Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management and controversies

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Abstract

Pancreatic endocrine tumors (PETs) can occur in as part of four inherited disorders including: Multiple Endocrine Neoplasia type 1 (MEN1), von Hippel-Lindau disease (VHL), neurofibromatosis 1(NF-1) [von Recklinghausen's disease] and the tuberous sclerosis complex (TSC). The relative frequency with which patients with these disorders develop PETs is MEN1>VHL>NF-1>TSC. Over the last few years there have been major advances in the understanding of the genetics and molecular pathogenesis of these disorders as well in the localization, medical and surgical treatment of the PETs in these patients. The study of the PETs in these disorders has not only provided insights into the possible pathogenesis of sporadic PETs, but have also presented a number of unique management and treatment issues, some of which are applicable to patients with sporadic PETs. Therefore the study of PETs in these uncommon disorders has provided valuable insights that in many cases are applicable to the general group of patients with sporadic PETs. In this article these areas are briefly reviewed as well as the current state of knowledge of the PETs in these disorders and the controversies that exist in their management are briefly summarized and discussed.

Keywords

pancreatic endocrine tumors; neuroendocrine tumors; multiple endocrine neoplasia type 1; von Hippel-Lindau disease; neurofibromatosis 1; tuberous sclerosis; gastrinomas; insulinomas; Zollinger-Ellison syndrome

I. Introduction

Pancreatic endocrine tumors (PETs) have long fascinated clinicians because some can release biologically active hormones that cause distinct syndromes that provide important insights into the biological effects of these hormones in man [1–3]. PETs can be divided into two general groups; functional PETs associated with symptoms due to ectopic secretion of hormones and nonfunctional PETs (NF-PET), which either don't secrete or the products secreted do not cause a clinical syndrome (i.e. pancreatic polypeptide [PPoma], chromogranin A, ghrelin, neurotensin, subunits of chorionic gonadotropin, neuron- specific enolase) [1–4]. Functional PETs include gastrinomas which ectopically releasing gastrin causing the Zollinger-Ellison syndrome (ZES) characterized by refractory peptic ulcer disease due to the gastric hypersecretion; insulinomas secreting insulin causing hypoglycemia; vipomas (Verner-

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Morrison syndrome, WHA syndrome, pancreatic cholera) secreting vasoactive intestinal peptide causing severe secretory diarrhea; glucagonomas secreting glucagon causing hyperglycemia, diabetes, and a characteristic skin rash, necrolytic migratory erythema; somatostatinomas secreting somatostatin causing diabetes, steatorrhea and gallstones and GRFomas secreting growth hormone-releasing factor (GRF) causing acromegaly [1,2,5,6]. Other less common functional PETs reported to cause specific syndromes secrete luteinizing hormone, erythropoietin, renin and PYY have been described [3], but in general too few cases have been described to fully establish a syndrome. Each patient with a PET has potentially two treatment problems: treatment of the hormone excess state if present, and treatment of the PET itself, because except for insulinomas, >50% of the different PETs are malignant [1,3,7]. In the last few years there have been marked advances in the treatment of the hormone excess states, the ability to localize these tumors and fully stage them and in treatment for advanced disease [8–10]. Another importance advance is increased understanding that a subset of these tumors has an inherited basis and the insights being provided by study of this subset (Table 1)[11,12].

There are four well-established diseases associated with inherited pancreatic endocrine tumors (PETs) (Table 1). These include Multiple Endocrine Neoplasia type 1 (MEN1)(Wermer's syndrome), von Hippel-Lindau disease (VHL), von Recklinghausen's disease (neurofibromatosis 1)(NF-1) and tuberous sclerosis. Each of these disorders shows autosomal dominant inheritance and the causative genes (*MEN1, VHL, NF1, TSC1/2*) (Table 1) all function as tumor suppressor genes [11,13–18]. While there are occasional reports of other familial occurrences of PETs (insulinomas) [19] or gastrointestinal carcinoid tumors [20], which share many clinical and pathologic similarities to PETs [21], these have not been investigated in detail genetically and it is unclear whether they have a distinct etiology not related to the above syndromes.

Within the last twenty years there have been considerable advances in both the clinical understanding of these diseases as well as their molecular basis and treatment. The genetic defect(s) causing each of these inherited PET syndromes has been elucidated (Table 1) and considerable advances have been made in understanding the cellular roles of the various altered proteins (Table 1) and how alterations might lead to the observed clinical abnormalities seen. These genetic changes also provide important insights into the role of some of these genes in the pathogenesis of sporadic PETs, a group of tumors for which the understanding of their pathogenesis has remained relatively unclear, because it does not depend on the common oncogenes and tumor suppressor genes frequently altered in the common gastrointestinal adenocarcinomas [11,12]. In the last few years there have been rapid advances in early diagnosis of these diseases and the associated PETs using genetic studies as well as improved imaging studies. These have led to a number of unique controversies over the treatment of PETs, especially when small, asymptomatic PETs are found in patients. In this article the information available on PETs in these inherited disorders will be briefly summarized, as well as the advances and controversies in diagnosis and treatment of PETs in these syndromes. Because PETs are much more a prominent part of the MEN1 syndrome than the other three syndromes (Table 1) and because the natural history of the PET in MEN1 patients is becoming the leading determinant of long term survival [22–25], the PETs in this disorder will be discussed in more detail.

II. Multiple Endocrine Neoplasia type 1 (MEN1)

II.A. General

MEN1 is characterized classically by tumors/hyperplasia of the parathyroid, enteropancreatic tissues and pituitary [13,14]. Increasingly, tumors are being described in a number of different tissues including the adrenal, thyroid, CNS, skin (angiofibromas, collagenomas), smooth muscle as well as foregut carcinoids (thymus, gastric, lung)(Table 2, Fig. 1).

II.B. Genetics/molecular pathogenesis

In 1988 [26] the *Men1* gene was mapped to chromosome region 11q13 using linkage analysis and in 1997 was cloned [27]. It spanned 10 exons (9 coding) and encoding for a 610 amino acid nuclear protein, menin, which was widely expressed in endocrine and nonendocrine tissues [14,27] (Fig. 2). The intracellular functions of menin have not been fully elucidated, however an increasing amount is known about the numbers of proteins it interacts with [28,28–33] (Fig. 2). Menin interacts with a large number of proteins, which have important effects on transcriptional regulation, genomic stability, cell division and cell cycle control [28,28–33] (Fig. 2).

In transcriptional regulation, menin interacts with the activating protein-1 transcription factor JunD and NF-κB resulting in inhibition of transcription caused by each of these proteins [28, 30–32]. Menin's interaction with SMAD proteins (SMAD 3 and SMAD1/5 complex) results in enhanced transcriptional activation and TGFβ signaling as well as interaction with the bone morphogenetic protein(BMP)-2 signaling pathway and it also interacts with Runx2, which is a target of TGFβ and BMP as well as with mouse placental embryonic expression gene protein (Pem)[28,32,34,35]. Menin's interacts with the homeobox-containing protein Pem can affect JNK and other MAP kinases signaling cascades [32,36]. The forkhead transcription factor CHES1 which forms a transcriptional repressor complex that includes mSin3a, histone deacetetylase (HDAC) and HDAC-2 interacts with menin in a S-phase checkpoint pathway related to the cellular DNA damage response seem after ionizing radiation [37]. Menin has been shown to bind in a histone methyltransferase complex containing MLL2, which is homologous to the mixed lineage leukemia (MLL) family of proteins that alter transcriptional activity [28, 31,38–40]. Menin in cooperative interaction with MLL proteins regulates cyclin-dependent kinase inhibitors, p27 and p18, which in turn regulate the clustered homeobox genes (Hox) which have important effects on proliferation [28,38–40]. Menin has been shown to interact directly with the estrogen nuclear receptor (ERalpha) and to acts as a co-activator for ER alpha mediated transcription; therefore it acts as a critical link between recruitment of histone methyltransferase complexes and nuclear receptor –mediated transcription [41] (Fig. 2).

Menin also has been shown to bind directly with double-stranded DNA, which is mediated by the positively charged residues in the NLSs in the COOH terminus of menin (Fig. 2) [42]. The NLSs are also important for interaction of menin with the insulin-like growth factor-2 (IGFBP-2) promoter resulting in repression of the expression of IGFBP-2 and in menin-mediated induction of caspases 8 expression, suggesting menin may act as a scaffold protein in coordinating activation and repression of gene transcription [43,44].

Menin associates with chromatin and nuclear matrix and from studies of menin in irradiated cells it has been proposed that menin might be important for repairing DNA damage [28]. Menin interacts with a 32-kD subunit of replication protein A (RPA2) which is required for DNA replication, repair and recombination [45] and the FANCD2 protein which is also involved in DNA repair and whose mutations result in the inherited cancer-prone syndrome, Fanconi's anemia[46], suggesting that menin plays an important role in genomic stability (Fig. 2) [45–47]. Menin also plays a role in cell division through its interaction with the non-muscle myosin II-A heavy chain protein (NMHC II-A) that is involved in cytokinesis and cell shape changes during cell division [48] and by interacting with the type III intermediate filament proteins, glial fibrillary acidic protein (GFAP) and vimentin [49]. The latter interaction demonstrates that the intermediate filament network may serve as a cytoplasmic sequestering network for menin at the S and early G2 phase of the cell cycle [49]. Menin also plays a role in cell cycle control through its interaction with the tumor metastases suppressor nm23/nucleoside diphosphate (NDP) kinase which is a multifunctional kinase which has been implicated in cell growth, differentiation, development and suppression of tumor metastases [50], as well as its interaction with the S-phase kinase ASK (Fig. 2) [51]. ASK, a component of the Cdc/ASK kinase complex,

is essential for cell proliferation, it is repressed by intact menin, but not by disease causing menin mutants, demonstrating a functional link between menin and ASK in the regulation of cell proliferation [51]. Studies also suggest functions of menin related to telomeres with menin localizing in telomeres during the prophase [52] and menin inhibiting telomere expression by functioning as a direct repressor of the hTERT, an essential telomeric protein component [53].

Recent data suggest that menin and its interaction with the above proteins play an important role in physiological regulation of growth, control of the cell cycle, genomic stability and are potentially important in bone development and multipotent mesenchymal stem cell differentiation [28,32]. Specifically, in the case of the pancreatic islets which may give rise to some PETs in MEN1 [54], recent studies [47,55,56] show the loss of menin increases β cell proliferation by disrupting menin's inhibitory effect on S-phase entry [47] and by disrupting menin-dependent histone methylation that maintains p27 and p18 inhibition of cyclin-dependent kinases [55].

Targeted disruption of the *Men1* gene [57–59] resulted in mice with a similar phenotype to the disease that develops in humans with tumors of the pancreas, parathyroid, pituitary, thyroid and adrenal. Conditioned knockout of the *Men1* gene [60,61] in pancreatic islets of the mouse, developed β cell hyperplasia and insulinomas in some animals by nine months. This late development of tumors even though both copies of the *Men1* gene were removed, suggested that additional somatic events are required for adenoma formation in *B* cells.

Mutations in the *Men1* gene are found in 78–93% of MEN1 families with 1336 different mutations reported which occur throughout the 9 exon-coding region [14,29,62]. Overall 23% of the mutations are nonsense mutations, 9% slice-site mutations, 41% frameshift mutations or insertions, 6% in –frame deletions/insertions, 20% missense mutations and 1% whole or partial gene deletions [29]. More than 75% of the mutations lead to truncated forms of menin [29]. In general there is no genotype phenotype correlation [29]. One study reported no association of the MEN1 mutation type with tumor behavior [63], however another study by Bartsch et al [64] reported that truncating mutations in the amino or COOH terminal regions of menin (exons 2,9,10) were associated with a significantly higher rate of malignant PETs (55 vs. 10%, p<0.05) and tended to have a shorter disease-free interval (26 vs. 92 mos, p=0.11).

PETs from patients with sporadic PETs (not due to MEN1) have loss of heterozygosity (LOH) at the MEN1 locus (11q13) in 5–93% and have a mutation in the *Men1* gene in 27–39% [13,29,65,66]. The presence of an MEN1 mutation in sporadic gastrinomas was not associated with more severe disease [66]. These results support the conclusion that alterations in the *Men1* gene may be important in the pathogenesis of a subset of sporadic PETs [11,29,65,66].

Global gene expression has been studied in a small number of MEN1 PETs (N=8) and compared to normal islets [67]. Four-five genes were over-expressed and 148 genes under-expressed compared to normal islets including 19 apoptosis-related genes [specially, IER3, DDT, PHLDS2, IAPP], which were under-expressed [67].

II.C. MEN1-clinical aspects (Figure 1 and Table 2, top)

The classical manifestations of MEN1 are parathyroid hyperplasia leading to hyperparathyroidism (HPT) (95–100), PETs (symptomatic in 20–70%) and anterior pituitary tumors (54–65%) [13,14,68](Table 2, Fig. 1). Adrenal tumors, thyroid adenomas, carcinoid tumors (thymic, gastric, pulmonary), skin tumors, CNS tumor and smooth muscle tumors also occur in a significant number of MEN1 patients (Table 2, Fig. 1). Classically, almost all patients are reported to initially present with HPT (Fig. 3 panels A, B), however in numerous recent series up to 40% of patients present with a functional PET (usually an insulinoma or gastrinoma) and the patients were frequently initially thought to have sporadic PETs [13,68–

[72]. In some of these cases the HPT is almost certainly missed. This occurs because, in most MEN1 patients, the HPT initially is mild and easily missed if careful assessments of parathyroid function are not performed with serum ionized calcium studies and assessment of intact plasma PTH levels using a sensitive IRMA assay [13,68,73]. This point is well shown in a recent study [68] of ZES/MEN1 patients (107 NIH, 1009 literature patients) in which in 44% and 47% of the MEN1 patients, the ZES was clinically evident before the diagnosis of HPT and in 20–25% it was diagnosed 5 years earlier. This study showed if careful assessment of parathyroid function was carried out in these patients only 8% of patients found to have MEN1 who presented with ZES did not have HPT identified at the initial evaluations [68]. The mean age of presentation in MEN1 patients not detected by genetic screening or family studies is 29–34 years old, the mean age of diagnosis is a decade later and the mean age of diagnosis for patients detected by biochemical screening in families is 25–29 years [68,74,75]

II.D. PET spectrum in MEN1 (Table 2, bottom)

II.D.1. PETs in MEN1: General—The most common PETs in MEN1 are nonfunctional tumors (80–100%), gastrinomas (mean-54% [range-20–61] and insulinomas (mean 18% [range-7–31%]) (Table 2). MEN1 is found in 10–54% (mean-25%) of all patients with gastrinomas [68,76] and 4% of insulinomas [77]. Other functional PETs also occur but are present in <5% (Table 2) [78]. The PETs characteristically are diagnosed between ages 30–50 [68,78–83] (Fig. 3A,B) although a wide range exists varying from 5–15 years for the youngest with the different PETs to 68 to 80 years for the oldest [68,78,81,84]. Both insulinomas and gastrinomas occur earlier in MEN1 patients than in patients with sporadic PETs and in a detailed study [85] in gastrinomas the difference was one decade (43.5 vs. 33.2 years) (Fig. 3C).

II.D.2. PETs in MEN1: pathology/origin of PETs—Except for gastrinomas and a rare somatostatinoma, all the other classes of PETs in MEN1 (Table 2) occur exclusively within the pancreas. In patients with ZES/MEN1 duodenal gastrinomas are present in 80–100% (Fig. 4A) and pancreatic gastrinomas in 0–15% in different series [79,86–89]. The most characteristic MEN1 pancreatic lesion is the presence of diffuse microadenomatosis (lesions <0.5 mm) (Fig. 5D) which are present in almost every case in various series (Fig. 5D) [89–91]. Macroadenomas frequently also occur (Fig. 5,A–D). The microadenomas primarily display a trabecular or mixed trabecular growth pattern surrounded by or interspersed with dense connective tissue [90,91]. Most of the micro- and macroadenomas produce multiple hormones/peptides on immunohistochemical staining with 100% positive for generic neuroendocrine markers (neurons-specific enolase, chromogranin A, synaptophysin) followed by glucagon producing tumors (37–52%), insulin (15–27%), pancreatic polypeptide (17–20%), somatostatin-producing (5%), gastrin (1%) and VIP-producing (1%) [90–92]. Studies of the duodenal gastrinomas in patients with ZES demonstrate they are usually small (<1 cm in diameter); they are multicentric (Fig. 4A–C), show trabecular and pseudoglandular histological patterns and stain positive for gastrin and occasionally for somatostatin [86,93,94]. Lymph node metastases occur in 45–85%% of gastrinomas despite their small size, although liver metastases are uncommon from the duodenal gastrinomas [86,94–96].

There is no agreement on which cell gives rise to PETs in MEN1. On study [97] concluded that the pancreatic PETs arise from acinar/ductal structures, not from pancreatic islet tissue. Another study identified monohormonal endocrine cell clusters in MEN1 pancreas [54] and found that all pancreatic microadenomas and 95% of the hormonal cell clusters had loss of one *Men1* allele and concluded that the microadenomas originated from islets. In a detailed study [98] of duodenal mucosa in patients with MEN1/ZES, all patients found to have proliferative, hyperplasic lesions consisting of gastrin cells in the nontumoral duodenal mucosa, similar to the gastric ECL cells seen in the gastric mucosa in patients with hypergastrinemia, as well as many having small microadenomas. Approximately 50% of the MEN1 duodenal

microadenomas showed allelic deletion of the *Men1* gene, whereas the endocrine cell precursor lesions retained heterozygosity [99]. These lesions were not seen in MEN1 patients without ZES or sporadic ZES patients, which led the authors to propose that these proliferative lesions likely preceded the development of the duodenal gastrinomas in MEN1 patients but not patients with sporadic duodenal gastrinomas [98].

The mean size of PETs in various studies was 2.4–4 cm [23,78,81,83,100,101]. However, the mean size varies markedly in the different PETs in MEN1 patients with gastrinomas averaging 0.7–1.2 cm in diameter (usually duodenal)[78,98,101], insulinomas 0.2–2 cm in diameter [78, 102], whereas with NF-PETs it was 3.1 cm [81,101], glucagonomas 3.25 cm [78], Vipomas 4 cm in diameter [78] and with somatostinomas 7 cm [78]. In most studies multiple pancreatic PETs are found at surgery (mean 2.9–4.8, range 1–10) [23,81,101].

II.D.3. PETs in MEN1: Natural history/prognostic factors—The age-specific clinical penetrance or recognition of any manifestation of MEN1 (positive clinically or biochemically), in patients with known MEN1, for patients <20 years old is 10% and 52%, respectively; for patients < 30 years old it is 25% and 87%, respectively and by age 50 years old, 85–80% of patients with MEN1 had clinical symptoms [103]. In one study the age specific penetrance of PETs in MEN1 patients was 15% at age 30, 49% at age 50 and 68% at age 70 [104] and in the large GTE study (134 patients) [81] it was 9% at 20 years, 53% at 50 years and 84% at 80 years. The type of *Men1* gene mutation did not affect the time course of penetrance of PETs [84]. The survival is reported to differ significantly (p=0.007) in one study [78] between MEN1 patients with different PET subtypes. Specifically, the relative 10 year survival rates were gastrinomas, insulinomas (82–91%)>NF-PETs (62%)>glucagonomas, VIPomas, somatostinomas (54%) [78] (Fig. 6, panel 1A). This result is also mirrored in the summary data of survival for any PET or different PETs from a number of studies in the literature (Table 4, Top). In patients with nonfunctional PETs, treatment options for the PET itself have to be considered because these are malignant in a percentage of patients (13%) (Table 3, bottom). Patients with functional PETs require two aspects of treatment: the hormone excess state must be treated and because a proportion of these tumors are also malignant (11–50% with the different PETs) (Table 3, bottom), in addition, treatment needs to be considered for the PET itself [1–3,23,105].

In the past the main cause of death was the hormone excess states including renal failure due to uncontrolled hyperparathyroidism and the inability to control the PET hormone excess-state in patients with functional PETs [72,106–110] (Table 4, bottom). This has largely changed over the last 20 years with effects of uncontrolled hyperparathyroidism, advanced pituitary disease or failure to adequately treat the PET hormone excess state becoming an uncommon cause of death [25,100,104,105,110–112]. This change has occurred because of increased use of careful serial assessments of parathyroid function, the use of appropriate surgical parathyroid resections (i.e. 3.5–4 gland resections), recognition with effective medical and surgical treatments of the pituitary disease, the increased diagnosis and effective surgical treatment of insulinomas and the development of effective medical treatments for the hormone excess states [88,113–115]. The latter includes particularly the development of effective drugs for treatment of the gastric acid hypersecretion seen in ZES and the development of long-acting somatostatin analogues (lanreotide, octreotide), which control the symptoms of most of the other functional PETs [3,116]. This was a particularly important advance in the case of ZES, which used to be the leading cause of MEN1 deaths (Table 4, bottom), because of its occurrence in more than one-half of MEN1 patients in most series (Table 2) and because of its high morbidity and mortality from untreated severe gastric acid hypersecretion [76,117–119] that occurs in most ZES patients [68,85,120]. The result of these changes is that increasingly the natural history of the PET is becoming the main determining factor for survival (Table 4, bottom) [23,105,109, 110]. A second important determinant of survival in subset of patients (3–8%) recently recognized is the development of thymic carcinoid tumors, especially in males (i.e. 89–100%

MEN1/thymic carcinoids in males), which occur later in the disease course usually after the onset of PETs or hyperparathyroidism (mean age diagnosis-50 years)(Fig. 1B) and which are particularly aggressive [68,109,121–123].

The current natural history, with more effective treatments as outline above, of MEN1 patients with or without PETs (except for those with MEN1/ZES, discussed in latter section) is not well defined by prospective studies. Patients with MEN1 are reported to have an increased incidence of premature death (mean age –46–54 years) with 28–100% of the patients dying from a MEN1-related cause and with PETs accounting for 19–100% of the MEN1 related deaths (Table 4, bottom) [104,109,110]. The overall 10 and 20 year survival from diagnosis for all MEN1 patients is 85 % and 64%% [100,110] and patients with PETs have a decreased survival (Fig. 6, panel 1A) [72,81,109,110]. The mean age at death in patients with NF-PETs is 43 [81] and with MEN1 with or without a PET is 47 years old [25]. The 5 and 10 year survival for MEN1 patients with any PET from a number of series is 82% [range 79–100%] and 75%, respectively (Table 4, top)(Fig. 6, panel 1A)[81,100,104,110,124,125]. In most [96,124,126] but not all [127] studies the survival rate of MEN1 patients with PETs is better than that of patients with sporadic PETs. At present the basis for this difference is not clear.

The extent of PET in MEN1 patients without gastrinomas in the literature is generally poorly studied. This has occurred because it has rarely been examined prospectively, all patients do not routinely undergo abdominal surgical exploration, and/or sensitive imaging modalities such positron emission tomography or somatostatin receptor scintigraphy (SRS) with SPECT imaging and CT/MRI fusing imaging, which might allow localization of small primaries and metastases, is not routinely available or used. In 8 different studies of MEN1 patients (Table 3, top) $52 \pm 12\%$ [range-38–70%] had a PET identified by conventional imaging studies (CT, MRI, Ultrasound) and $12 \pm 6\%$ [range 5.1–20%] had liver metastases detected. When the frequency of metastatic disease to the liver is compared in MEN1 patients with various functional or nonfunctional PETs, to the frequency seen in patients with sporadic PETs, in general it is reduced by more than one-half (Table 3, bottom panel). Specifically, the frequency of liver metastases in MEN1 patients with gastrinomas compared to patients with sporadic gastrinomas is reduced by 62%, with VIPomas or glucagonomas by almost 50%, with somatostatinomas by 30% and with nonfunctional PETs by 80% (Table 3, bottom panel). In contrast, the frequency of liver metastases in patients with insulinomas with MEN1 is not lower than that seen in series of patients with sporadic insulinomas, and may even be higher (i.e. 14% vs. 5%, Table 3, lower panel). At exploratory laparotomy in MEN1 patients with PETs without ZES the frequency of lymph node metastases is 16–33% [81,128,129].

Clinical prognostic factors for the growth of the PET/survival or development of liver metastases in MEN1 include (Table 5, top; Fig. 6, panel 3B): age>35 yrs at PET diagnosis [100,130]; history of a first degree relative with a PET malignancy [130]; presence of a nonfunctional PET or gastrinoma (Fig. 6, panel 1A) [81,100,130]; presence of a large PET (i.e. > 3 cm) in some studies [78,81], but not others [24] (Fig. 6, panel 3A); presence of liver metastases [81,100] (Fig. 6, panel 3B); or history of an unsuccessful curative resection [81,100]. Some [64,100] but not other [129] molecular studies have reported mutations of exon 2, 9 or 10 (truncating/frameshift) [64] or exon 2 [100] are associated with a more aggressive tumors and decreased survival. These results in MEN1 patients generally show similarities to the results of prognostic studies in sporadic PETs (Fig. 6, panel 2A), which have been much more extensively studied [7,12,124,131–135]. In sporadic PETs with multivariate analysis the presence of liver metastases (initially, their development, extent) has been the most important predictor of survival (p<0.00001) and to a lesser extent, poor differentiation and incomplete resection. In general, the presence of lymph node metastases has had minimal, if any, effect on survival in most studies [7,12,124,131–137], but not all [124,132,135]. In most studies the presence of liver metastases is associated with larger primary tumor size (>2–3 cm) [7,12,124,131–134,136], but

not all [124]. Other important predictors in a number of studies are the presence of distant metastases, incomplete tumor resections, or the presence of a nonfunctional PET rather than a functional PET [7,125,131,132,132,134,138] (Table 5, top). In contrast to MEN1 PETs, sporadic PETs have been well-studied for histological predictors of aggressive behavior (i.e. high proliferative index [Ki67, PCNA] or mitotic index, vascular/neural/capsular invasion, nuclear pleomorphism) [7,131–135,139] and numerous molecular studies have identified predictive factors (p53 over-expression, LOH or chromosomal losses at certain loci [1,3p, 3q, 6q] or chromosomal gains [17p, 17q, 20q], presence of aneuploidy, and altered expression of a number of genes detected by gene array expression studies [11,12,62,131,135,140–143]. In one study comparing sporadic PETs to normal islets, 667 genes were up-regulated [particularly BIN1, SERPINA10, LCK, BST2] and 223 genes down-regulated [143]. Comparison of metastatic to primary tumors showed no gene expression differences in one study [143], whereas in a second study [144] 65 genes were found overexpressed in metastatic PETs compared to well-differentiated non-metastatic PETs and 57 genes under-expressed. A number of different classes of genes were altered including growth factor-related genes (IGFBP1, IGFBP3, MET), developmental factors (TBX3, MEIS2), cytoskeletal factors (B1 tubulin, ACTN2), intracellular signaling and methyltransferases (DYRK1A, PK1B, AK2, MGMT, GAMT) and DNA repair/regulatory molecules (CHEK1, ZNF198) [144].

II.D.4. PETs in MEN1: Imaging—Numerous studies in both MEN1 patients and patients with sporadic PETs demonstrate that the relative order of sensitivity of conventional imaging studies for localizing a PET is angiography>CT, MRI> transabdominal ultrasound (US)[23,145–147]. These studies show sensitivity is in large part dependent on primary tumor size, with detection rates of <20–30% of PETs<1 cm in diameter, 30–50% 1–3 cm and >70% for >3 cm [146,147]. Therefore conventional imaging studies will miss most small PETs (<1 cm) and will not detect most duodenal gastrinomas [23,95,148–153] which are very frequently <0.5cm (Fig. 4A,B) [94,95,150]. Greater than 80% of PETs both in patients with or without MEN1 over-express somatostatin receptors (sst 2,3,5) that bind the synthetic somatostatin analogues, lanreotide or octreotide with high affinity and this can be used to image these tumors (using [111]Indium –labeled analogues) (Fig. 5A,B), to deliver somatostatin receptor-mediated radiotherapy (using [111]Indium, [90]Yttrium, [177]Lutetium-labeled analogues) and to treat the hormone excess state [146,154–160]. Somatostatin receptor scintigraphy (SRS) has greater sensitivity than conventional imaging studies in most reports [23,146,148,149,155,156,159], however, its sensitivity is also size dependent and it will miss 50% of small PETs/duodenal gastrinomas < 1 cm in diameter [149]. SRS is also the most sensitive modality for detection of liver metastases [23,156,161–163], the detection of distant metastases (bone, distant lymph nodes, soft tissues) [164,165] and has the advantage of allowing whole body imaging at one time. SRS is equally sensitive in all PETs except for insulinomas, which because of the low density of somatostatin receptors that bind ^{111}In penetreotide with high affinity, SRS is generally positive in <50% of the cases [155,157,166,167]. The presence of MEN1 can introduce an added element of confusion in the interpretation of the SRS for PET localization in these patients. Increased densities of somatostatin receptors not only occur on PETs, but they can also occur on other MEN1 related neuroendocrine tumors (carcinoids [gastric, thymic, bronchial] (Fig. 5A), CNS tumors, thyroid tumors)[122,155,157,168–171], as well as other neoplasms (breast, prostate, lymphomas) and in other diseases (granulomatous disease, inflammatory disorders, thyroid disease) [155,157,168]. These can lead to false positive SRS's for PETs, as well as various procedural aspects (isotope spill, retained isotope in gallbladder or intestine) or overexpression by normal tissues such as lymphocytes in injury (wound infection, abscess) [146,168]. In one prospective study [168] of patients with PETs primarily without MEN1, 12% of all SRSs were false positive, however with proper clinical correlation this was reduced to 3%. Therefore in MEN1 patients it is important to consider that the uptake in the upper abdomen or at a distant site suggesting distant metastases in a patient with a PET

could be another MEN1 related tumor (especially gastric carcinoid) (Fig. 5A), or another false positive cause. An example of such a patient is shown in Figure 4 (panel A) who had MEN1/ ZES with SRS showing possible tumor localization in four areas in the upper abdomen of which 3 were due to pancreatic PETs, but the fourth was due to gastric carcinoid.

Increasingly endoscopic ultrasound (EUS) is being used to evaluate the number, size, location and presence of PETs in patients with MEN1 [160,172–174]. EUS shows excellent sensitivity for detection of intra-pancreatic tumors (82–100%), however it is less useful for duodenal gastrinomas. which it frequently misses (>50% in most studies) [131,152,172,173,175–177]. In numerous studies EUS has greater sensitivity than SRS or conventional imaging studies for localizing primary PETs in patients with MEN1 [160,173,174]. EUS is able to detect smaller PETs than seen on SRS or conventional imaging studies in MEN1 patients, with a mean size of 0.6–1.1 cm [range 0.4–4 cm] in different studies [172,173,176], however in one study it missed a number of small PETs with a mean diameter of 3.2 mm (rang 2–6 mm) [173]. Furthermore, EUS was able to detect multiple PETs (mean 3 [range 1–9]) in 55–100% of MEN1 patients even when asymptomatic [160,172,176,176,178,179]. In various studies EUS detected PETs in 54–85% of MEN1 patients with non-functional PETs [172,176]. Recent studies show EUS also has excellent specificity and reproducibility with a mean coefficient of variation with serial measurements of $5.5 \pm 4.6\%$ for PETs <5 mm in diameter and $4.4 \pm 2.6\%$ for PETs > 5 mm in diameter [160,179]. This latter point is particularly important in MEN1 patients, because it has been proposed that serial EUS studies can be used to assess the growth of small PETs and determine when intervention should be considered [160,172,174,176,179]. This latter point will be discussed in more detail in the later sections [Sections II.E.3.b and II.F.2.c] dealing with the surgical treatment of small PETs in MEN1 patients.

Recently two other imaging approaches are being increasingly used which will likely play an important role in the future management of PETs in patients with MEN1: the use of positron emission tomographic scanning [180–183] and the use of image fusion or hybrid techniques that allow the SRS image to be fused with a CT or MRI image [184,185]. One of the main limitations of SRS is that only the anatomical area of the lesion is defined (i.e. pancreatic head area) and it does not allow clear definition of the exact anatomical location of the lesion seen (i.e. gastrinoma in pancreas or duodenal wall). The recent introduction of dual gamma camera/CT imaging systems allows the fusion of the CT result with the SRS result (SPECT/CT hybrid systems) allowing 3-dimensional localization that can define the exact location of the lesion seen [184,185]. Preliminary results suggest this methodology many alter the clinical approach [184,185] and affect the management of the PET in up to 64% of patients [184]. Positron emission tomographic scanning with ^{18}F-labelled deoxyglucose (FDG), which is widely used in various common tumors, does not work well for PET imaging with the exception of tumors with high proliferative activity and low differentiation, which are the minority [186,187]. Recent studies using ^{11}C-5-HTP, ^{11}C-labeled L-DOPA, ^{18}F-labeled L-DOPA or ^{68}Ga-DOTA-Tyr[3]-octreotide demonstrate increased sensitivity over SRS or conventional imaging studies for detecting both the primary PET site and the presence of liver metastases or distant metastases [180,181,183]. In the future both the SRS/CT hybrid scanning and positron emission tomography using these radiolabeled analogues, and particularly ^{68}Ga labelled somatostatin analogues which can be prepared using a reactor instead of requiring a cyclotron, will likely play an important role in the management of these patients.

II.E. Specific PET syndromes in MEN1

II.E.1. General: Specific PET syndromes—Three PET syndromes (gastrinomas, NF-PETs, insulinomas) present a number of special problems or issues either because of their frequency, insights provided or unique management issues and will be considered separately

in the next section. The medical and surgical treatment of all MEN1-related PETs as well as controversies in these treatments will be considered in separate latter sections.

II.E.2. Gastrinomas

II.E.2.a Gastrinomas in MEN1: General: Gastrinomas are PETs, which ectopically secrete gastrin-causing hypergastrinemia, which results in the Zollinger-Ellison syndrome (ZES), which is due to the gastric acid hypersecretion resulting in refractory peptic ulcer disease [68, 79,85,113,120]. In addition, the hypergastrinemia has trophic effects on the gastric mucosa resulting in increased parietal cell mass and proliferation of gastric enterochromaffin-like cells (ECL cells), which can result in gastric carcinoid tumors, a proportion (20–30%) of which are malignant [170,188–192]. Gastrinomas are the most common functional PET occurring in MEN1 patients and occur 3 times as frequent as insulinomas (54% vs. 18%) (Table 2) which is the reverse of their relative frequency in sporadic cases, where insulinomas are generally reported more frequently than gastrinomas [3,113]. One peculiarity of the gastrinoma in MEN1 patients compared to sporadic cases, is the presence of the hypercalcemia due to the concomitant hyperparathyroidism that is frequently present in the MEN1 patients (Fig. 1, 2; Table 2), can influence the secretory behavior of the gastrinoma [88,115,193]. After a successful parathyroidectomy in MEN1 patients with ZES, fasting gastrin levels and gastric acid secretory rates frequently fall, sometimes to normal ranges [88,115,193], and the secretin provocative test used to diagnose ZES [194] can become negative [193]; making it difficult to diagnose the gastrinoma post parathyroidectomy in some patients. Whether correction of the hyperparathyroidism affects the gastrinoma growth in MEN1 patients is unknown.

II.E.2.b. Gastrinomas in MEN1: Pathology: MEN1 is the cause of ZES in 20–25% of all ZES patients in most series [range 10–48%][85,87,113] and gastrinomas are the most common, functional tumor in MEN1 patients, occurring in slightly more than one-half of the patients (Table 2). The gastrinomas are primarily in the duodenum (65–100% in most series), are almost invariably multiple, are usually small (usually < 1 cm), and are most common in the first and second parts of the duodenum [23,86,95,105,195–199] (Fig. 4A–C). Recent studies in patients with sporadic gastrinomas demonstrate these tumors show a clear proximal distal gradient of occurrence in the duodenum with a frequency of: 1st part of the duodenum (D1) (56% of all sporadic duodenal gastrinomas)>D2 (31%) >D3>(7%), (D4 (6%)[150,200–203]. Recent data suggest a similar proximal distal localization gradient occurs for duodenal gastrinomas in MEN1 patients [199]. The duodenal gastrinomas are primarily submucosal in location, 34–85% are associated with lymph node metastases, whereas liver metastases are uncommon and only occur in 2–14 % of all patients (Table 2, bottom) at some time in the disease course and in 7% at diagnosis [23,80,86,95,105,195,198,203,204].

II.E.2.c. Gastrinomas in MEN1: Clinical: The mean age of onset of ZES in MEN1 patients is 33–39 years [80,85], and in one study was 10 years earlier than seen in patients with sporadic ZES (i.e., 33.2 vs.43.5 yrs)[85] (Fig. 3B, C). The presenting clinical symptoms of ZES in MEN1 patients do not differ generally from those in patients with sporadic ZES with pain, diarrhea (66–76%)>heartburn> nausea/vomiting> weight loss [85]. Similar to sporadic ZES, the vast majority have prominent gastric folds on endoscopy (95%), peptic ulcer disease (PUD) occurs in the majority (62%), only a minority develop PUD complications [perforation, bleeding (7–12%)], however they differ from sporadic ZES in manifestations of hyperparathyroidism (nephrolithiases-47% vs. 4%), or history of endocrinopathies (81% vs. 14%) [85]. The delay in diagnosis of ZES in MEN1 patients is not different from that for sporadic disease (5.5 years) [85,205]. Recently [206] MEN1/ZES patients were shown to have a 3-fold higher risk of severe esophageal reflux disease (GERD), 5-fold higher for development of the pre-malignant condition, Barrett's esophagus, and 8-fold higher for developing esophageal dysplasia. A detailed analysis [206] suggested the earlier onset of ZES in MEN1 patients and inadequate as

well as delayed treatment of the GERD, which can be more difficult to treat in MEN1/ZES patients than sporadic cases [113,207–209], were important contributing factors.

II.E.2.d. Gastrinomas in MEN1: Diagnosis of ZES: The diagnosis of ZES in MEN1 patients is similar to that in sporadic disease [210] in that it requires the demonstration of hypergastrinemia in the presence of hyperchlorhydria combined with other clinical or laboratory findings [5,87,210]. Similar to sporadic ZES, 97–99% of MEN1/ZES patients have elevated fasting serum gastrin (FSG) levels with a median increase of 6-fold [205], so this is usually the initial determination [87,205,210]. An exception to this is post successful parathyroidectomy, in MEN1/ZES patients, the FSG may return to normal, as well as the basal acid output and the secretin test becomes negative [88,88,115,193] masking the diagnosis of gastrinoma. No level of FSG alone is diagnostic of ZES because achlorhydria, presence of antral G cell hyperplasia, other diseases or the presence of H. pylori can all increase FSG [5,113,210–213]. Similar to sporadic ZES, MEN1/ZES patients have marked basal acid hypersecretion [120] (mean increase -4 fold, 37.5 mEq/hr), however acid secretion rates are rarely measured, so this assessment is uncommonly used in the diagnosis. Recent studies suggest the following criteria for diagnosis of ZES in MEN1 patients; if the FSG≥10fold increased (40% of ZES) and the gastric pH is ≤2 (occurs 100% ZES patients), the diagnosis is established (after excluding retained antrum syndrome by history) [5,87,120,194,205,210,214]; if the FSG is ≤10 fold increased and gastric pH≤2, then a secretin test (≥120 pg/ml increase is positive [194]) and basal acid output (positive >15 mEq/hr) should be done [5,87,120,194,205,210]. Using the above criteria for the secretin provocative test 94% of MEN patients will have a positive test with 100% specificity [194]. Besides confusion post parathyroidectomy, as discussed above, the use of potent acid suppressant drugs such as proton pump inhibitors (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole) (PPIs) can confound the diagnosis, because they can cause hypergastrinemia secondary to achlorhydria/hypochlorhydria, and thus they need to be carefully stopped for at least a week to allow assessment [5,210,212].

II.E.2.e. Gastrinomas in MEN1: natural history and prognostic factors (Table 5): The natural history/prognostic factors for gastrinomas are considered separately from the other PETs, for a number of reasons. First, they are the most frequent malignant tumor causing clinical problems in MEN1 patients (Table 2). Second, they arise from the duodenum not the pancreas as the other PETs. Third, there have been extensive studies (clinical, laboratory, molecular) of the natural history/prognosis in sporadic ZES [7,12,96,131,215–217], which is also caused by primarily duodenal gastrinomas (>60% recent studies) [86,87,93,95,200], that can be used for comparison. Overall survival in MEN1/ZES in is 90–96% at 5 yrs, 75–95% at 10 years and 58–90% at 20 years. [80,96,105,126,218]. In the NIH series where no patient died of acid-related conditions the survival in MEN1/ZES patients was 5 years-96%, 10 years 96% and 20 years (90%) [23,96,105].

Prognostic factors for MEN1/ZES include the presence of liver metastases (p=0.0012) and on univariate analysis the presence of male gender, the development of liver metastases (p=0.012), young age of onset or diagnosis (i.e. <30 years) (p=0.03) or the presence of a large primary tumor (>3 cm) (Table 5, bottom). These results are similar to studies with sporadic ZES where the presence, development or extent of liver metastases (Fig. 6, panel 2A) are the most important predictors of survival [96,105,113,157,215,219]. In addition numerous predictors of aggressive tumor growth and/or the development liver metastases or survival have been described for sporadic gastrinomas including clinical factors [female gender, short disease duration at diagnosis of ZES, development of bone metastases and/or ectopic Cushing's syndrome, control of acid hypersecretion]; laboratory [marked increase gastrin]; histopathological [low % nontetraploid aneuploid or high stem-line aneuploidy, nonduodenal location, tumor size>3 cm, rapid tumor growth], and molecular [high HER2/neu expression,

high 1q LOH, high EGF receptor expression] [96,105,131,164,215,216,220–229]. In three studies the presence of lymph node metastases had no effect on survival [96,229,230], in a second study [215] their presence had a weak effect on survival (p=0.03) and in a third study the 20 year survival was 83% in patients with lymph node metastases only [231]. A particular important predictor for development of liver metastases in patients with sporadic ZES is the location of the primary gastrinoma [96,204,215,229]. Duodenal and pancreatic gastrinomas showed equal rates of metastases to the lymph nodes (47–48%) [96], however, liver metastases occurred much more frequently in pancreatic gastrinomas than duodenal gastrinomas (47% vs. 5%, p<0.00001, [96]. In general pancreatic gastrinomas are large (95% > 3 cm) [96] while duodenal gastrinomas are small (80%<1cm) [96] and it was unclear [96] whether the gastrinoma size or location was the critical determinant of the high metastatic rate to the liver. It is also unclear whether gastrinomas in the duodenum and pancreas in MEN1/ZES patients behave in a similar fashion to the sporadic cases, because there are too few pancreatic gastrinomas in MEN1/ZES described to determine the behavior pattern.

In some studies ZES in MEN1 patients was associated with a significantly lower metastatic rate to the liver compared to the sporadic form of ZES (6% vs. 22%) [96], whereas in others the liver metastatic rate did not differ [230]. However during follow-up over a 9 year period both groups of ZES had the same rate of development of metastatic liver disease ((9%-MEN1/ZES and 5% for sporadic ZES) [96].

Prospective studies of both sporadic ZES and MEN1/ZES (Fig. 6, panel 1B) provide evidence for two forms of the disease: one characterized by aggressive tumor growth and the other by either no tumor growth or nonaggressive growth [96,105,215,216,232]. With MEN1/ZES 14% of patients have tumors demonstrating aggressive growth) Fig. 6, panel 2A) [105], whereas with sporadic ZES in 24% aggressive growth is seen [96,215].

II.E.3. Nonfunctional PETs (NF-PETs) in MEN1

II.E.3.a NF-PETs in MEN1: General: NF-PETs are PETs, which cause no hormonal symptoms. Immunocytochemically almost all synthesize multiple peptides and many secrete pancreatic polypeptide (50–70%) (PPomas), chromogranin A (44%) [233,234] and other hormones which don't cause symptoms [235–238]. NF-PETs occur histologically in 80–100% of MEN1 pancreases as multiple, microadenomas (<0.5 cm) [89–91] with 55–82% of patients also having macroadenomas (>1 cm) [90,91]. These pancreatic microadenomas on immunocytochemistry (IHC) show multiple hormone production in 38–100% with neuron-specific enolase IHC seen in 100%, PP (20–75%), glucagon (24–52%), insulin (15–42%), somatostatin (3–58%), gastrin (4–33%) and <1–8% (VIP, neurotensin) [89–92]. As is apparent the term NF-PET is a misnomer in that even though these PETs usually produce by IHC multiple peptides, because no clinical symptoms of hormone excess occur, they are clinically NF-PETs. An additional unusual feature is that even though these adenomas are found histologically in almost every MEN1 patient, in series reporting the presence of NF-PETs detected by conventional imaging studies they are present in only 1.1% [74], 4% [14] (Fig. 1) and 18% [81] of all the MEN1 patients. EUS has increased sensitivity and is able to detect multiple PETs (mean 3 [range 1–9]) in 55–100% of MEN1 patients even when asymptomatic [160,172, 176,176,178,179].

II.E.3.b NF-PETs in MEN1: clinical/pathology: In the GTE series of 579 MEN1 patients, NF-PETs were the most frequent PET, occurring in 3% of patient's age 20 yrs, 34% aged 50 yrs and 53% of patients aged 80 yrs [81]. NF-PETs are diagnosed at an average age of 36.2 years with and average time from MEN1 diagnosis to NF-PET diagnosis of 5 years [range 0–33] [81]. Most were primarily discovered by imaging studies with symptoms occurring in only 0–13% (Table 2) [81]. In various series only 9–19% of the NF-PETs were associated with liver

metastases (Table 3, bottom), 14–33% with lymph node metastases [63,81] and in the GTE series of 108 NF-PETs/MEN1, there was a correlation of primary size (p<0.01) with the frequency of liver metastases. Specifically, only 4% of patients with NF-PETs ≤1 cm in diameter had liver metastases, 10% with 1.1–2 cm, 18% with 2.1–3 cm and 43% with NF-PETs> 3cm [81]. Patients with NF-PETs with MEN1 had a similar survival curve to patients with gastrinomas with MEN1 and each had a significantly shorter life expectancy than MEN1 patients with no PET (Fig. 6, panel 1A) [81]. However, MEN1 patients with NF-PETs ≤2 cm did not have a decreased survival (Fig. 6, panel 3A) [128] so the decrease in overall survival of NF-PET patients was due to decreased survival occurring in the patients with larger NF-PETs [81,128]. Biochemical screening by some using a standardized meal test [236,239], but not others [235, 240], as well as the routine use of EUS [160,172,174,175,178], has allowed the detection of NF-PETs in patients with negative conventional imaging modalities and at an earlier age, often in the third decade.

Recently, using serial imaging studies (especially EUS), the natural history of NF-PETs in MEN1 patients has been examined in a number of studies [174,176,241]. In various studies [128,241] 8% of the NF-PETs and in 7% [241] and 38% [176] of the patients with a NF-PET, there was an increased in tumor size over a 4–7 year follow-up. In one study [241] none of the PETs ≤2cm in size increased in size over a 6 year follow-up, whereas in a second study [174] of 20 MEN1 patients with NF-PETs<1.5 cm followed over a 20 month period, the largest tumor increased 1.3%/mo with an annual tumor incidence rate of 0.62 new tumor/patient/year. Over a 4–7 year period 38–100% of the patients developed new NF-PETs and in some patients the growth was rapid [174,176,241]. The conclusion of a number of these studies is that small NF-PETs appear to generally show indolent growth, however, in some patients faster growing tumors occur [174,241], and thus regular follow-up EUS's were recommended with the frequency depending of the NF-PET's size. The results above demonstrate that although 55–82% of MEN1 patients have macroadenomas histologically, in most series they are not detected by routine conventional imaging studies, they are rarely symptomatic, however with EUS they can be detected in most patients. At present the treatment of NF-PETs, especially if small (≤ 2cm in diameter) is controversial [63,64,64,81,100,128,174,176,198,239,241,242] and will be discussed in the general surgery section below.

II.E.4. Insulinomas in MEN1

II.E.4.a Insulinomas in MEN1: General/Clinical/pathology: Insulinomas are PETs secreting insulin, which results in hypoglycemic symptoms [6,243]. Insulinomas occur in slightly less that one-fifth of MEN1 patients (18%, Table 2, bottom) and MEN1 is an uncommon cause of insulinoma in most large series of insulinomas patients (sporadic and MEN1) accounting for only 4% [77]. Insulinomas are diagnosed at a mean age of 36.4 yrs in MEN1 patients in one study [82], at 24 yrs old in a second study [244] and at 34 yrs in a review of 53 cases in the literature [245]. In 14–29.5% of patients the insulinoma was the initial revelation of MEN1 [244,245] and the insulinoma was associated with another functional tumor in 34% of patients (ZES>glucagonoma≫VIPoma) in one study [82], in 10% in a second study (ZES, glucagonoma-1 case each) [244] and in 42% in a third study (all ZES) [245].

Insulinomas in MEN1 patients, similar to patients with sporadic insulinomas (Table 3, bottom) have a low rate of malignancy, with 14% of patients showing liver metastases in the large GTE study of 44 MEN1 insulinoma patients [82], 5% (1/19 patients) in a review of the Mayo clinic cases [244], 0% (0/7 and 0/10, patients) in three studies [24,64,197] and in 20% of 43 cases in the literature [245]. In two series [24,244] 10% of the insulinoma patients had lymph node metastases, whereas in another study (0%) (0/6 patients [64] had lymph node metastases. In MEN1, in contrast to sporadic cases [6,77,243], in most studies the insulinomas are reported to be multiple (76–89%) [244,245] and they are usually small (mean size-0.6 cm [range 0.2–1.6 cm]) [244]. The

insulinomas are relatively evenly distributed throughout the pancreas similar to their localization in sporadic disease [6,77,243–245].

The importance of tumor localization, medical and surgical treatment will be consider in the following sections dealing with treatment of PETs in MEN1.

II.F. Treatment of PETs in MEN1

II.F.1. Treatment of PETs: General

In functional PETS the hormone excess-state needs to be diagnosed and controlled acutely and long-term until possible tumor resection. In both functional and NF-PETs treatment directed at the PET per se needs to be considered, because a percentage of these tumors are malignant (Table 3, bottom) and they are an increasingly prominent cause of death in these patients (Table 4, bottom; Fig. 6, panels 1A, 1B, 3B). Furthermore, in the case of some functional PETs (insulinomas, VIPomas, glucagonomas, somatostatinoma), surgical resection has a high probability of cure [64,78,82,102,197,244–248].

PETs in MEN1 present special diagnostic and treatment problems because of their invariable multiplicity. This leads to the need to determine which of the multiple PETs that might be present is the functional PET(s) responsible for the functional syndrome so it can be removed at surgery. Furthermore, the multiplicity of the PETs in the pancreas means that cure of all NF-PETs is not possible without total pancreatectomy. Furthermore, the invariable multiplicity of duodenal gastrinomas is one of the main contributors to the inability to cure patients with MEN1/ZES patients long-term (Fig. 6, panel 2A) [23,64,94,95,131,197,199,249] without aggressive resections such as a Whipple procedure (Table 6).

II.F.2. Treatment of PETs hormone-excess state: Medical

II.F.2.a Gastrinomas: In ZES/MEN1 patients in older studies (Table 4, bottom), the complications of the severe peptic ulcer disease due to the unchecked gastric acid hypersecretion, were the main cause of death and total gastrectomy was the only proven effective treatment [117–119]. With the development of potent acid suppressant drugs such as the histamine H_2 receptor antagonists in the 1970 (cimetidine, ranitidine and later others) and more recently inhibitors of the H+K+ ATPase (or proton pump inhibitors [PPIs])(omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole), the acid secretion can now be controlled in almost every patient by once or twice a day dosing [5,116,207,209,250–253]. Acute control of the gastric hypersecretion is now simplified with the availability of parental PPIs which can be given every 4–8 hours and which have largely replaced the parenteral histamine H_2 receptor antagonists, which were effective, but high doses administered by continuous infusion were required [254–259]. Oral PPIs are safe and effective long-term in MEN1/ZES patients and tachyphylaxis does not develop, however the hypercalcemia due to the hyperparathyroidism makes the patients less sensitive to antisecretory drugs [88,115,193], with the result higher doses with more frequent PPI dosing is required, both initially and long -term in MEN1/ZES patients than in patients with sporadic ZES [207,209,250].

II.F.2.a Other PETs-treatment of hormone excess-state: Insulinomas in MEN1 patients, similar to sporadic disease, are almost invariably treated surgically, except for the small percentage with metastatic disease to the liver (Table 3, bottom) [6,243,260]. Initially, to control the hypoglycemia prior to surgery, diazoxide combined with frequent feedings is generally used (50–60% respond)[6,243,260] and some use long-acting somatostatin analogues such as octreotide or lanreotide [6,243,260]. The somatostatin analogues need to be used with care, because in some cases they may make the hypoglycemia worse by suppressing counter-regulatory hormones (glucagon, etc) and also some insulinomas have very low densities of

sst$_{2, 3,5}$ somatostatin receptors that bind octreotide/lanreotide with high affinity and thus these agents are effective in only 40–50% of patients[6,155,157,166,167,243,260–262].

With all other functional PETs in MEN1 (VIPomas, glucagonomas, GRFomas, somatostatinomas), the drugs of choice for control of the hormone excess-state prior to surgery or in patients who are not cured surgically are long acting somatostatin analogues (octreotide/lanreotide) [1,263,264]. For long-term treatment, depot forms of these two drugs are now increasingly used which require once a month dosing (octreotide-LAR, lanreotide autogel)[1,263,264].

II.F.2. Treatment of PETs: Surgical

II.F.2.a General: controversies: Whereas there is no controversy in the need for surgical treatment of a PET causing direct tumor -related symptoms or for a number of functional PETs in MEN1 (insulinoma, glucagonoma, vipoma, somatostatinoma, GRFoma) which can frequently be cured [64,78,82,102,197,244–248], the role of surgery in patients with some familial MEN1 pancreatic and duodenal neuroendocrine tumor (NET) syndromes, especially with small NF-PETs (<2 cm) or gastrinomas is controversial[63,64,64,81,83,95,100,128,131, 174,176,198,239,241,242,246,265,266]. The controversy not only involves the timing of surgery, if any, but also the type of operation that should be routinely performed. This controversy has resulted in some groups recommending surgery not be routinely done in patients with MEN1/ZES or NF-PETs without direct tumor symptoms (pain, etc) [267,268], others recommend surgery only be performed if PETs are found of a certain size on preoperative imaging studies (>2 or >3 cm)[23,94,95,128,218], whereas still others recommend that all such MEN1 patients with a PET undergo surgical exploration [269,270]. The controversy on the type of operation involves how aggressive surgery should be for gastrinomas in the pancreatic head area and also whether routine distal pancreatectomy should be performed at the time of surgery in any MEN1 patient, to reduce the amount of pancreatic tissue that could potentially develop new PETs in the future [23,64,95,271,272]. These controversies have occurred because the hormone-excess state in MEN1/ZES/NF-PET patients can be either controlled or requires no treatment; the tumors are invariably multiple and frequently small, making cure unlikely without aggressive surgery; most patients with small gastrinomas/NF-PETs have a 15 year life-expectancy > 90% (Fig. 1B, 3A, 3B)[23,83,96,105,128] and because the natural history of these PETs is to a large extent unknown, as well as their importance as a cause of death in MEN1 patients. Recent studies show that malignant neuroendocrine tumors (NETs) are becoming the main determinant of long-term survival in MEN1 patients and a prominent role is played by malignant PETs (Table 4, bottom). Because numerous studies show a subset of these patients develop aggressive PETs or PETs with rapid growth [23,25,105,109,128,130, 273,274] and because of the increasing importance of PETs as a determinant of survival (Table 4), almost all investigators agree surgical treatment is indicated for some patients with MEN1/ZES or NF-PETs, but there is no agreement on which group of these patients.

The role of surgery is becoming more clearly defined, in some cases, as we have better understanding of surgical outcomes and the natural history of neuroendocrine tumors in the familial setting. For example, in patients with ZES/MEN1 controversies about the role of surgery has clearly changed with the development of new drugs to treat gastric acid hypersecretion. Initially surgery for ZES in MEN-1 patients was designed to control the severe peptic ulcer disease and total gastrectomy was required, as lesser procedures resulted in recurrent symptoms [76,117,119]. Initially, the gastrinomas were seldom found at surgery because surgeons focused primarily on the pancreas [113,118,196,275,276]. Now it is clear that the most MEN1 gastrinomas (>80%) are in the duodenum and not the pancreas [86,93,94, 248]. This inability to find tumor in the early operations, further supported the use of total gastrectomy. However, since PPIs have been developed to effectively control the acid

hypersecretion without symptoms or complications in all patients with ZES, surgery can now focus on removal of the gastrinoma for potential cure of ZES and control of the tumoral process. This is still controversial, because recent studies show that MEN1 ZES patients are seldom cured by simple resection of duodenal tumor (Table 6, top panel).

However, the role of surgery is becoming less well defined in other cases, such as with NF-PETs in MEN1 patients or the role of when patients should be re-operated. With the increased routine use of sensitive imaging modalities in MEN1 patients, especially with endoscopic ultrasound, the presence and location of NF-PETs is being better defined and the detection rate is approaching the 80% penetrance seen in some autopsy studies [160,172,176,176,178,179]. This has raised a new set of controversies about whether these small asymptomatic PETs should be routinely removed or how they should be managed [128,160,172,176,176,178,179,273]. With an increasing numbers of MEN1 patients with PETs undergoing initial surgery that does not result in cure (i.e. especially patients with gastrinomas, NF-PETs), there is an increasing question of when re-operation for a PET is indicated [277–279]. At present there are no studies specifically on MEN1 patients with PETs that provide enough information on this point to address this question, whose importance will increase in the future as these patients continue to live longer.. A similar question exists in patients with sporadic PETs (especially gastrinomas where long-term up >50% are not cured) [277–279], however the limited information is unlikely to be applicable to MEN1 patients with PETs because of the difference in multiplicity of tumors, different PET natural history and differ surgical cure rates with PETs (especially gastrinomas/NF-PETs). Because the controversies and role of surgery differ in the different PETs in MEN1 patients, they will be considered briefly, separately below.

II.F.2.b Surgery for localized gastrinomas: Since 1990 it is appreciated that the majority (>80%) of gastrinomas in patients with MEN-1/ZES arise in the duodenum [86,87,276]. Prior to 1990 this lack of knowledge of the location of the primary gastrinoma very likely contributed to the low cure rate in MEN1/ZES patients (Table 6, top) and the controversy at that time about the value of routine surgical exploration in MEN1/ZES. With this increased appreciation of the duodenal location of the gastrinomas and the routine use of duodenotomy at the time of surgery, which increases the number of duodenal tumors found and cure-rate in sporadic ZES patients [95,150,150,153,276,280–282], it was hoped that a similar increase in cure rate would be seen in MEN1/ZES patients. However, this was not the case [23,94,95], because even with a duodenotomy the 5 year cure rate in MEN1/ZES patients is very low or zero, without aggressive resections such as pancreaticoduodenectomy (Fig. 3B). This likely occurs because duodenal gastrinomas in MEN1/ZES patients, in contrast to sporadic ZES, are invariably multiple, frequently very small and thus difficult to find even with a duodenotomy (Fig. 4A, B), and are associated with lymph node metastases in 50–86% of cases [23,86,93–96,150,201]. Since gastrinomas in MEN-1 are usually in the gastrinoma triangle [268] that includes the head of the pancreas and the duodenum, some advocate the use of more radical procedures like Whipple pancreaticoduodenectomy for improved cure-rate [150,198,269,283,284].

Pancreaticoduodenectomy has been performed in a limited of MEN1/ZES patients and generally results in a high (77–100%) cure rate (Table 6). However, most experts do not recommend Whipple pancreaticoduodenectomy for the surgical management of gastrinoma [22,23,83,129,150,248]. This recommendation is made both because of the increased understanding of the natural history of MEN1/ZES patients with PET <2 cm on imaging and because of the possible side-effects of Whipple resections. A recent study [23] reports the disease-related survival in patients with MEN1/ZES with PETs<2 cm on imaging and no surgery is 100% at 15 years [23]. Numerous studies show that lymph node metastases may develop in a proportions of these patients [23,86,94] however in a most studies, they alone are not associated with decreased survival [96,113,218,231,232], only the development of liver metastases [7,113,215,218]. A large prospective study showed duodenal gastrinomas

metastasize to the liver with a 10-fold lower frequency than pancreatic PETs and liver metastases are uncommon in patients with duodenal gastrinomas (1–5%) [88,96]. A Whipple procedure is clearly associated with a higher complication and death rate than simple excision or enucleation of pancreatic and duodenal tumors. Whipple resections may have long-term complications like weight loss, diabetes and malabsorption and the frequency of these or other late complications is largely unknown. Furthermore, Whipple resection makes subsequent re-operation much more difficult. Finally, liver metastases occurring after Whipple procedure cannot be treated with chemo-embolization, because of an increased risk of ascending infection. Nevertheless, because of the dramatic increase in cure rate and the ability to totally remove the entire gastrinoma triangle, Whipple pancreaticoduodenectomy is clearly indicated in some patients with gastrinoma. It is recommended to be considered in MEN-1 ZES patients with good health and a large pancreatic head or duodenal tumor that is not able to be simply excised; multiple localized lymph nodes; or if the patient is not cured after removal of a duodenal or pancreatic head gastrinoma and develops recurrent tumor that is increasing in size and localized to the gastrinoma triangle.

At present the operative approach that is most widely used in patients with MEN1/ZES includes the use of intra-operative ultrasound, enucleation of tumors in the pancreatic head, duodenotomy and excision of duodenal wall tumors, systematic removal of lymph nodes around the pancreas, along the celiac trunk and hepatic ligament with or without routine distal pancreatectomy-splenectomy [23,64,95,271,272]. The role of the routine distal pancreatectomy is controversial and will be discussed in the surgical treatment of NF-PETs below. At present most recommend that [23,94,95,218,285] an operation be performed only in MEN1/ZES patients with imaged tumor>2cm, because of the low possibility of cure (Table 6), their excellent long term survival and quality of life with smaller tumors [23], the morbidity of more advanced surgical procedures and the lack of evidence that routine exploration in this group of patients extends life. Others [248,286] recommend such a procedure be performed in all MEN1/ZES patients. At present without long-term prospective studies and a clear definition of the importance of duodenal gastrinomas in altering survival these different approaches will not be easily resolved.

II.F.2.c Surgery for NF-PETs in MEN1: Similar to gastrinomas in MEN1/ZES patients there is no general agreement on the approach to small NF-PETs (<2 cm) in MEN1 patients [63, 128,160,172,176,176,178,179,241,266,270]. All agree that NF-PETs >2–3 cm should be routinely removed from MEN1 patients, even if asymptomatic, because numerous studies demonstrate that pancreatic PETs of this size are associated with an increased incidence of liver metastases/decreased survival [7,24,96,215,218,241]. Furthermore, studies show that the decreased survival of MEN1 patients with NF-PETs (Fig. 6, panel 1A)[273] is not due to the PETs<2 cm (Fig. 6, panel 3A) [128], but instead to the inclusion of patients with NF-PETs >2 cm in diameter. It is not proven in MEN1 patients that the removal of larger PETs (>2 cm) will prevent the subsequent development of liver metastases and increase disease-related survival, however recent studies in patients with sporadic gastrinoma show the routine surgical removal of the primary PET decreases the subsequent rate of developing liver metastases and increases survival [225,226]. Controversy exists for the small NF-PETs (<2 cm) in asymptomatic MEN1 patients, because a recent GTE study [128], demonstrated that, similar to the finding with small gastrinomas in MEN1 patients [23], there was no decrease in survival in patients with small NF-PETs (<2 cm) with MEN1 (Fig. 6, panel 3A) [128]. Furthermore, a second study [241]demonstrated no growth of NF-PETs<2cm in MEN1 patients and no patient developed liver metastases on follow-up. Recently it has been proposed that serial EUS studies could be used to assess the growth of small NF-PETs and determine when intervention should be considered [160,172, 174,176,179]. Recent studies show EUS also has excellent specificity and reproducibility for assessing the size of pancreatic PETs with a mean coefficient of variation with serial measurements of $5.5 \pm 4.6\%$ for PETs <5 mm in diameter and $4.4 \pm 2.6\%$ for PETs > 5 mm

in diameter [160,179]. Such serial studies may be helpful in identifying the subset of small NF-PETs that demonstrate rapid growth [241], however at present no study has established criteria that have been evaluated serially in a large number of patients.

There is also controversy whether the standard operation in MEN1 patients with NF-PETs or for any PET, should include a routine distal pancreatectomy with some advocating this procedure [22,64,248,271,272] and others not [23,94,287]. The National Comprehensive Cancer network guidelines for surgery for MEN1 patients with PETs recently recommend the use of routine distal pancreatectomy [288]. Although it seems logical that this approach may reduce the subsequent development of PETs that could be clinically significant, it has not been shown to extend life or decreases the liver metastases rate that is the primary determinant of long-term survival. In one study [23] in which distal pancreatectomy was not routinely performed, the 15 year survival rate was 92%. It was recommended that distal pancreatectomy not be performed, because of the excellent survival without it, its possibility of leading to the development of glucose intolerance, increasing the complication rate and reducing the possibility of a subsequent pancreaticoduodenectomy, if it is needed [23]. The possibility of such routine resections leading to glucose intolerance or diabetes is receiving increased attention, because a recent study shows MEN1 patients have an increased occurrence of glucose intolerance and diabetes [289]. Furthermore, whereas it is reported that such surgery rarely results in the development of diabetes by some [22], a number of studies indicate that impairment of glucose intolerance after such a procedure is relatively common and therefore raise questions about its routine use [100,241,289].

II.F.2.d Surgery for Insulinomas in MEN1: The surgical cure rate in patients with sporadic insulinoma is nearly 100% as they are usually benign and simply enucleated or resected [6,264,290]. With MEN1, most patients (61–100%) are still cured by removal of a dominant pancreatic PET (Table 6), but some will develop recurrent hypoglycemia or show persistent hypoglycemia suggesting the presence of other or multiple pancreatic insulinomas (Table 6) [82,102,244–246]. The role of surgery is more critical in these patients than those with gastrinomas, as the medical management of the hypoglycemia is less efficacious than the acid management of gastrinoma and the possibility of long-term cure is much higher with simple PET enucleation (Table 6). Although a number of studies [244,245] report multiple PETs removed at surgery in MEN1 patients with insulinomas and the implication is that most of these patients have multiple insulinomas, this is not clearly established. Insulinoma patients typically have a dominant NET that secretes excessive insulin and causes the neuroglycopenic symptoms and the resected pancreas contains other smaller PETs. However, the other NETs may not be secreting insulin. Immunohistochemistry for insulin is seldom done in prior series so it is impossible to determine if these other tumors are insulinomas.

II.F.2.d Surgery for other PETs in MEN1: Even though Vipomas, somatostatinomas glucagonomas and GRFomas are uncommon in MEN1 patients (Table 2) they can cause severe symptoms, which may or may not be well controlled with long acting somatostatin analogues. These patients may be cured [70,78,101,196] and therefore if the PET or its metastases are resectable, these patients should have a surgical exploration and tumor resection whenever possible.

II.F.3. Treatment of advanced disease in patients with PETs/MEN1—Metastatic disease to the liver or distant sites occurs in a proportion of MEN1 patients with different PETs, although it is at a lower rate in MEN1 PETs than seen in sporadic PETs. (Table 3). In many patients the metastatic disease shows either no growth or indolent growth and no immediate anti-tumor treatment, except to control the hormone excess-state, is needed [105,216,218]. However, in a subset of patients (Fig 5, panel 1B) aggressive tumor growth occurs [100,105, 197,218]. Both in these patients, those with tumor symptoms due to the metastatic disease or

those with the hormone-excess state poorly controlled, anti-tumor treatment is indicated. In most patients the liver metastases are diffuse and surgical resection is only possible in <15% [105,131,291,292]. Numerous treatments are reported to be effective including cytoreductive surgery, chemotherapy [primarily streptozotocin/doxorubicin], biotherapy with somatostatin analogues or interferon, chemoembolization of the liver, treatment with [111]Indium-, [90]Yttrium-, [177]Lutetium-labeled somatostatin analogues, and various new agents (temozolamide, thalidomide, VEGFR inhibitors, tyrosine kinase inhibitors, mTor inhibitors). These treatments will not be further discussed here, because they are similar to those used in malignant sporadic PETs and have been covered in a number of recent reviews [8,18,154,291–295].

IV. Von Hippel-Lindau Disease (VHL)

IV.A. General

VHL is an autosomal dominant neoplastic disorder due to germline mutations in the VHL gene on chromosome 3p25 (Table 1) [15,296]. Germline mutations in this gene lead to benign and malignant tumors in a number of tissues as well as cyst development in a number of organs [15,296]. Characteristically, VHL patients develop hemangioblastomas of the retina (25–60%) and craniospinal region [cerebellum (44–72%), brainstem (10–25%), spinal cord (13–50%)]; endolymphatic sac tumors (10%); renal cell carcinomas or cysts (25–60%); pheochromocytomas (10–20%); and epididymal cytadenomas (25–60%) [15,296]. Pancreatic tumors or cysts develop in 35–77% of patients in most series with the majority being cysts, with the pancreatic tumors including cytadenomas (12 %), hemangioblastomas (<1%), adenocarcinomas (<1%) and PETs (Table 1)[15,296–305,305–310]

IV.B. Genetics/molecular pathogenesis

The *VHL* gene encodes for a 232 amino acid protein, pVHL which forms a complex with various proteins including elongin B and C and cullin 2 which determines ubiquitin-dependent proteolysis of large cellular proteins (Table 1) [15,296]. In normal oxygen levels, this complex targets and degrades hypoxia-inducible factors 1 and 2 (HIF1 and 2). Altered pVHL, as occurs in VHL, can lead to increased HIF effects because of failure to degrade it, which include increased glucose uptake, increased expression of angiogenic, growth and mitogenic factors including VEGF, PDGFβ, TGF α and erythropoietin [15,296]. The exact mechanism by which this results in the formation of PETs is not clear.

Although PETs develop in VHL patients there is no evidence of mutations in the *VHL* gene in a subset of sporadic PETs [12,142]. In one study of sporadic PETs [142], 33% had 3p LOH which is the region of the *VHL* gene, but no mutations were found in any sporadic PET in the *VHL* gene, leading to the proposal that there may be another tumor suppressor gene adjacent to *VHL* gene that could play a role in the PET formation in this subset of patients. This latter proposal was supported by a study of a VHL kindred [311] with prominent PET formation, which showed 3p LOH proximal to the VHL locus, also suggesting this area might contain an unknown tumor suppressor gene, besides *VHL*, which is critical for the PET formation in VHL patients.

IV.B. PETs in VHL

IV.B.1. PETs in VHL.General/pathology—PETs develop in 10–17% of VHL patients (Table 1) and they are almost invariably nonfunctional and usually asymptomatic, although they may occasional cause pancreatitis or a mass causing pain [15,296–309,312]. In 7.6% of patients only the pancreas is affected [297]. In almost every series 100% of the PETs are NF-PETs [297,300,306,312]. The mean age of diagnosis of the PET is 29–38 years and the majority of patients, in contrast to those with MEN1, have a single PET (67–70%) [299–301,306,312].

Malignant PETs occur in 8%–50 % with metastases to the liver in 9–37% [297,299–302,306, 312]. The mean size of the PETs is 2.6–4.3 cm (range-1–10 cm) [301,306] and in various studies 52–70%, 28–33% and 7–21% are located in the pancreatic head, body and tail, respectively [297,298,301,306]. IHC demonstrated chromogranin A in 78–100%, synaptophysin (100%), neuron specific enolase (100%), with 35% demonstrating focal staining for pancreatic polypeptide, insulin, somatostatin, and/or glucagon and 0% for gastrin [297,306,307].

IV.B.2 PETs in VHL. Natural history and prognosis—In one study of 30 patients with VHL with PETs, 7%(2/30) died of metastatic disease due to the PET during follow-up [306] and in a second study [312] 2% (2/108) died of metastatic disease due to the PET. In both studies [306,312] the size of the primary PET correlated with the presence of hepatic metastases (mean-5 cm-liver metastases vs. 2 cm, no metastases, p=0.0013). No patient in these two studies [298,306] with a primary <3 cm had hepatic metastases and in a third study [312] metastases were much more frequent in patients with primary tumors >3 cm (69% vs. 19%, P<0.005). PETs <3 cm demonstrated a longer mean doubling time (mean 2.5 vs. 1 yr) than did larger PETs (≥3cm) [298] and the mean doubling time of the primary tumor was 8-times faster in patients with metastatic disease than those without metastatic disease (334 days vs. 2628 days, p<0.001) [312]. The mean age of death of VHL patients from any cause is 40–48 years [313–315] and the PET is, in general, an uncommon cause of death in VHL patients, with most dying of metastatic renal cell cancer or complications of the cerebellar hemangioblastomas [18,313–315].

IV.B.3 PETs in VHL. Treatment of the PETS—Similar to NF-PETs, the indications for treatment of PETs in VHL depends on two factors: whether the PET is symptomatic and the perceived risk of malignancy. Functional PETs have only very rarely been reported in VHL [300,301,315] and thus 100% are NF-PETs clinically. Nevertheless, they can on occasion (<5% in most series) cause symptoms because of expansion or local invasion (pancreatitis, pain, etc) [297,300,309] and this would be an indication for surgical treatment. Because most PETs in VHL remain asymptomatic, show indolent growth, and no liver metastases are reported in patients with PETs <3 cm, three series recommend that only PETs≥ 3 cm should be routinely resected [297,306,312]. A recent study [312] of 108 patients with VHL and PETs reported all patients with metastatic disease had at least two of three important factors associated with malignancy: a primary tumor>3 cm, mutation in exon 3 of the *VHL* gene or a primary tumor doubling time >500 days. This study [312] recommended that VHL patients without 2 of these three PET prognostic factors could be followed. One study [306] recommended that VHL patients with PETs < 1cm be followed at 12-month intervals with serial CT scans and patients with PETs 1–3 cm should be monitored and resection is recommended if growth to >2 cm. With the accuracy of EUS and its increased availability, the growth of these PETs could be much more carefully assessed and it is likely in the future, similar to the case with NF-PETs in MEN1 patients discussed above, that criteria could be developed to better select these patients for surgery.

V. Von Recklinghausen's syndrome [neurofibromatosis 1 (NF-1)]

V.A. General

NF-1 is a relatively common disorder occurring in 1-4,000-5000 live births and is due to alterations in the *NF-1* gene on chromosome 17q11.2, which encodes for a 2485 amino acid protein, neurofibromin (Table 1) [16,316,317]. The principal clinical manifestations are: cafe au lait macules (>99%), neurofibromas (cutaneous>99%, deep-seated-44%), skin-fold freckling (85%), iris Lisch nodules (iris hamartomas seen on slit lamp examination) (>95%), optic pathway gliomas (15%) and bony dysplasia (sphenoid wing and bowing of long bones of the bones) [16,316]. CNS abnormalities are common with learning problems (30–60%), attention deficit hyperactivity disorder (38%) and epilepsy (6–7%) [16,316,317]. Renal artery stenosis

(2%), pheochromocytomas (2%) and an increase risk of hypertension are important clinically in some patients [16,316,317].

V.B. Genetics/molecular pathogenesis

Neurofibromin, acts as a tumor suppressor, and is especially widely expressed in the nervous system. Neurofibromin affects cell proliferation/growth and signaling by regulating the activation of p21 ras by its Ras GTPase protein-activating activity, binding microtubules, modulating adenylate cyclase activity, interacting with the cellular cytoskeleton and by interacting through a signaling pathway with tuberin, the TSC2 gene product, it regulates mTor, which is a serine-threonine kinase that regulates cell growth and proliferation (Table 1) [316–318].

V.C. PETs in NF-1

V.C.1 PETs in NF-1: Clinical, pathology—PETs, almost exclusively duodenal somatostatinomas, occur in NF-1 patients, but are relatively uncommon (0–10%) (Table 1) [87,319–323]. However, NF-1 accounted for 48% of the total duodenal somatostatinomas reported in the literature in one review [322] and 23% [324] of all ampullary carcinoid tumors. In NF-1 rare patients are reported with pancreatic somatostatinomas (16 times less common than duodenal somatostinomas) [322], ZES [325,326], an insulinoma [327–329] or a nonfunctioning pancreatic PET [330] and increasing numbers are reported with GI stromal tumors [331,332] which have been suggested to be the most common NF-1 associated GI tumor.

Characteristically these duodenal somatostatinomas occur in the periampullary region [87,319–323] and have a mean size of 2.8 cm (range 1–5 cm) [322]. In one series of 71 cases of ampullary PETs reviewed in the literature [333] 18% were caused by NF-1. These ampullary somatostinomas are almost always hormonally silent and do not cause a functional somatostatinoma syndrome [87,333,334]. In contrast to other duodenal neuroendocrine tumors, these periampullary tumors more frequently present with jaundice, cause biliary dilatation, pancreatitis and can cause pain, nausea, bleeding or vomiting [87,332,335,336]. Duodenal somatostatinomas my be suspected histologically because they may show a glandular pattern with psammoma bodies (63%) [87,322,334,337,338]. Metastases to liver and/or lymph nodes occur in 30% [322]. Duodenal somatostatinomas in patients with NF-1 are similar to sporadic duodenal somatostatinomas in most respects [size, psammoma body presence, metastatic rate], however they are less likely to produce other hormones on IHC examination (18% vs. 43%) [322]. In contrast, both NF-1 and sporadic duodenal somatostatinomas differ from sporadic pancreatic somatostatinomas in a number of respects [322] including: frequency of producing the clinical somatostinoma syndrome (1–2% vs. 66%), tumor size (2.8 vs. 5.9 cm), psammoma body production (61% vs. 0%) and presence of metastases (30% vs. 71%) [322].

V.C.2 PETs in NF-1: Treatment—NF1 patients have a 10–15 year decrease in life-span (median age of death-59 years) [339], with the most common cause of death being malignancy [339–341]. In one series 1 of 11 deaths (9%) was due to a PET [341], whereas in a large population study [339] malignant neoplasms of the connective tissue or other soft tissues were an increased cause of death by 34 times compared to a non-NF-1 patients and CNS tumor 5.5 times increased, but GI/pancreatic tumors were not an increased cause of death [339]. Nevertheless, because duodenal somatostatinomas are malignant in 30%, because of their periampullary location they can grow and cause symptoms, and because tumor size is not a good predictor of tumor behavior with periampullary tumors [333,342], many experts recommend either a Whipple resection or pylorus-sparing pancreatico-duodenectomy be performed, particularly for PETs>2cm [324,343]. However, satisfactory local resections [324,343,344] (especially with PETs <2 cm) inducing endoscopic resection [344], have been reported. Therefore, if after careful

EUS examination, only local disease is seen which is thought locally resectable, then a more conservative approach could be considered.

VI. Tuberous sclerosis [Bourneville's disease)

VI.A. General/genetics/molecular pathogenesis

Tuberous sclerosis is an autosomal dominant neuro-cutaneous multi-system disorder, which is due to mutations in one of two genes, the tuberous sclerosis complex 1 gene (TSC1)(encoding for hamartin) or TSC2 (encoding for tuberin) (Table 1) [17,345,346]. TSC is characterized by the development of hamartomas in almost every organ and patients develop disabling neurological features (epilepsy, mental retardation, autism), dermatological features (facial angiofibromas, hypomelanotic macules, shagreen patch, ungula fibromas); and tumor-like hamartomatous lesions (cortical tubers, cardiac rhabdomyomas, subependymal nodules, renal angiomyolipomas and lymphangiomyomastosis) [17,345,346].

The products of the TSC1 and TSC2 genes, hamartin and tuberin form a dimer, which is important in the PI3K signaling pathway [17,345,346]. They are also important for regulation of the small GTPase, rheb, which is turn is involved in regulating mTOR activity and through this cascade and others can affect protein translation and protein synthesis, growth and proliferation, cellular energy levels and nutrient availability (Table 1) [17,345,346].

VI.B. PETs in TSC

PETs both functional [347–352] and nonfunctional [353–356] are reported in a small percentage of patients with TSC usually occurring in patients with TSC2 [354]. In TSC patients with functional PETs,, tumors reported include gastrinomas causing ZES [347] and insulinomas [348–352]. In patients with a functional tumor, the hormone excess state needs to be controlled medically and/or surgically as discussed above with MEN1. Furthermore, in some TSC patients the PETs are malignant [353,355] so that appropriate surgical treatment of the PETs should be considered.

Acknowledgements

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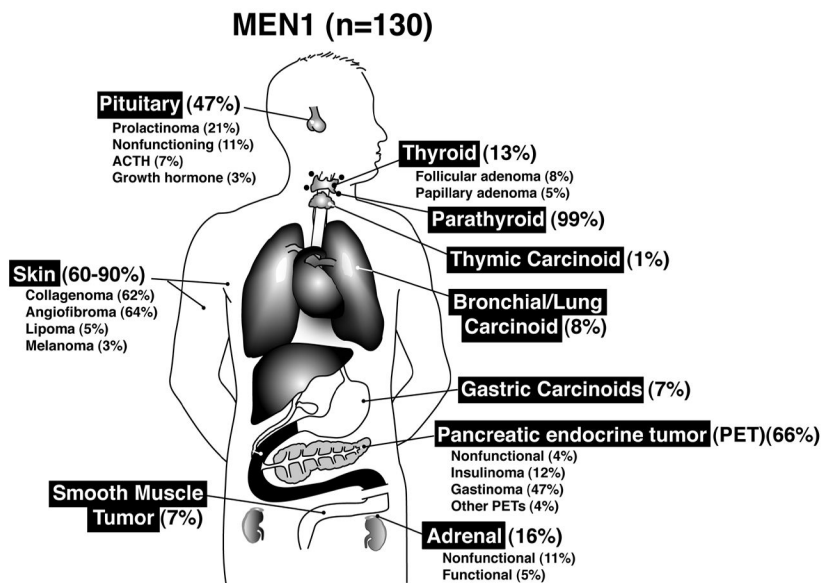
MEN1 (n=130)

Pituitary (47%)
Prolactinoma (21%)
Nonfunctioning (11%)
ACTH (7%)
Growth hormone (3%)

Thyroid (13%)
Follicular adenoma (8%)
Papillary adenoma (5%)

Parathyroid (99%)

Thymic Carcinoid (1%)

Skin (60-90%)
Collagenoma (62%)
Angiofibroma (64%)
Lipoma (5%)
Melanoma (3%)

Bronchial/Lung Carcinoid (8%)

Gastric Carcinoids (7%)

Pancreatic endocrine tumor (PET)(66%)
Nonfunctional (4%)
Insulinoma (12%)
Gastrinoma (47%)
Other PETs (4%)

Smooth Muscle Tumor (7%)

Adrenal (16%)
Nonfunctional (11%)
Functional (5%)

Figure 1.
Location and frequency of tumors/hyperplasia in patients with MEN1. Location and frequency are graphed from the data for the 130 MEN1 patients reported in [14]. Percentage refers to percent of the total 130 patients with the tumor in the indicated location.
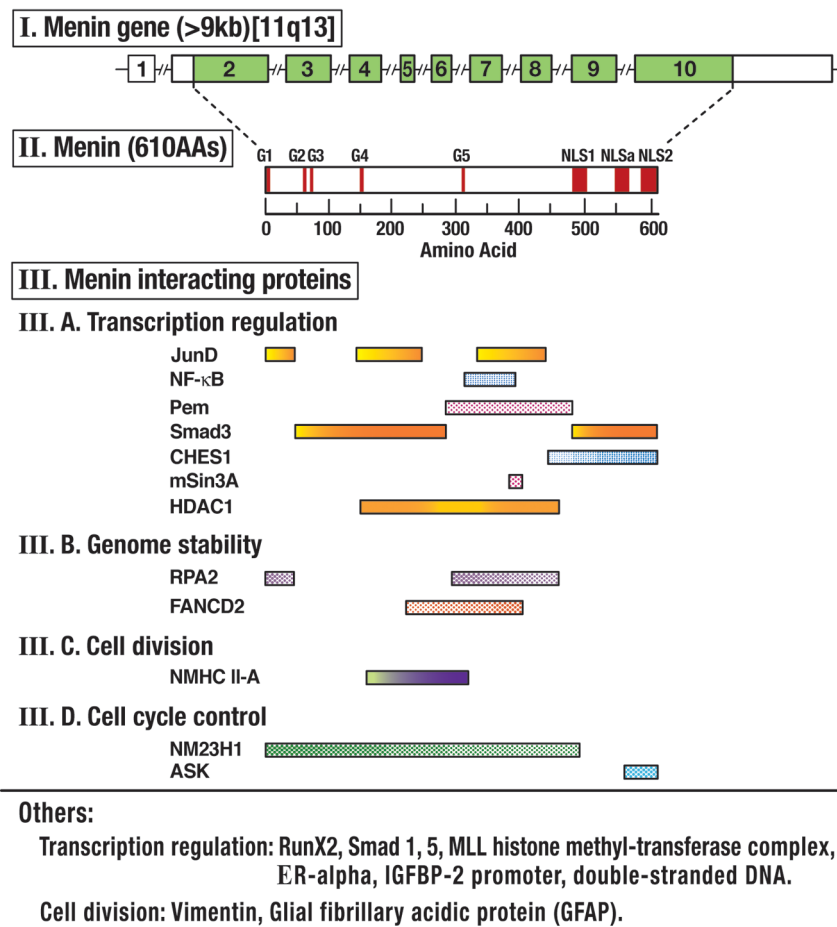
Figure 2.
Representation of the genomic organization of the *MEN 1* gene, its encoded protein, menin, and the menin regions that interact with different proteins grouped according to their main functional activity. The 10-exon gene has a 1.8-kb coding region (shaded) from 9 exons, which encode for the 610 amino acid protein, menin. Menin has 3 nuclear recognition signals (NLS) and five putative guanosine triphosphatase (GTPase) sites indicated by the bars. Regions which have been implicated in binding to different interacting proteins are shown and they are divided by their main intracellular function. Abbreviations are explained in text and individual menin interactions discussed. Figure drawn form data in [28–33] and references in text.
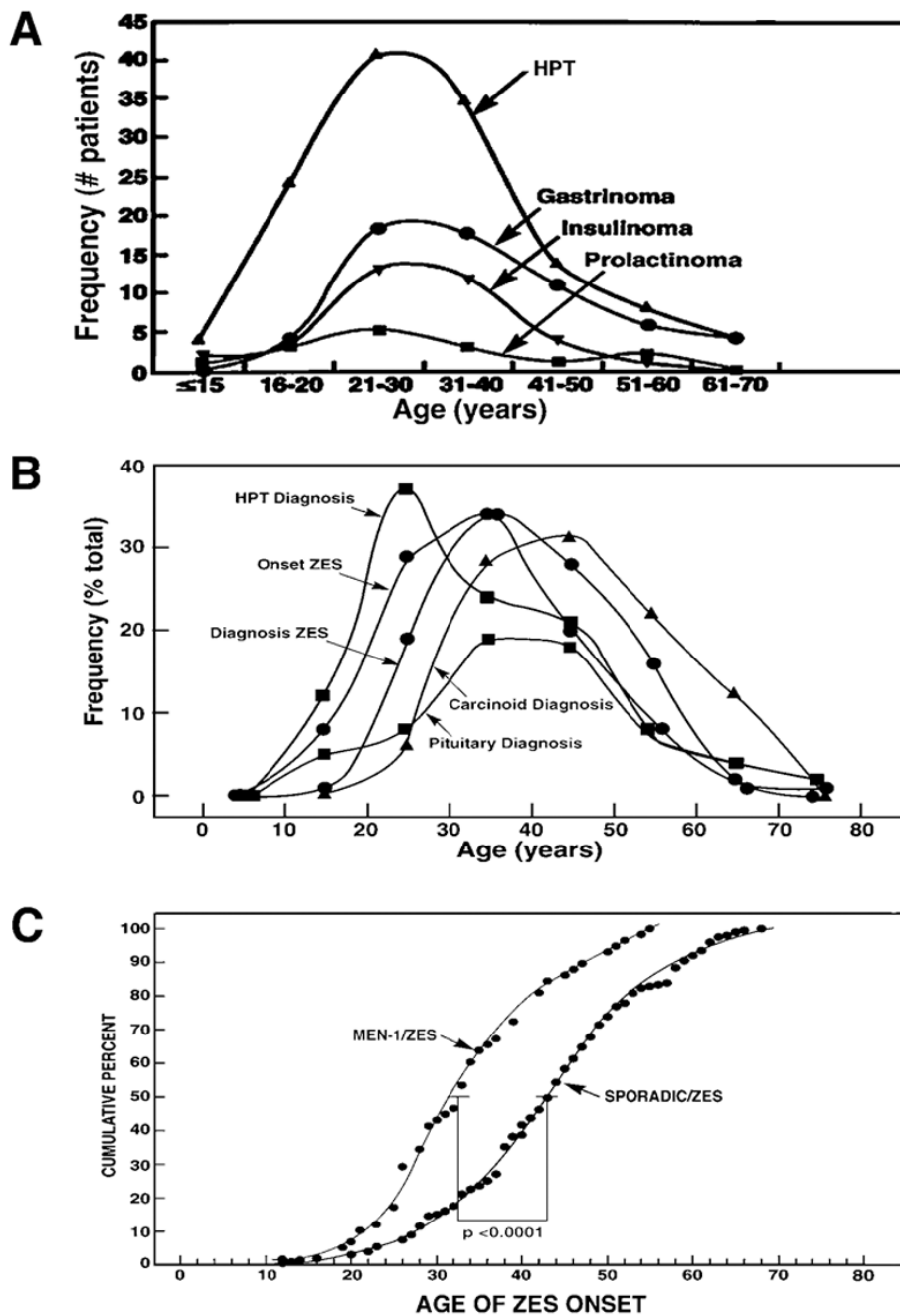
Figure 3.
Age of diagnosis or onset of various PETs and other manifestations of MEN1 in all MEN1 patients (A, top) or MEN1/ZES patients (B, Middle) and comparison of age onset of ZES in MEN1 patients and patients with sporadic ZES. Panel A is drawn form data in [14], panel B from [68] and panel C from [85].
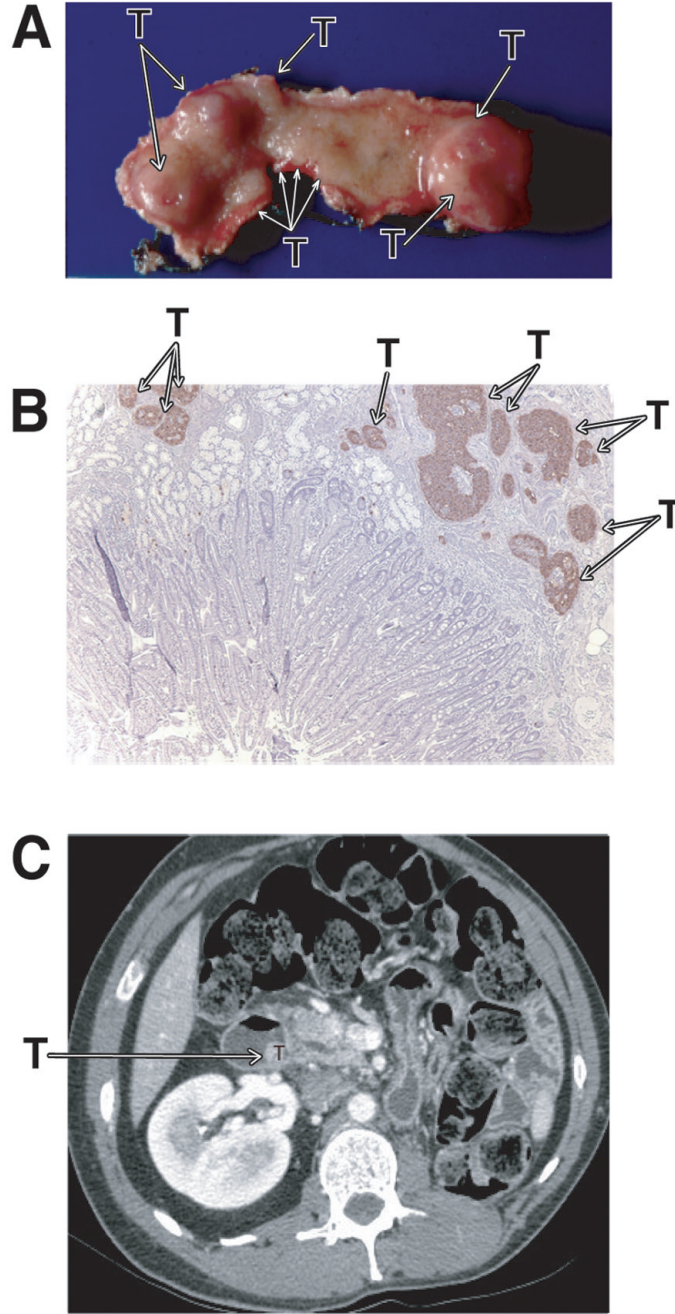
Figure 4.
Characteristic multiplicity of duodenal gastrinomas PETs in MEN1/ZES patients and its appearance on CT scan. Panels A (gross specimen) and B (IHC-gastrin stain) show multiple small and larger duodenal gastrinomas (T=tumors) which limits the ability to cure patients MEN1/ZES patients with tumor enucleation [95] (see Figure 2B). Panel 1C shows the appearance of a duodenal gastrinoma which is projecting into the lumen but arises submucosally [93,98, 201].
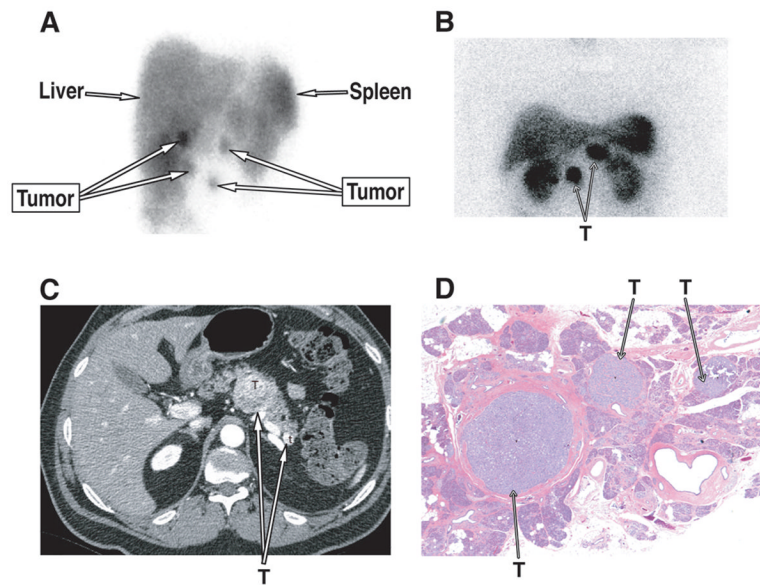
Figure 5.
Characteristic multiplicity of pancreatic PETs in MEN1 patients and the ability to image them. Panel 1A show an anterior somatostatin receptor scintigraphy (SRS) SPECT image demonstrating 4 tumors in this patient with MEN1/ZES. The tumor in the lower right was not in the pancreas but a gastric carcinoid, demonstrating the importance of not assuming all positive abdominal lesions are PETs in MEN1 patients. Panels 1B (SRS), 1C (CT) and 1D (histology) from a different patient show the multiple, intrapancreatic PETs (T=tumor) that are frequently seen in MEN1 patients.
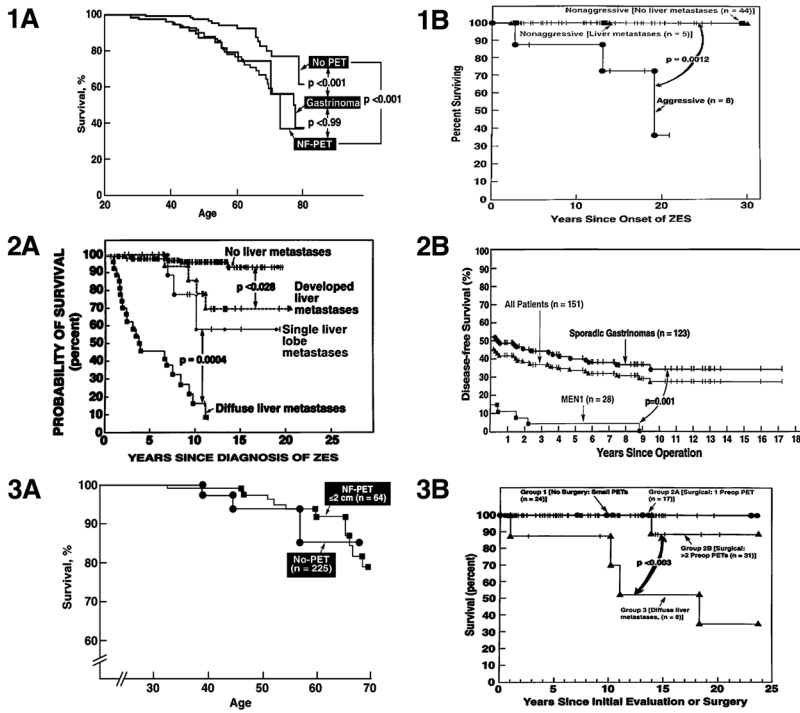
Figure 6.
Effect of various factors on survival in patients with PETs with MEN1 (1A, 1B, 2B, 3A, 3B) or without MEN1 (2A, 2B). Panels 1A, 3A show the effect of type of PET or lack of size of NF-PET on survival in MEN1 patients and are drawn from data in [81,128]. Panels 1B, shows survival in patients with MEN1/ZES with (15%) or without (85%) aggressive tumors and is drawn from data in [105]. Panel 2A shows the effect presence or extent of liver metastases in patients with sporadic ZES and is drawn form data in [96,215]. Panel 2B compares the disease-free survival rate in patients with ZES with sporadic ZES or MEN1/ZES and is drawn from [95]. Panel 3B shows the difference in survival for MEN1/ZES patients with no surgery with tumors <2 cm, (Group 1); group 2 with surgery with no liver metastases with a single (group 1A) or >2 PETs (2B) prior to surgery and group 3 with diffuse liver metastases and no surgery (drawn from data in [23].

Table 1

Inherited PET syndromes

Syndrome	Frequency	Location/type genetic abnormality	Altered protein function(s)	Frequency PETs	Type PET
Multiple Endocrine Neoplasia type 1 (MEN1)(Wermer's syndrome)	Prevalence-1–10 per 100,000	11q13(encodes 610 amino acid protein, menin)	Nuclear location; exact function unclear- interacts JunD, NFκB, SMAD signaling pathways. Effects cell cycle, growth, genomic stability, and apoptosis.	80–100% (microscopic)20–80% (clinical)	Nonfunctional (NF)(microscopic)>functional (20–80%)
Von Hippel-Lindau disease (VHL)	Prevalence-2–3 per 100,000	3p25(encodes 232 amino acid protein, [pVHL])	Interacts elongins which act as transcriptional regulators that degrades HIF, regulates cell cycle, VEGF	10–17%	>98% NF
Von Recklinghausen's Disease (neurofibromatosis 1, NF-1)	Prevalence-1 per 4–5,000	17q11.2 (encodes2485 amino acid protein neurofibromin)	Ras GTPase-activating activity, bind microtubules, modulates adenylate cyclase, mTor-regulates growth, cell cytoskeleton	Uncommon (0–10%)	Duodenal somatostatinomas, rare PETs
Tuberous sclerosis (Bourneville's disease)	Prevalence-1 per 10,000	9q34 (TSC1) (encodes 1164 amino acid protein, hamartin) 16p13(TSC2) (encodes 1807 amino acid protein, tuberin)	Interact PI3K signaling pathway regulating GTPase, mTor for which plays a key role in growth, energy regulation, response to hypoxia, nutrients	Uncommon	Rarely develop functional, NF PETs

Abbreviations. PET-pancreatic endocrine tumor; NF- nonfunctional PET; TSC-tuberous sclerosis complex, mTor-mammalian target of rapamycin; HIF, hypoxia-inducible factor; VEGA-vascular endothelial growth factor; PI3K-phosphoinositide 3-kinase;

Table 2

Frequency of general manifestations and of different PETs in MEN1

I. **General: MEN1 manifestations**[1,2]

1. Parathyroid hyperplasia (95–100%)

2. PET (80–100%) (symptomatic-20–70%)

3. Anterior pituitary tumor (54–65%-usual, range 16–100%)

4. Adrenal adenomas (27–36%) [Symptoms <2%]

5. Carcinoids

    a. gastric [ECLomas](7–35%)[symptomatic<5%]

    b. Lung (0–8%)

    c. Thymic (0–8%)

6. Thyroid adenomas (0–10%)[Symptomatic<1%]

7. Skin-angiofibromas (88%)>collagenomas (72%)>café-au-lait macules (38%)>lipomas (34%)[symptoms <1%]

8. CNS tumors (meningiomas (0–8%)[symptoms-<1%]. ependymomas, schwannoma

9. Smooth muscle tumors (leiomyomas, leiomyosarcomas)(1–7%) [symptoms <5%]

II. **PETs**[1,2]

1. Nonfunctional (80–100%-microscopic) [0–13% symptomatic, large]

2. Gastrinomas (mean 54%, range-20–61%)

3. Insulinomas (mean 18%, range-7–31%)

4. Glucagonomas (mean 3%, range-1–6%)

5. VIPomas (mean, 3%, range-1–12%)

6. GRFomas (<1%)

7. Somatostatinomas (0–1%)

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[1]Data means [ranges] of series in the literature and are from 13,14,68,74,78,80–82,84,357

[2]Shown are both the frequency reported in various series and when known the percentage that cause symptoms.

Abbreviations: CNS-central nervous system; VIPoma-vasoactive intestinal peptide secreting tumor; GRFoma-Growth hormone releasing factor secreting tumor;

Table 3

Frequency of liver metastases and tumor extent at diagnosis in MEN1 patients

I. Conventional imaging results (CT, MRI, Ultrasound) and/or laparotomy[1]

No. MEN1 patients	% PET imaging	Imaging used	% with liver Metastases	Mean Age (yrs)	Year, Reference
41	39%	CT, US	10%		1996, 270
69	40%	CT, US, Lap	20%	46	1998, 130
20	70%	CT, US, MRI	20	29	1998, 75
8	38%	CT, MRI	15%		1998, 104
130	66%	CT, US, MRI			1998, 14
36	55%	CT, US, MRI		51	1999, 233
580	53%	CT, US, MRI	8.2%	40	2004, 78
118	56%	CT, US, MRI	5.1%	37	2004, 100

II. Metastatic PET to liver at Diagnosis in MEN1 compared to patients without MEN1 (sporadic)[1]

PET	% with Liver Mets		MEN1 reference
	Sporadic[1]	MEN1	
A. Functional			24,64,82,197,244,245
Insulinoma	5% [5–15]	0%–20%	
Gastrinoma	34% [13–53]	11%	23,24,68,79,80,88,218,358
Vipoma	60% [40–70]	0 (0/2)–33%(1/3)	24,78
Glucagonoma	60% [50–80]	40% (2/5)	78
Somastatinoma	>70%	50% (1/2)	233
GRFoma	>60%	unknown	
B. Nonfunctional			100
(NF-PET, PPoma, NToma, ghrelin-secreting, etc).	60% [9–91]	19%	24,63,81,100

[1] Series reporting percentage of total MEN1 patients with PET by imaging study with percentage with liver metastases and age of patient at time of identification of PET.

[1] Sporadic data from 2,113,136,215,264,359.

Abbreviations: NF-PET-nonfunctional PET; NToma-neurotensin-secreting PET; PPoma-pancreatic polypeptide-secreting PET)

Table 4

Survival and cause of death in patients with MEN1 with PETs

A. Survival in MEN1 patients with different PETs

PET	Survival (%) Years Follow-up			References
	5	10	20	
Any PET	82 ± 6	75 ± 5	52 ± 13	100,100,104,110,125.360
NF-PET	74 ± 16	49 ± 14	ND	78,81,100,125
Gastrinoma	89 ± 8	83 ± 9	67 ± 18	78,80,81,105,126,218,265,361
Insulinoma	95 ± 8	94 ± 1	92 ± 3	78,82,101,244
Glucagonoma,				78
VIPoma, SSoma	100	54	54	

B. Cause of death in MEN1 patients

Died/total (%)	MEN1 Related death (%)	PET related death (%)	ZES related death (%)	Malignant PET related death (%)	Mean age death (%)	Year of study	ref
8/42 (19)	100	100	88	12	-	1964	106
12/36 (33)	100	83	75	16	-	1978	107
11/-	100	100	91	9	-	1979	108
15/52 (29)	100	87	73	14	41	1989	71
46/-	43	30	4	26	51	1993	109
59/-	46	30	10	20	55	1998	25
7/34 (20)	86	71	0	71	50	1998	104
60/233 (26)	28	19	2	17	-	2000	110
8/57 (14) [a]	38	38	0	38	-	2002	105
30/84 (34)	57	33	13	20	51	2003	111
16/55 (29) [b]	81	62	-	62	-	2006	100
16/82 (20)	68	82	27	73	60	2007	112

Abbreviations: SSoma-somatostatinoma, NF-PET-nonfunctional PET

[a] all patients in this series had gastrinomas;

[b] All patients in this series had a PET

Table 5

Prognostic factors/characteristics of aggressive PETs and Gastrinomas in MEN1

I. All PETs in MEN1 patients
  A. Clinical/histologic Tumoral Features
    A.1. Univariate analysis
      Presence of a 1st degree relative with PET malignancy (odds ratio=3.7, p<0.05) [130]
      Advanced age (p<0.05) [100,130]
      Presence of a NF-PET (p<0.01) [81,100]
      Presence of a gastrinoma (p<0.01) [81,130]
      Primary tumor size >3 cm (p<0.01) [78,81,134,218]
      Presence of liver metastases (p<0.01) [81,134]
      Noncurative resections (p<0.01) [81]
      Presence of a VIPoma, SSoma, glucagonoma (p=0.01) [78]
      Poor tumor differentiation (p=0.019) [134]
    A.2. Multivariate analysis
      Liver metastases (p=0.002) [100,134]
      Advanced age (0.0003) [100]
      Presence of a NF-PET (p=0.037) [100]
      Successful surgical resection (p=0.0043) [100]
  B. Molecular Biologic Features
      Presence of *MEN1* gene truncations/frameshift mutation in exon 2,9,10[64] or exon 2 mutation [100]
II. Gastrinomas in MEN1 patients[a]
  A. Clinical Tumoral Features
    A.1. Univariate analysis
      Presence of a large gastrinoma (>3 cm) (p<0.005) [218]
      Male gender (p=0.022) [218]
      Young age (<30 yrs old) of onset or diagnosis of ZES (p=0.03) [105]
      Diagnosis 20 yrs prior to report (p=0.008) [218]
      Development/presence of liver metastases (p=0.0012 23,105,218
    A.2. Multivariate analysis
      Presence of a large primary gastrinoma (>3 cm) (p<0.0001) [105,218]
      Development/presence of liver metastases (p=0.0012 23,105,218

Table 6

Surgical Cure Rate in MEN1 and ZES with and without pancreaticoduodenectomy, and MEN1 and insulinoma.

MEN1/ZES - NON-PANCREATICODUODENECTOMY		
Author (year)	**# patients**	**Long-term # disease –free (%)**
van Heerden (1986) [275]	25	0 (0))
Samaan (1989) [75]	5	0 (0)}
Pipeleers-Marichal (1990) [86]	4	2 (50)
Cherner (1992) [362]	1	0 (0)
Farley (1992) [127]	15	0 (0)
Grama (1992) [197]	12	0 (0)
Melvin (1993) [126]	19	1 (5)
Mignon (1995) [361]	36	1 (3)
MacFarlane (1995) [94]	10	0 (0)
Thompson (1997, 1998) [248,271]	27	9 (33)
Kisker (1998) [363]	2	0 (0)
Jordan (1999) [364]	3	0 (0)
Norton (1999) [95]	28	2 (6)
Bartsch (2000) [64]	7	3 (42)
Kato (2000) [365]	2	2 (100)
Norton (2001) [23]	48	0 (0)
Thodiyl (2001) [366]	1	0 (0)
Gauger and Thompson (2001) [367]	37	13 (33)
MEN1/ZES - PANCREATICODUODENECTOMY		
Waddell (1968) [368]	1	1 (100)
Lind (1989) [369]	1	1 (100)
Pipeleers-Marichal (1990) [86]	2	2 (100)
Delcore (1992) [370]	2	2 (100)
Stadil (1995) [283]	3	3 (100)
Schroder (1996) [371]	1	1 (100)
Phan (1997) [284]	6	6 (100)
Jordan (1999) [363]	1	0 (0)
Bartsch (2000) [64]	3	3 (100)
Kato (2000) [365]	2	2 (100)
Norton (2001) [23]	2	0 (0)
Sarmiento (2002) [372]	1	1 (100)
Tonelli (2006) [101]	13	10 (77)
Bartsch (2005) [373]	4	4 (100)
MEN1/INSULINOMA		
Rasbach (1985) [102]	12	10 (83)
Sheppard (1989) [196]	3	3 (100)
Jadoul (1990) [247]	2	2 (100)
Demeure (1993) [245]	6	5 (83)
O'Riordain (1994) [244]	19	17 (89)
Thompson (1998) [248]	6	6 (100)
Cougard (2000) [82]	44	27 (61)
Bartsch (2005) [101]	4	4 (100)
Fernandez-Cruz (2005) [373]	2	2 (100)
Tonelli (2006) [198]	3	3 (100)
Norton (2006) [246]	7	6 (86)