Section-- Diffuse Hormonal Systems and Endocrine Tumor Syndromes

Chapter 5. MULTIPLE ENDOCRINE NEOPLASIA TYPE I and II

E.C. Feliberti, R.R. Perry, A.I. Vinik **Department of Surgery, Eastern Virginia Medical school, Norfolk VA 23507. Email : felibeec@evms.edu.**

Updated 7.19.13

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

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] [2] [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 islets, and pituitary glands. Hyperparathyroidism occurs in about 90% of patients, endocrine pancreatic tumors 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 was usually identified during the third or fourth decade of life. However, with the advent of biochemical screening, it is now typically detected earlier [6] [7] [8]. Approximately one third of patients with gastrinomas are associated with MEN-1 [9] [10] [11] [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 tumor types identified in MEN-1 patients include non-functioning tumors, vipomas, glucagonomas, somatostatinomas, and Ppomas [15] [16] [17]. More than one clinical syndrome may develop in the same patient either synchronously, or more often metachronously. Some patients may have lymph node or liver metastases with no clinical manifestations.

It has become apparent that gastrinomas in MEN-1 patients are often located in the duodenum. These tumors are small, usually multiple, and may be associated with pancreatic gastrinomas as well [14] [15] [18]. 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 gastrinoma in MEN-1, but not sporadic duodenal gastrinomas [19]. Patients with clinical syndromes usually have discrete tumors rather than diffuse islet cell disease as the cause of the syndrome [20] [21]. 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 [22]. 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] [23] [24] [25] [17]. 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 [26]. 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 [27].

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 and has recently 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 without significant clustering. There are no true "hot spots". Up to 20% of mutations involve intron sequences, thus these regions must be searched for germ

line mutations [32]. About 70% of the mutations are non-sense and frame shift mutations, resulting in truncation of the protein product. Despite detailed study, no correlation between the genetic mutation and the phenotypic expression has been identified [33]. However, the likelihood of finding a mutation appears to correlate with the number of MEN-1 associated tumors, and the presence of a family history [34]. About 20% of MEN-1 kindreds lack an identified mutation in the MEN-1 gene.

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 [35]. 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 [27] [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 [36]. Menin interacts with the transcription factor Jun-D [37], suggesting a potential role in transcriptional regulation. Menin has been shown to bind directly to double stranded DNA, with regulatory effects on cell proliferation [38]. Menin interacts with activator S-phase kinase (ASK) with regulatory effects on cell proliferation [39]. 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 [40]. 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 [41]. 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. For example, 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 throughout the gene [42]. MEN-1 mutations are identified less often in sporadic insulinoma, 17% in one series [43]. Mutations in the MEN-1 gene are believed to be an early event, since mutations have been identified in both benign and malignant pancreatic endocrine tumors [44]. Thus, the MEN-1 gene appears to 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. Two 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%) [45]. 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 [46] . 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.

Diagnosis of MEN1

A diagnosis of MEN1 can be established by any one of three criteria recommended by a recent consensus: 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 [47]. 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 [48]. 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 measurements of intact PTH, serum calcium, prolactin, somatomedin C, glucose, insulin, pro-insulin, gastrin, pancreatic polypeptide, glucagon, 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. Those family members who carry the mutated MEN-1 gene should undergo yearly biochemical screening from childhood and continued for life. Indeed, genetically positive patients have biochemical evidence of neoplasia an average of 10 years prior to clinically evident disease [49]. Early detection and early treatment of endocrine abnormalities should reduce morbidity and mortality from this disease. Peptic ulcer disease, renal complications, and malignant tumors are the common causes of morbidity and mortality in MEN-1 patients [50].

Clinical Presentation and Therapy

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 pancreatic endocrine tumors 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 [51]. However, some groups have had good results using endoscopic ultrasound for identifying pancreatic endocrine tumors in patients with MEN-1, even when tumors are small [52] [53] [54]. Although somatostatin receptor scintigraphy may identify occult lesions, the false positive and false negative rates are considerable [55]. 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-DOTOTOC) 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 [56].

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. Because the various components may present sequentially, surgical procedures involving different endocrine organs may be required over a period of many years.

The hyperparathyroidism and resulting hypercalcemia in MEN-1 patients is usually mild and only slowly progressive. 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 [57]. Sestamibi scans are not useful in MEN-1 patients prior to initial operation, however they may sometimes be useful in reoperative cases [58]. 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 [59]. Controversy persists regarding the use of subtotal versus total parathyroidectomy in MEN-I patients. A small study of 16 patients suggests that intraoperative PTH measurements may be useful in these patients [60]. 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% [61] [62] [63]. Total parathyroidectomy with forearm auto transplantation is associated with lower persistent hyperparathyroidism of 0% and lower long term recurrence rates in some series [64] [65] [66], but not in others [63]. If the disease should recur, it is a simple matter to remove a portion of the transplanted 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 parathyrodectomy with autotransplantation ranges from 22 to 36% compared to approximately 10% with subtotal parathyroidectomy [67] [63] [66]. 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.

The surgical management of MEN-1 patients with pancreatic disease remains controversial [20] [21] [68] [47]. 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. Thus, a cure can only be achieved in a minority of patients. Fortunately, patients with a functional tumor can be successfully managed medically. Thus, there is little need or justification for total pancreatectomy in these patients. A selective surgical approach, nonetheless, may be justified. It must be remembered that the majority of duodenal gastrinomas are malignant, and that eventually metastases to lymph nodes and/or liver develop in many or most of these patients [69] [70].

There is no universal agreement as to the indications for surgery for pancreatic disease in MEN-I patients [71] [47]. Current recommendations for surgical therapy for MEN1 gastrinomas include pancreatic tumors greater than 2 cm and duodenal tumors with accurate preoperative localization [47]. Many believe that patients suspected of having duodenal gastrinomas should be explored, because of the high risk of malignancy. Patients with larger lesions of the pancreas also 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 [72]. This was confirmed in a French multi-center trial involving 71 patients. However, resecting the lesions did not prevent subsequent liver metastases [73]. Another study in 48 patients, however, showed no correlation between pancreatic tumor size and metastases in MEN-1 patients [74]. Patients in whom a discrete anatomic abnormality is identified, which is functionally active, can also 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.

Some groups have recommended an aggressive surgical approach in selected MEN-1 patients with hypergastrinemia [20] [21] [75] [47]. 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 [76]. After a Kocher manuever 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 [77]. These tumors may be as small as 1-2 mm. A peripancreatic lymph node dissection is routinely performed in patients with duodenal tumors or pancreatic tumor with an incidence of regional lymph node metastasis between 53 and 68% and lymph node only disease occurring in 3-12% of patients [44] [76]. 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 surgically with lesser procedures. Most patients can be rendered eugastrinemic 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 [76]. Long term, many or most such patients do recur with new primary tumors, and with no patients disease free at 5 years. 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 [78].

Other pancreatic tumors occurring in MEN1 include insulinomas and non-functioning tumors and less commmonly glucagonomas. Unlike patients with sporadic insulinoma, MEN-1 patients with hyperinsulinism tend to be younger at time of diagnosis and usually have multiple tumors.

However, if these tumors can be identified and removed, the syndrome is cured, and recurrences are rare. The role of surgery for non-functioning pancreatic tumors is more controversial. Malignant pancreatic neuroendocrine tumors are the leading casue of death in MEN1 patients. [16] [79] [80]. An updated consensus recommended surgery for tumors that are more than 1 cm in size and /or shows significant growth over 6-12 months [47]. These tumors tend to be limited to the pancreas and are multifocal. Thus, more extensive pancreatic resections are recommended. 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%) [16]. Complications include 20% chance of developing diabetes mellitus, steatorrhea, and dumping syndrome [81]. Patients with locally advanced and/or metastatic disease can be treated with targeted chemotherapeutic agents. The tyrosine kinase receptor inhibitor sunitinib has been shown in a prospective randomized trial to increase overall survival and prolong progression-free survival. [82]. Another randomized trial reported that patients with pancreatic neuroendocrine tumors treated with everolimus, an inhibitor of the mammlain target of rapamycin, experienced a doubling of median progression-free survival [83].

Pituitary tumors are the least common of the 3 signature tumors characteristic of MEN1 with an incidence ranging from 30-50% [84] [85]. 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 39% on pathology [86]. Patients with prolactinoma 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%) [84]. Transsphenoidal 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 [87]. Patients with Cushing's disease are best treated with transphenoidal 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 [22].

Carcinoid tumors can occur in more than 3% of patients with MEN1. These tumors can 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 can portend a poor prognosis [88] [89] [80] [79]. Periodic chest CT 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 surprisingly significant rate [47] [80] [90]. Bronchial carcinoids occur in about 5% of MEN-1 patients, occur primarily in females, and appear to have a much more benign clinical course [91]. 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, including metastases to the liver [92]. Surgical resection should be considered for carcinoid tumors when they are identified. Serial measurements of chromogranin A levels may be useful for following those patients with pancreatic endocrine tumors [93].

Cutaneous lesions, especially angiofibromas and collagenomas are quite common in MEN-1 patients, occurring in more than 60%, and these lesions are usually multiple [94].

Follow-up

Patients diagnosed with MEN1 or are carriers of mutant MEN1 gene are recommended to undergo periodic examination, biochemical screening and imaging [47]. Biochemical screening includes measurement of serum calcium, PTH, gastrin, fasting glucose, insulin, chromogranin A, pancreatic polypeptise, glucagon, VIP, prolactin and IGF-1 annually. MRI or CT 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 [54]. 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 pancreatic endocrine tumors. Such a program was reported to reduce the annual screening cost from 2,100 euro per patient to 700 euro [54].

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 [95]. 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 [96] [97]. Approximately 70% of MEN1 patients will die directly related to MEN1

[17]. With the advent of effective medical therapy to manage gastrinoma, the mortality associated with MEN1 has shifted to other malignant tumors. The development of thymic carcinoid tumors is associated with an increased risk of death [17] [79]. 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 [17] [16].

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2A, 2B, AND NON-MEN FAMILIAL MEDULLARY THRYOID CARCINOMA

These syndromes have been described in nearly all ethnics group throughout the world. All three syndromes have autosomal dominant transmission patterns. Thus, children of affected individuals have a 50% chance of inheriting the genetic abnormality. The penetrance is virtually 100% by biochemical screening, however only 60-70% develop clinically apparent syndromes [3] [98]. About 25% of patients with medullary thyroid carcinoma have one of these familial syndromes. Because MTC is rare, the occurrence of two MTC's in a single family should raise suspicions of a familial syndrome. Up to 23% of pheochromocytoma patients also have a familial disorder, mainly either MEN-2 or von-Hippel-Lindau disease [99] [100].

Virtually 100% of patients with MEN-2A have C-cell hyperplasia or MTC, 50% have pheochromocytoma, and 20-30% have hyperparathyroidism. Some patients with MEN-2A develop Hirschsprung's disease, which frequently precedes the development of MEN-2 [101]. Patients with MEN-2B also have a 100% incidence of MTC, and frequently have pheochromocytomas. They also have a characteristic physical appearance at birth or shortly thereafter with mucosal neuromas of the eyelids, lips, and tongue, marfanoid habitus, and hyperflexible joints [102] [103]. They do not have the marfanoid lens or aortic abnormalities. Patients may also have abnormal gastrointestinal motility, due to wide spread

ganglioneuromatosis of the gastrointestinal tract. Thus, even at a young age, patients with MEN-2B may have troubles with diarrhea, constipation, colonic dilatation, or even present with megacolon. A review of the literature shows that diverticulosis, diverticulitis, abscess and other complications have also been noted [104]. Patients with MEN-2B seldom have hyperparathyroidism. Patients with non-MEN familial medullary thyroid carcinoma have medullary thyroid carcinoma, but none of the other associated endocrine or neural-tissue involvement [105].

Pathology

The major difference in patients with familial compared to the sporadic forms of these tumors is the multifocal nature of the lesions, the presence of hyperplastic states as precursors to frank tumors and different clinical behaviors.

Patients with genetic forms of MTC have diffuse bilateral C-cell hyperplasia of the thyroid, or frank MTC. The hyperplasia may not be apparent on routine histologic examination, thus immunostaining for calcitonin is essential in order to make the diagnosis. Detailed immunostaining may also reveal occult MTC. C-cell hyperplasia and occult MTC are consistently curable by total thyroidectomy, unlike clinically apparent MTC, where cure is infrequent [106] [107]. Patients with MEN-2A and 2B also may have adrenal hyperplasia preceding the development of pheochromocytoma. However, the clinical significance and management of adrenal hyperplasia in these patients is controversial.

Genetics

The gene for all three diseases is the RET proto-oncogene, located at the centrometric region of chromosome 10 (10q11-2). The RET proto-oncogene gene is a transmembrane tyrosine kinase with a long extracellular domain, a single transmembrane region, and two cytosplasmic tyrosine

kinase domains. The oncogene contains 21 exons spanning more than 60kb of genomic DNA. It is expressed in tissues of neural crest origin, and appears to have important function in cell migration and development. Ligands which bind to RET together with specific co-receptors include glial cell line-derived neurotrophic factor (GDNF), neurturin, artemin, and persephrin [108]. All MEN-2A families studied thus far have mutations of the RET proto-oncogene, but a few families with MEN-2B or non-MEN FMTC do not have such mutations. The vast majority of MEN-2A or FMTC patients will have a mis-sense mutation in the extracellular domain at a single codon (609, 611, 618, 620, or 634) [109]. Eighty-five percent of MEN-2A mutations occur at codon 634, whereas only 30% of mutations in non-MEN FMTC occur at codon 634 [110]. Patients with MEN-2B typically have a point mutation in the intracellular kinase catalytic domain, most commonly a substitution of threonine for methionine at codon 918. A study of this mutation in transgenic mice revealed that it predisposes the mice to MTC [111]. RET mutations in MEN-2 typically result in constitutive activation. Different mutations lead to different levels of activation, which may have an affect on the clinical spectrum [112]. Mutations in the RET proto-oncogene are noted occasionally in patients with sporadic MTC, and rarely in patients with sporadic pheochromocytoma. Inactivating mutations in the extracellular domain of the RET proto-oncogene have been identified in patients with Hirschsprung's disease. Thus, the RET proto-oncogene appears to be associated with growth regulation of neuroendocrine cells. Mutations of the RET proto-oncogene act in a dominant fashion. Both peripheral leukocytes and tumors from patients with these syndromes contain a normal allele of the RET gene. Other genetic abnormalities identified in patients with MEN-2 and non-MEN FMTC include LOH at chromosome 1p, 22q, 17p or 3p. Thus, multi-step carcinogenesis may be applicable to patients with MEN-2.

Data are accumulating regarding genotype-phenotype correlations and mutations in various RET codons. For instance, the rare codon 768 and 804 mutations are associated with non-MEN

FMTC, and these patients would not be expected to develop pheochromocytoma or hyperparathyroidism. However, current data are insufficient to determine the risk of pheochromocytoma in a given patient or family. Thus, all patients need to be carefully followed for the development of these tumors [108]. This may change in the future. A recent study showed that 20 of 21 patients with pheochromocytoma and MEN-2 had codon 634 or 918 mutations[94]. MTC aggressiveness may be related to the particular mutation in the codon [113]. The specific mutation in codon 634 in patients with MEN-2A may have an impact on tumor aggressiveness [114]. It is uncertain as to why the same point mutation can result in different clinical manifestations in the same family or in different families. This suggests that other genetic changes or modifiers are responsible for phenotypic differences. Alterations in the TGF-beta pathway, and increased expression of chondromodulin-1 may help explain the earlier onset of malignancy and skeletal abnormalities in MEN-2B compared to MEN-2A [115].

Clinical Features

Biochemically, the tumors that arise in patients with these genetic syndromes are similar to those with the sporadic forms of the tumors. There are no distinct biochemical markers that allow identification of familial versus non-familial forms of the tumors.

Familial MTC tends to occur at a younger age than sporadic MTC. The clinical presentation and behavior differ with each of the clinical syndromes. Peak incidence of MTC is in the second and third decades for patients with MEN-2A. The cancer usually behaves in a relatively indolent fashion, even though it can metastasize early. Survival for patients with MEN-2A and MTC is somewhat better than for patients with sporadic MTC. A small subset of patients with MEN-2A have MTC which behaves very aggressively. Thus, there is a need for an aggressive surgical approach early on, to prevent widespread metastatic disease.

MTC in MEN-2B occurs in the first and second decades of life. It tends to be more aggressive and lethal [25] [116], and death from metastatic diseases has been reported in young children [117]. When MEN-2B is diagnosed, even in infants, surgical treatment for MTC should be performed as early as possible.

In non-MEN familial MTC, the peak incidences is in the fourth to fifth decade. MTC in this disorder behaves in the least aggressive fashion [105]. Although lymph node metastases are frequent, the disease usually follows an indolent course, and virtually never results in death.

Pheochromocytoma in MEN-2A and 2B has a peak incidence in the fourth and fifth decades. Although it may be detected at the same time as MTC, pheochromocytoma tends to develop at a later age than the thyroid disease [118]. Occasionally, pheochromocytoma is identified in childhood. These tumors are often bilateral and multiple. They are only occasionally malignant [119] [120] [121]. Classically, the ratio of norepinephrine to epinephrine is lower in the genetic forms of pheochromocytoma than in the sporadic form. Common early symptoms in these patients include palpitations, headaches, and anxiety. With aggressive family screening, some patients are identified who have no symptoms from the tumor. In patients in whom the disorder is not recognized, a hypertensive crisis may be induced by an operation or by childbirth.

Primary hyperparathyroidism (PHPT) in MEN2A is typically diagnosed at a median age of 37 years and most patients (68%) are asymptomatic at time of diagnosis [122].

Screening and Diagnosis

Patients diagnosed with either MTC or pheochromocytoma should be studied for the possibility of MEN-2. A negative family history is not reliable, since about 40% of MEN-2A gene carriers do not develop clinically apparent disease. Thus, family members should be screened for both tumors. In a study of 174 patients with MTC screened for pheochromocytoma, 5 cases were

identified in known MEN-2 families, and another 5 index cases were found, leading to the discovery of 5 new MEN-2 families [123].

In the past, members of MEN-2A and non-MEN FMTC families underwent yearly calcium/pentagastrin stimulation tests, starting before the age of five. However the identification of mutations of the RET proto-oncogene has virtually eliminated the need for calcium pentagastrin stimulation tests. Genetic screening with mutational analysis can identify gene carriers with extremely high accuracy. Multiple studies have confirmed that using molecular biology techniques, the index case of a new family, and every gene carrier in a known family of MEN-2A, can be identified with 100% accuracy [124] [125] [126] [127]. The accuracy for identifying patients with MEN-2B and non-MEN FMTC is not quite as high, because of the small number of families that do not have the common RET proto-oncogene mutations. Members of MEN-2A families who are not gene carriers by genetic screening do not need to undergo biochemical testing. The accuracy of screening by direct analysis of RET proto-oncogene mutations for non-MEN FMTC still needs to be confirmed.

The biochemical diagnosis is similar to patients with sporadic disease. Patients with clinical MTC have elevated serum calcitonin. Pheochromocytoma is identified by elevated urinary epinephrine, norepinephrine, or VMA. Measurements of plasma normetanephrine and metanephrine may be more sensitive at detecting pheochromocytoma than urinary testing [128]. Patients with subclinical MTC usually do not have elevated basal serum levels of calcitonin. However, patients with C-cell hyperplasia or subclinical MTC increase calcitonin levels in response to calcium and/or pentagastrin. The combination test described by Wells and colleagues result in less false negatives than tests performed with either of the two agents alone [129]. This test consists of a 50 second infusion of calcium gluconate (2mg of elemental calcium/kg) followed by a 10 second bolus of pentagastrin (Peptavalon, Ayerst, 0.5mg/kg). Calcitonin levels are measured at 0, 2, 3.5, and 5 minutes, and generally peak at the 2 or 3.5

minute points. Pentagastrin is however, no longer available and reliance has to be placed on calcium infusion alone. Physicians screening patients for MTC must be thoroughly familiar with the particular calcitonin assay being used, as normal ranges vary somewhat. In general, normal females do not have a stimulated calcitonin level greater than 29 pg/ml, and in males the normal limit is 106 pg/ml. False positive results are uncommon. They occur in a small number of patients with normal thyroid glands, including the 5% of normal patients who have C-cell hyperplasia [106] [107] [130]. Provocative tests becomes abnormal at an average age of about 8-9 in gene carriers of MEN-2A.

Surgical Management

Patients with MEN-2 syndromes must be screened for possible pheochromocytomas, before undergoing thyroidectomy for MCT. If pheochromocytoma is identified, surgery for this should always take precedence over any neck procedure, to avoid a potential hypertensive crisis following induction of anesthesia. Once a diagnosis of pheochromocytoma is established biochemically, non-invasive localization and the subsequent surgical approach is carried out as previously described for sporadic pheochromocytoma. Pheochromocytomas in MEN-2 patients almost always occur bilaterally, however they often do not occur synchronously. The contralateral adrenal lesion can develop many years later. Fortunately, pheochromocytomas in these patients are usually benign. Thus, surgery can be reserved for those patients with demonstrated elevated catecholamine secretion and with a discrete tumor or tumors, or symptoms. Useful tests in these patients include MIBG scans, CT scans, or MRI. Imaging studies usually reveal an abnormality when biochemical testing is abnormal [124]. Patients who present with bilateral disease should undergo bilateral adrenalectomy. Patients with unilateral disease should undergo unilateral adrenalectomy. Cortical-sparing adrenalectomy is an option in patients who require bilateral adrenal resection, resulting in 65% of patients corticosteroid independent, and a low (approximately 10%) recurrence rate [131]. These patients need to

undergo yearly biochemical monitoring, to detect recurrent pheochromocytoma in the remaining adrenal gland. Interestingly, only one third to one half of these patients need a second surgery for recurrent pheochromocytoma in the remaining adrenal gland.

The primary management for genetic forms of MTC is total thyroidectomy. The goal is to do surgery before there are any clinical signs of disease, thus resulting in a high rate of cure. Patients with C-cell hyperplasia and microscopic MTC are consistently curable by total thyroidectomy, whereas patients with higher stage disease are not [129] [132]. Because of the field defect in the entire thyroid, and the multifocal nature of MTC in the genetic syndromes, total thyroidectomy is essential. Every effort must be made to leave no thyroid tissue or capsule behind. Failure to remove all thyroid tissue inevitably leads to recurrence [133] [134]. This point cannot be overemphasized. In addition to total thyroidectomy, central compartment lymph nodes should be excised, similar to the procedure done in patients with sporadic disease. In MEN-2 patients diagnosed by provocative testing, there are usually no palpable thyroid abnormalities, and the central lymph nodes are usually free of disease. For patients with involved central compartment lymph nodes, ipsilateral or bilateral modified neck dissection should be considered.

The timing of surgery depends on the particular syndrome. Patients with MEN-2A with positive biochemical screening should undergo total thyroidectomy no later than age 6. MTC in MEN-2B occurs at a younger age and is much more aggressive than in MEN-2A. As soon as the typical phenotype is recognized, total thyroidectomy should be performed, preferably before age 2, even if calcitonin levels are normal [135]. Two large European studies suggest that the particular codon affected can be used to help determine the timing of thyroidectomy [136] [137]. The American Thyroid Association (ATA) has published consensus guidelines for the management of MTC and prophylactic treatment of MEN2 patients based on the codon position of the RET mutation [138]. A risk level was assigned to each codon based on its known clinical

aggressiveness (level A – least aggressive, level D – most aggressive) and recommendations were made based on risk level. ATA risk level D mutations include codon 883 and 918 (>95% MEN2B harbor this codon) and these patients are recommended to undergo prophylactic thyroidectomy before age 1. Patients with ATA risk level C (codon 634) should undergo total thyroidectomy before age 5, while patients with ATA risk level B and A may delay total thyroidectomy after age 5 in select cases.

The advent of genetic screening of first degree family members of those with newly discovered MTC has led to earlier diagnosis and treatment. Patients operated on who have C-cell hyperplasia or microscopic MTC have greater than a 90% cure rate. Provocative testing has been particularly useful in MEN-2A family members who lack the characteristics phenotypic features found in MEN-2B patients. Unfortunately, some patients do have distant metastases when first diagnosed, thus preventing any chance for cure [116].

Hyperparathyroidism is present about 20-30% of patients with MEN-2A, however it rarely occurs in MEN-2B patients. Surgery for MEN-2A parathyroid disease usually takes place during total thyroidectomy for MTC and is similar to that for patients with MEN-1 parathyroid disease. Subtotal parathyroidectomy or total parathyroidectomy with autotransplantation into the forearm muscle can be performed in hypercalcemic patients [126] [139]. Recurrence rarely occurs, even with long term follow-up. The surgical treatment of normocalcemic patients is controversial. One or two parathyroid glands may be found to be abnormal in normocalcemic MEN-2A patients. In patients whose family history reveals little hyperparathyroidism, more conservative surgery consisting of removal of the enlarged glands only can be considered. It should be noted that hyperparathyroidism rarely occurs after total thyroidectomy for C-cell hyperplasia detected by screening, even when the parathyroid glands are left in place.

Treatment of recurrent or metastatic disease

The morbidity and mortality in patients with MEN-2 is due to recurrent medullary thyroid carcinoma. A study of 104 patients with sporadic and hereditary MTC revealed that patient age at presentation and tumor stage were the only independent predictors of survival [140]. The treatment of recurrent disease in patients with the genetic syndromes is similar to the sporadic counterparts. A study from the French Calcitonin Study Group involving 226 sporadic and heredity MTC patients showed that patients with preoperative calcitonin levels <50 pg/ml were more likely to normalize postoperatively [141]. If calcitonin levels remain elevated postoperatively, an aggressive approach may be considered in selected patients with disease confined to the neck. Prior to considering neck re-exploration, the evaluation should be thorough to exclude distant disease. In addition to CT or MRI of the neck, chest, and abdomen, laparoscopy has been advocated to exclude occult liver metastases [142]. Alternatively selected venous sampling can be performed for calcitonin. When elevated levels are isolated to one or both sides of the neck, modified unilateral or bilateral neck dissection is then performed. Such surgery can be performed by experienced groups with low morbidity [143]. There appears to be little role for the use of external beam radiation therapy in these patients [144]. There are few data on the use of combination chemotherapy in patients with systemic disease [145] [146] [147] [148]. A variety of combinations including CVD have had limited success.

Better understanding of the molecular aberrations associated with RET mutations and its receptor tyrosine kinase has led to exciting therapeutics in MEN2 patients. Studies of small molecule tyrosine kinase inhibitors (TKI) targeting the RET tyrosine kinase have shown promising results. Vandetanib is an orally available TKI that competes with ATP and blocks autophosphorylation and signal transduction. It targets RET-dependent tumor cell proliferation as well as vascular endothelial growth factor dependent tumor angiogenesis and epidermal growth factor receptor. A phase 3 trial with vandetanib at 300 mg/day in advanced medullary thyroid carcinoma showed an improved progression-free survival, an increased objective

response and a significant biochemical response [149]. Within the study were 33 patients with hereditary medullary thyroid carcinoma who had a 46% objective response rate, similar to the entire cohort. Those patients with the mutation M918T had a higher response rate than those who did not. Sunitinib (37.5 mg/ daily) and sorafenib (400 mg twice daily) have also shown modest efficacy in refractory and metastatic MTC in phase 2 trials [150] [151].

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] Benya RV, Metz DC, Venzon DJ, Fishbeyn VA, Strader DB, Orbuch M *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.

[7] 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.

[8] 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.

[9] 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.

[10] 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.

[11] 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.

[12] Thompson NW, Lloyd RV, Nishiyama RH, Vinik AI, Strodel WE, Allo MD *et al.* MEN I pancreas: a histological and immunohistochemical study. World J Surg 1984; **8:** 561-574.

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

[14] Pipeleers-Marichal M, Somers G, Willems G, Foulis A, Imrie C, Bishop AE *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.

[15] 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.

[16] Kouvaraki MA, Shapiro SE, Cote GJ, Lee JE, Yao JC, Waguespack SG *et al.* Management of pancreatic endocrine tumors in multiple endocrine neoplasia type 1. World J Surg 2006; **30**(5)**:** 643-653.

[17] Goudet P, Murat A, Binquet C, Cardot-Bauters C, Costa A, Ruszniewski P *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.

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

[19] Anlauf M, Perren A, Meyer CL, Schmid S, Saremaslani P, Kruse ML *et al.* Precursor lesions in patients with multiple endocrine neoplasia type 1-associated duodenal gastrinomas. Gastroenterology 2005; **128**(5)**:** 1187-1198.

[20] 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.

[21] Norton JA, Doppman JL, Collen MJ, Harmon JW, Maton PN, Gardner JD *et al.* Prospective study of gastrinoma localization and resection in patients with Zollinger-Ellison syndrome. Ann Surg 1986; **204**(4)**:** 468-479.

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

[23] BALLARD HS, FAME B, HARTSOCK RJ. FAMILIAL MULTIPLE ENDOCRINE ADENOMA-PEPTIC ULCER COMPLEX. Medicine (Baltimore) 1964; **43:** 481-516.

[24] 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.

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

[26] 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.

[27] 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.

[28] 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.

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

[30] Chandrasekharappa SC, Guru SC, Manickam P, Olufemi SE, Collins FS, Emmert-Buck MR *et al.* Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science 1997; **276**(5311)**:** 404-407.

[31] Calender A. Molecular genetics of neuroendocrine tumors. Digestion 2000; **62 Suppl 1:** 3-18.

[32] Mutch MG, Dilley WG, Sanjurjo F, DeBenedetti MK, Doherty GM, Wells SA, Jr. *et al.* Germline mutations in the multiple endocrine neoplasia type 1 gene: evidence for frequent splicing defects. Hum Mutat 1999; **13**(3)**:** 175-185.

[33] Agarwal SK, Lee BA, Sukhodolets KE, Kennedy PA, Obungu VH, Hickman AB *et al.* Molecular pathology of the MEN1 gene. Ann N Y Acad Sci 2004; **1014:** 189-198.

[34] 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.

[35] Crabtree J, Scacheri P, Ward J, Garrett-Beal L, Emmert-Buck M, Edgemon K *et al.* A mouse model of multiple endocrine neoplasia, type 1, develop multiple endocrine tumors. PNAS 98[3], 1118-1123. 1-30-2001.

Ref Type: Generic

[36] Cavallari I, D'Agostino DM, Ferro T, Rosato A, Barzon L, Pasquali C *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.

[37] Agarwal SK, Guru SC, Heppner C, Erdos MR, Collins RM, Park SY *et al.* Menin interacts with the AP1 transcription factor JunD and represses JunD-activated transcription. Cell 1999; **96**(1)**:** 143-152.

[38] La P, Silva AC, Hou Z, Wang H, Schnepp RW, Yan N *et al.* Direct binding of DNA by tumor suppressor menin. J Biol Chem 2004; **279**(47)**:** 49045-49054.

[39] Schnepp RW, Hou Z, Wang H, Petersen C, Silva A, Masai H *et al.* Functional interaction between tumor suppressor menin and activator of S-phase kinase. Cancer Res 2004; **64**(18)**:** 6791-6796.

[40] Milne TA, Hughes CM, Lloyd R, Yang Z, Rozenblatt-Rosen O, Dou Y *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.

[41] 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.

[42] Goebel SU, Heppner C, Burns AL, Marx SJ, Spiegel AM, Zhuang Z *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.

[43] Zhuang Z, Vortmeyer AO, Pack S, Huang S, Pham TA, Wang C *et al.* Somatic mutations of the MEN1 tumor suppressor gene in sporadic gastrinomas and insulinomas. Cancer Res 1997; **57**(21)**:** 4682-4686.

[44] 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.

[45] Hao W, Skarulis MC, Simonds WF, Weinstein LS, Agarwal SK, Mateo C *et al.* Multiple endocrine neoplasia type 1 variant with frequent prolactinoma and rare gastrinoma. J Clin Endocrinol Metab 2004; **89**(8)**:** 3776-3784.

[46] Hannan FM, Nesbit MA, Christie PT, Fratter C, Dudley NE, Sadler GP *et al.* Familial isolated primary hyperparathyroidism caused by mutations of the MEN1 gene. Nat Clin Pract Endocrinol Metab 2008; **4**(1)**:** 53-58.

[47] Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR *et al.* Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 2012; **97**(9)**:** 2990-3011.

[48] 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.

[49] Lairmore TC, Piersall LD, DeBenedetti MK, Dilley WG, Mutch MG, Whelan AJ *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.

[50] 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.

[51] 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.

[52] 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.

[53] Langer P, Kann PH, Fendrich V, Richter G, Diehl S, Rothmund M *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.

[54] Waldmann J, Fendrich V, Habbe N, Bartsch DK, Slater EP, Kann PH *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.

[55] 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.

[56] Froeling V, Elgeti F, Maurer MH, Scheurig-Muenkler C, Beck A, Kroencke TJ *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.

[57] Doherty GM, Lairmore TC, DeBenedetti MK. Multiple endocrine neoplasia type 1 parathyroid adenoma development over time. World J Surg 2004; **28**(11)**:** 1139-1142.

[58] 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.

[59] Lafferty FW. Primary hyperparathyroidism. Changing clinical spectrum, prevalence of hypertension, and discriminant analysis of laboratory tests. Arch Intern Med 1981; **141**(13)**:** 1761-1766.

[60] Tonelli F, Spini S, Tommasi M, Gabbrielli G, Amorosi A, Brocchi A *et al.* Intraoperative parathormone measurement in patients with multiple endocrine neoplasia type I syndrome and hyperparathyroidism. World J Surg 2000; **24**(5)**:** 556-562.

[61] Arnalsteen LC, Alesina PF, Quiereux JL, Farrel SG, Patton FN, Carnaille BM *et al.* Long-term results of less than total parathyroidectomy for hyperparathyroidism in multiple endocrine neoplasia type 1. Surgery 2002; **132**(6)**:** 1119-1124.

[62] Lambert LA, Shapiro SE, Lee JE, Perrier ND, Truong M, Wallace MJ *et al.* Surgical treatment of hyperparathyroidism in patients with multiple endocrine neoplasia type 1. Arch Surg 2005; **140**(4)**:** 374-382.

[63] Norton JA, Venzon DJ, Berna MJ, Alexander HR, Fraker DL, Libutti SK *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.

[64] 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.

[65] 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.

[66] 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.

[67] 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.

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

[69] 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.

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

[71] 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.

[72] Norton JA. Surgical treatment and prognosis of gastrinoma. Best Pract Res Clin Gastroenterol 2005; **19**(5)**:** 799-805.

[73] Cadiot G, Vuagnat A, Doukhan I, Murat A, Bonnaud G, Delemer B *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.

[74] 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.

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

[76] 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.

[77] Norton JA, Fraker DL, Alexander HR, Gibril F, Liewehr DJ, Venzon DJ *et al.* Surgery increases survival in patients with gastrinoma. Ann Surg 2006; **244**(3)**:** 410-419.

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

[79] 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 2012.

[80] Goudet P, Murat A, Cardot-Bauters C, Emy P, Baudin E, du Boullay CH *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.

[81] You YN, Thompson GB, Young WF, Jr., Larson D, Farley DR, Richards M *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.

[82] Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C *et al.* Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011; **364**(6)**:** 501-513.

[83] Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van CE *et al.* Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011; **364**(6)**:** 514-523.

[84] Verges B, Boureille F, Goudet P, Murat A, Beckers A, Sassolas G *et al.* Pituitary disease in MEN type 1 (MEN1): data from the France-Belgium MEN1 multicenter study. J Clin Endocrinol Metab 2002; **87**(2)**:** 457-465.

[85] Trump D, Farren B, Wooding C, Pang JT, Besser GM, Buchanan KD *et al.* Clinical studies of multiple endocrine neoplasia type 1 (MEN1). QJM 1996; **89**(9)**:** 653-669.

[86] Trouillas J, Labat-Moleur F, Sturm N, Kujas M, Heymann MF, Figarella-Branger D *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.

[87] Ezzat S, Snyder PJ, Young WF, Boyajy LD, Newman C, Klibanski A *et al.* Octreotide treatment of acromegaly. A randomized, multicenter study. Ann Intern Med 1992; **117**(9)**:** 711-718.

[88] Ferolla P, Falchetti A, Filosso P, Tomassetti P, Tamburrano G, Avenia N *et al.* Thymic neuroendocrine carcinoma (carcinoid) in multiple endocrine neoplasia type 1 syndrome: the Italian series. J Clin Endocrinol Metab 2005; **90**(5)**:** 2603-2609.

[89] Gibril F, Chen YJ, Schrump DS, Vortmeyer A, Zhuang Z, Lubensky IA *et al.* Prospective study of thymic carcinoids in patients with multiple endocrine neoplasia type 1. J Clin Endocrinol Metab 2003; **88**(3)**:** 1066-1081.

[90] 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.

[91] Sachithanandan N, Harle RA, Burgess JR. Bronchopulmonary carcinoid in multiple endocrine neoplasia type 1. Cancer 2005; **103**(3)**:** 509-515.

[92] Norton JA, Melcher ML, Gibril F, Jensen RT. Gastric carcinoid tumors in multiple endocrine neoplasia-1 patients with Zollinger-Ellison syndrome can be symptomatic, demonstrate aggressive growth, and require surgical treatment. Surgery 2004; **136**(6)**:** 1267-1274.

[93] Nehar D, Lombard-Bohas C, Olivieri S, Claustrat B, Chayvialle JA, Penes MC *et al.* Interest of Chromogranin A for diagnosis and follow-up of endocrine tumours. Clin Endocrinol (Oxf) 2004; **60**(5)**:** 644-652.

[94] Asgharian B, Turner ML, Gibril F, Entsuah LK, Serrano J, Jensen RT. Cutaneous tumors in patients with multiple endocrine neoplasm type 1 (MEN1) and gastrinomas: prospective study of frequency and development of criteria with high sensitivity and specificity for MEN1. J Clin Endocrinol Metab 2004; **89**(11)**:** 5328-5336.

[95] Jensen RT. Management of the Zollinger-Ellison syndrome in patients with multiple endocrine neoplasia type 1. J Intern Med 1998; **243**(6)**:** 477-488.

[96] Dean PG, van Heerden JA, Farley DR, Thompson GB, Grant CS, Harmsen WS *et al.* Are patients with multiple endocrine neoplasia type I prone to premature death? World J Surg 2000; **24**(11)**:** 1437-1441.

[97] Doherty GM, Olson JA, Frisella MM, Lairmore TC, Wells SA, Jr., Norton JA. Lethality of multiple endocrine neoplasia type I. World J Surg 1998; **22**(6)**:** 581-586.

[98] Easton DF, Ponder MA, Cummings T, Gagel RF, Hansen HH, Reichlin S *et al.* The clinical and screening age-at-onset distribution for the MEN-2 syndrome. Am J Hum Genet 1989; **44**(2)**:** 208-215.

[99] Neumann HP, Berger DP, Sigmund G, Blum U, Schmidt D, Parmer RJ *et al.* Pheochromocytomas, multiple endocrine neoplasia type 2, and von Hippel-Lindau disease. N Engl J Med 1993; **329**(21)**:** 1531-1538.

[100] Raue F, Frank-Raue K, Grauer A. Multiple endocrine neoplasia type 2. Clinical features and screening. Endocrinol Metab Clin North Am 1994; **23**(1)**:** 137-156.

[101] Cohen MS, Phay JE, Albinson C, DeBenedetti MK, Skinner MA, Lairmore TC *et al.* Gastrointestinal manifestations of multiple endocrine neoplasia type 2. Ann Surg 2002; **235**(5)**:** 648-654.

[102] Kahiri M, Dexter R, Burzynski N, et al. Mucosal neuroma, pheochromocytoma, and medullary thyroid carcinoma. MEN type III. Medicine 1975; **54:** 89.

[103] Williams ED, Pollock DJ. Multiple mucosal neuromata with endocrine tumours: a syndrome allied to von Recklinghausen's disease. J Pathol Bacteriol 1966; **91**(1)**:** 71-80.

[104] Grobmyer SR, Guillem JG, O'Riordain DS, Woodruff JM, Shriver C, Brennan MF. Colonic manifestations of multiple endocrine neoplasia type 2B: report of four cases. Dis Colon Rectum 1999; **42**(9)**:** 1216-1219.

[105] Farndon JR, Leight GS, Dilley WG, Baylin SB, Smallridge RC, Harrison TS *et al.* Familial medullary thyroid carcinoma without associated endocrinopathies: a distinct clinical entity. Br J Surg 1986; **73**(4)**:** 278-281.

[106] Baylin S, Mendelsohn G. Medullary thyroid carcinoma: a model for the study of human tumor. In Owens AJ, Coffey D, Baylin S eds. *Tumor Cell Heterogeneity, Origins and Implications*. New York: Academic Press 1982.

[107] Gagel RF, Tashjian AH, Jr., Cummings T, Papathanasopoulos N, Kaplan MM, DeLellis RA *et al.* The clinical outcome of prospective screening for multiple endocrine neoplasia type 2a. An 18-year experience. N Engl J Med 1988; **318**(8)**:** 478-484.

[108] Airaksinen MS, Titievsky A, Saarma M. GDNF family neurotrophic factor signaling: four masters, one servant? Mol Cell Neurosci 1999; **13**(5)**:** 313-325.

[109] Noll WW. Utility of RET mutation analysis in multiple endocrine neoplasia type 2. Arch Pathol Lab Med 1999; **123**(11)**:** 1047-1049.

[110] Eng C. RET proto-oncogene in the development of human cancer. J Clin Oncol 1999; **17**(1)**:** 380-393.

[111] Acton DS, Velthuyzen D, Lips CJ, Hoppener JW. Multiple endocrine neoplasia type 2B mutation in human RET oncogene induces medullary thyroid carcinoma in transgenic mice. Oncogene 2000; **19**(27)**:** 3121-3125.

[112] Ponder BA. The phenotypes associated with ret mutations in the multiple endocrine neoplasia type 2 syndrome. Cancer Res 1999; **59**(7 Suppl)**:** 1736s-1741s.

[113] Yip L, Cote GJ, Shapiro SE, Ayers GD, Herzog CE, Sellin RV *et al.* Multiple endocrine neoplasia type 2: evaluation of the genotype-phenotype relationship. Arch Surg 2003; **138**(4)**:** 409-416.

[114] Punales MK, Graf H, Gross JL, Maia AL. RET codon 634 mutations in multiple endocrine neoplasia type 2: variable clinical features and clinical outcome. J Clin Endocrinol Metab 2003; **88**(6)**:** 2644-2649.

[115] Jain S, Watson MA, DeBenedetti MK, Hiraki Y, Moley JF, Milbrandt J. Expression profiles provide insights into early malignant potential and skeletal abnormalities in multiple endocrine neoplasia type 2B syndrome tumors. Cancer Res 2004; **64**(11)**:** 3907-3913.

[116] Norton JA, Froome LC, Farrell RE, Wells SA, Jr. Multiple endocrine neoplasia type IIb: the most aggressive form of medullary thyroid carcinoma. Surg Clin North Am 1979; **59**(1)**:** 109-118.

[117] Kaufman FR, Roe TF, Isaacs H, Jr., Weitzman JJ. Metastatic medullary thyroid carcinoma in young children with mucosal neuroma syndrome. Pediatrics 1982; **70**(2)**:** 263-267.

[118] Nguyen L, Niccoli-Sire P, Caron P, Bastie D, Maes B, Chabrier G *et al.* Pheochromocytoma in multiple endocrine neoplasia type 2: a prospective study. Eur J Endocrinol 2001; **144**(1)**:** 37-44.

[119] van Heerden JA, Roland CF, Carney JA, Sheps SG, Grant CS. Long-term evaluation following resection of apparently benign pheochromocytoma(s)/paraganglioma(s). World J Surg 1990; **14**(3)**:** 325-329.

[120] Keiser H, Dopopman J, Robertson W, Linehan W, Averbuch S. Diagnosis, localizaton, and management of pheochromocytoma. In Lack EE ed. *Pathology of the Adrenal Glands*. New York: Churchill Livinstone, 1 1990.

[121] Shapiro B, Fig LM. Management of pheochromocytoma. Endocrinol Metab Clin North Am 1989; **18**(2)**:** 443-481.

[122] Kraimps JL, Denizot A, Carnaille B, Henry JF, Proye C, Bacourt F *et al.* Primary hyperparathyroidism in multiple endocrine neoplasia type IIa: retrospective French multicentric study. Groupe d'Etude des Tumeurs a Calcitonine (GETC, French Calcitonin Tumors Study Group), French Association of Endocrine Surgeons. World J Surg 1996; **20**(7)**:** 808-812.

[123] Bonnin F, Schlumberger M, Gardet P, Tenenbaum F, Lumbroso J, Leclere J *et al.* Screening for adrenal medullary disease in patients with medullary thyroid carcinoma. J Endocrinol Invest 1994; **17**(4)**:** 253-257.

[124] Lips CJ, Landsvater RM, Hoppener JW, Geerdink RA, Blijham G, van Veen JM *et al.* Clinical screening as compared with DNA analysis in families with multiple endocrine neoplasia type 2A. N Engl J Med 1994; **331**(13)**:** 828-835.

[125] McMahon R, Mulligan LM, Healey CS, Payne SJ, Ponder M, Ferguson-Smith MA *et al.* Direct, non-radioactive detection of mutations in multiple endocrine neoplasia type 2A families. Hum Mol Genet 1994; **3**(4)**:** 643-646.

[126] O'Riordain DS, O'Brien T, Grant CS, Weaver A, Gharib H, van Heerden JA. Surgical management of primary hyperparathyroidism in multiple endocrine neoplasia types 1 and 2. Surgery 1993; **114**(6)**:** 1031-1037.

[127] Wells SA, Jr., Chi DD, Toshima K, Dehner LP, Coffin CM, Dowton SB *et al.* Predictive DNA testing and prophylactic thyroidectomy in patients at risk for multiple endocrine neoplasia type 2A. Ann Surg 1994; **220**(3)**:** 237-247.

[128] Eisenhofer G, Lenders JW, Linehan WM, Walther MM, Goldstein DS, Keiser HR. Plasma normetanephrine and metanephrine for detecting pheochromocytoma in von Hippel-Lindau disease and multiple endocrine neoplasia type 2. N Engl J Med 1999; **340**(24)**:** 1872-1879.

[129] Wells SA, Jr., Dilley WG, Farndon JA, Leight GS, Baylin SB. Early diagnosis and treatment of medullary thyroid carcinoma. Arch Intern Med 1985; **145**(7)**:** 1248-1252.

[130] Snow KJ, Boyd AE, III. Management of individual tumor syndromes. Medullary thyroid carcinoma and hyperparathyroidism. Endocrinol Metab Clin North Am 1994; **23**(1)**:** 157-166.

[131] Yip L, Lee JE, Shapiro SE, Waguespack SG, Sherman SI, Hoff AO *et al.* Surgical management of hereditary pheochromocytoma. J Am Coll Surg 2004; **198**(4)**:** 525-534.

[132] Delius RE, Thompson NW. Early total thyroidectomy in patients with multiple endocrine neoplasia IIb syndrome. Surg Gynecol Obstet 1989; **169**(5)**:** 442-444.

[133] Harness JK, Fung L, Thompson NW, Burney RE, McLeod MK. Total thyroidectomy: complications and technique. World J Surg 1986; **10**(5)**:** 781-786.

[134] Russell CF, van Heerden JA, Sizemore GW, Edis AJ, Taylor WF, ReMine WH *et al.* The surgical management of medullary thyroid carcinoma. Ann Surg 1983; **197**(1)**:** 42-48.

[135] Wells SA, Jr., Franz C. Medullary carcinoma of the thyroid gland. World J Surg 2000; **24**(8)**:** 952-956.

[136] Gimm O, Ukkat J, Niederle BE, Weber T, Thanh PN, Brauckhoff M *et al.* Timing and extent of surgery in patients with familial medullary thyroid carcinoma/multiple endocrine neoplasia 2A-related RET mutations not affecting codon 634. World J Surg 2004; **28**(12)**:** 1312-1316.

[137] Machens A, Niccoli-Sire P, Hoegel J, Frank-Raue K, van Vroonhoven TJ, Roeher HD *et al.* Early malignant progression of hereditary medullary thyroid cancer. N Engl J Med 2003; **349**(16)**:** 1517-1525.

[138] Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H *et al.* Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009; **19**(6)**:** 565-612.

[139] Mallette LE. Management of hyperparathyroidism in the multiple endocrine neoplasia syndromes and other familial endocrinopathies. Endocrinol Metab Clin North Am 1994; **23**(1)**:** 19-36.

[140] Kebebew E, Ituarte PH, Siperstein AE, Duh QY, Clark OH. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. Cancer 2000; **88**(5)**:** 1139-1148.

[141] Cohen R, Campos JM, Salaun C, Heshmati HM, Kraimps JL, Proye C *et al.* Preoperative calcitonin levels are predictive of tumor size and postoperative calcitonin normalization in medullary thyroid carcinoma. Groupe d'Etudes des Tumeurs a Calcitonine (GETC). J Clin Endocrinol Metab 2000; **85**(2)**:** 919-922.

[142] Tung WS, Vesely TM, Moley JF. Laparoscopic detection of hepatic metastases in patients with residual or recurrent medullary thyroid cancer. Surgery 1995; **118**(6)**:** 1024-1029.

[143] Moley JF, Dilley WG, DeBenedetti MK. Improved results of cervical reoperation for medullary thyroid carcinoma. Ann Surg 1997; **225**(6)**:** 734-740.

[144] Samaan NA, Schultz PN, Hickey RC. Medullary thyroid carcinoma: prognosis of familial versus sporadic disease and the role of radiotherapy. J Clin Endocrinol Metab 1988; **67**(4)**:** 801-805.

[145] Averbuch S, Wu L, Pertsemlidis D, Drakes T. Cyclophosphamide (C), vincristine (V), and dacarbazine (D) for advanced neuroendocrine carcinomas. Proc Am Soc Clin Oncol 1990; **9:** 382.

[146] Petursson SR. Metastatic medullary thyroid carcinoma. Complete response to combination chemotherapy with dacarbazine and 5-fluorouracil. Cancer 1988; **62**(9)**:** 1899-1903.

[147] Shimaoka K, Schoenfeld DA, DeWys WD, Creech RH, DeConti R. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. Cancer 1985; **56**(9)**:** 2155-2160.

[148] Wu LT, Averbuch SD, Ball DW, de BA, Baylin SB, McGuire WP, III. Treatment of advanced medullary thyroid carcinoma with a combination of cyclophosphamide, vincristine, and dacarbazine. Cancer 1994; **73**(2)**:** 432-436.

[149] Wells SA, Jr., Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M *et al.* Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 2012; **30**(2)**:** 134-141.

[150] Carr LL, Mankoff DA, Goulart BH, Eaton KD, Capell PT, Kell EM *et al.* Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid cancer

and metastatic medullary carcinoma of the thyroid with functional imaging correlation. Clin Cancer Res 2010; **16**(21)**:** 5260-5268.

[151] Lam ET, Ringel MD, Kloos RT, Prior TW, Knopp MV, Liang J *et al.* Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer. J Clin Oncol 2010; **28**(14)**:** 2323-2330.