MULTIPLE ENDOCRINE NEOPLASIA TYPE I

Aaron I. Vinik, MD, PhD, FCP, MACP, FACE, Murray Waitzer Endowed Chair for Diabetes Research, Professor of Medicine/Pathology/Neurobiology, Director of Research and Neuroendocrine Unit Division of Endocrine and Metabolic Disorders, Eastern Virginia Medical School
Roger R. Perry, MD, FACS, Robert L. Payne, Jr. Professor of Surgery, Division of Surgical Oncology, Eastern Virginia Medical School, Norfolk, VA
Marybeth Hughes, MD, FACS, Chief Division of Surgical Oncology, Eastern Virginia Medical School, Norfolk, VA
 Eric Feliberti, MD, FACS, Associate Professor, Division of Surgical Oncology, Eastern Virginia Medical School, Norfolk, VA

ABSTRACT

MEN-1 syndrome is a rare autosomal dominant disease with a high degree of penetrance, characterized by hyperplasia and/or neoplasia of the parathyroid, pancreatic islet cells, and pituitary, usually prolactinomas. Hyperparathyroidism occurs in about 90%, pNETs in 60% and pituitary adenomas in 40% of patients. The most common pNET is a gastrinoma frequently found in the duodenum but others include non-functioning tumors, vipomas, glucagonomas, somatostatinomas and Ppomas. Tumors may function synchronously or meta-synchronously. More than one syndrome may occur in the same patient and metastases may secrete different hormones. In women with MEN-1 breast carcinoma is increased 2.8 fold. MEN-1 is a tumor suppressor gene on (11q13), and there are more than 300 different MEN-1 germ line mutations and about 20 % of MEN kindred have no mutation. Tumors have loss of zygousity and the allelic loss is from the unaffected parent. The protein encoded is menin that binds to double stranded DNA and is a tumor suppressor. MEN-1 gene mutations are also found in non-syndromic tumors. Diagnosis of MEN requires presence of the gene mutation without signs or symptoms, an individual with the disease and the same disease in a 1st degree relative, or an individual who has two or more of the clinical syndromes. Biochemical testing should include PTH, prolactin, fasting gastrin and a secretin/calcium provocative test. Tumor localization requires endoscopic ultrasound, Octreoscan and PET/CT using Ga-68-Dota(-D-)-Phe(1)-Tyr(3)-octreotide (Ga-68-DOTATOC) to image neuroendocrine tumors with a reported sensitivity and specificity of 91.7% and 93.5%, respectively have altered management in 47.6% of MEN1 patients However this has not been found uniformly. Surgical management of the parathyroid usually involves total parathyroidectomy with implant of parathyroid in the forearm, allowing local excision in the case of recurrence. Localizing the pancreatic tumors requires THPVS and only the producing tumor(s) should be removed. The larger the tumor the more likely are metastasis! In general prognosis is good and the 15 year survival is 93%. Symptoms and secretions can be controlled. Mortality has shifted to thymic and carcinoid tumors.

INTRODUCTION

The tumors which comprise the MEN syndromes arise from APUD neuroendocrine cells. Each of the syndromes is inherited as an autosomal dominant trait. Advances in molecular biology and genetics have led to the identification of specific genetic defects which will improve the understanding and ability to diagnose these tumors. There are three distinct MEN syndromes as well as non-MEN familial medullary thyroid carcinoma.

MEN-1 syndrome is quite rare. It has an incidence of 0.25% determined from postmortem studies, and an estimated prevalence of between 0.02 and 0.2 per thousand (1-3). It is inherited in an autosomal dominant pattern, with a high degree of penetrance. MEN-1 is characterized by hyperplasia and/or neoplasm of the parathyroid glands, pancreatic islet cells, and pituitary glands. Hyperparathyroidism occurs in about 90% of patients, pancreatic neuroendocrine tumors (pNETs) in 60% of patients, and pituitary adenomas in 40% of patients (2) (4) (5). Hyperparathyroidism is usually the first manifestation of the syndrome. However, the presence of hyperparathyroidism may not be detected until clinical disease of the pancreas or pituitary has brought the patient to medical attention. The presence of hyperparathyroidism may also be detected when screening immediate family members of those with proven MEN-1. MEN-1 patients with hyperparathyroidism typically have multiple gland nodular hyperplasia. The disease usually takes a slow but progressive course. The individual gland involvement is often variable and asymmetric, resulting in enlargement of only one or two glands. Hyperparathyroidism is commonly diagnosed during the second decade of life.

The most frequent islet cell neoplasm in patients with MEN-1 is gastrinoma. This is usually identified during the third or fourth decade of life. However, with the advent of biochemical screening, it is now typically detected earlier (6-8). Approximately one third of patients with gastrinomas are associated with MEN-1 (9-12). However, fewer than 5% of insulinomas are found in MEN-1 patients (13). Gastrinomas in MEN-1 syndrome are usually small, multiple adenomas in the pancreas or duodenum (14). The malignant potential of MEN-1 associated gastrinomas is probably less than sporadic tumors. Other types of pNETs identified in MEN-1 patients include non-functioning tumors, vipomas, glucagonomas, somatostatinomas, and Ppomas (15) (16). More than one clinical syndrome may develop in the same patient either synchronously, or more often meta-synchronously. Some patients may have lymph node or liver metastases with no clinical manifestations.

It has become apparent that gastrinomas in MEN-1 patients are most often located in the duodenum. These tumors are small, usually multiple, and may be associated with pancreatic gastrinomas as well (14) (16). Immunohistochemical studies of the pancreas from MEN-1 patients demonstrate that most tumors that stain positively for gastrin are in the duodenum, or in the head or uncinate process of the pancreas (12). It has been shown that proliferative gastrin cell changes in the duodenal mucosa precede the development of duodenal gastrinomas in MEN-1, but not sporadic duodenal gastrinomas (17). Patients with clinical syndromes usually have discrete tumors rather than diffuse islet cell disease as the cause of the syndrome (18) (19). Even though diffuse islet cell dysplasia is found in most patients, these cells do not stain

for either gastrin or insulin. At least 50% of patients with elevated serum gastrin have metastases already (7).

Pituitary tumors are common in patients with MEN-1, and may be micro or macro adenomas (1) (2). The tumors are generally functionally active and often secrete prolactin (20). Less commonly, the pituitary tumors may secrete ACTH leading to Cushing's syndrome, or growth hormone leading to acromegaly. It is especially important to establish that Cushing's syndrome in the MEN-1 patient is pituitary dependent (i.e., Cushing disease) rather than pituitary independent caused by an adrenal adenoma, an islet cell tumor, or a bronchial carcinoid tumor secreting ACTH or corticotrophin-releasing factor.

There is an increased frequency of adrenal lesions in patients with MEN-1 syndrome occurring in approximately 18% of MEN1 patients (13) (21) (22) (23) (16). The patients may have functional or non-functional adrenal cortical hyperplasia or adenomas. There is some evidence to suggest that the frequency of adrenal cortical carcinoma is increased in MEN-1 patients.

Carcinoid tumors also occur more frequently in MEN-1 patients (24). Although they have been reported in a variety of locations, bronchial carcinoids occur more commonly in women, and thymic carcinoids occur more commonly in men. Patients with MEN-1 and gastrinoma who are on long term H2 blockers or proton pump inhibitors may develop gastric carcinoids (25).

Female MEN1 patients are at increased risk of invasive breast cancer, with a relative risk of 2.83, and occurring at a mean age of 48 years, compared to 60-65 years in the general population (26) . This risk is not related to other known breast cancer risk factors (27). Thus, earlier breast cancer screening must be considered an integral part of the management of these patients.

As one can gather from all of the above, management of these patients is not straightforward. These complex and challenging patients should be seen, evaluated, and treated by an experienced multidisciplinary team.

GENETICS

The MEN-1 gene locus was first mapped to the long arm of chromosome 11 (11q13), by Larsson et al (28). The gene is a tumor suppressor gene   which has been identified and cloned (29) (30). The gene contains 10 exons and spans 10kb of genomic DNA. More than 300 different MEN-1 germ line mutations have been identified thus far (31). The mutations are spread over the entire genome including the intronic and promoter regions without significant clustering (32). There are no true "hot spots". As up to 20% of mutations involve intron sequences, it is important that these regions be searched for germline mutations (33). About 70% of the mutations are nonsense and frame shift mutations, resulting in truncation of the protein product. About 20% of MEN-1 kindreds lack an identified mutation in the MEN-1 gene. Thus, despite advances in the understanding of the genetics of MEN1, clinical diagnostic criteria remain important in making the diagnosis (32).

Despite detailed study, no clinically relevant correlation between the genetic mutation and the phenotypic expression has been identified (34) (32). However, data about genetic mutations and disease modification are slowly emerging. The likelihood of finding a mutation appears to correlate with the number of MEN-1 associated tumors, and the presence of a family history (35). A recent study suggests that the *p27* tumor suppressor gene may act as a disease modifier in patients with MEN1 germline mutations, with patients possessing the *p27* rs2066827 variant more likely to have tumors in 3 or 4 glands vs one or 2 glands (36). Patients with MEN1 mutations leading to CHES1 loss of interaction (LOI) have higher rates of functional pNETs (70% vs 34%), malignant pNETs (37% vs 9%), and increased pNET-related mortality (20% vs 4.5%) (37). It has also been shown that MEN1 patients with mutations in the JunD interacting domain have a higher risk of disease-associated death (38).

Endocrine tumors from MEN-1 patients have loss of heterozygosity (LOH). The allelic loss is always from the normal chromosome belonging to the unaffected parent, analogous to the second hit in retinoblastoma. A mouse model of MEN-1 has been generated through homologous recombination (39). Tumors in these mice show loss of the wild-type MEN-1 allele, as would be expected in a tumor suppressor gene.

The gene product has been identified and is a 610 amino acid protein called menin (28) (30). Menin is a nuclear protein, the function of which is unknown. It has no homology to known proteins. There are different patterns of expression in pancreatic exocrine and islet cells (40). Menin interacts with the transcription factor Jun-D (41), suggesting a potential role in transcriptional regulation. Menin has been shown to bind directly to double stranded DNA, with regulatory effects on cell proliferation (42). Menin interacts with activator S-phase kinase (ASK) with regulatory effects on cell proliferation (43). It appears that regulation of cyclin-dependant kinase inhibitor transcription by cooperative interaction between menin and mixed lineage leukemia (MLL) proteins plays a major role in menin-related tumor suppression (44). Menin has been shown to interact with numerous proteins including JunD, and nuclear factor - KappaB, Smad3, Pem, Nm23H1, glial fibrillary acidic protein, vimentin, and probably p53 (45). About 25 protein partners for menin have been identified, but the importance of many of these interactions remains unknown (46). Thus, the effects of menin on transcriptional regulation and cellular proliferation appear to be complex due to its effects on multiple pathways.

Deletions of chromosome 11q13 have also been found in a significant portion of sporadic adenomas of the parathyroid gland, pancreas, and pituitary gland. Among sporadic tumors, *MEN1* mutations are described as occurring in 10-20% of parathyroid adenomas, 10-50% of pNETs depending on the histologic type, and 25-35% of bronchial carcinoids (46). In one study, mutations of the MEN-1 gene have been identified in 31% of sporadic gastrinomas. However, the mutations are clustered between amino acids 66-166, unlike MEN-1, where mutations are scattered through the gene (47). MEN-1 mutations are identified less often in sporadic insulinoma, 17% in one series (48). Mutations in the MEN-1 gene are believed to be an early event, since mutations have been identified in both benign and malignant pNETs (49). MEN1 mutations were identified in 7 of 55(13%) of patients with sporadic pulmonary carcinoids, and those patients with mutations had a worse prognosis (50).Thus, the MEN-1 gene appears to

4

play an important role in both sporadic and familial endocrine tumorigenesis. A variety of other chromosomes and genetic changes may also be involved, such as PRAD1 in parathyroid adenoma, and Gs L-chain gene in pituitary adenoma. A recent study identified 3 new miRNA's which appear to be involved in MEN1 parathyroid neoplasia (51).The MEN1 gene may also play a role in the development of other tumor types . A study of human melanomas and melanoma cell lines showed that MEN1 acts as a melanoma tumor suppressor by stimulating transcription of genes involved in homologous recombination-directed DNA repair (52).

Several variants of MEN1 syndrome have been described. MEN1 Burin is characterized by a high incidence of prolactinomas (40%) and a low incidence of gastrinomas (10%) (53). No characteristic gene mutation has been identified in affected individuals. Familial isolated hyperparathyroidism is another MEN1 variant characterized by the development of hyperparathyroidism without other endocrinopathies in affected individuals (54). This autosomal dominant variant is notable for mild missense or in-frame deletions in the MEN1 gene as opposed to nonsense mutations seen in approximately 80% of MEN1 patients. A syndrome named MEN4 is notable for a predisposition to parathyroid adenomas, pituitary adenomas, and pNETS, is associated with germline *CDKN1B* mutations, but appears clinically indistinguishable from MEN1 (55).

DIAGNOSIS AND SCREENING

A diagnosis of MEN1 can be established by any one of three criteria recommended by a consensus statement: 1.) An individual with a known MEN1 gene mutation but does not have clinical or biochemical evidence of disease, 2.) An individual with one MEN1-associated tumor and a first degree relative diagnosed with MEN1, and 3.) An individual with at least two MEN1-associated tumors (56) In patients without a family history, the diagnosis of MEN-1 requires a high level of clinical suspicion. Patients presenting with hyperparathyroidism or hypergastrinemia should be carefully questioned regarding a family history (57). Furthermore, patients who present with pituitary adenoma may have a higher frequency of MEN1 than previously appreciated, 7.7% in a recent study (58). If after careful questioning MEN-1 syndrome is suspected, then biochemical screening should be performed. A biochemical screening program which gives the highest yield   includes measurement of serum calcium, intact PTH, gastrin, fasting glucose, insulin, proinsulin, chromogranin A, pancreatic polypeptide, glucagon, VIP, IGF-1, prolactin, somatomedin C, and ingestion of a test meal followed by measurement of pancreatic polypeptide and gastrin. If biochemical testing indicates the presence of MEN-1, this can be confirmed by genetic testing for mutations in the MEN-1 gene.

Once MEN-1 is diagnosed in the proband, genetic counseling and genetic testing should be considered in all family members. Patients diagnosed with MEN1 or are carriers of a mutant MEN1 gene are recommended to undergo physical examination, biochemical screening and imaging (56).Those family members who carry the mutated MEN-1 gene should undergo yearly biochemical screening as discussed above from childhood and continued for life. Indeed, genetically positive patients have biochemical evidence of neoplasia on average of 10 years prior to clinically evident disease (53). The importance of beginning screening at an early age in

identified *MEN1* carriers is further illustrated by a study of 19 patients ages 12-20 (59). They found pNETs in 42% (8 of 19), all non-functional, with 3 patients undergoing resection for large (>2cm) tumors. Serial measurements of chromogranin A levels may be useful for following patients with pNETs (60).

However, biochemical screening alone, even with a combination of markers, is insufficient to diagnose the presence of pNETS, due to relatively low sensitivity (61). Thus, imaging remains a critical component of the evaluation and follow-up of these patients. MRI of the pancreas, adrenal glands and pituitary should be done every 1 to 3 years and CT or MRI for thymic and bronchial carcinoid tumors every 1-2 years. A critical prospective assessment of such a screening program at one center found that most tumors in MEN1 patients were found at initial assessment and new pancreatic tumors were the most common tumors found on follow-up screening most reliably by endoscopic ultrasound (62). Based on this, they advocated for a more streamlined screening process including : 1) Serum measurement of calcium, gastrin, pancreatic polypeptide and prolactin every 3 years, 2) Endoscopic ultrasound of the pancreas every 3 years, 3) CT of the chest and abdomen in patients with prior pancreatic resections or with bronchial or thymic carcinoids and 4.) somatostatin receptor scintigraphy in patients with malignant pNETs. Such a program was reported to reduce the annual screening cost from 2,100 euro to 700 euro per patient (62).

Breast cancer is more common and occurs at an earlier age in female MEN1 patients (26) (27). Thus, earlier initiation of breast cancer screening should be considered in the management of female MEN1 patients. So far there are no data to suggest an increase in breast cancer risk in male MEN1 patients.

Early detection and early treatment of the endocrine abnormalities should reduce morbidity and mortality from this disease. Traditionally, peptic ulcer disease, renal complications, and malignant tumors were the common causes of morbidity and mortality in MEN-1 patients (54). However, with improved medical management, malignant tumors have become the predominant cause of morbidity and mortality (see Prognosis section below).

CLINICAL PRESENTATION AND MANAGEMENT

The diagnostic and therapeutic approach to MEN-1 patients is determined by the presence of a clinical syndrome or a clearly elevated hormonal level. The diagnosis is similar to patients with sporadic tumors. For example, hyperparathyroidism is diagnosed by the presence of hypercalcemia associated with elevated or non-suppressible intact PTH levels. Diagnosis of gastrinoma is confirmed by measurements of serum gastrin, the secretin stimulation test, and measurements of basal and stimulated gastric acid output. Insulinoma is diagnosed by the detection of increased insulin or pro-insulin levels with associated hypoglycemia. Pituitary adenomas usually have elevated serum prolactin or somatomedin C.

The localization procedures for patients with MEN-1 associated endocrine tumors are similar to patients with the sporadic counterparts. There are some problems unique to patients with MEN-

1. For instance, the pNETs in MEN-1 patients are particularly challenging due to their small size, frequent duodenal location, and multiplicity. The main role of imaging in these patients may be to identify those with liver metastases (56). However, some groups have had good results using endoscopic ultrasound for identifying pNETs in patients with MEN-1, even when tumors are small (63) (64) (62). Although somatostatin receptor scintigraphy may identify occult lesions, the false positive and false negative rates are considerable (65). A study of 49 adult MEN1 patients, 25 with pancreatic lesions identified on conventional imaging, suggests FDG-PET/CT may be useful for identifying those pNETs with increased malignant potential, as more aggressive lesions tended to be FDG-avid (66).Thus, no one imaging modality is consistently useful, and frequently multiple imaging methods are required.

A more recent imaging technique is PET/CT using radiolabelled gallium-68 attached to octreotide as Ga-68-Dota(-D-)-Phe(1)-Tyr(3)-octreotide (Ga-68-DOTATOC) to image neuroendocrine tumors with a reported sensitivity and specificity of 91.7% and 93.5%, respectively and altered management in 47.6% of MEN1 patients (67) . A subsequent study has failed to confirm these findings. In 33 patients with MEN1, DOTATOC-PET-CT failed to detect 62% of tumors found on conventional imaging, with the majority of missed lesions pNETs (68). And although more liver and lymph node metastases were detected in patients with known metastatic disease, in no patient was management altered. The conflicting data suggest more study and perhaps refinement of the technique will be required to determine the precise role and usefulness of DOTATOC-PET-CT in MEN1 patients.

In general, the management of patients with MEN-1 syndrome is the same as for each sporadic tumor comprising the syndrome. Thus, the surgical treatment is dependent on the phenotypic expression in the individual patient. MEN-1 patients must be followed for life for involvement of the parathyroid glands, endocrine pancreas, the pituitary gland, the adrenal glands, the thymus, and for bronchial carcinoids as previously noted above. Because the various components may present sequentially, surgical procedures involving different endocrine organs may be required over a period of many years.

PARATHYROID DISEASE

The hyperparathyroidism and resulting hypercalcemia in MEN-1 patients is usually mild and only slowly progressive. That does not mean that the hyperparthyroidism is insignificant. A recent study compared bone density measurements in 14 MEN1 hyperparathyroid and 104 sporadic hyperparathyroid patients. Z-scores were significantly lower in the lumbar spine, total hip and femoral neck in the MEN1 patients, with less bone density recovery 1 year postoperatively compared to the sporadic group (69).

Patients with gastrinoma and hyperparathyroidism may require more urgent parathyroidectomy since hypercalcemia increases gastrin secretion and worsens peptic ulcer disease. Patients with MEN-1 and hyperparathyroidism have hyperplasia. Although some patients at the time of diagnosis may have normal sized glands in addition to grossly enlarged glands, the normal sized glands will enlarge given time (70). Sestamibi scans are not felt to be useful in MEN-1

patients prior to initial operation, however they may sometimes be useful in re-operative cases (71). Because supernumerary glands are identified in as many as 6-20% of MEN-1 patients, cervical thymectomy is an essential component of the neck exploration in these patients (72).

Controversy persists regarding the use of subtotal versus total parathyroidectomy in MEN-I patients. A small study of 16 patients suggests that intraoperative PTH (IOPTH) measurements may be useful in these patients (62). Subtotal parathyroidectomy, leaving only a small remnant of one gland in place, is associated with persistent hyperparathyroidism in 12% of patients and long term recurrence rates ranging from 7 to 44% (73) (67) (74). For patients who develop persistent/recurrent hyperparathyroidism after subtotal parathyroidectomy, preoperative imaging studies are helpful. However, even an aggressive imaging strategy may miss the site of disease, thus IOPTH measurements should be routinely performed in operative patients (75). Even with preoperative imaging and IOPTH, the 30 patients in their study underwent 69 reoperations, with a recurrence in 4 (13%). This again illustrates the challenge presented by these patients.

One group has advocated unilateral neck clearance as an alternative to subtotal or total parathyroidectomy. Unilateral clearance was offered to selected patients with concordant preoperative sestimibi scan and ultrasound showing a single enlarged parathyroid gland. The results in the 8 patients who underwent unilateral clearance were comparable to the 16 who underwent subtotal parathyroidectomy at a mean follow-up of 47-68 months (76).

Total parathyroidectomy with forearm auto transplantation is associated with lower persistent hyperparathyroidism of 0% and lower long term recurrence rates in some series (77) (78) (79), but not in others (74). If the disease should recur, it is a simple matter to remove a portion of the transplanted parathyroid tissue under local anesthesia. Disadvantages are that patients will require vitamin D and oral calcium for at least 3 months or longer, until the transplant functions. In addition, some patients are rendered permanently hypoparathyroid, unless subsequent transplant of cryopreserved parathyroid tissue is successful.

The risk of hypoparathyroidism after total parathyroidectomy with autotransplantation ranges from 22 to 36% compared to approximately 10% with subtotal parathyroidectomy (80) (74) (79). Thus, the risk of permanent hypoparathyroidism with total parathyroidectomy and auto transplantation needs to be balanced against the risk of recurrent hyperparathyroidism with subtotal parathyroidectomy. Although there are good arguments on both sides, at this time the balance appears to be leaning more towards subtotal parathyroidectomy as the preferred approach.

PANCREATIC NEUROENDOCRINE TUMORS (pNETs)

The surgical management of MEN-1 patients with pancreatic disease remains controversial (18) (19) (81) (56). There is no universal agreement as to the indications for surgery (74) (56). Nearly all MEN-1 patients with pancreatic disease have diffuse islet cell dysplasia, such as nesidioblastosis, islet cell hyperplasia, microadenomatosis, and/or discrete islet cell tumors. A

cure can only be achieved in a minority of patients. Fortunately, most patients with a functional tumor can be initially managed medically while the indications for surgery, and the risks and benefits of surgery are ascertained. There is little need or justification for total pancreatectomy. A selective surgical approach, nonetheless, may be justified. Patients in whom there is a discrete anatomic abnormality which is functionally active, may be considered for exploration. The importance of aggressive preoperative localization studies in MEN-1 patients considered for exploration cannot be over emphasized. Other factors which need to be considered are the patient's age, overall medical condition, and the difficulty in managing the patient medically. Prior to offering the patient surgery, it should be noted that the morbidity of major pancreatic resection can be considerable in the MEN1 population, with 10-86% of patients having impaired glucose tolerance or diabetes after major pancreatectomy (82). Furthermore, it is not clear that surgical intervention has a major impact on tumor-related mortality (83).

Many groups, including our own, and many guidelines use tumor size as an indication for selecting patients for surgery (56). Patients with larger lesions of the pancreas have a greater risk of malignancy and liver metastases. Patients with pancreatic tumors 2-3 cm in size have regional lymph node metastases in 50-70% of cases and tumors greater than 4 cm have a 25-40% risk of hepatic metastases (84). This was confirmed in a French multi-center trial involving 71 patients. However, resecting the primary lesions did not prevent subsequent liver metastases (85). Further clouding the issue is a study in 48 patients which showed no correlation between pancreatic tumor size and metastases in MEN-1 patients (86). One group favors a selective but aggressive approach, recommending surgery for patients with a clinical syndrome, tumor size more than 1.5-2cm, or with a significant increase in size over 12 months (87). In their study of 77 MEN1 patients, 50 patients underwent surgery consisting of removal of all functioning lesions, and all measurable disease in the pancreas, regional lymph nodes, and liver. Of note, 12/27 patients in the non-surgical group, and 18/50 patients in the operative group showed evidence of pNET progression. Overall, only 2 (2.6%) of their patients died related to pNET progression, both with gastrinoma (87). Thus, it has been difficult to prove that an aggressive surgical approach in MEN1 patients, even in those with larger pNETs, provides a survival advantage.

Current recommendations for surgical therapy for MEN1 gastrinomas include pancreatic tumors greater than 2 cm and duodenal tumors (18) (19) (79) (55). Many believe that patients suspected of having duodenal gastrinomas should be explored, because of the high risk of malignancy. Eventually metastases to lymph nodes and/or liver develop in many or most of these patients (88) (89). Localization studies should be performed in patients prior to surgery. During the operation, a thorough examination of the duodenum and pancreas must be done since 35% of patients thought to have solitary tumors are found to have multifocal disease (90) . After a Kocher maneuver is performed, the duodenum can be evaluated by a combination of palpation, endoscopic transillumination, intraoperative ultrasound and longitudinal duodenotomy along the anterolateral side of the second portion of the duodenum (91). These tumors may be as small as 1-2 mm. A peripancreatic lymph node dissection is routinely performed as there is an incidence of regional lymph node metastasis in 53 - 68% and lymph node only disease in 3-12% of patients (49) (92). Tumors identified in the head of the pancreas or uncinate process by palpation or intraoperative ultrasound are enucleated if possible. More extensive procedures

such as pancreaticoduodenectomy and distal pancreatectomy with splenic preservation are reserved for those patients whose disease cannot be eradicated with lesser procedures. Most patients can be rendered eugastrinemic, at least initially, with this approach. Patients with two or more lesions, or with large lesions, who underwent a thorough exploration, aggressive resection, and lymph node dissection, appear to have survival comparable to those without identified tumor or those with more limited disease (92). Unfortunately, many or most patients recur with new primary tumors and/or distant disease , with no patients disease free at 5 years (82). Because of the lack of clear benefit, other groups favor a more conservative approach, believing that most MEN-1 gastrinomas patients are not curable. Patients with unresectable disease, metastatic disease, or recurrent disease can in many instances be successfully managed medically, with histamine II receptor blockers or proton pump inhibitors (93).

Other pancreatic tumors occurring in MEN1 include insulinomas, non-functioning tumors and less commonly glucagonomas. Unlike patients with sporadic insulinoma, MEN-1 patients with hyperinsulinism tend to be younger at the time of diagnosis and usually have multiple tumors. However, if the responsible tumors are successfully identified and removed, the syndrome is cured, and recurrences are rare. Long-term medical management of hyperinsulinism and hypoglycemia can prove challenging. Thus, a surgical approach must be strongly considered in patients who are medically able. Techniques such as transhepatic portal venous sampling (THPVS) may be useful preoperatively to regionalize the source(s) of hyperinsulinism and help tailor the surgical approach. A study of 12 patients with MEN-1 and insulinoma who underwent aggressive surgery revealed multiple insulinomas in 5 patients, insulin-positive lymph node metastases in two patients, and not surprisingly, multiple non-functioning tumors in all patients (94). No patients developed clinical recurrence at a mean follow-up of 85 months, supporting a role for aggressive identification and resection of all insulin producing lesions, including with pancreaticoduodenectomy, if required.

The role of surgery for non-functioning pancreatic tumors remains controversial. Malignant pancreatic neuroendocrine tumors are the leading cause of death in MEN1 patients (15) (95) (96). An updated consensus recommended surgery for tumors that are more than 1 cm in size and /or show significant growth over 6-12 months (56).These tumors tend to be limited to the pancreas and are multifocal. Thus, more extensive pancreatic resections including total pancreatectomy if required to remove all lesions have been recommended by some. Distal pancreatectomy with enucleation of tumors in the head of the pancreas has resulted in a prolonged median survival of 22 years and an increased chance of being disease free at 10 years compared to enucleation alone (84% v 50%) and a lower incidence of distant metastasis (9% v 50%) (15). Complications include a 20% chance of developing diabetes mellitus, steatorrhea, and dumping syndrome (97). Thus, aggressive surgery in even the best of hands is associated with significant morbidity. A study of 46 MEN1 patients with non-functional pNETs prospectively followed for a mean of 10.7 years showed low disease specific mortality, thus the authors favor a conservative approach for tumors $\leq$ 2cm (98). Indeed, given the morbidity of surgery in this patient population, we believe that an aggressive approach to resect all non – functioning pNETs is seldom, if ever, indicated.

Patients with locally advanced and/or metastatic disease can be treated with targeted chemotherapeutic agents similar to patients with sporadic disease. The tyrosine kinase receptor inhibitor sunitinib has been shown in a prospective randomized trial to increase overall survival and prolong progression-free survival (99). Another randomized trial reported that patients with pancreatic neuroendocrine tumors treated with everolimus, an inhibitor of the mammalian target of rapamycin, experienced a doubling of median progression-free survival (100).

PITUITARY TUMORS

Pituitary tumors are the least common of the 3 signature tumors characteristic of MEN1 with an incidence ranging from 30-50% (101) (102). The pituitary adenomas are more aggressive, with a higher risk of progression/recurrence, but there is not an increased risk of pituitary carcinoma compared with the general population (103). Most patients with MEN-1 associated pituitary disease have a prolactinoma occurring in approximately 60% of patients followed in frequency by tumors that secrete growth hormone in 25% of cases and ACTH in 5% of cases. Pituitary tumors in MEN1 patients are predominantly macroadenomas in 85% and demonstrate plurihormonal expression in 39% on pathology (104). Patients with prolactinomas should initially be treated with bromocriptine or other dopamine analogs. Both the prolactin level and tumor size will decrease in many patients. However, the response rate appears to be lower in MEN-1 patients (42%), compared to non-MEN-1 patients (90%) (101). Trans-sphenoidal hypophysectomy is reserved for prolactinoma patients who fail to respond to medical therapy. Surgery is the treatment of choice for growth hormone-secreting pituitary adenomas. An alternative is octreotide, which reduces tumor size and circulating growth hormone and somatomedin C levels in a significant number of patients (105). Patients with Cushing's disease are best treated with trans-sphenoidal hypophysectomy. Radiation therapy can be used as an alternative to surgery, or in patients who have failed other modalities. The use of modern stereotaxic radiosurgery can minimize the problem of hypopituitarism, often seen after conventional radiation therapy (20).

OTHER LESIONS

Carcinoid tumors occur in more than 3% of patients with MEN1. These tumors may be located in the thymus, bronchial tree, and stomach among other sites. Thymic carcinoids develop in 2.8%-11% of MEN-1 patients, occur predominantly in males, have very aggressive behavior, and may portend a poor prognosis (106) (84) (96) (95) . A recent study of 9 MEN1 patients with thymic carcinoids included 3 women, certainly a higher percentage than most studies (107). Periodic chest CT or MRI scans should be used in the follow-up of MEN-1 patients, to help detect the development of thymic carcinoids. Prophylactic transcervical thymectomy has been recommended at the time of parathyroidectomy in MEN1 patients; however, thymic carcinoid tumors can occur after transcervical thymectomy at a surprising rate (56) (96) (108). Bronchial carcinoids occur in about 5% of MEN-1 patients, occur primarily in females, and appear to have a much more benign clinical course (109). Gastric carcinoids can occur in 15-50% of MEN-1 gastrinoma patients, and traditionally have been felt to be benign. However, patients with longstanding MEN-1 gastrinomas may develop gastric carcinoids with aggressive behavior,

11

including metastases to the liver (110). Surgical resection should be considered for gastric carcinoids when they are identified.

As previously noted in this chapter, adrenal lesions occur in up to 18% of MEN1 patients. These lesions include primarily functional or non-functional adrenal cortical hyperplasia or adenomas, with management similar to those of sporadic lesions. Cutaneous lesions, especially angiofibromas and collagenomas are quite common in MEN-1 patients, occurring in more than 60%, and these lesions are usually multiple (111).

PROGNOSIS

The prognosis of MEN-1 patients is generally good. In a large series of gastrinoma patients, patients with MEN-1 had a 15 year survival of 93%, compared to 68% in sporadic patients (90). However, one cannot take a cavalier attitude towards this disorder. Studies have clearly shown that MEN-1 patients have an increased risk of premature death, often related to metastatic islet cell tumor (91) (112). A study of 220 pNET patients from the Dutch National MEN1 database revealed that 34(15%) developed liver metastases, and 16 of these patients died after a median follow-up of 4 years (113). Approximately 60-70% of MEN1 patients who die will die directly related to MEN1 (96) (82). With the advent of medical therapy to control the hypersecretory states of gastrinoma and other functional pNETs, and improved management of hyperparathyroidism and the pituitary tumors, the mortality associated with MEN1 has shifted to malignant pNETs and thymic carcinoids (82). The development of thymic carcinoid tumors is associated with an increased risk of death (96) (95). Glucagonomas, Vipomas, somatostatinomas and non-functioning pancreatic endocrine tumors in MEN1 have also been reported to confer a 3-4 fold increase risk of death (96) (15). Thus better strategies are needed to identify those patients whose tumors will exhibit more aggressive behavior, and thus merit more aggressive surgical treatment and closer follow-up.

REFERENCES

1. Brandi ML. Multiple endocrine neoplasia type I: general features and new insights into etiology. J Endocrinol Invest 1991; 14(1):61-72.
2. Eberle F, Grun R. Multiple endocrine neoplasia, type I (MEN I). Ergeb Inn Med Kinderheilkd 1981; 46:76-149.
3. Thakker RV, Ponder BA. Multiple endocrine neoplasia. Baillieres Clin Endocrinol Metab 1988; 2(4):1031-1067.
4. Oberg K, Skogseid B, Eriksson B. Multiple endocrine neoplasia type 1 (MEN-1). Clinical, biochemical and genetical investigations. Acta Oncol 1989; 28(3):383-387.
5. Samaan NA, Ouais S, Ordonez NG, Choksi UA, Sellin RV, Hickey RC. Multiple endocrine syndrome type I. Clinical, laboratory findings, and management in five families. Cancer 1989; 64(3):741-752.
6. Skogseid B, Rastad J, Oberg K. Multiple endocrine neoplasia type 1. Clinical features and screening. Endocrinol Metab Clin North Am 1994; 23(1):1-18.

7. Gibril F, Schumann M, Pace A, Jensen RT. Multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome: a prospective study of 107 cases and comparison with 1009 cases from the literature. Medicine (Baltimore) 2004; 83(1):43-83.

8. Eriksson B, Skogseid B, Lundqvist G, Wide L, Wilander E, Oberg K. Medical treatment and long-term survival in a prospective study of 84 patients with endocrine pancreatic tumors. Cancer 1990; 65(9):1883-1890.

9. Friesen SR. The development of endocrinopathies in the prospective screening of two families with multiple endocrine adenopathy, type I. World J Surg 1979; 3(6):753-764.

10. Lamers CB, Buis JT, van TJ. Secretin-stimulated serum gastrin levels in hyperparathyroid patients from families with multiple endocrine adenomatosis type I. Ann Intern Med 1977; 86(6):719-724.

11. Thompson NW, Lloyd RV, Nishiyama RH et al. MEN I pancreas: a histological and immunohistochemical study. World J Surg 1984; 8:561-574.

12. Howard TJ, Passaro E Jr. Gastrinoma. New medical and surgical approaches. Surg Clin North Am 1989; 69(3):667-681.

13. Pipeleers-Marichal M, Somers G, Willems G et al. Gastrinomas in the duodenums of patients with multiple endocrine neoplasia type 1 and the Zollinger-Ellison syndrome. N Engl J Med 1990; 322(11):723-727.

14. Wynick D, Williams SJ, Bloom SR. Symptomatic secondary hormone syndromes in patients with established malignant pancreatic endocrine tumors. N Engl J Med 1988; 319(10):605-607.

15. Kouvaraki MA, Shapiro SE, Cote GJ et al. Management of pancreatic endocrine tumors in multiple endocrine neoplasia type 1. World J Surg 2006; 30(5):643-653.

16. Goudet P, Murat A, Binquet C et al. Risk factors and causes of death in MEN1 disease. A GTE (Groupe d'Etude des Tumeurs Endocrines) cohort study among 758 patients. World J Surg 2010; 34(2):249-255.

17. Doherty GM. Multiple endocrine neoplasia type 1: duodenopancreatic tumors. Surg Oncol 2003; 12(2):135-143.

18. Anlauf M, Perren A, Meyer CL et al. Precursor lesions in patients with multiple endocrine neoplasia type 1-associated duodenal gastrinomas. Gastroenterology 2005; 128(5):1187-1198.

19. van Heerden JA, Smith SL, Miller LJ. Management of the Zollinger-Ellison syndrome in patients with multiple endocrine neoplasia type I. Surgery 1986; 100(6):971-977.

20. Norton JA, Doppman JL, Collen MJ et al. Prospective study of gastrinoma localization and resection in patients with Zollinger-Ellison syndrome. Ann Surg 1986; 204(4):468-479.

21. McCutcheon IE. Management of individual tumor syndromes. Pituitary neoplasia. Endocrinol Metab Clin North Am 1994; 23(1):37-51.

22. Ballard HS, Fame B, Hartsock RJ. Familial multiple endocrine adenoma- peptic ulcer complex. Medicine (Baltimore) 1964; 43:481-516.

23. Maton PN, Gardner JD, Jensen RT. Cushing's syndrome in patients with the Zollinger-Ellison syndrome. N Engl J Med 1986; 315(1):1-5.

24. Schimke RN. Multiple endocrine neoplasia: how many syndromes? Am J Med Genet 1990; 37(3):375-383.

25. Farhangi M, Taylor J, Havey A, O'Dorisio TM. Neuroendocrine (carcinoid) tumor of the lung and type I multiple endocrine neoplasia. South Med J 1987; 80(11):1459-1462.

26. Dreijerink KM, Goudet P, Burgess JR, Valk GD. Breast-cancer predisposition in multiple endocrine neoplasia type 1. N Engl J Med 2014; 371(6):583-584.

27. van Leeuwaarde RS, Dreijerink KM, Ausems MG et al. MEN1-Dependent Breast Cancer: Indication for Early Screening? Results From the Dutch MEN1 Study Group. J Clin Endocrinol Metab 2017; 102(6):2083-2090.

28. Cadiot G, Laurent-Puig P, Thuille B, Lehy T, Mignon M, Olschwang S. Is the multiple endocrine neoplasia type 1 gene a suppressor for fundic argyrophil tumors in the Zollinger-Ellison syndrome? Gastroenterology 1993; 105(2):579-582.

29. Larsson C, Skogseid B, Oberg K, Nakamura Y, Nordenskjold M. Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. Nature 1988; 332(6159):85-87.

30. The European Consortium on MEN1. Linkage disequilibrium studies in multiple endocrine neoplasia type 1 (MEN1). Hum Genet 1997; 100(5-6):657-665.

31. Chandrasekharappa SC, Guru SC, Manickam P et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science 1997; 276(5311):404-407.

32. Hyde SM, Cote GJ, Grubbs EG. Genetics of Multiple Endocrine Neoplasia Type 1/Multiple Endocrine Neoplasia Type 2 Syndromes. Endocrinol Metab Clin North Am 2017; 46(2):491-502.

33. Calender A. Molecular genetics of neuroendocrine tumors. Digestion 2000; 62 Suppl 1:3-18.

34. Mutch MG, Dilley WG, Sanjurjo F et al. Germline mutations in the multiple endocrine neoplasia type 1 gene: evidence for frequent splicing defects. Hum Mutat 1999; 13(3):175-185.

35. Agarwal SK, Lee BA, Sukhodolets KE et al. Molecular pathology of the MEN1 gene. Ann N Y Acad Sci 2004; 1014:189-198.

36. Longuini VC, Lourenco DM, Jr., Sekiya T et al. Association between the p27 rs2066827 variant and tumor multiplicity in patients harboring MEN1 germline mutations. Eur J Endocrinol 2014; 171(3):335-342.

37. Bartsch DK, Slater EP, Albers M et al. Higher risk of aggressive pancreatic neuroendocrine tumors in MEN1 patients with MEN1 mutations affecting the CHES1 interacting MENIN domain. J Clin Endocrinol Metab 2014; 99(11):E2387-E2391.

38. Thevenon J, Bourredjem A, Faivre L et al. Higher risk of death among MEN1 patients with mutations in the JunD interacting domain: a Groupe d'etude des Tumeurs Endocrines (GTE) cohort study. Hum Mol Genet 2013; 22(10):1940-1948.

39. Ellard S, Hattersley AT, Brewer CM, Vaidya B. Detection of an MEN1 gene mutation depends on clinical features and supports current referral criteria for diagnostic molecular genetic testing. Clin Endocrinol (Oxf) 2005; 62(2):169-175.

40. Crabtree J, Scacheri P, Ward J et al. A mouse model of multiple endocrine neoplasia, type 1, develop multiple endocrine tumors. PNAS 2001; 98(3):1118-1123.

41. Cavallari I, D'Agostino DM, Ferro T et al. In situ analysis of human menin in normal and neoplastic pancreatic tissues: evidence for differential expression in exocrine and endocrine cells. J Clin Endocrinol Metab 2003; 88(8):3893-3901.

42. Agarwal SK, Guru SC, Heppner C et al. Menin interacts with the AP1 transcription factor JunD and represses JunD-activated transcription. Cell 1999; 96(1):143-152.

14

43. La P, Silva AC, Hou Z et al. Direct binding of DNA by tumor suppressor menin. J Biol Chem 2004; 279(47):49045-49054.

44. Schnepp RW, Hou Z, Wang H et al. Functional interaction between tumor suppressor menin and activator of S-phase kinase. Cancer Res 2004; 64(18):6791-6796.

45. Milne TA, Hughes CM, Lloyd R et al. Menin and MLL cooperatively regulate expression of cyclin-dependent kinase inhibitors. Proc Natl Acad Sci U S A 2005; 102(3):749-754.

46. Oberg K. The genetics of neuroendocrine tumors. Semin Oncol 2013; 40(1):37-44.

47. Poisson A, Zablewska B, Gaudray P. Menin interacting proteins as clues toward the understanding of multiple endocrine neoplasia type 1. Cancer Lett 2003; 189(1):1-10.

48. Goebel SU, Heppner C, Burns AL et al. Genotype/phenotype correlation of multiple endocrine neoplasia type 1 gene mutations in sporadic gastrinomas. J Clin Endocrinol Metab 2000; 85(1):116-123.

49. Zhuang Z, Vortmeyer AO, Pack S et al. Somatic mutations of the MEN1 tumor suppressor gene in sporadic gastrinomas and insulinomas. Cancer Res 1997; 57(21):4682-4686.

50. Swarts DR, Scarpa A, Corbo V et al. MEN1 gene mutation and reduced expression are associated with poor prognosis in pulmonary carcinoids. J Clin Endocrinol Metab 2014; 99(2):E374-E378.

51. Luzi E, Ciuffi S, Marini F, Mavilia C, Galli G, Brandi ML. Analysis of differentially expressed microRNAs in MEN1 parathyroid adenomas. Am J Transl Res 2017; 9(4):1743-1753.

52. Fang M, Xia F, Mahalingam M, Virbasius CM, Wajapeyee N, Green MR. MEN1 is a melanoma tumor suppressor that preserves genomic integrity by stimulating transcription of genes that promote homologous recombination-directed DNA repair. Mol Cell Biol 2013; 33(13):2635-2647.

53. Hao W, Skarulis MC, Simonds WF et al. Multiple endocrine neoplasia type 1 variant with frequent prolactinoma and rare gastrinoma. J Clin Endocrinol Metab 2004; 89(8):3776-3784.

54. Hannan FM, Nesbit MA, Christie PT et al. Familial isolated primary hyperparathyroidism caused by mutations of the MEN1 gene. Nat Clin Pract Endocrinol Metab 2008; 4(1):53-58.

55. Thakker RV. Multiple endocrine neoplasia type 1 (MEN1) and type 4 (MEN4). Mol Cell Endocrinol 2014; 386(1-2):2-15.

56. Thakker RV, Newey PJ, Walls GV et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 2012; 97(9):2990-3011.

57. Wang EH, Ebrahimi SA, Wu AY, Kashefi C, Passaro E Jr, Sawicki MP. Mutation of the MENIN gene in sporadic pancreatic endocrine tumors. Cancer Res 1998; 58(19):4417-4420.

58. Nunes VS, Souza GL, Perone D, Conde SJ, Nogueira CR. Frequency of multiple endocrine neoplasia type 1 in a group of patients with pituitary adenoma: genetic study and familial screening. Pituitary 2014; 17(1):30-37.

59. Goncalves TD, Toledo RA, Sekiya T et al. Penetrance of functioning and nonfunctioning pancreatic neuroendocrine tumors in multiple endocrine neoplasia type 1 in the second decade of life. J Clin Endocrinol Metab 2014; 99(1):E89-E96.

60. Thompson NW, Bondeson AG, Bondeson L, Vinik A. The surgical treatment of gastrinoma in MEN I syndrome patients. Surgery 1989; 106:1081-1085.

15

61. Qiu W, Christakis I, Silva A et al. Utility of chromogranin A, pancreatic polypeptide, glucagon and gastrin in the diagnosis and follow-up of pancreatic neuroendocrine tumours in multiple endocrine neoplasia type 1 patients. Clin Endocrinol (Oxf) 2016; 85(3):400-407.

62. Waldmann J, Fendrich V, Habbe N et al. Screening of patients with multiple endocrine neoplasia type 1 (MEN-1): a critical analysis of its value. World J Surg 2009; 33(6):1208-1218.

63. Marx SJ, Vinik AI, Santen RJ, Floyd JC, Jr., Mills JL, Green J. Multiple endocrine neoplasia type I: assessment of laboratory tests to screen for the gene in a large kindred. Medicine (Baltimore) 1986; 65:226-241.

64. Lairmore TC, Piersall LD, DeBenedetti MK et al. Clinical genetic testing and early surgical intervention in patients with multiple endocrine neoplasia type 1 (MEN 1). Ann Surg 2004; 239(5):637-645.

65. Wilkinson S, Teh BT, Davey KR, McArdle JP, Young M, Shepherd JJ. Cause of death in multiple endocrine neoplasia type 1. Arch Surg 1993; 128(6):683-690.

66. Kornaczewski Jackson ER, Pointon OP, Bohmer R, Burgess JR. Utility of FDG-PET Imaging for Risk Stratification of Pancreatic Neuroendocrine Tumors in MEN1. J Clin Endocrinol Metab 2017; 102(6):1926-1933.

67. Froeling V, Elgeti F, Maurer MH et al. Impact of Ga-68 DOTATOC PET/CT on the diagnosis and treatment of patients with multiple endocrine neoplasia. Ann Nucl Med 2012; 26(9):738-743.

68. Albers MB, Librizzi D, Lopez CL et al. Limited Value of Ga-68-DOTATOC-PET-CT in Routine Screening of Patients with Multiple Endocrine Neoplasia Type 1. World J Surg 2017; 41(6):1521-1527.

69. Silva AM, Vodopivec D, Christakis I et al. Operative intervention for primary hyperparathyroidism offers greater bone recovery in patients with sporadic disease than in those with multiple endocrine neoplasia type 1-related hyperparathyroidism. Surgery 2017; 161(1):107-115.

70. Thompson NW. Current concepts in the surgical management of multiple endocrine neoplasia type 1 pancreatic-duodenal disease. Results in the treatment of 40 patients with Zollinger-Ellison syndrome, hypoglycaemia or both. J Intern Med 1998; 243(6):495-500.

71. Gauger PG, Scheiman JM, Wamsteker EJ, Richards ML, Doherty GM, Thompson NW. Role of endoscopic ultrasonography in screening and treatment of pancreatic endocrine tumours in asymptomatic patients with multiple endocrine neoplasia type 1. Br J Surg 2003; 90(6):748-754.

72. Langer P, Kann PH, Fendrich V et al. Prospective evaluation of imaging procedures for the detection of pancreaticoduodenal endocrine tumors in patients with multiple endocrine neoplasia type 1. World J Surg 2004; 28(12):1317-1322.

73. Yim JH, Siegel BA, DeBenedetti MK, Norton JA, Lairmore TC, Doherty GM. Prospective study of the utility of somatostatin-receptor scintigraphy in the evaluation of patients with multiple endocrine neoplasia type 1. Surgery 1998; 124(6):1037-1042.

74. Norton JA, Venzon DJ, Berna MJ et al. Prospective study of surgery for primary hyperparathyroidism (HPT) in multiple endocrine neoplasia-type 1 and Zollinger-Ellison syndrome: long-term outcome of a more virulent form of HPT. Ann Surg 2008; 247(3):501-510

75. Keutgen XM, Nilubol N, Agarwal S et al. Reoperative Surgery in Patients with Multiple Endocrine Neoplasia Type 1 Associated Primary Hyperparathyroidism. Ann Surg Oncol 2016; 23(Suppl 5):701-707.
76. Kluijfhout WP, Duh QY. Unilateral Clearance for Primary Hyperparathyroidism in Selected Patients with Multiple Endocrine Neoplasia Type 1: Reply. World J Surg 2017; 41(1):329.
77. Doherty GM, Lairmore TC, DeBenedetti MK. Multiple endocrine neoplasia type 1 parathyroid adenoma development over time. World J Surg 2004; 28(11):1139-1142.
78. Shepherd JJ, Burgess JR, Greenaway TM, Ware R. Preoperative sestamibi scanning and surgical findings at bilateral, unilateral, or minimal reoperation for recurrent hyperparathyroidism after subtotal parathyroidectomy in patients with multiple endocrine neoplasia type 1. Arch Surg 2000; 135(7):844-848.
79. Tonelli F, Marcucci T, Fratini G, Tommasi MS, Falchetti A, Brandi ML. Is total parathyroidectomy the treatment of choice for hyperparathyroidism in multiple endocrine neoplasia type 1? Ann Surg 2007; 246(6):1075-1082.
80. Lafferty FW. Primary hyperparathyroidism. Changing clinical spectrum, prevalence of hypertension, and discriminant analysis of laboratory tests. Arch Intern Med 1981; 141(13):1761-1766.
81. Tonelli F, Spini S, Tommasi M et al. Intraoperative parathormone measurement in patients with multiple endocrine neoplasia type I syndrome and hyperparathyroidism. World J Surg 2000; 24(5):556-562.
82. Jensen RT, Norton JA. Treatment of Pancreatic Neuroendocrine Tumors in Multiple Endocrine Neoplasia Type 1: Some Clarity But Continued Controversy. Pancreas 2017; 46(5):589-594.
83. Donegan D, Singh ON, Rodriguez-Gutierrez R et al. Long-term outcomes in patients with multiple endocrine neoplasia type 1 and pancreaticoduodenal neuroendocrine tumours. Clin Endocrinol (Oxf) 2017; 86(2):199-206.
84. Norton JA. Surgical treatment and prognosis of gastrinoma. Best Pract Res Clin Gastroenterol 2005; 19(5):799-805.
85. Prinz RA, Gamvros OI, Sellu D, Lynn JA. Subtotal parathyroidectomy for primary chief cell hyperplasia of the multiple endocrine neoplasia type I syndrome. Ann Surg 1981; 193(1):26-29.
86. Wells SA, Jr., Gunnells JC, Gutman RA, Shelburne JD, Schneider AB, Sherwood LM. The successful transplantation of frozen parathyroid tissue in man. Surgery 1977; 81(1):86-90.
87. Giudici F, Cavalli T, Giusti F et al. Natural History of MEN1 GEP-NET: Single-Center Experience After a Long Follow-Up. World J Surg 2017; Published online: 20 April 2017(DOI 10.1007/s00268-017-4019-2).
88. Arnalsteen LC, Alesina PF, Quiereux JL et al. Long-term results of less than total parathyroidectomy for hyperparathyroidism in multiple endocrine neoplasia type 1. Surgery 2002; 132(6):1119-1124.
89. Lambert LA, Shapiro SE, Lee JE et al. Surgical treatment of hyperparathyroidism in patients with multiple endocrine neoplasia type 1. Arch Surg 2005; 140(4):374-382.

90. Norton JA, Alexander HR, Fraker DL, Venzon DJ, Gibril F, Jensen RT. Comparison of surgical results in patients with advanced and limited disease with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome. Ann Surg 2001; 234(4):495-505.

91. Norton JA, Fraker DL, Alexander HR et al. Surgery increases survival in patients with gastrinoma. Ann Surg 2006; 244(3):410-419.

92. Hellman P, Skogseid B, Oberg K, Juhlin C, Akerstrom G, Rastad J. Primary and reoperative parathyroid operations in hyperparathyroidism of multiple endocrine neoplasia type 1. Surgery 1998; 124(6):993-999.

93. Vassilopoulou-Sellin R, Ajani J. Islet cell tumors of the pancreas. Endocrinol Metab Clin North Am 1994; 23(1):53-65.

94. Tonelli F, Giudici F, Nesi G, Batignani G, Brandi ML. Operation for insulinomas in multiple endocrine neoplasia type 1: When pancreatoduodenectomy is appropriate. Surgery 2017; 161(3):727-734.

95. Horiuchi K, Okamoto T, Iihara M, Tsukada T. An analysis of genotype-phenotype correlations and survival outcomes in patients with primary hyperparathyroidism caused by multiple endocrine neoplasia type 1: the experience at a single institution. Surg Today 2013; 43:894.

96. Goudet P, Murat A, Cardot-Bauters C et al. Thymic neuroendocrine tumors in multiple endocrine neoplasia type 1: a comparative study on 21 cases among a series of 761 MEN1 from the GTE (Groupe des Tumeurs Endocrines). World J Surg 2009; 33(6):1197-1207.

97. You YN, Thompson GB, Young WF, Jr. et al. Pancreatoduodenal surgery in patients with multiple endocrine neoplasia type 1: Operative outcomes, long-term function, and quality of life. Surgery 2007; 142(6):829-836.

98. Triponez F, Sadowski SM, Pattou F et al. Long-term Follow-up of MEN1 Patients Who Do Not Have Initial Surgery for Small </=2 cm Nonfunctioning Pancreatic Neuroendocrine Tumors, an AFCE and GTE Study: Association Francophone de Chirurgie Endocrinienne & Groupe d'Etude des Tumeurs Endocrines. Ann Surg 2017.

99. Raymond E, Dahan L, Raoul JL et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011; 364(6):501-513.

100 Yao JC, Shah MH, Ito T et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011; 364(6):514-523.

101. Norton JA, Doppman JL, Jensen RT. Curative resection in Zollinger-Ellison syndrome. Results of a 10-year prospective study. Ann Surg 1992; 215(1):8-18.

102. Trump D, Farren B, Wooding C et al. Clinical studies of multiple endocrine neoplasia type 1 (MEN1). QJM 1996; 89(9):653-669.

103. Cuny T, Barlier A. The significance of MEN1 mutations in pituitary carcinomas. Biomark Med 2013; 7(4):567-569.

104. Trouillas J, Labat-Moleur F, Sturm N et al. Pituitary tumors and hyperplasia in multiple endocrine neoplasia type 1 syndrome (MEN1): a case-control study in a series of 77 patients versus 2509 non-MEN1 patients. Am J Surg Pathol 2008; 32(4):534-543.

105. Thom AK, Norton JA, Axiotis CA, Jensen RT. Location, incidence, and malignant potential of duodenal gastrinomas. Surgery 1991; 110(6):1086-1091.

106. Norton JA, Jensen RT. Resolved and unresolved controversies in the surgical management of patients with Zollinger-Ellison syndrome. Ann Surg 2004; 240(5):757-773.

107. Christakis I, Qiu W, Silva Figueroa AM et al. Clinical Features, Treatments, and Outcomes of Patients with Thymic Carcinoids and Multiple Endocrine Neoplasia Type 1 Syndrome at MD Anderson Cancer Center. Horm Cancer 2016; 7(4):279-287.

108. Lim LC, Tan MH, Eng C, Teh BT, Rajasoorya RC. Thymic carcinoid in multiple endocrine neoplasia 1: genotype-phenotype correlation and prevention. J Intern Med 2006; 259(4):428-432.

109. Cadiot G, Vuagnat A, Doukhan I et al. Prognostic factors in patients with Zollinger-Ellison syndrome and multiple endocrine neoplasia type 1. Groupe d'Etude des Neoplasies Endocriniennes Multiples (GENEM and groupe de Recherche et d'Etude du Syndrome de Zollinger-Ellison (GRESZE). Gastroenterology 1999; 116(2):286-293.

110. Lowney JK, Frisella MM, Lairmore TC, Doherty GM. Pancreatic islet cell tumor metastasis in multiple endocrine neoplasia type 1: correlation with primary tumor size. Surgery 1998; 124(6):1043-8, discussion.

111. Benya RV, Metz DC, Venzon DJ et al. Zollinger-Ellison syndrome can be the initial endocrine manifestation in patients with multiple endocrine neoplasia-type I. Am J Med 1994; 97(5):436-444.

112. Maton PN, Gardner JD, Jensen RT. Diagnosis and management of Zollinger-Ellison syndrome. Endocrinol Metab Clin North Am 1989; 18(2):519-543.

113. Conemans EB, Nell S, Pieterman CRC et al. Prognostic factors for survival of MEN1 patients with duodenopancreatic tumors metastatic to the liver: Results from the DMSG. Endocr Pract 2017; 23(6):641-648.

19