEN1-ZES and no imageable pancreatic tumors have a 10-year survival rate of 100%. In the presence of diffuse distant metastases, 10-year survival is still 54% (LE: 2b) [273]. Other groups favor a surgical approach to aim at biochemical cure and to prevent the development of liver metastases [56, 202, 266, 272, 278], since R0/R1 resection of MEN1-ZES has been demonstrated to significantly prolong survival compared to non-surgery or R2 resection [279] and since surgery has proven to prevent the development of liver metastases [280]. In a study carried out by the NIH [280], only 3% of surgically treated patients with MEN1-ZES developed liver metastases compared to 23% of non-surgically treated patients during follow-up ($p = 0.003$) (LE: 3) [279].

Several retrospective series have confirmed that surgery prevents the development of liver metastases in 90 to 100% of patients during long-term follow-up (LE: 2b) [21, 56, 68, 202]. In addition, normalization of serum gastrin levels in MEN1 patients following gastrinoma resection has been suggested to result in regression and/or prevention of type 2 gastric NENs, which may occur in some patients due to chronic gastrin stimulation of the enterochromaffin cells to proliferate (LE: 3) [280].

Timing of Surgery

The adequate indication for and extent of surgery in ZES remain a matter of controversy. Some groups have demonstrated in small cases series that PPD as an initial procedure at the time of biochemical evidence of ZES, even without positive imaging studies, resulted in a high rate of biochemical cure, ranging from 77 to 92% without mortality after a median of three to seven years (LE: 3) [56, 202, 272, 278].

Other groups [96, 273, 275] have recommended surgery for MEN1-ZES if imaging visualizes a pancreatic lesion > 20 to 30 mm in size, as the risk for liver metastases then increases significantly [230]. It may be speculated that ***the vast majority of patients*** in those studies [273, 275] ***had duodenal gastrinomas and that the imaged, supposedly "pancreatic gastrinomas",*** which were not proven based on histopathology including IHC for gastrin expression, ***were most likely NF-P-NENs.*** Therefore, the correct interpretation of such imageable "pancreatic tumors" (> 20 mm) in MEN1-ZES has to be related to NF-P-NENs and not to gastrinoma. Nevertheless, the presence of an ***imageable pancreatic lesion > 20 mm*** in MEN1-ZES may be a ***useful surrogate parameter to indicate surgery***, based on the good rate of long-term survival in this setting of up to 100% at ten years (LE: 2b) [96, 273].

Type of Surgery

Enucleation

The extent of surgery is another controversial issue in MEN1-ZES. Most experts agree that the very rare "pancreatic gastrinomas" should be either enucleated, whenever technically feasible, or removed by formal pancreatic resection, both combined with systematic lymphadenectomy [281].

Thompson Procedure

The most commonly proposed operation for duodenal gastrinomas includes duodenotomy with excision of the duodenal wall tumors, enucleation of any tumors of the pancreatic head, and peripancreatic lymph node dissection with distal pancreatectomy ("Thompson procedure") or without [266, 273, 281, 282]. No controlled comparative studies have evaluated these two procedures and thus there is only weak data to give preference to one procedure over the other [39].

Based on retrospective cohort studies, there seems to be no difference regarding the cure rate and the prevention of liver metastases (LE: 3) [266, 272, 273, 280, 282]. These procedures rarely provide cure, with no more than 30% of the patients showing a negative secretin test five years postoperatively, but they prevent the development of liver metastases in most patients over long-term follow-up [55, 56, 266, 272, 273, 281, 282].

It also has to be considered that the Thompson procedure involves a significant risk of postoperative pancreoprivic diabetes mellitus (around 30%) and of completion pancreatectomy (up to 16%) during long-term follow-up [55, 56, 266, 272, 282].

PPD

Therefore, some groups prefer PPD as the first-line procedure for MEN1-ZES [56, 202, 272, 278]. There are several reasons for this strategy: First, since more than 90% of MEN1 gastrinomas arise in the duodenum, and proliferative gastrin cells in the normal duodenal mucosa are the precursors of these tumors, long-term cure is only possible if the organ of origin is removed given the inherited predisposition. Second, PPD allows radical excision of the peripancreatic lymph nodes and of P-NENs possibly prevalent in the head of the pancreas, thus clearing the entire gastrinoma triangle. Third, cephalic macroscopic P-NENs can also be treated by PPD by extending the procedure to include part of the pancreatic body.

Small cases series with 3 to 13 patients evaluating PPD as initial procedure for MEN1-ZES have yielded a high rate of biochemical cure after a median of three to seven years, ranging from 77 to 92% [56, 202, 272, 278]. Although the PPD procedures provide the greatest likelihood of cure for MEN1-ZES, they are potentially associated with increased operative mortality and long-term morbidity. However, a recent study on 27 patients with MEN1-ZES demonstrated that the perioperative complication rate tended to be even higher in the non-PPD group. The rate of postoperative diabetes mellitus and the need for completion pancreatectomy during follow-up was also higher in the non-PPD resection group [272]. Nevertheless, long-term results regarding quality of life after PPD resections are still lacking. In this regard, it also has to be taken into account that lesser operations are associated with excellent long-term survival [273].

PPTD

PPTD has been described as an alternative surgical procedure for duodenal MEN1-ZES. Five of seven patients having undergone this procedure were biochemically cured after two to six years [202]. The authors stated that PPTD is a less invasive procedure than PPD, with no complications in their series. However, they also noted that regional lymph node dissection may not be as complete with PPTD compared to PPD. This may be the reason for the fact that two of their seven patients developed ZES recurrence due to liver or distant lymph node metastases within three years postoperatively. Based on these data, the value of PPTD for the treatment of MEN1-ZES cannot yet be determined.

TP

TP as an initial procedure for MEN1-ZES should be avoided whenever possible, since resulting "brittle" diabetes (labile diabetes, hard-to-control diabetes with large and rapid swings in blood glucose levels) significantly reduces patients' quality of life and is associated with serious morbidity during long-term survival. Thus, this procedure should be definitively restricted to very rare conditions, such as malignant ZES with multiple large P-NENs throughout the entire pancreas.

In a current review of the literature, Bartsch and Albers [283] analyzed postoperative complications, mortality and morbidity, the postoperative development of liver metastasis , and the cure rates after "less than PPD" (Table 11) and "after PPD" (Table 12). All studies included provided the required data.

Table 11. ZES in MEN1: Results of "less than PPD"

See review by [283]

Author [**reference**]†	***n***	**Secretin test** (normal at last FU)	**Postop complications**	**Mortality**	**Liver mets. postop**	**FU** months (median)
MacFarlane [104]	10	0 (0%)	No data	0	0/10 (0%)	18
Thompson [266]	40	13 (3.25%)	17 (42.5%)	0	1/40 (2.5%)	126
Mignon [284]	36	1 (2.8%)	13 (36.1%)	0	5/36 (13.9%)	95
Norton [273]	48	2 (4.2%)	14 (29.2%)	0	3/48 (6.3%)	122
Dickson [278]	11	3 (27.3%)	no data	0	1/11 (9.1%)	44
Lopez [272]	9	3 (33.3%)	5 (55.6%)	0	0/9 (0%)	136
Total (*n*)	**154**	**22/154**	**49/133**	**0/154**	**10/154**	**108.5**
%		**14.3**	**36.9**	**0**	**6.5**	

†Only studies that provided required data

FU: follow-up; mets.: metastases; postop: postoperative.

Table 12. ZES in MEN1: Results of "after PPD"

See review by [283]

Author† **(reference)**	***n***	**Secretin test** (normal at last FU)	**Postop complications**	**Mortality**	**Liver mets. postop**	**FU** months (median)
Stadil [285]	3	3 (100%)	1/3 (33.3%)	0	0	60–132
Tonelli [56]	13	10 (76.9%)	5/13 (38.5%)	0	1 (7.7%)	6–36
Dickson [278]	3	3 (100%)	No data	0	0	12–48
Imamura [202]	3	3 (100%)	1/3 (33.3%)	0	0	48–221
Lopez [272]	13	12 (92.3%)	4/13 (30.8%)	0	0	6–132
Total (*n*)	**35**	**31/35**	**11/32**	**0**	**1/35**	**6–221**
%		**(88.6%)**	**(34.4%)**	**0**	**(2.9%)**	

†Only studies that provided required data ; FU: follow-up; mets.: metastases; postop: postoperative.

Surgical Re-exploration in MEN1-ZES

At present, the indications for surgical re-exploration and the type of operation, including completion pancreatectomy, are largely undefined in MEN1-ZES [281], as only few retrospective studies with between two and twelve patients have dealt with this problem (LE: 3) [55, 277, 282, 286].

The indication for re-exploration was a biochemically proven recurrence of ZES in combination with imageable disease (e.g., CT/MRI or SRS). The operations included redo duodenotomy with lymphadenectomy, resection of lymph node or liver metastases, and PPD resection or completion pancreatectomy. In these series, up to 50% of patients with MEN1-ZES who had undergone reoperations were given total pancreatectomy. The biochemical cure rate varied between 0% (0 of 2 patients) [286] and 75% (3 of 4) [55], and none of the patients developed liver metastases during 100 months' long-term follow-up. Based on the very limited data, it is recommended that the indication for re-exploration in MEN1-ZES should be considered with caution, especially since the symptoms can be well controlled with medical treatment and long-term survival without distant metastases is excellent. The surgical procedure should be individualized according to preoperative findings, previous DP resections, the patient's history (e.g., age, pre-existing insulin-dependent diabetes) and the patient's preference. Completion pancreatectomy should be avoided, if technically possible and justified from an oncological perspective.

Role of Surgery in the Treatment of Advanced MEN1-ZES

Approximately 24% of patients with MEN1-ZES develop an aggressive course of disease with distant metastases leading to death (LE: 2a) [287]. No reliable marker or parameter has so far been identified to indicate an aggressive course of disease in MEN1-ZES. The most important determinant of survival in patients with MEN1-ZES is the presence or development of hepatic metastases [230, 276, 287]. Furthermore, the extent of liver metastases in ZES also seems to be important, as patients with single-lobe involvement or less than five metastases have been seen to experience significantly better 15-year survival rates (60%) compared to those with diffuse liver metastases (15%) [276].

Unfortunately, only up to 20% of ZES patients with advanced disease have limited hepatic disease type 1 or 2 [276, 281] according to the ENETS classification [288], with no other distant metastases (e.g., bone metastases). In various retrospective studies including patients with MEN1-ZES, surgery has resulted in cure in a few subjects, and 5-year survival rates of approx. 70% have been reported after resection of liver metastases [289].

However, these results are difficult to interpret with regard to MEN1-ZES. In no controlled trials have the groups been appropriately matched to control groups without cytoreductive surgery. This makes patients with resectable disease incomparable to those with unresectable disease and differences in survival may be independent of surgery. This holds especially true for patients with advanced MEN1-ZES at the time of diagnosis, since those most likely belong to the 24% of patients with an aggressive course of disease [287].

Patients with advanced F-NENs other than gastrinoma may benefit from symptom control post resection, whereas in patients with MEN1 gastrinoma, in whom symptoms are usually well controlled with PPI treatment, the value of surgery is almost entirely assessed by its effect on survival. At present, there are insufficient data for MEN1-ZES to unequivocally determine in which patient cytoreductive surgery for liver metastases should be performed. However, most of the retrospective surgical studies on advanced P-NENs [289] have shown that these resections can be performed with acceptable morbidity and low mortality and that they potentially prolong survival. Therefore, it can be recommended that surgery be considered in MEN1-ZES patients with advanced disease confined to the liver if at least 90% or all of the identifiable tumor burden can safely be removed [288]. A multidisciplinary approach, including surgical and non-surgical treatment options, should always be discussed on a tumor board basis and be balanced prior to any surgical resection.

Prognostic Factors Influencing Survival

Medical therapy is recommended and clinically necessary in all patients with ZES. Surgery may be considered in a subgroup of patients (see discussion above). A recently published population-based cohort study assessed prognostic factors of survival in patients with MEN1-related gastrinomas based on FSG levels and/or pathology. The 5- and 10-year overall survival rates were 83% and 65%, respectively. The prognostic factors associated with overall survival were initial FSG levels ≥ 20x upper limit of normal (HR 6.2 [95% CI 1.7-23.0]), pancreatic NEN ≥ 20 mm (HR 4.5 [1.5-13.1]), synchronous liver metastases (HR 8.9 [2.1-36.7]), gastroduodenoscopy suspicious for gastric NENs (HR 12.7 [1.4-115.6]), and multiple concurrent NENs (HR 5.9 [1.2-27.7]). The authors concluded that the prognostic factors influencing the reduced life expectancy of patients with MEN1 gastrinoma are FSG levels and pancreatic NENs ≥ 20 mm. FSG levels might guide surveillance intensity, step-up to additional diagnostics, or provide arguments in selecting patients who might benefit from surgery [290].

Insulinoma / Rare F-P-NENs (VIPoma - Glucagonoma - Somatostatinoma)

Francesco Tonelli

Insulinoma

Insulinomas are the second most frequent F-DP-NENs in MEN1, occurring in approx. 15% of patients. ***The target organ*** of insulinoma (provoking hypoglycemic syndromes) ***is the pancreas.*** [74]. [48, 110, 291, 292]. Insulinomas can represent the first clinical manifestation of the MEN1 syndrome in at least 15% of the affected patients [11, 15, 44, 79, 293].

A NEN is classified as insulinoma if diffuse positivity of the neuroendocrine cells for insulin is found at IHC [54, 69, 266, 294-297]. However, there seems to be no clear relationship between IHC expression and biochemical or clinical diagnosis [298]. Furthermore, identification of insulinoma on pathology is challenging because NF-DP-NENs might also express insulin and some insulinomas might not express insulin [299].

In MEN1 insulinoma, ***the indication for early surgery after biochemical confirmation of organic hyperinsulinism is generally advocated because of the lack of effective medical treatment. Successful surgery in time avoids neurological complications of hormone excess*** (e.g., brain damage by glycopenic attacks)[110, 291, 300-303].

The size of insulinomas varies from a few millimeters to 20 mm or more and multiple insulinomas may be found alongside NF-P-NENs [54, 294, 296, 297]. Some authors have suggested that a dominant lesion with a dimension of at least 10 mm is responsible for hyperinsulinism, also in the presence of multiple NENs (LE: 4) [74, 295]. It is unclear whether only the dominant P-NEN is responsible for hypoglycemia. It is probable that also micro-insulinomas (less than 5 mm in diameter) are present and cause hyperinsulinism besides a larger insulinoma. This is because the persistence of hypoglycemia after enucleation of a single insulinoma larger than 10 mm is accompanied by a percentage of persistence of the syndrome much lower than the percentage of the discovered multiple insulinomas.

Preoperative Localization

(also see Methods to Diagnose and Follow Up DP-NENs: Cross-Sectional and Functional Imaging)

In the MEN1 pancreas, more than one macroscopic tumor and several microadenomas are the rule. Therefore, it is sometimes difficult to distinguish insulinomas from other P-NENs by pre- or intraoperative imaging techniques (EUS/CT/MRT/PET or intraoperative US) or by localization/regionalization) procedures (SACI test).

The recent advances in noninvasive imaging by both HRCT and MRI allow a very high detection rate with close to 100% sensitivity of various macroadenomas (LE: 3) [152]. EUS is able to visualize NENs even if they are around 5 mm in diameter [153]. The EUS appearance of an insulinoma is a rounded, homogeneously hypoechoic lesion with distinct margins. However, it does not differ in its aspect from other NF-P-NENs.

Most importantly, intraoperative findings, based on intraoperative US and/or bimanual palpation, are used to diagnose preoperatively not localized insulinoma and subsequently guide intraoperative surgical decision-making. In at least 5%, insulinomas are very small and therefore invisible and impalpable or are isoechogenic, so that even intraoperative US assessments can be negative.

To classify a P-NEN as insulinoma is not feasible with cross-sectional imaging, and the possibility must theoretically be entrusted to specific diagnostic techniques, such as the following.

EUS- (or CT-) guided FNB, which allows samples to be taken for IHC examinations documenting insulin. However, this procedure is rarely employed in MEN1 patients [44, 225, 304], because it is difficult or impossible to examine several pancreatic lesions, especially if the nodules are small. The study published by Kann [305] analyzed patients with sporadic insulinoma. However, the results may also suggest for MEN1 insulinoma that EUS-FNA could be an effective tool in the diagnostic work-up. Carried out in institutions with extensive EUS expertise, it may be helpful in questionable imaging situations where an accurate preoperative diagnosis should help to localize the insulinoma within multiple P-NENs, thus affecting the therapeutic strategy.

Insulinomas with a diameter of less than 5 mm can be "detected" with SACI (LE: 3; [306]; also see Methods to Diagnose and Follow Up DP-NENs: Cross-Sectional and Functional Imaging). However, applying the SACI test, the insulin-hypersecreting lesion cannot be "localized" definitively, but can be "regionalized" in the pancreas, assigning the insulin-secreting tumor to the right or left pancreatic region. This is based on an increase in hepatic vein insulin levels as an expression of the increase in insulin levels in the venous effluent of the pancreatic veins draining a specific pancreatic region (head, body, tail), stimulated by calcium applied into the pancreatic artery. A two-fold increase in the insulin concentration from baseline regionalizes the given insulinoma within the anatomic region. Sung et al. [307] suggested to document not only the level of insulin, but also of C-peptide to achieve better sensitivity of the examination. Indeed, although the secretion ratio of C-peptide to insulin is 1:1, the ratio in serum is completely different with a value of 5 to 15:1 in favor of C-peptide. Their observation should be confirmed by additional investigations, as other authors [308] have failed to identify significant differences in the sensitivity of the test related to insulin or C-peptide levels. SACI requires specific expertise that may be available only in specialized centers.

Over the past twenty years, 14 cases of MEN1 insulinomas have been documented in the literature and the examinations by SACI test were inconclusive in two of these cases [295, 308, 309]. False-negatives due to technical flaws and anatomical variants of pancreatic vascularization or false-positives involving insulinoma regionalization in a wrong pancreatic region are both possible. Furthermore, it is unclear whether the SACI test may also evidence small insulinomas eventually detected on the histological examination of the resected pancreas and how more than one insulinoma scattered throughout different parts of the pancreas may possibly be regionalized. The technique is operator-dependent, requires a high level of expertise and may sometimes result in misleading or inconclusive results [308].

THPVS has been widely used in the past in sporadic hyperinsulinism. Its application in MEN1 is rare, if ever at all performed. The technique is invasive with low accuracy. It is mentioned here to theoretically complete the localization/regionalization methods.

GLP-1R imaging by ^{68}Ga-exendin-4 PET/CT (also see Methods to Diagnose and Follow Up DP-NENs: Cross-Sectional and Functional Imaging). Insulinomas express more GLP-1Rs than SSTRs and, therefore, receptor-targeted imaging with agonists for GLP-1Rs has been proposed and employed over the past years. Several ligands for GPL-1Rs are available. ^{68}Ga-DOTA-exendin-4 PET/CT has been seen to correctly localize insulinomas in almost all patients affected by sporadic or MEN1 insulinomas [194, 310]. The selectivity of this tracer or others specific for insulinoma cells must be shown with further clinical experiences. Antawi et al. [194] recently evaluated the sensitivity of ^{68}Ga-DOTA-exendin-4 PET/CT in the detection and localization of insulinoma in six patients with MEN1 and organic hyperinsulinism. Functional imaging by ^{68}Ga-DOTA-exendin-4 PET allowed to distinguish solitary and multiple insulinoma from other P-NENs within a MEN1 pancreas in the study. The sensitivity to correctly localize the insulinomas was 90%. The combination with MRI additionally allowed to determine the size of the insulinomas and other P-NENs.

Functional and morphological imaging may individually guide the surgical strategy in patients with MEN1 and organic hyperinsulinism and, as a consequence, should improve the postoperative results. Since all of these location and regionalization studies are rarely employed and available to an only limited extent, it is difficult to analyze their definitive value and accuracy in localizing insulinomas in MEN1. In a great majority of patients, surgery has to be carried out without knowledge of the definitive site, size and/or the number of insulinoma(s). Therefore, surgery should be performed in centers with experience.

Surgical Treatment

No specific surgical procedure is recommended in MEN1 insulinomas. An individualized surgical approach has to be choosen, based on the location and size of the suspected insulinoma as well as of the

presence of other F-DP-NENs (e.g., gastrinoma) and additional NF-P-NENs with an indication for surgery (e.g., size > 20 mm). The selected surgical procedure should both yield a high probability to cure hyperinsulinism and preserve the exocrine and endocrine pancreatic functions at a high rate.

Enucleation may be an attractive pancreatic parenchyma-sparing strategy and has been proposed by several authors in the case of a single or dominant insulin-hypersecreting P-NEN [55, 295].

Distal pancreatectomy is considered to be the procedure of choice as it yields a high rate of cure in several series [56, 300, 302, 311-317].

Distal pancreatectomy exposes patients to the risk of secondary diabetes and exocrine secretion deficit because of the more extended tissue resection, especially in the context of MEN1, for which additional surgery is frequently required [312, 318].

Data concerning the modality, morbidity and the biochemical long-term result of surgical treatment can be retrieved from thirteen retrospective case series [54, 110, 266, 294-297, 300, 313, 314, 319, 320] [321]. Several of these publications are based on experience with less than ten patients and some show follow-up periods shorter than ten years (Table 13).

Limited Pancreatic Resection

Enucleation: ***In cases of a solitary tumor or one dominant tumor (> 10 mm) besides some other small DP-NENs (≤ 5 mm), enucleation or segmental pancreatic resection with the dominant tumor(s) is recommended whenever technically feasible***. A distance to the main pancreatic duct ≥ 3 mm is favorable not to damage the duct. In order to avoid overextensive pancreatic resections, a distance to the main pancreatic duct < 3 mm may be accepted. However, a higher rate of pancreatic fistula has to be taken into account.

Enucleation as the standard treatment does not appear to be the optimal strategy for all patients with MEN1 insulinoma (LE: 4). Besides the risk of damage to the main pancreatic duct or vessels, the potential drawbacks of enucleation include the difficulty to treat multiple and/or deep NENs, the risk of leaving small unexplored insulinomas behind, which may be responsible for the persistence or recurrence of hyperinsulinism, and theoretically inappropriate treatment of malignant insulinoma. Therefore, enucleation is accompanied by a substantial risk of secondary surgery either for treating the persistence/recurrence of insulinomas or for the growth of neglected and untreated NF-NENs or coexisting duodenal gastrinomas (LE: 4). Recently, however, some investigators [79, 295] chose insulinoma enucleation especially in young patients who manifested hypoglycemia as the first symptom in the absence of other evident DP-NENs. The recurrence rate in the setting of MEN1 patients is acceptable (1/7 patients according to Bartsch et al. [295]). Larger insulinomas located in the pancreatic tail,

especially adjacent to the main pancreatic duct, should be treated by minimal resection to reduce complications (pancreatic fistula) preserving the spleen.

All types of limited pancreatic resection can be followed by the persistence of organic hyperinsulinism [301]. The cure rates for MEN1 insulinoma after limited pancreatic resection (enucleation or minimal resection) are reported at approx. 60% (Table 13). In long-term follow-up, the occurrence of postoperative diabetes mellitus is rare (3%, Table 13).

Furthermore, patients submitted to limited surgery will more frequently be prone to the growth of F- or NF-DP-NENs than those submitted to distal pancreatectomy [294, 295, 314].

Extended Procedures

Distal pancreatectomy: Studies with more than ten patients presenting with insulinoma and other NF-DP-NENs [110, 312, 314, 320, 322] have recommended ***distal pancreatectomy with/without enucleation of additional NENs in the pancreatic head (Thompson procedure)*** as the treatment of choice for MEN1 insulinoma. It ***is favored because the more extensive procedure theoretically prevents the persistence or recurrence of hyperinsulinism in patients with multiple insulinomas*** [54, 294, 296, 297, 314] and because the identification of the insulinoma may be difficult in the presence of multiple DP-NENs. It is also supposed to be a preventive operation, since removing pancreatic tissue new DP-NENs from developing. The majority of distal pancreatic resections are performed preserving the splenic vessels and spleen [54].

The long-term cure rates of hyperinsulinism after this procedure are excellent, ranging from 83 to 100% (Table 13). Insulin-dependent diabetes mellitus is documented in approx. 20%. The development of new or persisting NENs in the pancreatic remnant leads to the danger of malignant behavior and may result in a totalization of pancreatectomy in long-term follow-up.

Regardless of the surgical technique applied, ***surgery usually includes peripancreatic lymphadenectomy in lesions close to or > 20 mm, also in insulinoma, as malignancy or malignant behavior during short or medium follow-up is to be expected.***

Enucleation or distal pancreatic resection: Published recently, there are two retrospective multicenter studies [297] [321] evaluating more than 50 patients and comparing morbidity and the long-term metabolic outcome defined as the rate of persisting and recurring hypoglycedmia after insulinoma enucleation and distal pancreatectomy (with and without enucleation of NENs in the pancreatic head) to better asses the most performed surgical procedures.

Vezzosi, Cardot-Bauters et al. 2015 analysed 73 patients following the patients in median of 9.0 years. Distal pancreatectomy was associated with the highest rate of symptom-free survival. Recurrent hypoglycemic episodes were documented in 8.7% of cases after distal pancreatectomy and in 33.3% after conventional distal pancreatectomy / TP. Enucleation was associated with a

significantly higher recurrence of hypoglycemia than distal pancreatectomy. The recurrences were 0% in the case of distal pancreatectomy and enucleation of additional tumors in the pancreatic head. The risk of recurrence increased from 0 to 11% in patients who had distal pancreatectomy and enucleation in comparison with those who had distal pancreatectomy alone.

The authors concluded that enucleation appears to be an alternative in patients in whom the first goal is to achieve a low rate of comorbidity and control of hypoglycemic symptoms. However, as cure after distal pancreatectomy was more frequently observed than after enucleation alone, this signifies that in MEN1 patients presenting with hypoglycemic symptoms, the concept of a single insulinoma should be revised and enucleation, if chosen, should be considered and explained to the patient as a palliative procedure even in the setting of symptomatic cure.

Analyzing 63 patients with localized and 33 pateints with multiple insulinoma, van Beek et al.[321] concluded recently that surgery for MEN1-related insulinoma is more successful than previously thought. After a median follow-up of 8 (range 1–22) years, 7/96 (7%) patients had hypoglycemia.

One patient (1%) had persistent hypoglycemia and six (6%) had recurrent hypoglycemia. Of those with recurrent hypoglycemia, four had a new insulinoma and two developed insulin-producing liver metastases.

The estimated 10-year hypoglycemia-free and insulinoma-free survival rates were 91% (95% CI 80-96) and 93% (83-97), respectively.The estimated 10-year hypoglycaemia-free survival rate was 96 %(84-98) for patients with localized insulinoma and 81 %(58-92) among those with multifocal insulinomas.

Of those patients with localized disease, 46 patients underwent pancreatic resection and 17 enucleation. One of these patients had persistent disease and one developed recurrent insulinoma. Enucleation was compared with resection (distal pancreatectomy or Whipple/PPPD) demonstrating recurrent hypoglycemia in 1/17 (5.9%) after enucleation and persistent disease in 1/46 (2.2%) after resection.

No postoperative death was documented in this large series. Postoperattive pancreatic fistulae were noticed in 16/87 (18.4%). No relevant differences in the rate of complications were observed between enucleation and resection. No bile leak or postoperative bleeding was identified.

Enucleation for patients with MEN1 and a localized insulinoma seems preferable if surgically feasible, as it is associated with a high rate of cure of hypoglycemia, low risk of recurrent disease and absence of long-term complications. The feasibility of enucleation depends on insulinoma size, location and relation to the main pancreatic duct and should be the preferred procedure in young patients expecting further surgical procedures in the course of the disease. Enucleation might be considered as an alternative when long-term comorbidity is a major concern. Of the 15 patients aged less than 21 years at the time of surgery, two developed recurrent insulinoma [321].

There are fewer recurrent hypoglycemic episodes after distal pancreatectomies in comparison with enucleations. In patients with multifocal disease (F- besides NF-DP-NENs), a more aggressive approach

applying distal pancreatectomy combined with enucleation of tumors in the head seems advisable. For surgical decision making, the precise localization of insulinoma(s) within multiple DP-NENs is particularly important in assisting to plan individual surgical procedures. The better availability of GLP-1R imaging by ^{68}Ga-exendin-4 PET/CT is a promising localization modality to support tissue-preserving surgery.

PPD: PPD with or without pylorus preservation is rarely employed (Table 13). ***PPD may be indicated in patients with large insulinoma involving most of the pancreatic head and independent of size in one or more tumors located deep in the pancreatic tissue close to the main pancreatic duct.*** The presence of enlarged lymph nodes at risk of being metastatic lesions visualized around the DP block and the evidence of duodenal gastrinomas enforce this more radical surgical concept [54]. PPD can be combined with enucleations of macroadenomas in the (left) pancreatic remnant and can be accompanied by excellent results [296].

Persistent or recurrent hyperinsulinism is generally due to indicating this type of surgery in very advanced and possibly malignant tumors. Indeed, T3 insulinomas (according to the UICC pTNM classification) are associated with a significantly higher risk of recurrence compared to T1-T2 insulinomas [297].

Intraoperative Assessment of Successful Hyperinsulinism Treatment

Considering the risk of persistent hypoglycemia, intraoperative confirmation of complete resection of the functioning lesions is an important aspect in warranting surgical success. The intraoperative assessment of both serum glucose and insulin levels has been investigated. Glucose level monitoring has been the most frequently employed method, yet it is an object of criticism due to the necessity to avoid glucose infusion during surgery with the subsequent risk of severe hypoglycemia and a high rate of false-negative results [74, 323].

Furthermore, more than one hour is necessary to observe a clear increase in blood sugar following surgical success. Insulin levels have also been proposed and used for more than two decades prevalently in sporadic insulinomas. Rapid intraoperative blood insulin monitoring is possible with the immunochemiluminescent assay [324]. With this method, insulin has been shown to decrease 15 to 20 minutes after tumor resection. There is very little experience in MEN1 patients [74, 323]. Proye et al. [323] analyzed eight cases of MEN1 insulinomas with a correct prediction of favorable surgical outcome in only five cases. Confounding data from this assay can be observed when the basal insulin level is normal or when insulin is released into the blood by surgical manipulation. Therefore, it seems more adequate to determine insulin levels during pancreatic manipulation in an attempt to acquire a feasible basal reference and evaluate the insulin/glucose ratio, as it is less influenced by the previously cited bias. Giudici et al. [54] identified perfect accuracy with the latter method used in five MEN1 patients (LE: 4). However, more experience with this method is needed to further confirm the technique.

Short- and Long-Term Postoperative Complications

No postoperative death was documented (Table 13)

All surgical procedures are at risk for pancreatic fistula or pancreatitis [325]. In particular, the rate of pancreatic fistula (grades A, B and C) observed in recent reviews of large institutional experiences with surgery for endocrine pancreatic tumors is often higher than that of surgery for pancreatic adenocarcinoma [326]. Van Beck and coworkers observed postoperattive pancreatic fistulae in 16/87 (18%.4) [321].

The less frequent use of PPD probably reflects the fear that this more complex operation can be more frequently followed by major postoperative complications than enucleation or distal pancreatectomy. Indeed, the rates of morbidity and mortality after PPD have been dramatically reduced in current surgical practice, particularly at dedicated centers. Moreover, the rate and the severity of pancreatic fistulae are similar when PPD is compared to the other procedures (LE: 4) [327]. In particular, postoperative complications cannot be avoided with enucleation, and it is surprising that the rate of fistula is also higher with this procedure than with resection of the left or the right pancreas [327, 328].

The MEN1 pancreas harbors all the factors responsible for the occurrence of fistula: the softness of the pancreatic parenchyma, the small diameter of the Wirsung duct, in addition to macro- and microscopic pancreatic alterations due to the presence of multiple NENs. The remnant pancreatic volume following surgery is another risk factor, and the volume is certainly higher after enucleation than after resection.

Pancreatic resection may induce the development of diabetes. Since the impairment of glucose metabolism is a common event after any type of pancreatic resection [329], diabetes is expected to develop after resective surgery for MEN1 insulinomas (Table 13). It has also been observed that MEN1 gene mutation carriers have decreased insulin sensitivity and a higher prevalence of impaired fasting glucose compared to controls [330].

However, available data on the prevalence of diabetes in MEN1 patients submitted to pancreatic resection are limited. The development of diabetes is rarely referred to in European or North American case series, but is common in Japanese patients, probably reflecting a relatively low insulin secretion potency among Asians compared to the European and American populations [331].

In the series by van Beek and coworkers, no patients who underwent enucleation developed exocrine pancreatic insufficiency or new-onset diabetes [321]. New-onset diabetes was only observed after distal pancreatectomy with or without enucleation, and occurred in 27% [290].

Prospective follow-up studies are needed to better clarify the real risk of developing diabetes after pancreatic resection in MEN1 patients.

Prognosis

The majority (more than 90%) of insulinomas exhibit benign biological behavior. The rate of malignancy ranges from 4.5 to 27% (Table 14). Malignancy of insulinomas is documented by metastasis in peripancreatic (regional) lymph nodes and more rarely by invasion of the surrounding tissues and/or hepatic metastasis. In the postoperative course, six patients in the series by van Beek et al. [321] developed liver metastases, of whom two had insulin-producing liver metastases. Nine patients died during follow-up, but no deaths were insulinoma-related.

Considering that MEN1 insulinoma is rarely malignant, the prognosis following curative surgery is good and even better than that observed in other F- or NF-DP-NENs. ***However, the association of insulinoma with other DP-NENs significantly increases the risk of death*** [28].

Persistent and Recurrent Organic Hyperinsulinism

Surgical reintervention (enucleation, resection) is also recommended with a curative intent for persisting or locally and distally recurrent insulinoma. However, in highly selected situations (patient refusal of reoperation, avoidance of TP, patient ineligibility for surgery because of locally very advanced tumor, unresectable bilateral liver or extrahepatic metastasis), medical treatment – including administration of diazoxide or alternatives such as radio frequence or ethanol ablation transcatheter arterial (chemo)embolization (TAE), radioembolization (RFA), or peptide radio-receptor-therapy (PRRT) may be indicated [101].

Lee et al. [304] reported for the first time a patient with MEN1 whose multiple insulinomas were treated by EUS-guided ethanol ablation. This case demonstrated that EUS-guided ethanol ablation may be an alternative choice in highly selected cases, allowing avoidance of the morbidity associated with total pancreatectomy. The experience of some more MEN1 patients have recently been summarized [228].

In general, EUS-guided RFA of P-NENs is a minimally invasive, safe and technically feasible procedure for selected patients, leading to complete relief of the symptoms of hypoglycaemia also in MEN1-related insulinoma [332].

(Also see Conservative (Medical) Treatment Options in F-DP-NENs)

Rare F-DP-NENs

Less than 3% of DP-NENs produce and secret glucagon (glucagonoma), VIP (VIPoma) or somatostatin (somatostatinoma) [26]. NENs may secret ectopic hormones such as GHRH (GHRHoma), ACTH (ACTHoma), calcitonin or PTHrP are also exceptionally reported. ***All these NENs arise in the pancreas with the exception of somatostatinoma***, which may also be located in the duodenum or in the first jejunal loop.

Glucagonoma

Glucagonomas occur commonly before the age of 40. The characteristic sign (necrolytic migratory erythema) may be absent and the diagnosis is made by the presence of hyperglucagonemia (levels > 1000 pg/ml). The development of clinical manifestations and malignancy are related to the size of the tumor. A tumor less than 20 mm in diameter has a low incidence of symptoms and malignancy, but when tumor size is more than 50 mm in diameter, two thirds of glucagonomas are symptomatic and malignant (LE: 4) [231]. The liver is the most common site for distant metastases.

VIPoma

VIPoma is clinically charcacterized by the WDHA syndrome with hyponatremia, hypokalemia, achlorhydria and dehydration. Cardiac arrhythmia or ischemic stroke can be the presenting symptoms. The severe electrolytic imbalance [333] must be corrected before surgery. The majority of VIPomas are larger than 30 mm in diameter, malignant and associated with synchronous or metachronous liver metastases (LE: 4) [110].

Somatostatinoma

This tumor is particularly rare, affecting less than 1% of MEN1 patients. The somatostatinoma syndrome is commonly absent or incomplete and diagnosis is based on high levels of somatostatin in the plasma or somatostatin-immunoreactive cells within the tumors (80 to 100%). The majority of somatostatinomas are diagnosed in the fifth decade of life [138]. Either the pancreas or the duodenum and first jejunal loop may be the site of the tumor. Most frequently, somatostatinomas localized in the duodenum or the jejunum have small dimensions (around 0.5 to 1 mm), are multiple and represent an incidental finding in MEN1 patients suffering from ZES due to duodenal gastrinoma. Metastases in the peripancreatic lymph nodes are found, but usually are positive for gastrin and not for somatostatin [138]. Pancreatic somatostatinomas have large dimensions (30 to 50 mm), are frequently multiple and may metastasize to peripancreatic lymph nodes and the liver (LE: 4) [59, 138].

Surgical Treatment of Rare Functioning Tumors

Even at an advanced stage, there is general agreement to recommend surgery for these rare functioning pancreatic tumors [26, 59]. Surgical exploration must be carried out with the intention to perform radical resection of the primary tumor and eventually its metastases. The type of pancreas resection is related to tumor localization. Both PPD and distal pancreatectomy are required, and total pancreatectomy may usually be omitted. Extensive lymphadenectomy is useful, especially for somatostatinoma and glucagonoma which have a propensity for lymph node spread. Surgical resection of hepatic metastases may be indicated (LE: 4).

Prognosis

The majority of "rare" F-DP-NENs show malignant biological behavior. Prognosis is poor, probably because of large tumor size and the high rate of metastasis at the time of diagnosis (Table 14). Survival is similar to that in patients with non-functioning tumors [59]. The natural course of these tumors is also very slow in the presence of distant metastases, and 10-year survival rates approach 50 to 60% [26, 59]. Visceral metastases (with the highest prevalence in the liver) are usually documented if the tumor dimension exceeds 30 mm and may be the cause of death in approximately half of the affected patients [59]. The symptoms and biochemical alterations disappear quickly with complete resection. Prolonged remission of symptoms is also achieved with aggressive, but not total, cytoreduction.

Table 13. Insulinoma in MEN1: Enucleation vs. pancreatic resection

	Enucleation/ Minimal pancreatic resection	**Distal pancreatectomy**	**Distal pancreatectomy and enucleation**	**Pancreaticoduodenectomy**	**Pancreaticoduodenectomy and enucleation**
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Patients	37	54	45	8	4
Persistent/recurrent hyperinsulinism*	16/37* (43.2)	7/54 (13.0)	0/45 (0)	3/8 (37.5)	0/4 (0)
Diabetes mellitus**	1/33 (3.0)	18/81 (22.2)		1/12 (8.3)	
Postoperative mortality*	0	0	0	0	0

* Ref: [266, 294-297, 300, 313, 314, 320]

**Ref: [266, 294] not included; data not related

Table 14. Pathological characteristics of insulinoma and other rare F-P-NENs within the MEN1 syndrome

F-NEN type	Mean age at diagnosis years (range)	Sex M/F	Size mm (range)	Lymph node metastasis	Liver metastasis	References
Insulinoma	25 (8-67)	1/1.3	(3-21)	(0-18%)	rare	[26, 54, 110, 294, 295, 297, 314]
VIPoma	31 (15-47)	1/1	(3-250)	33%	22%	[55, 59, 236, 333, 334]
Glucagonoma	31 (19-51)	1/0.5	(9-110)	11%	33%	[59, 266]

NF-DP-NENs

Gerard M. Doherty

The focus of MEN1 management is currently on the prevention or delay of death from malignancy. MEN1 requires experience and judgment to balance the risks of disease against the effects of treatment. In the absence of a functional endocrine syndrome that requires operative intervention, one must make some judgment about when to intervene for the NF-DP-NENs. [335].

The indication to treat surgically asymptomatic NF-NENs depends on the initial size, imaging findings (signs of invasion, regional and/or distant metastasis), and the further growth rates of borderline-sized tumors during follow-up.

There is limited data on the most accurate methods for the management of asymptomatic NENs, especially for the many NF-DP-NENs that are smaller than 10 mm or between 15 and 20 mm and that are discovered very early in the disease process. With increasing sensitivities of radiological screening, especially using EUS, more of these small NF-DP-NENs are currently diagnosed [80]. They are usually indolent and demonstrate slow growth, with a doubling time of 5 to 10 years [47]. However, they may account for a significant proportion of MEN1-related morbidity and mortality [28, 29]. Therefore, there is an ongoing controversy as how to surgically treat these small NF-DP-NENs, discovered during screening and routine follow-up, and when best to intervene. An important area of debate over the last two decades has been the identification of triggers for intervention.

There are currently several different recommendations for the management of MEN1 patients with small NF-DP-NENs [336, 337]. The Clinical Practice Guidelines for MEN1 by Thakker et al. [150] suggest to consider surgical resection for NF-P-NENs that are larger than 10 mm in size, as do the Uppsala group [338], the Marburg group [68] and the MEN consortium in Japan [339]. Lopez et al. have recently recommended surgical treatment for NF-DP-NENs in MEN1 with a size between 10 and 20 mm and rapid progression, defined by 5 mm tumor growth annually (LE: 3b) [340]. The NCCN in the USA has supported the same concept (www.nccn.org, version 1.2019).

The goal of treatment is to reduce morbidity and mortality due to metastatic disease while preserving as much pancreatic tissue as possible and avoiding complications of surgical intervention. Respecting the complexity of pancreas surgery and its attendant alterations to quality of life, the morbidity and mortality associated with pancreatic surgery may be significant, even when the procedure is performed in experienced centers [232, 341, 342]. Some subjects may develop complications that include diabetes mellitus, steatorrhea, and early and late dumping syndromes [343]. Prophylactic TP is not a reasonable option for the prevention of death from MEN1 pancreas malignancy. Most groups have

now converged around using some identification of gross tumor above 20 mm in size, or smaller with growth under observation, as the indication for pancreatic intervention [39, 55].

Once the decision to intervene for pancreas tumors is made, the most commonly performed operation to try to prevent or delay death from DP-NENs in MEN1 is to remove all of the demonstrable tumors from the pancreas and duodenum while preserving some pancreatic parenchyma for endocrine function. This approach is generally customized for various tumor patterns, but the most common operation is the "Thompson procedure" (a distal pancreatectomy with enucleation of tumors in the proximal pancreas or duodenum). This general strategy – to "reset the clock" by resecting the multiple sites of developing DP-NENs – appears to delay, but not completely eliminate, recurrences, reoperations and deaths from DP-NEN, while preserving some pancreatic parenchyma for endocrine function. The alternative of TP has mainly been employed when that is required for complete tumor resection.

The experience with this approach has been fairly consistent across case series over the past three decades (Table 15). In a series from the University of Michigan, 39 patients were operated upon between 1967 and 2003 [344]. When reported in 2004, seven patients had died, while just eight were alive with no evidence of disease, and this group had a relatively short median follow-up of 4.9 years. Fifteen patients had had 30 reoperations for recurrent disease. The long-term effects of surgery and the disease were significant, including four patients who were permanently disabled due to the operation or the disease, 16 patients requiring daily insulin, and nine using oral antihypoglycemic agents. At the follow-up of this same series in 2009, there were 49 patients in total who had had surgery, including eight who had required completion pancreatectomy for recurrent disease in the remnant pancreas [282]. The overall impression from this series is that, of the patients who initially had localized disease and had operative treatment, few went on to develop metastatic disease under observation. Most, however, developed new disease in the remnant pancreas and went on to require more therapy for that reason.

In a similar series from the MDACC, 38 patients had initial MEN1 pancreas operations. Three of these were TPs, while 35 were tailored procedures given the site(s) of disease: 4 tumor enucleations, 4 PPDs and 27 distal pancreatectomies with proximal enucleations. With a progression-free survival median of 12.5 years, 20% required reoperation for recurrence in the pancreas at a median of 7.8 years. Five of these subjects underwent completion pancreatectomy and two were able to have lesser resections with preservation of some pancreatic parenchyma. The median time needed for reoperation was much shorter (< 5 years) for patients who had tumor enucleation only as their initial procedure. The overall disease progression rate was 35%, reflecting a number of patients whose follow-up was less than the median duration of progression-free survival [78].

A complicated but informative study from the GTE published in 2006 included data from 108 patients, of whom 43 had pancreatic surgery. Thirty-two of the operations were done with curative intent. Though the study does not have as many clinical details due to its multi-institutional design, it does have the strength of a cohort of patients who did not have tumors that reached the indications for operation. The follow-up data show that there was no difference in tumor progression in the pancreas, or death, between the patients who had a resection compared to those who did not have larger or more advanced lesions. One interpretation of this finding is that the operation achieved its goal of returning the patients' future clinical course to that followed by those who had not yet developed progressive tumors [30].

The most recently available surgical series is from Marburg. The authors reported 38 initial operations, which included five PPDs, 25 distal pancreatectomies and eight tumor enucleation procedures. There were no primary TPs. After 9.1 years of median follow-up, the in-pancreas recurrence rate was 63%; ten patients (26%) had been re-explored, including three completion pancreatectomies. There was limited information reported on the timing of recurrences, though the anecdotal data presented suggest long intervals [55].

Other studies in the area contain too few patients or too little follow-up to be informative as to the efficacy of the approach studied. Careful review of these reports generates the clinical impression that pancreatic resection may in fact result in delay or prevention of the development of metastatic disease. However, the occurrence of new lesions within the pancreas appears to be only limited by time. Given sufficient time and follow-up, it appears that nearly all patients will recur in the pancreas. What is still unknown is how many of these patients will go on to develop life-threatening metastatic disease [331, 345].

Selection of initial TP versus less-than-total pancreatectomy hinges less upon the oncologic effectiveness of the operation than it does upon the real or perceived benefits of retaining pancreas function for some period, and the potential risk of subsequent operations (Table 16). An important measure of the efficacy of a management strategy may be the number of episodes of care, as well as the length of good quality-of-life time between those episodes – so-called "reoperation-free survival". Maximizing this measure may be an important goal in the management of these patients.

Nell et al. recently analyzed short- and long-term morbidity after pancreatic surgery of NF-DP-NENs in MEN1 and concluded that surgery is associated with high rates of major short- and long-term complications [342]. The frequency of early postoperative complications, the new onset of diabetes mellitus, and exocrine pancreatic insufficiency was analyzed in 61 patients who had undergone various types of surgery. The patients were young (median age 41 years) with low preoperative risk scores. Median NF-P-NEN size on imaging was 22 mm (3 to 157 mm). Thirty-three percent (19/58 patients) developed major early Clavien-Dindo grade III to IV complications, mainly consisting of ISGPS grade

B/C pancreatic fistulae. Twenty-three percent (14/61 patients) developed endocrine or exocrine pancreas insufficiency. The development of major early postoperative complications was independent of NF-P-NEN tumor size. Twenty-one percent (12/58 patients) developed multiple major early complications. The findings have to be taken into account in the shared decision-making process when MEN1 NF-P-NEN surgery is considered [342].

It was shown recently that the overall prognosis of DP-NENs in MEN1 is good with repeated surgeries at recurrence. Therefore, minimal resection with strict follow-up is recommended rather than extensive pancreatic resections for consideration of recurrence [346]. ***The ability to obtain more definitive answers to the questions regarding the best management scheme is limited both by the relative rarity of the disease and the long interval before the outcome of a strategy becomes clear***. Ongoing follow-up of these carefully studied series will be critical to our improved understanding of the efficacy of these strategies. The strategies may change further over time as our understanding of the long-term life course affected by current management approaches becomes clearer, and as we develop more granular information about molecularly defined subsets of tumor behavior [103, 347].

Surgery for MEN1 DP-NENs requires a multidisciplinary approach with the patient at the center. Striking a balance between the timing and extent of a given surgical procedure, the attendant risk of complications and risk to life of the DP-NEN is complex, with limited outcome data on which to base treatment recommendations [348].

Sometimes less is more. In a systematic review and exploratory meta-analysis of the English language literature, sole enucleation conferred similar survival rates to major pancreatic resection. However, the former is associated with a lower risk of postoperative endocrine insufficiency and a higher risk of recurrence but not reoperation. At any rate, the significant heterogeneity identified in the reporting of this data necessitates large, multicenter, prospective comparative studies with long-term follow-up to allow a definitive conclusion as to whether the initial surgical intervention for MEN1 associated DP-NENs should be enucleation or resection. The available data suggests that the former, where it can be safely performed, is probably the better option [349].

Table 15. NF-P-NENs in MEN1: Pancreas resection and follow-up

Venue; date	***n***	**Primary procedures**	**Follow-up (median, y)**	**Recurrence**
University of Michigan, USA [103, 344]; 2004, 2009; LE: 4	49	All distal pancreatectomies with enucleations	4.8 - 9.9	- 21% recurrence-free with shorter follow-up - 38% reoperation rate - 8/49 completion pancreatectomies
MD Anderson, USA [234]; 2006; LE: 4	38	- 3 TPs - 4 enucleations only - 4 Whipple procedures - 27 distal pancreatectomies with enucleations	7.8	- 12.5 y median progression-free survival - 20% reoperation rate - 35% overall rate of disease progression
GTE, France [55]; 2006; LE: 3b	43	- 5 biopsies only - 2 biopsies and bypasses - 9 enucleations only - 5 Whipple procedures -21 distal pancreatectomies +/- enucleations	6	- 32 operations, curative intent - 2 reoperations - progression-free survival same as cohort without tumors requiring resection
Matsumoto, Japan [39]; 2007; LE: 4	7	Not clear	Not reported	Not reported

Aristotle University, Greece [342]; 2007; LE: 4	4	- 4 distal pancreatectomies with enucleations	Short – followed for 2, 2, 4 and 5	Follow-up too short for analysis
Marburg, Germany [345]; 2011; LE: 4	38	- 8 enucleations only - 5 Whipple procedures - 25 distal pancreatectomies with enucleations	9.1	- 63% pancreas recurrence - 26% reoperation rate including 3 completion pancreatectomies - No deaths from pancreas tumors

LE: Level of evidence

Table 16. Comparison of pancreatic resection options

Feature	**TP**	**Less-than-total resection**
Completeness	High	? 100% recurrence in pancreas given time
Complexity	Higher	High
Reoperation risk	Negligible	~ 40%
Quality of life	Diabetes uniform	Diabetes common
Exocrine function	None	Usual
Risk of metastases	Low	Low
Death from disease	Rare	Rare

Laparoscopic/Robotic Surgical Techniques

Detlef K. Bartsch and Bruno Niederle

Laparoscopic resection and enucleation of DP-NENs can be performed safely with the potential patient benefit of successful minimally invasive surgery (LE: 2b) [350-352].

In a recently published meta-analysis with overall limited conclusions, laparoscopic pancreatic surgery was associated with a reduced complication rate and shorter length of hospital stay than open pancreatic surgery [353]. In a retrospective study analyzing laparoscopic pancreatic resection and tumor enucleation and including 65 patients with P-NENs, the overall morbidity rate of endoscopic procedures was 42%, with a surgical morbidity rate of 21% and postoperative pancreatic fistula formation in 21% of the subjects. The laparoscopic enucleations were associated with a higher rate of postoperative pancreatic fistula formation than were laparoscopic resections (LE: 4) [352].

In response to the recent considerable controversy surrounding the costs and surgical outcomes of laparoscopic distal pancreatectomy versus open distal resection in P-NENs, Xourafas et al. [354] showed that ***the laparoscopic procedure was cost-neutral and that it significantly reduced postoperative morbidity without compromising oncologic outcomes or survival*** (LE: 4).

Only two reports in the literature have described laparoscopic surgery in patients with MEN1 [340, 355]. In the first report [355], laparoscopic spleen-preserving distal pancreatectomy was performed in two patients with MEN1 insulinomas, in one patient with and in the other without splenic vessel preservation. The latter patient developed a 40-mm splenic infarct that was managed conservatively. The authors concluded that laparoscopic enucleation and laparoscopic spleen-preserving distal pancreatectomy are feasible and safe and achieved cure in the two patients with multiple insulinomas associated with MEN1. However, the risk of pancreatic leakage after laparoscopic enucleation remains high, and laparoscopic spleen-preserving distal pancreatectomy (with splenic vessel preservation) may be associated with splenic infarction.

In the second retrospective study [340], 33 MEN1 patients with insulinomas (n = 9) or NF-P-NENs > 10 mm in size (n = 24) underwent either open surgery (21 patients [64%], group 1) or a minimally invasive approach (12 patients [36%], either laparoscopic [n = 8] or robotically assisted [n = 4], group 2). Both groups were comparable regarding age, gender, and the number and size of pancreatic tumors. In both groups, hyperinsulinism was cured in all patients (9/9, 100%) and all NF-DP-NENs > 10 mm were resected. Group 2 had a significantly shorter duration of surgery (200 vs. 260 min; p = 0.036), less intraoperative blood loss (120 vs. 280 ml; p < 0.001), and a shorter hospital stay (11 vs. 15.5 days; p = 0.034). The rate of patients with postoperative complications, especially postoperative pancreatic fistulas, was not significantly different between the groups (62% in group 1 vs. 67% in group 2;

p = 0.74). The authors concluded that minimally invasive distal pancreatic resections and enucleations are feasible and safe in MEN1 patients with insulinomas or NF-DP-NENs.

Insulinoma and NF-DP-NENs

Endoscopic enucleation is safely indicated for sporadic, solitary, superficial or pedunculated NENs of all pancreatic regions. In MEN1, however, F- and NF-DP-NENs are multiple with a high potential of malignant behavior of gastrinoma, VIPoma, glucagonoma, somatostatinoma and NF-P-NENs > 20 mm. Extended lymph node dissection is not recommended in insulinoma and NF-P-NENs ≤ 20 mm with an overall low malignant potential.

Laparoscopic procedures can be applied if the same radical extent of surgery (primary tumor, lymph nodes) is feasible as when applying open procedures or in those guided by a palliative intent (with/without splenectomy).

In the presence of potentially multiple insulinomas or multiple NF-DP-NENs, the majority of endocrine surgeons favor an extended exploration of the entire gland for NENs in open surgery. However, ***laparoscopic approaches may be applied in selected patients by surgeons highly experienced in endoscopic procedures, as well as in intraoperative EUS.***

Gastrinoma

There are case reports on the laparoscopic excisions of D-NENs. ***The value of laparoscopic surgery in gastrinoma is questionable and may be hazardous***, as the primary is often not seen on preoperative imaging studies and the tumors are located in the submucosa of the duodenum. Most MEN1 gastrinomas occur multiply and at times grow invasively beyond the submucosa, which makes both identification and endoscopic removal difficult. At least 80% of MEN1 gastrinomas have lymph node metastases, necessitating lymphadenectomy and frequently resulting in accompanying P-NENs which also require treatment.

The laparoscopic approach may only be performed if the gastrinoma is preoperatively well localized in the pancreatic head or in the anterior duodenal wall (LE: 4) [356] and the surgeon is familiar with the techniques of laparoscopic peripancreatic lymphadenectomy.

Presently, ***final recommendations for laparoscopic surgery cannot be given either for sporadic disease or for MEN1.*** Although laparoscopic and robotic PPD resections may be feasible and safe (LE: 3), they are technically demanding [357, 358].

Moreover, prospective randomized trials have yet to establish that the postoperative morbidity and mortality rates are at least equal to open surgery. Successful endoscopic removal of sporadic duodenal

gastrinomas using snare polypectomy or robotic-assisted endoscopic mucosectomy have been described in few cases (LE: 4) [359, 360].

No experiences with these techniques in MEN1-ZES have so far been published. Endoscopic local excision of duodenal gastrinomas should not be performed, since approx. 80% of MEN1 gastrinomas have lymph node metastases at the time of diagnosis and any type of endoscopic muscosal resection would be oncologically inadequate [272].

Advanced Local and Distal Disease

Massimo Falconi

Dy et al. [361] recently analyzed 30 MEN1 patients who had undergone synchronous and metachronous resection of metastatic tumors separate from the site of primary disease of the pancreas and/or duodenum, including resection of lymph nodes and liver metastases. Synchronous metastases were identified in 19 patients (63.3%), whereas 11 (36.7%) had metachronous disease. R0 resection was achieved in 93% of the patients. Estimated 10-year survival was 86.4% with no factors predictive of overall survival. The disease-free interval at 1, 5 and 10 years was 89%, 50% and 19%, respectively, with recurrences occurring at a median of 5.4 years. Synchronous metastases and non-functioning tumors were more likely to recur, whereas age and the sites of metastases did not influence recurrence. The authors concluded that patients with MEN1 benefit from resection of metastatic neuroendocrine disease. At the time of diagnosis of MEN1, extended lymph node and liver metastasis were documented in 6 to 59% of the patients [55, 361]. In 15 to 19%, liver metastasis developed during follow-up [30, 58].

Due to the rarity of P-NENs in general and MEN1 pancreatic disease in particular, with its disease complexity (most importantly: P-NENs are distributed throughout the pancreas with one "dominating" tumor larger than 20 mm), there are no clear recommendations with respect to the indication, timing and type of (palliative) pancreatic surgery in the presence of unresectable hepatic metastases. The presence of F- and NF-DP-NENs, patient characteristics (such as age, general condition) and tumor grading strongly influence individual decision-making. The indication for palliative surgery should always be discussed within a multidisciplinary team considering all therapeutic (alternative) options and should be recommended for tumors refractory to non-surgical treatments [288].

Pancreatic Surgery in Patients with Unresectable Liver Metastasis

Several small, uncontrolled, single-center or retrospective studies and one meta-analysis considering patients affected by sporadic NF-P-NENs have suggested a possible benefit of surgical resection of the primary tumor, even in the presence of disseminated liver metastasis (LE: 3; GR: B) [339, 362-366]. Because DP-NENs in MEN1 and sporadic P-NENs do not significantly differ in terms of prognosis, the same benefits may be expected in MEN1 patients after palliative surgery [53].

Palliative local pancreatic surgery for F- and NF-DP-NENs in MEN1 patients is indicated only for well differentiated (G1) or moderately differentiated (G2) tumors with liver metastasis in the absence of

extrahepatic metastases and peritoneal spreading (LE: 3; GR: B) [289, 362, 366-368]. In addition, surgical resection of the primary tumor in the presence of unresectable liver metastases should be carried out to yield a low morbidity rate and be performed in high-volume referral centers [289, 362, 364, 366, 367].

Liver Surgery in Patients with R0 Resection of the Dominating P-NEN

The extent of liver metastases seems to be important, since survival has been seen to differ significantly between patients with single-lobe or less than five metastases and patients with diffuse liver metastases [248].

Liver metastases in MEN1 patients are bilobar in 80% of the subjects. At present, there are insufficient data for MEN1 to unequivocally determine in which patient cytoreductive surgery of liver metastases should be performed. However, according to most studies, resection of liver metastases can be performed with a low rate of complications and morbidity [289].

It can be postulated that in patients with advanced MEN1-ZES disease confined to the liver, surgery can be considered, if at least 90% of identifiable tumor burden can be safely removed [369]. In the case of surgical resection of liver metastasis, the probability to achieve a R0 resection in the liver is low (approx. 10%) [184, 289, 364, 367, 370]. In patients with G1 or G2 F- and NF-P-NENs, resectable liver metastases and no extrahepatic metastasis, liver resection should be considered as the primary treatment [31, 184].

Cytoreductive (debulking) surgery is an alternative option to locoregional therapies and could be considered in patients with uncontrolled F-NENs and unresectable liver metastasis. It aims to provide relief from the symptoms of hormonal hypersecretion, to limit the disease to the liver, and to prevent life-threatening and obstructive complications such as bleeding, acute pancreatitis, jaundice or intestinal occlusion (LE: 3; GR: B) [74, 371, 372]. Debulking surgery may be considered in patients with non-functioning tumors if the disease is not progressive over a six-month period and the subjects suffer from symptoms related to tumor burden. It remains unclear whether debulking surgery is of benefit in asymptomatic patients, since comparative trials in systemic therapy are lacking.

Natural Course – Conservative Treatment

Natural Course of Untreated NF-DP-NENs and Follow-up Protocols of Treated DP-NENs

Gerlof D. Valk

As a result of the genetic background, F- and NF-DP-NENs may recur, grow and metastasize [30, 64, 84, 373].

Prognosis

MEN1 patients are living longer than in the past; however, their life expectancy is still shortened (with a mean age at death of 55 years) [29]. This study as well as the recent literature reported that two thirds of MEN1 patients currently die from a MEN1-related cause, and in 40-45%, the principal cause is P-NEN related.

Apart from thymic NENs, metastatic DP-NENs are the most important disease-related cause of death in patients with MEN1. Therefore, consequent follow-up examinations are mandatory to prevent progressive disease.

The high prevalence and variable malignant potential of F- and NF-DP-NENs decreasing patients' life expectancy outline the need for consistent follow-up protocols [374]. In a recently published study, the prognosis of MEN1-affected and MEN1-non-affected patients with DP-NENs did not differ significantly. Analyzing DP-NENs according to disease outcome, it was shown that recovered and stable P-NENs in MEN1-affected patients, compared to MEN1-non-affected subjects, are diagnosed at a lower age ($p = 0.04$ / $p = 0.002$) and are more frequently multifocal lesions ($p = 0.009$ / $p = 0.002$) [53].

The estimated 10-year survival rates were 23 to 62% [59, 78] and 100% in a recent small patient series ($n = 25$, median follow-up: 109 months), in which patients underwent surgery for NF-DP-NENs when size surpassed 10 mm [55]. In the nationwide Dutch MEN1 study, from the moment of diagnosing DP-NENs in patients without liver metastasis, the 5- and 10-year survival rates were 95 and 86%, respectively, compared to 65 and 50% for patients with liver metastasis [58].

The high prevalence and malignant potential of DP-NENs decreasing MEN1 patients' life expectancy outline the need for an evidence-based follow-up protocol. The most important ***prognostic factors*** to be used in follow-up and as a consequence of clinical decision making in MEN1-related NF-DP-NENs are ***tumor size, grading*** (mitotic count/Ki-67 index) and ***annual growth rate*** [55, 250, 375]. A larger

tumor size seems associated with a higher rate of metastasis and a decrease in overall survival [30, 58, 83, 248].

Diagnosis and Follow-up of New F- and NF-DP-NENs Based on the Biochemical Evaluation of Fasting GI Hormone Profile and Follow-up Imaging

Current clinical practice guidelines advise biochemical evaluation of fasting GI tract hormone profiles and routine imaging during follow-up of DP-NENs in MEN1 patients [11]. Therefore, it seems plausible that after a DP-NEN is diagnosed, specific markers and imaging techniques can be used for follow-up as proxy for measuring increase in tumor load or biochemical activity (LE: 5).

Optimal radiological follow-up of NF-DP-NENs has not yet been established [93]. For the detection of new NF-DP-NENs, EUS has the highest sensitivity. A combined strategy of EUS and MRI seems to be the most useful. However, MRI seems to be cost-effective for follow-up and could be alone utilized in patient surveillance.

Functional imaging (e.g., with ^{68}Ga octreotate-DOTA-PET-CT) could be added if NF-DP-NENs are diagnosed to identify metastasis during follow-up [93]. A recent systematic review evaluated the available scientific evidence concerning the accuracy of the tumor markers PP, CgA and glucagon, measured alone or in combination, for diagnosing DP-NENs in MEN1 [93]. A total of 11 studies were included for risk of bias assessment from an extensive search through the literature. Based on the two studies with maximum applicability and at lowest risks of bias, it was concluded that these tumor markers, even when measured in combination, should not be used in MEN1 DP-NEN screening programs [75, 85]. ***At present, no data are available concerning the usefulness of these tumor markers for the follow-up of DP-NENs in patients with MEN1.***

Natural Course of MEN1-Related DP-NENs

Growth Rate and New Tumor Formation

In a recent systematic review, eight studies were identified assessing the natural course of MEN1-related DP-NENs [93]. ***The annual growth rate of NF-DP-NENs, as measured by means of EUS and conventional imaging (MRI/CT scan), varied between 0.1 and 1.32 mm per year*** [93]. In the population-based Dutch MEN1 study of 99 patients with 115 NF-DP-NENs smaller than 20 mm, the overall growth rate was 0.4 mm per year using conventional imaging. However, a growth rate of 1.6 mm per year was found in a subgroup of 35 tumors in 34 patients, whereas the majority of tumors showed no growth. In the subgroup of growing tumors, missense mutations were associated with faster growth [259].

In the French cohort, DP-NENs were also stable in a large proportion of patients [375]. The indolent course of the tumors was in line with the outcomes of a smaller and older prospective study [331]. The fastest DP-NEN growth rate (1.22 mm/year) was found in a retrospective investigation applying EUS and including 11 patients. Although 61% of the tumors were stable during follow-up, new lesions identified at follow-up had a significantly faster growth rate compared with the index lesions [226]. However, in a larger EUS-based study, the overall annual growth rate was 0.21 mm per year with an absence of growth in the newly identified lesions during follow-up [49]. In an older study of 28 patients with DP-NENs with 6 mm median tumor size, only 13% showed tumor growth [80]. Indolent courses were also found in the other EUS-based studies [47, 376].

Lopez et al. [55] followed nine MEN1 patients with only small (< 10 mm) NF-DP-NENs in terms of tumor growth, formation of new NENs and functionality. The baseline tumor diameter was determined with a median of 4.5 mm (range 1.1-8.8 mm) as determined by EUS. Over a period of median 84 months (range 2-120 months), the tumors grew by a median of 0.6 mm according to 16% per year with respect to the baseline tumor diameter (4.5 mm [range 1.1-8.8 mm]), and 4 patients (44.4%) developed new additional DP-NENs. However, none of these patients developed a hormonal syndrome or a size of > 10 mm in diameter that would indicate surgery following our strategy.

Comments on Growth Rates and the Formation of New DP-NENs

Overall, the natural course of MEN1-related NF-DP-NENs seems to be relatively indolent and these tumors grow slowly. The outcomes of available studies may be confounded by indication, as especially patients with faster-growing tumors were operated and not included in these studies. This may have led to an underestimation of growth. However, at the long-term follow-up of patients with small NF-DP-NENs (< 20 mm), only a small proportion (14 to 16%) undergoes surgery [259, 375].

Based on the available evidence documenting an overall indolent nature of NF-DP-NENs, especially in NENs < 20 mm, intensive follow-up does not seem to be necessary once it is established that tumors do not show a tendency towards rapid growing and frequency of DP-NENs imaging might be decreased (LE: 2a and 4).

Factors Influencing Prognosis

Irrespective of the indolent course of DP-NENs, liver metastasis develops in 15 to 19% of the patients suffering from NF-DP-NENs [30, 275]. ***The presence of liver metastasis is the most important prognostic factor related to overall survival in patients with MEN1-related DP-NENs*** [29, 30, 58, 78, 275]. ***In NF-DP-NENs, larger tumor size was associated with a higher rate of metastasis and a decrease in overall survival*** [30, 58, 83, 248]. Although mitotic count and Ki-67 have proven to be important prognostic factors in sporadically occurring DP-NENs, these measures have only been assessed in one study

of 76 MEN1 patients who had undergone surgery. In this study, more than 80% of the DP-NENs were WHO grade 1, 16% WHO grade 2, and only one of the tumors was a WHO grade 3 NEN. ***A high mitotic count in large (> 20 mm) NF-DP-NENs was associated with poor prognosis.*** This association was not seen for WHO grade based on Ki-67 [248].

Grade 2 NF-DP-NENs should be considered high risk [250].

In general, especially in the older trials, ***small patient groups were frequently studied and the outcomes are therefore at risk of bias***. In addition, most studies were retrospective and only few truly population-based. ***The available literature must therefore be interpreted with some caution.***

Medical Treatment Options

F-DP-NENs

Tetsuhide Ito, Lingaku Lee and Robert T. Jensen

The improvement of hormone excess at the time of diagnosis by medical treatment is mandatory to prevent the development of complications from hormone excess prior to surgery and to other therapies directed against the functioning tumor (e.g., embolization) (LE: 2b) [26, 29, 100, 102, 103, 150].

Gastrinoma

In MEN1-ZES patients, gastric acid hypersecretion is almost universally present at diagnosis [91, 377, 378], and older studies demonstrated very high complication rates and high mortality if such hypersecretion is not under control [Ellison and Wilson 1964, Jensen, Gardner et al. 1983, Ito, Igarashi et al. 2013, Norton, Krampitz et al. 2015, Jensen and Norton 2017]. Prior to the development of gastric-acid antisecretory drugs effective in ZES, the principal cause of death in MEN1 patients was complications of the gastric acid hypersecretory state, not the malignant nature of the tumor itself [103, 105, 112, 377, 379]. The drugs of choice to control gastric acid hypersecretion are PPIs (e.g., omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole) (LE: 2a) [100, 102, 380-382]. PPIs have revolutionized the symptomatic treatment of patients with ZES. For most ZES patients, PPIs are usually started at a dose corresponding to 60 mg/day of omeprazole. Acid suppression allows peptic lesions to heal and prevents their recurrence. The long-term oral antisecretory treatment has remained effective for over ten years without development of tachyphylaxis [383].

Antisecretory drug requirements can change with time, and patients with ZES are recommended to have their acid-secretory control checked every six to twelve months. SAs have also been applied to control acid secretion by reducing circulating gastrin levels.

Although histamine H_2-receptor antagonists are also effective, frequent (four- to six-hourly) and high doses are required, as well as frequent dose adjustments, particularly with changes in parathyroid hyperfunction (LE: 2a) [99, 100, 116, 117]. In contrast, because of their long duration of action, twice-a-day PPI dosing is usually sufficient, and tachyphylaxis occurs rarely (LE: 2a) [100, 384, 385]. For patients requiring parenteral drugs, either histamine H_2-receptor antagonists or PPIs can be used [100, 128, 386]. Parenteral PPIs are the drugs of choice in these settings, such as during surgery. Because of

their long duration of action, intermittent administration (every six to eight hours) is possible and continuous infusions are not required, as is the case with H_2-receptor antagonists [100, 128, 386]. Complications may arise if continuous infusions are interrupted (LE: 2a) [100, 128, 386].

Long-term treatment with PPIs has proven safe and effective, with dose changes required infrequently (LE: 2a) [100, 128, 384, 385]. With prolonged use, low serum vitamin B_{12} levels have been reported in patients with ZES (LE: 2b) [383, 387]. In non-ZES patients with prolonged PPI use, an increased occurrence of several important potential side-effects (bone fractures, hypomagnesemia, increased GI infections, renal toxicities) have been reported, although these are controversial and not proven, while not having been specifically reported in MEN1-ZES patients [100, 382, 383]. ***Usually, PPIs are first-line options for symptom control but can be complemented by adding SAs [388].***

Insulinoma

It was supported by older studies [29] that hypoglycemic complications were not an infrequent cause of death in MEN1 patients with insulinoma, primarily due to an inability to control hypoglycemic complications. Presently, effective therapies can be used to reduce mortality [28, 29, 96, 110], Diazoxide is the drug of choice. In patients not responsive to or intolerant of diazoxide (10%), an SA may be indicated to prevent hypoglycemia.

Persistent and Recurrent Gastrinoma and Insulinoma

Curative surgery is always the treatment of choice and may theoretically solve the hormone excess involved in removing a given F-DP-NEN. However, after extended surgical resection, the state of hormone excess may remain a problem, as patients with MEN1-ZES are rarely cured [26, 70, 74, 295, 296, 314]. A recently published case report highlighted the potential role of optimal tumor cytoreduction and LAR octreotide to control disease progression in a patient with MEN1 and ZES with locally advanced gastrinoma and secondary large neuroendocrine gastric tumors [389]. Furthermore, a similar situation may occur in insulinomas, with a percentage of patients continuing to require treatment of the hormone excess state following surgery [297]. While resections/enucleations have usually been curative in smaller studies [26, 70, 74, 295, 296, 314] 20 to 30% of patients in some larger MEN1 collective series developed recurrences or had persistent hyperinsulinemias after surgery [110, 297]. In MEN1 patients with insulinomas prior to surgery, hypoglycemia is controlled by frequent feedings and/or the use of diazoxide [101, 114, 136, 390].

Diazoxide, a non-diuretic thiazide analog, has potent hyperglycemic effects. It directly inhibits insulin release from beta cells through the stimulation of alpha-adrenergic receptors and also has an extra-pancreatic hypoglycemic effect that enhances glycogenolysis. Diazoxide should be initiated at a dose of 3 to 8 mg/kg per day divided into 3 or 4 daily doses. If not effective, the analog can be increased to a maximum daily dose of 15 mg/kg. The adverse effects include sodium retention/edema and GI symptoms such as nausea and hirsutism. Approximately 60% of insulinoma patients respond to diazoxide and some subjects have been treated with it for over 20 years.

Verapamil, prophanolol, phenytoin and glucocorticoids have occasionally been reported to be effective in insulinoma patients, but they may only have minor hypoglycemic effects and their successes are anecdotes [391, 392]. In patients not cured, diazoxide may continue to remain effective in controlling hypoglycemia (LE: 2b) [114, 136, 390, 393].

At times, the use of long-acting SAs (lanreotide or octreotide) is recommended [101, 114, 136, 390]. The long-acting SA octreotide has shown to control hypoglycemia in a number of cases of insulinoma. The response rate of insulinomas to SAs is likely lower than that of other F-DP-NENs, as insulinomas frequently have low levels of SSTR2. Because SAs also decrease glucagon and growth hormone secretion, administration may occasionally worsen hypoglycemia and patients should be well controlled before leaving the hospital. Therefore, it might be of value to start with octreotide at the dose of 100 μg to follow glucose and insulin levels and then, if the effect is positive, to switch to a long-acting SA, either octreotide LAR or lanreotide LAR [382, 386, 391, 394]. The use of SAs needs to be carefully monitored because in some patients, blood glucose control may deteriorate further due to overinhibition of insulin counter-regulatory mechanisms [114].

Recently, the mTOR inhibitor everolimus has demonstrated significant efficacy in controlling hypoglycemia in patients with metastatic insulinomas refractory to other therapies [101, 114, 395]. Everolimus blocks the release and decreases the synthesis of insulin, while also having a positive effect on peripheral glucostasis [101, 396].

In patients with metastatic insulinomas, PRRT with ^{177}Lu-DOTA SAs has been reported to be highly effective at controlling hyperglycemia [101]. In patients with localized insulinomas who are not surgical candidates, recent studies have reported that ablation with EUS using primarily ethanol injections is safe and effective [101] (also see the section on Surgical Strategies for F- and NF-DP-NENs: Insulinoma).

Rare F-DP-NENs

Glucagonoma

The initial medical treatment is directed at relieving symptoms, restoring nutritional status and controlling hyperglycemia. Long-acting SAs have been useful in controlling symptoms in patients with glucagonoma. For instance, rash was observed to improve with octreotide treatment in most patients with a rate of disappearance of up to 30%. Octreotide also improves other symptoms. Diabetes mellitus is not improved by octreotide [388].

VIPoma

The medical treatment of this syndrome includes long-acting SAs which control diarrhea in 70 to 100% of the patients. With time, resistance develops and other treatments might be added. In patients with non-responding diarrhea, IFN-alpha can be added with good control of the clinical symptoms including diarrhea [397].

Other options are cytotoxic treatment including streptozotocin plus/minus 5-FU or doxorubicin or temozolomide plus/minus capecetabine. Everolimus is also quite effective in controlling the clinical symptoms related to VIP production by reducing circulating VIP levels. PRRT with ^{177}Lu-DOTA SAs has been reported to be highly effective at controlling diarrhea, especially in patients with metastatic disease [101, 114].

Somatostatinoma

Some DP-NENs immunologicaly show somatostatin staining and are called somatostatinomas, but they do not have elevated plasma somatostatin levels or cause symptoms. Somatostatin overproduction occurs rarely, especially in patients with pancreatic tumors, and they present with gall stones, severe malnutrition or diabetes mellitus (somatostatinoma syndrome). Knowledge about tumor biology, treatment, survival and prognostic factors is limited [114, 398, 399].

Recently, one male subject without the full somatostatinoma syndrome was diagnosed within the MEN1 syndrome [400].

Medical treatment includes the same type of treatment as for NF-DP-NENs for asymptomatic somatostatinoma. For symptomatic patients with the somatostatinoma syndrome, treatment with SAs may have clinical benefit [114, 388].

Functioning Distant Metastasis

In patients with F-DP-NENs and unresectable metastatic disease, the functional syndrome often needs to be specifically dealt with, as it may not be controlled by the antitumor agents used [101, 401]. Control of the hormone excess state is similar to that outlined above for non-metastatic MEN1 patients with F-DP-NENs, with PPIs for gastrinomas and SAs for both their antitumor effects and antisecretory

effects in the other F-DP-NEN syndromes [101, 401]. In some patients, the antisecretory effects of somatostatin may be insufficient, and recent studies have shown that everolimus can be effective in some of these subjects (particularly with metastatic insulinomas and VIPomas). In some patients, sunitinib can have antisecretory effects. PRRT with ^{177}Lu-labeled SAs appears to be highly effective in such patients with or without MEN1 to control the hormone excess state quickly and independently of its effect on tumor growth [101, 402-404].

SA Treatment in Small (≤ 20 mm) NF-(G1/G2) DP-NENs

Marianne Pavel and Kjell Öberg

Although several studies have demonstrated that NF-DP-NENs ≤ 20 mm yield a low oncological risk and that progression-free survival may be identical in patients undergoing active surveillance compared to surgery [83, 405], concerns over unpredictable tumor progression or the development of distant metastases affect patients as well as their referring physicians, not only following active surveillance.

SAs have shown promising results with regard to progression-free survival in patients with metastatic NENs of the midgut [406-411], where a median time to progression was seen at 12.1 months in patients without treatment compared to 29.7 months in the treatment group [407]. The same has also been documented for DP-NENs [412], suggesting SAs should be considered as an early first-line treatment in this population [413].

The attitude towards active medical treatment has changed with the recently published results of the CLARINET study, including advanced NF-DP-NENs and demonstrating an antitumor effect by using Lanreotide Autogel® 120 mg [407]. Patients will be put on continued treatment with SAs to prevent further tumor development and metastatic disease [410].

SAs and MEN1

Treating DP-NENs, two experimental studies demonstrated the antisecretory, antiproliferative and proapoptotic activity of SAs in MEN1 mouse models [414, 415].

Recently, Lopez et al. [416] evaluated the chemopreventive effects of a long-acting SA on the development of P-NENs in a genetically engineered MEN1 knockout mouse model in comparison to a placebo group. The size and number of P-NENs were evaluated. The median tumor size of treated P-NENs was statistically significantly smaller after 6, 9, 12, 15 and 18 months. Comparing the amount of tumors in both groups, a significant reduction was achieved in treated MEN1 mice. Immunostaining showed no significant difference in the expression of the apoptosis marker caspase-3, but a significant difference in Ki-67 index as a marker for tumor cell proliferation. The authors concluded that long-acting SAs may be an effective chemopreventive approach to delay the progression of MEN1-associated P-NENs.

However, there is limited clinical experience with SAs in MEN1 and DP-NENs [417-419]. In a retrospective study of 40 patients with early-stage DP-NENs and MEN1, treatment with SAs was shown to be safe and effective, resulting in long-time suppression of tumor and hormonal activity and a 10%

objective response. The authors suggested initiating therapy with SAs early-on in patients with MEN1-related DP-NENs [419]. Apart from this clinical study, there is one case report on SAs for MEN1-related insulinoma [418].

A longitudinal, open-label investigation, the LARO-MEN1 study, was conceived to assess whether early medical treatment with long-acting SAs could act as a preventive approach in small, MEN1-related GEP-NENs. The results have recently been published [417]. Thirty consecutive patients affected by MEN1 were screened and eight patients with small (< 20 mm) NENs and abnormal laboratory values of at least one of the GEP hormones were administered octreotide acetate LAR formulation (10 mg i.m. every 28 days). Octreotide LAR was effective in decreasing GEP hormones and overall safe in the majority of patients over up to six years of treatment, also maintaining the disease stable in terms of tumor size. The positive outcomes of this study in MEN1 patients reinforce the results obtained in advanced NENs on the use of SAs, opening to the option of preventive SA (Octreotide LAR®, Lanreotid Autogel®) use which would be aimed to delay or even avoid surgery in these patients [417].

As shown recently [420], a 43-year-old male with a history of MEN1 and multiple subcentimeter NENs with elevation of PP was treated with octreotide therapy, leading to a reduction and normalization of PP levels. The patient tolerated octreotide therapy but self-discontinued octreotide after 24 months with a rise in PP levels off-therapy. The tumors remained stable in size through 40 months of imaging follow-up.

However, clinical experience remains limited in MEN1 DP-NENs and no final recommendations can thus be given. Recently, the CLARINET study indicated that metastatic DP-NENs with a Ki-67 proliferation of up to 10% can be successfully treated with Lanreotide Autogel® 120 mg once a month. This result raises the question whether this compound can also be used in an adjuvant setting to inhibit the development of new DP-NENs and growth of overt DP-NENs in patients with MEN1. Such a study has not yet been conducted but should be performed in a randomized controlled fashion, comparing observation with SA therapy.

The SANO trial – a prospective, randomized, controlled multicenter study – was designed to clarify the possible benefits of SA compared to no treatment with regard to progression (tumor growth) and the development of new DP-NENs and regional and/or distant metastasis in patients with MEN1 [421]. With the same intention, Faggiano et al. [422] recently evaluated the efficacy of SA Lanreotide Autogel® (120 mg every 28 day; LAN group) in MEN1-related P-NENs in a prospective study enrolling 23 patients in the LAN group and 19 patients in the group with active surveillance, not receiving any therapy (AS group). The median follow-up was 73 months. As a whole, 91 P-NENs were identified at initial imaging. The median rate of progression-free survival was significantly longer in the LAN than in the AS group (median not reached vs. 40 months, $p < 0.001$). In the LAN group, four patients had an objective tumor

response, 15 patients had stable disease, while four had tumor progression. In the AS group, 13 patients had P-NEN progression, while six were stable.

The findings highlight that this SA is effective as an antiproliferative therapy in MEN1-related P-NENs < 20 mm, suggesting the use of these compounds to arrest the development of tumor lesions as well as to delay or avoid pancreatic surgery.

Biotherapy – Targeted Therapy – Radiotherapy – Liver-Directed Therapies

Marianne Pavel and Kjell Öberg

In locally advanced and/or metastasized and therefore non-resectable/non-curable F- and NF-DP-NENs related to MEN1, ***treatment includes biotherapy*** (for example, SAs, inhibitors of receptors, and monoclonal antibodies), ***chemotherapy and radiological therapy*** [423] (Figure 1). However, ***there is a lack of clinical trials with a greater number of MEN1-patients with DP-NENs, but instead various case reports revealing the efficacy of these treatment regimes.***

F-DP-NENs

Insulinomas

Malignant insulinomas continue to be extremely rare tumors. To be considered malignant, insulinomas must show evidence of local invasion into the surrounding soft tissue, or lymph node or liver metastasis must be verified [424]. The major sites of metastasis or recurrence are regional lymph nodes and the liver. In many patients with malignant insulinomas, the tumors are unresectable and medical treatment is limited in its ability to prevent hypoglycemic episodes [425, 426].

Long-acting SAs have been seen to control hypoglycemia in a number of "malignant" insulinomas [391, 394].

Targeted agents such as everolimus, an oral inhibitor of mTOR pathway [427], ***have recently demonstrated significant efficacy in controlling hypoglycemia in patients with metastatic insulinomas refractory to other therapies*** [Kouvaraki, Ajani et al. 2004, [396]. The drug blocks the release and decreases the synthesis of insulin, while also having a positive effect on peripheral glucostasis. Another option may be the application of the antiangiogenic drug and tyrosine kinase inhibitor sunitinib (Raymond, Dahan et al. 2011)

Cytotoxic treatment is mainly applied in metastatic insulinomas, especially ***including streptozotocin in combination with 5-FU or doxorubicin*** [428]. Objective responses have been reported in up to 40% of patients with various types of malignant DP-NENs.

Another chemotherapy applied in metastatic insulinomas is temozolomide, alone or in combination with capecitabine. This therapy has identified objective responses in the range of 30 to 75% in DP-NENs [429-431].

Gastrinomas

Compared with SAs, ***PPIs control acid secretion better by reducing circulating gastrin levels for symptom control but may also help to reduce tumor growth*** [388]. Other options such as ***everolimus or sunitinib are applied in metastatic gastrinomas, as well as cytotoxic treatment including streptozotocin plus 5-FU or doxorubicin or temozolomide plus capecitabine***. ***Radioactive treatments with SA-based radioactive peptides such as ^{177}Lu and ^{90}Y have been applied with significant efficacy*** in patients with malignant gastrinomas as well as insulinomas [48, 432, 433].

Glucagonomas

Everolimus and sunitinib are therapies for particular metastatic glucagonomas and are both registered for ***DP-NENs***. Cytotoxic treatments with streptozotocin plus 5-FU/doxorubicin or temozolomide plus/minus capecitabine are valid alternatives. This type of tumor is also sensitive to PRRT with ^{177}Lu-DOTATATE and ^{90}Y-DOTATOC.

VIPomas

The treatment options for unresectable DP-NENs are cytotoxic treatment including ***streptozotocin plus/minus 5-FU or doxorubicin or temozolomide plus/minus sapecitabine***. Everolimus is also quite effective in controlling the clinical symptoms related to VIP production by reducing the circulating VIP levels. Finally, PRRT can be applied in these patients with clinical benefit.

Somatostatinomas

The medical treatment includes the same type of treatment as for NF-DP-NENs (see below).

Other F-DP-NENs, including GRFomas, ACTHomas, PTHrP-producing tumors and CCKomas, are altogether very rare manifestations of DP-NENs in the MEN1 setting and should be treated according to the same protocols as for other MEN1 DP-NENs, as discussed previously [398, 399, 434].

NF-DP-NENs including PPomas

NF-PPomas are nearly universal in patients with MEN1 [293, 435]. ***Metastatic NF-DP-NENs are commonly treated with the cytotoxic agent streptozotocin plus 5-FU or doxorubicin or temozolomide plus capecitabine.*** Due to problems in many countries to obtain streptozotocin, more and more patients are now starting on everolimus or sunitinib as a first-line medication [436].

It was shown recently that everolimus may offer prolonged tumor control in P-NENs with germline mutations (MEN1 or VHL) compared to sporadic ones. However, the small number of patients and the retrospective nature of this study precludes any definitive conclusions [437][438, 439].
Promising data have evolved with regard to PRRT using SA-based agents such as ^{90}Y-DOTATOC or ^{177}Lu-DOTATATE in the treatment of P-NENs [404, 440]. PRRT is recommended as second-line treatment after failure of medical therapy as an alternative option to everolimus.

PRRT can be considered in both F-PNENs and NF-P-NENs with high and homogenous expression of SSTRs, irrespective of the site of the primary tumour. Up to now, and with the exception of four case reports, there is limited experience in applying PRRT in advanced MEN1 F- and NF-DP-NENs as first-line treatment [403, 441]. In these patients, good palliative response to PRRT was observed without any major haematological or renal toxicity.

However, the optimal sequencing with targeted drugs and/or chemotherapy and/or PRRT needs to be defined in DP-NENs when data from prospective randomized trials with PRRT in DP-NENs become available [288].

Liver-Directed Therapies (Embolization, Chemoembolization, Radioembolization, RFA)

In selected patients with partially resectable or unresectable liver metatstasis of DP-NENs, ***liver-directed therapies generally include TAE, TACE, radioembolization or SIRT as well as RFA*** may be discussed. However, little is known in patients with MEN1 [101, 442].

TAE and TACE can be safely performed since NEN metastases in the liver are highly vascular and derive their blood supply primarily from the hepatic artery, whereas the normal liver parenchyma is supplied primarily by the portal vein. The procedure is performed percutaneously with occlusion of the feeding vessel(s) (TAE) with/without co-administration of chemotherapeutic agents (TACE, usually doxorubicin, streptozotocin, fluorouracil or cisplatinum). The procedures can reduce the hepatic tumor mass to 80% of the patients with a duration of up to 45 months [442].

Radiofrequency ablation (SIRT) involves use of ^{90}Y microspheres with either resin microspheres (SIR-Spheres) or ^{90}Y glass microspheres (TheraSpheres). The procedure can be repeated taking one lobe at the time. The response rates have been up to 75-80% and lasted for 20-40 months [442].

RFA is mostly performed in combination with surgery, especially to remove isolated metastases. Besides the use of RFA as an antitumor treatment, a number of studies have reported enhanced symptomatic control of F-P-NENs [443, 444].

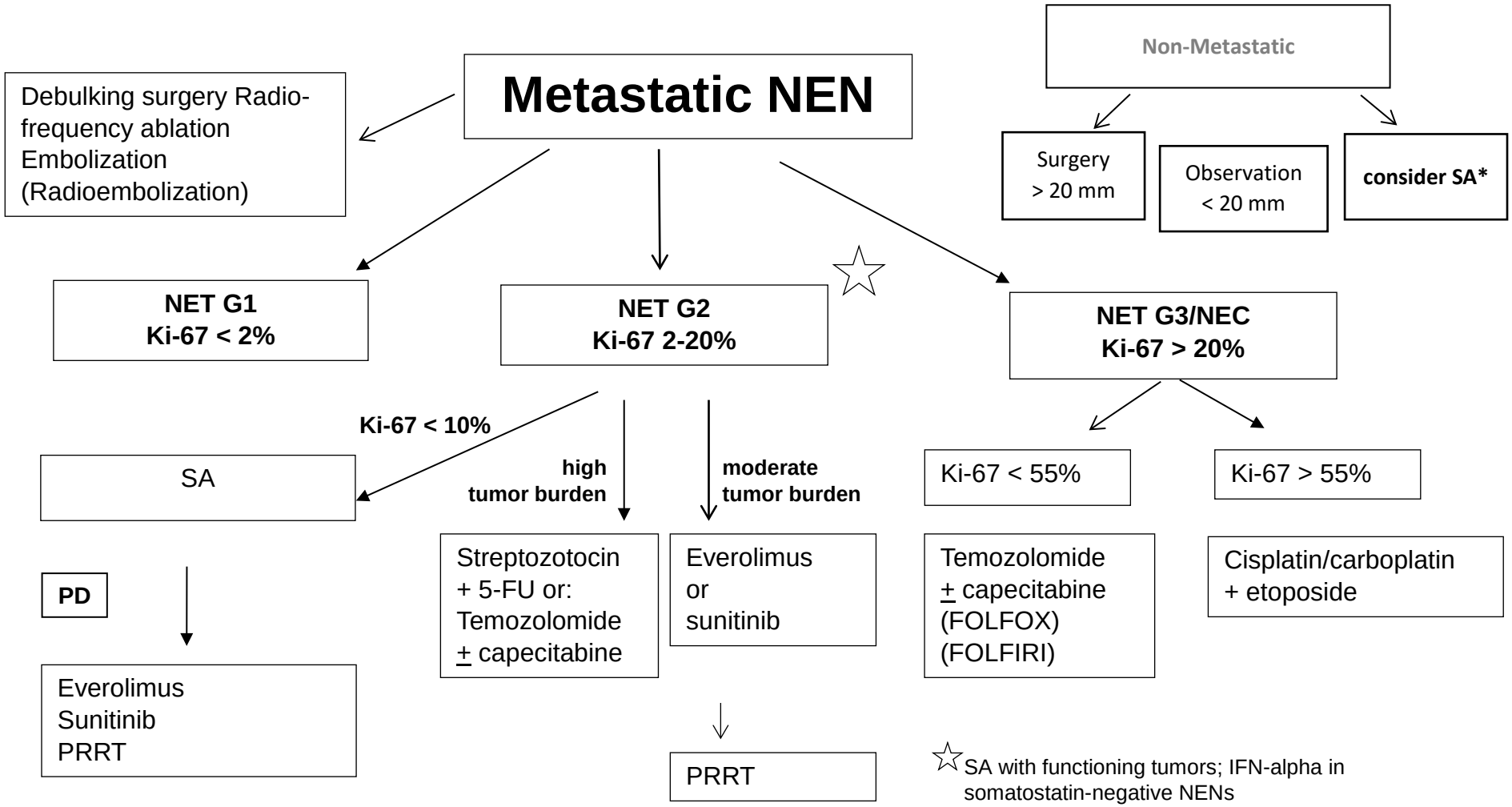
Metastatic NEN
Debulking surgery Radio-frequency ablation Embolization (Radioembolization)
Non-Metastatic
Surgery > 20 mm
Observation < 20 mm
consider SA*
NET G1 Ki-67 < 2%
NET G2 Ki-67 2-20%
NET G3/NEC Ki-67 > 20%
Ki-67 < 10%
high tumor burden
moderate tumor burden
SA
PD
Everolimus Sunitinib PRRT
Streptozotocin + 5-FU or: Temozolomide ± capecitabine
Everolimus or sunitinib
PRRT
Ki-67 < 55%
Ki-67 > 55%
Temozolomide ± capecitabine (FOLFOX) (FOLFIRI)
Cisplatin/carboplatin + etoposide
SA with functioning tumors; IFN-alpha in somatostatin-negative NENs

Figure 1. Treatment algorithm for locally advanced and/or metastasized F-DP-NENs and NF-DP-NENs within MEN1

FOLFIRI: folinic acid – fluorouracil – irinotecan; FOLFOX: folinic acid – fluorouracil – oxaliplatin; IFN-alpha: interferon alpha; Ki-67: Kiel-67 protein; NEN: neuroendocrine neoplasia; NET: neuroendocrine tumor; NEC: Neuroendocrine carcinoma; PRRT: peptide radioreceptor therapy; SA: somatostatin analog; 5-FU: 5-fluorouracil

* if locally advanced, unresectable, multiple tumors or surgery not feasible, preferably within a clinical trial

**modified by data from [445].

Gastropancreatic NENs in MEN1 can be responsible for liver metastases. Such metastases can be the dominant part of the disease as well due to the tumor burden itself or the symptoms related to such liver metastases. Intra-arterial therapies are commonly used in the liver only or liver-dominant disease and encompass TACE, TAE and RE. TACE performed with drug emulsified in Lipiodol has been used for the past 20 years with reported overall survival rates in the range of 3-4 years, with up to 75% objective response. Response to TACE is higher when treatment is used as a first-line therapy and the degree of liver involvement is lower. The benefit of TACE over TAE has not been proven in randomized studies, but reported in retrospective studies, namely in P-NENs. RE has provided early interesting results that need to be further evaluated in terms of benefit and toxicity. RFA allows control of small-size and numbered liver metastases, with low invasiveness. The ideal metastases to target are one metastasis < 50 mm, or three metastases < 30 mm, or a sum of diameter of all metastases below 80 mm. Ablation therapies can be applied in the lung or in the bones when needed, and more invasive surgery should be probably saved for large-size metastases. Even if the indication of image-guided therapy in the treatment of GEP-NEN liver metastases needs to be refined, such therapies allow for a manageable invasive set of treatments able to address oligometastatic patients in the liver, lung and bones. These treatments applied locally will save the benefit and the toxicity of systemic therapy for more advanced stages of the disease.

Based on the grade and stage of the DP-NEN, various options (and their combinations) are considered: besides surgical excision (either curative or for debulking aims), biological drugs (SSAs), targeted therapies (mTOR inhibitors or tyrosine kinases (TK)/receptors inhibitors), PRRT, chemotherapy and liver-directed therapies may be used. However, treatment of MEN1-related NENs patients is even more challenging, as the multifocal tumours with co-existing foci of heterogeneous biology and malignant potential tend to be more resistant to conventional therapies and therefore may be associated with a poorer prognosis.

Clinical data using standard therapeutic options in MEN1-related NENs are scarce. Recent preclinical studies have identified potentially new targeted therapeutic options for treating MEN1-associated NENs, such as epigenetic modulators, Wnt pathway-targeting β-catenin antagonists, Ras signalling modulators, Akt/mTOR signalling modulators, novel SAs, antiangiogenic drugs and MEN1 gene replacement therapy. In a recently published review, these novel therapeutic opportunities for NENs developing in the context of MEN1, with an emphasis on pancreatic NENs, as they are the most frequent ones studied to date are summarized [446].

DP-NECs (G3)

Marianne Pavel and Kjell Öberg

As shown recently, approximately 1% of DP-NENs within MEN1 was graded G3 [248]. Reviewing the literature, no patients with MEN1 and DP-NECs have been clinically reported. However, G3 tumors are a domain for medical treatment following the recommendations for treating sporadic P-NECs. The important recommendations concerning DP-NENs have recently been summarized [447].

For NECs, the guidelines generally summarize that systemic chemotherapy is indicated in advanced inoperable disease, provided that the given patient has adequate organ function and performance status (Figure 1). Otherwise, the patient should be rapidly referred for consideration of palliative chemotherapy. The combination of cisplatin and etoposide, or alternative regimens substituting carboplatin for cisplatin or irinotecan for etoposide, is recommended as first-line therapy. Since the response rates to these regimens are lower in patients with a Ki-67 value in the lower range of G3 (20 to 55%), other treatment options may be explored in such subjects (especially for NECs of a GI origin). While second-line regimens have not been evaluated rigorously, the options still include temozolomide-, irinotecan- and oxaliplatin-based schedules as main alternatives. There are no data to support the use of SAs or PRRT in patients with NECs expressing SSTRs. Prophylactic cranial irradiation is not indicated in patients with limited-stage disease in complete remission [447].

Special Feature

Pregnancy and DP-NENs

Bruno Niederle

Although there seems to be no adverse impact of the genetic background of MEN1 on patient fertility [448], ***the concurrence of pregnancy and MEN1 is very rare.***

Reviewing the literature, only anecdotical reports have been published with more or less details concerning F- and NF-DP-NENs in MEN1 [449] [450, 451].

Stewart et al. [449] reported two 29-year-old females and their three pregnancies. In one patient, the gastrinoma was diagnosed nine years before pregnancy and was never localized. Initial treatment was parathyroidectomy, resulting in a sufficient decrease in acid secretion, and only low doses of ranitidine were needed during pregnancy. The second patient had two pregnancies five and seven years after diagnosis of MEN1-ZES and curative resection of the gastrinoma. She required no acid antisecretory drugs during pregnancy due to the marked decrease in acid after the curative resection. All three pregnancies were uneventful and the three neonates healthy. Neither an exacerbation nor a recurrence of hormone excess was reported.

Mistry and coworkers [451] reported a 31-year-old primigravida with a confirmed diagnosis of MEN1 two years prior to conception. MRI for recurrent migraines identified a pituitary macroprolactinoma, PHPT, secondary hypothyroidism, a "pancreatic" gastrinoma and a non-functioning adrenal adenoma. In view of the findings of fetal growth restriction after 34 weeks and a raised umbilical artery Doppler pulsatility index, a decision was made for delivery by Caesarean section at 35+1 week's gestation. A baby boy was born in good condition and was initially treated with intravenous calcium. The neonate was breastfed and was later discharged with cholecalciferol and vitamin D supplements. Both the mother and baby had an otherwise unremarkable recovery. Maternal serum-corrected calcium was stable at 2.54 mmol/l. Nothing was reported concerning the course of the mentioned "gastrinoma".

Daglar et al. [450] reported the course of pregnancy with MEN1 syndrome (ongoing medical therapy of a prolactinoma, surgically treated PHPT). During screening for pancreatic manifestation, two hypodense lesions measuring 6 mm each in the junction of the pancreatic head and neck were depicted by CT and were suspected to be NENs. No biopsy was carried out to confirm NEN. At the age of 29 years, the patient was followed up as of the first trimester. She was admitted to the hospital at week 38 because of a premature rupture of membranes. US showed that the fetus size was consistent with gestational age. The biochemical test results were uneventful and a healthy baby girl was delivered vaginally.

There are no guidelines as how to advise young females with genetically confirmed MEN1 with respect to planning conception and, in unplanned pregnancy, how to follow NEN and pregnancy. The treatment and follow-up protocols are to consider the functionality (cured or persisting disease) as well as the grade and the stage of the DP-NEN. Based on these basic points, the arguments for and against pregnancy are to be discussed with the patient. They influence the sequence of necessary diagnostic follow-up intervals, the methods as well as the type and timing of treatment.

The challenging management of an unplanned, intact pregnancy is to respect the clinical course of both the mother and fetus without affecting one another.

Maternal MEN1 is associated with an increased risk of gestational diabetes, hypertensive disorders and low neonatal birthweight, but not with an increased miscarriage rate. Whilst hypercalcaemia worsens during the second trimester, most pregnancies progressed without overt complications or requirement for intervention [452].

An individualized, multidisciplinary approach is to be developed involving gynecologists and neonatologists along with medical oncologists, endocrinologist, surgeons and anesthesiologists. The patient´s family is also to be included when decisions for pregnancy are made, and a series of legal, ethical, religious, personal and emotional factors are to be taken into account.

F-DP-NENs and Pregnancy

F-DP-tumors identified in advance of pregnancy should be considered for surgical resection whenever feasible. A recurrence of cured hormone excess has not been reported to be triggered by pregnancy [449].

Gastrinoma

Measurements of serum gastrin and gastric pH are the keystones in the diagnostic work-up for gastrinoma also suspected during pregnancy. Serum gastrin concentrations appear to be unaffected by pregnancy [453]. Complications of acid hypersecretion frequently cause diarrhea and malabsorption, which could severely compromise nutritional status during pregnancy. ***Symptoms may be usefully controlled by the use of gastric antisecretory drugs, either prescribing H_2-receptor antagonists or PPIs [449] H_2-receptor antagonists are the preferred conservative treatment. There were no side effects of ranitidine in pregnancy [454]***

A recent meta-analysis [455] ***revealed an increased risk of congenital malformations associated with PPI use during pregnancy,*** in particular when based on case-control studies, although power was

low in all subgroup analyses. ***These findings suggest that PPIs should ideally be restricted to welldescribed indications if no other available treatment options are available and if the benefits outweigh the risks.*** No conclusions could be drawn for the other pregnancy outcomes.

Hyperparathyroidism with resultant hypercalcemia increases gastrin secretion from the gastrinoma [116] and also decreases the sensitivity of the acid-secretory process to antisecretory agents by an unknown mechanism [456]. ***Restoring normocalcemia by parathyroid surgery, recommended at the latest when serum calcium is persistently greater than 2.75 mmol/l and ideally performed in the second trimester*** [457]**,** could affect the need for antisecretory drugs and should be the first step in treating MEN1-ZES [449], while at once avoiding complications during and after pregnancy [458, 459].

Insulinoma

There are no reports in the literature of insulinoma during pregnancy in connection with MEN1. However, ***diagnosis is frequently delayed because mild hypoglycemia is common in early pregnancy and the symptoms of nausea, weakness and hypotension are mistaken for those of normal pregnancy.*** Furthermore, symptoms may improve during the second and third trimesters with the rise in insulin resistance, such that the diagnosis is often only established in the postpartum period when a rebound in insulin sensitivity occurs [460, 461].

Insulinomas are diagnosed on the basis of the 72-hour fast test. Pregnancy does not appear to influence the suppressive effect of hypoglycemia on insulin secretion [460], although the decision to perform such a test during pregnancy should take into account maternal and oetal well-being in addition to clinical need, since the test is not without risk and must be done under close supervision.

In the majority of patients, therapeutic management is convenient considering the less aggressive behavior of insulin-producing tumors. However, ***uncontrolled hypoglycemia caused by the insulinoma during pregnancy may cause fetal demise. Maintaining and monitoring reasonable levels of blood glucose through reduced and frequently administered meal portions serves to avoid complications. Surgical treatment in localized tumors remains the only curative method. It often has to be scheduled after birth or, if the situation requires, as late as possible after the fetus is of a convenient age (usually after 28 weeks of pregnancy).***

In pregnant patients who refuse the surgical procedure, when the tumor is not identified or in the case of metastasis of malignant insulinoma, medical treatment is used if the symptomatology is easy to control with conservative therapy. ***Diazoxide is the first line of medical treatment. In the case of inefficiency, the second line of therapy is SAs.*** No severe side effects have been reported applying these drugs during pregnancy.

NF-DP-NENs and Pregnancy

In female patients with NF-DP-NENs ≤ 20 mm, who require only surveillance but no other active treatment, there are theoretically no clear contraindications against pregnancy. The natural course of the NF-NEN may depend on a more or less aggressive genetic and biological background (grading) but is not influenced by pregnancy *per se*. ***There is no clear evidence that NENs progress more rapidly during pregnancy*** [462].

Asymptomatic, localized NENs > 20 mm may be best monitored closely with no intervention during pregnancy. Surgical resection of NENs, which is recommended in non-pregnant patients with localized disease, should be postponed until after delivery. However, due to the high malignancy rate and poor prognosis of large NENs with severe local symptoms, an aggressive surgical resection may be indicated in selected patients. Even distal extended pancreatic resections can be performed during pregnancy without any harmful effects on the fetus, but should be performed in specialized centers [463].

Women with metastasizing disease requiring ongoing treatment do not commonly desire pregnancy due to the burden of the disease and additional treatments. If they strongly wish to become pregnant, they should be generally advised against pregnancy by the supporting team of physicians.

If a patient with metastatic disease exhibits satisfactory treatment response regardless of clear disease burden and very strongly desires pregnancy, pausing treatment may be attempted to identify whether the tumor burden remains stable. lf the tumor is stable, pregnancy should be possible and may theoretically be discussed with the patient and her family. However, ***metastatic disease makes pregnancy a challenging issue and may increase the risk of fetal demise.*** lf required to stabilize metastatic disease, liver-directed therapies as well as PRRT using radioactive pharmaceuticals or chemotherapeutic agents and systemic therapies with targeted agents such as everolimus and sunitinib may be teratogenic.

Monitoring response to therapies by imaging may be limited in pregnancy as CT and nuclear imaging should be used with caution during pregnancy [464].

Neonates

Children with a MEN1+ parent ***are disproportionately vulnerable postpartum***. Neonates of MEN1+ mothers remain vulnerable despite contemporary care. The excess risk was not fully explained by maternal MEN1 or antenatal hypercalcemia [465].

Lactation

In women without active treatment, there are no contraindications to breast feeding. In patients with progressive disease requiring active treatment, breast feeding is generally challenging due to concern about drug excretion into breast milk, radioactivity exposure and logistics. Patients requiring SA treatment only may breastfeed safely.

Statements

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Author Contributions

B.N. and A.S. developed the project idea underlying this consensus statement. All authors participating in the statement are members of the ESES and/or ENETS which are responsible for the contents of the subtopic manuscripts. The authors drafted the individual manuscripts; their corresponding addresses are listed in the online Supplement, Addendum 2. B.N. revised the overall consensus statement. B.N. and A.S. designed and prepared and all authors approved the final version of the consensus statement. D.O´T. (ENETS), D.S.-C. (ESES), R.V.T., G.Th., G.Tr. and B.W. served as external reviewers.

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Addenda

Addendum 1 - Alphabetical List of Authors and External Reviewers

Addendum 2 - Subtopics / Authors

Addendum 3 – Levels of Evidence / Grades of Recommendation

Addendum 4 – Table and Figure Legends

Addendum 5 – Abbreviations

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Addendum 2: Subtopics / Authors

SA treatment in small (≤ 20 mm) NF-(G1/G2) DP-NENs	M. Pavel, K. Öberg	93 - 95
Biotherapy – Targeted Therapy – Radiotherapy – Liver-Directed Therapies	M. Pavel, K. Öberg	96 - 101
DP-NECs (G3)	M. Pavel, K. Öberg	102
Special feature		
Pregnancy and DP-NENs	B. Niederle	103 - 107
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Addendum 3 – Levels of Evidence / Grades of Recommendation

Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009) (for definitions of terms used, see glossary at http://www.cebm.NEN/?o=1116)

Levels of evidence

Level	Therapy/Prevention, Etiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centers	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with > 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multiway sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level > 2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level > 2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., < 80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation	Exploratory** cohort study with good††† reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including

		of CDR† or validated on split-sample§§§ only			multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick**, March 2009.**

Notes

Users can add a minus-sign "-" to denote that the LE fails to provide a conclusive answer because of: ***EITHER*** a single result with a wide Confidence Interval ***OR*** a Systematic Review with troublesome heterogeneity.

Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all

	worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)
‡	See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in < 80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is > 80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1 - 5 years chronic)

Grades of recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

"Extrapolations" refers to data that is used in a situation that has potentially clinically important differences compared to the original study situation.

Original - http://www.cebm.NEN/index.aspx?o=1025

Addendum 4 – Table and Figure Legends

Addendum 5 – Abbreviations

ACTH	Adrenocorticotropic hormone
ACTHoma	Adrenocorticotropic hormone-producing tumor
AJCC	American Joint Committee on Cancer
ALT	Alternative lengthening of telomeres
ATRX	Alpha thalassemia/mental retardation syndrome
CCKoma	Cholecystokinin-producing tumor
CEBM	Centre for Evidence-Based Medicine
CgA	Chromogranin A
CHES1	Checkpoint suppressor 1
CI	Confidence interval
CLARINET study	Lanreotide Antiproliferative Response in Patients with Gastroentero-pancreatic Neuroendocrine Tumor study
CNB	Core needle biopsy
CT	Computed tomography
DAXX	Death domain-associated protein gene
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTANOC	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-1-Nal3-oc-treotide
DOTATATE	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-octreotate
DOTATOC	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-Tyr3-oc-treotide
DP	Duodenopancreatic
EBM	Evidence-based medicine
ENETS	European Neuroendocrine Tumor Society
ESES	European Society of Endocrine Surgeons
EUS	Endoscopic ultrasound
F-	Functioning
FDG	Fluoro-2-deoxy-D-glucose
F-DOPA	F-fluoro-L-phenylalanine
FISH	Fluorescence in situ hybridization
FNAB	Fine-needle aspiration biopsy
FOLFIRI	Folinic acid – fluorouracil – irinotecan

FOLFOX	Folinic acid – fluorouracil – oxaliplatin
FSG	Fasting serum gastrin
GEP	Gastroenteropancreatic
GHRH	Growth hormone-releasing hormone
GHRHoma	Growth hormone-releasing hormone-secreting tumor
GI	Gastrointestinal
GLP-1R	Glucagon-like peptide-1 receptor
GR	Grade of recommendation
GRFoma	Growth hormone-releasing factor tumor
GTE	Groupe d'étude des Tumeurs Endocrines
HR	Hazard ratio
HRCT	High-resolution computed tomography
IFN-alpha	Interferon alpha
IHC	Immunohistochemistry
ISGPS	International Study Group of Pancreatic Surgery
IU	International unit
JunD	JunD proto-oncogene
LAR	Long-acting release
LARO-MEN1 study	Long-Acting Release in Patients with Multiple Endocrine Neoplasia type 1 study
LCNEC	Large-cell neuroendocrine carcinoma
LE	Level of evidence
MDACC	MD Anderson Cancer Center
MEN1	Multiple endocrine neoplasia type 1
MI	Mitotic index
MINEN	Mixed neuroendocrine/non-neuroendocrine neoplasia
MRI	Magnetic resonance imaging
mTOR	Mechanistic target of rapamycin
NCCN	National Comprehensive Cancer Network
NDC	National Drugs Code
NEC	Neuroendocrine carcinoma
NEN	Neuroendocrine neoplasia
NET	Neuroendocrine tumor

NETest	Neuroendocrine neoplasms test
NF-	Non-functioning
NIH	National Institutes of Health
OMIM	Online Mendelian Inheritance in Man
PC	Pancreatic cholera
PET	Positron emission tomography
PHPT	Primary hyperparathyroidism
PP	Pancreatic polypeptide
PPD	Partial pancreaticoduodenectomy (Whipple procedure)
PPI	Proton pump inhibitor
PPoma	Pancreatic polypeptide-secreting tumor
PPPD	Pylorus-preserving pancreaticoduodenectomy
PPTD	Pancreas-preserving total duodenectomy (Imamura procedure)
PPV	Positive predictive value
PRRT	Peptide radioreceptor therapy
PTHrP	Parathyroid hormone-related protein
RE	Radioembolization
RFA	Radiofrequency ablation
SA	Somatostatin analog
SACI	Selective arterial calcium injection
SANO trial	Somatostatin Analog versus No treatment trial
SASI	Selective arterial secretin injection
SCNEC	Small-cell neuroendocrine carcinoma
SIR	Selective internal radiation
SIRT	Selective internal radiation therapy
SPECT	Single-photon emission computed tomography
SRI	Somatostatin receptor imaging
SRS	Somatostatin receptor scintigraphy
SSTR	Somatostatin receptor (subtype)
SUVmax	Maximum standardized uptake value
TACE	Transarterial chemoembolization
TAE	Transarterial embolization
THPVS	Transhepatic portal venous sampling
TNM	Tumor-node-metastasis classification of malignant tumors

TP	Total (duodeno)pancreatectomy
UICC	Union for International Cancer Control
US	Ultrasonography
VHL	Von Hippel-Lindau disease
VIP	Vasoactive intestinal peptide
VIPoma	Vasoactive intestinal peptide-secreting tumor
WDHA	Watery diarrhea - hypokalemia - achlorhydria
WHO	World Health Organization
ZES	Zollinger-Ellison syndrome
5-FU	5-fluorouracil
11C-5-HTP	11C-5-hydroxytryptophan
18-FDG	18-fluoro-2-deoxy-D-glucose
^{68}Ga	Gallium-68
^{90}Y	Yttrium-90
^{111}In	Indium-111
^{177}Lu	Lutetium-177