Surgical Management of MEN-1 and -2: State of the Art

Göran Åkerström, MD, PhD*, Peter Stålberg, MD, PhD

KEYWORDS

- Multiple endocrine neoplasia type 1
- Multiple endocrine neoplasia type 2
- Surgical treatment • Genetic diagnosis
- Surveillance

MEN TYPE 1

MEN-1 is an autosomal-dominant syndrome comprising endocrine tumors of the parathyroid, the endocrine pancreas-duodenum, and the anterior pituitary. In addition to these classical lesions there is increased incidence of foregut carcinoids (in the thymus, bronchial tree, and the stomach); adrenocortical hyperplasia; and nonendocrine tumors, such as meningioma, ependymoma, leiomyoma, lipoma, facial angiofibroma, and collagenoma.

MEN-1 occurs as a result of inactivating mutations of the *MEN-1* tumor suppressor gene on chromosome 11q13 encoding for menin.[1] Menin has a role for DNA replication and repair, and is involved in transcriptional regulation and histone modification. MEN-1 is relatively rare, with a prevalence of 2 to 3 per 100 000, and is equally common in males and females. The MEN-1 gene is a complex gene, with more than 1000 mutations identified in different families, without strong genotype-phenotype correlations.[2] The disease expression is variable even within families. Complete *MEN-1* gene sequencing is the best method of diagnosis, and can reveal mutations in 70% to 90% of typical MEN-1 cases. A multiplex ligation-dependent probe amplification (MLPA) assay is recently used for detection of large deletions occurring in 4% of MEN-1 cases.[3] Because genetic diagnosis is difficult negative genetic testing cannot exclude the syndrome, unless mutation is known in the family. In absence of genetic diagnosis MEN-1 can be diagnosed if a patient has tumors in two of the three classical endocrine organs (parathyroid, pancreas-duodenum, or pituitary) or has family history of MEN-1 and one such tumor.[4]

Surveillance and screening for MEN-1 endocrine tumors is recommended in presymptomatic gene carriers, because biochemical abnormalities can be detected decades before clinical symptoms become overt.[4,5] Delaying screening until

Department of Surgery, University Hospital, Uppsala, 751 85 Sweden
* Corresponding author.
E-mail address: goran.akerstrom@surgsci.uu.se (G. Åkerström).

Surg Clin N Am 89 (2009) 1047–1068
doi:10.1016/j.suc.2009.06.016 surgical.theclinics.com
0039-6109/09/$ – see front matter

clinical symptoms develop can be associated with morbidity and mortality from MEN-1–related neuroendocrine pancreatic and thymic tumors.[4–6] Screening is done by a combination of biochemical tests and imaging studies aimed to reveal presence of any of the three classical endocrinopathies (**Table 1**), and is initiated in children during the first decade of life.[7]

Primary HPT

Primary HPT (pHPT) is the most common and generally first detected endocrinopathy in MEN-1, often possible to diagnose at approximately 20 years of age, and affecting more than 95% of patients by the age of 40 years.[4–7] MEN-1 pHPT accounts for 2% to 4% of all pHPT cases, and affects approximately 10% of patients with hyperplasia and multiglandular parathyroid disease. MEN-1 has been the most common of the familial pHPT syndromes, and the most important to exclude, and should be suspected in all cases with multiglandular involvement, or recurrent HPT. Younger patients may frequently (approximately 10%) be index cases for MEN-1 kindreds.[4–9] Screening with serum calcium may reveal MEN-1 in patients with pancreatic or pituitary tumors, or foregut carcinoids.

Symptoms are similar as in sporadic pHPT, with decrease in bone mineral density, nephrolithiasis in some patients, common fatigue, muscle weakness, asthenia, mild depression, and typical concentration difficulty. Bone mineral density decrease may be detected already at around 40 years of age.[10] Because hypercalcemia stimulates gastrin, early parathyroid surgery has been recommended in patients with MEN-1–associated Zollinger-Ellison syndrome (ZES), although similar effect is obtained by proton pump inhibitors.[11,12]

The diagnosis of pHPT is made by demonstration of raised ionized or total-albumin corrected serum calcium together with inappropriately raised serum parathyroid hormone (PTH).

Surgical Management

MEN-1 cases have markedly asymmetric nodular hyperplasia, where multiple monoclonal tumors develop from polyclonal hyperplasia (**Fig. 1**).[11,13] Lesions may occur asynchronously, and normal glands can especially in younger patients coexist with enlarged ones. Some patients initially have single gland enlargement, easily misinterpreted as adenoma, when associated glands have normal size and histology.

MEN-1 patients have aggressive HPT, with high recurrence rate. The authors routinely use surgeon-performed preoperative ultrasound to have glandular localization depicted before surgery, although bilateral neck exploration is required for primary explorations.[11,14] Surgery is regarded as palliative, and aims to map the location of four parathyroid glands, also for forthcoming reoperations. To ensure removal of the largest, most severely diseased glands it is crucial to refrain from glandular excision until both sides of the neck have been explored.[11] The surgeon should then remove the largest glands in radical parathyroidectomy, and explore common ectopic sites, possibly harboring supernumerary glands, occurring normally in up to 15%.[14–16] Cervical thymectomy and clearance of perithyroid fat is performed to remove supernumerary glands and parathyroid cell clusters, which may grow as a result of the genetic stimulation.[15]

Resections less than subtotal parathyroidectomy are associated with high frequency of persistent or recurrent HPT in MEN-1.[14,16–20] Subtotal parathyroidectomy implying 3 to 3.5 gland resection (combined with cervical thymectomy) is now the commonly recommended operation.[14] The smallest, most normal gland is

Table 1
MEN-1 screening

Tumor	Age to Begin Screening (y)	Biochemical Tests (Annually)	Imaging (Every 3 y)
Parathyroid	10	Serum calcium, (parathyroid hormone)	None
Gastrinoma	20	Serum gastrin	None
Insulinoma	5	Fasting serum glucose and insulin	None
Nonfunctioning pancreaticoduodenal tumors	20	Pancreatic polypeptide, proinsulin, insulin, glucagon, vasoactive intestinal polypeptide, chromogranin A	Endoscopic ultrasound (Octreoscan, CT)
Anterior pituitary	5	Prolactin, insulinlike growth factor-1	Brain MRI
Foregut carcinoid	20	None	CT

Data from Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type1 and type2. J Clin Endocrinol Metab 2001;86:5658–71.

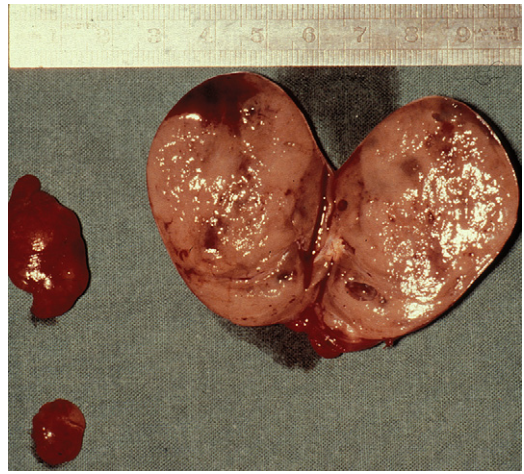

Fig. 1. Asymmetric enlargement of parathyroid glands in a patient with MEN 1–associated HPT and multiglandular parathyroid hyperplasia. The larger gland may be easily mistaken to represent a single adenoma. (*From* Åkerström G, Juhlin C. Surgical management of multiglandular parathyroid disease. In: Randolph GW, editor. Surgery of the thyroid and parathyroid glands. Philadelphia: WB Saunders; 2003. p. 529–48; with permission.)

selected as remnant, with circulation verified before removing other glands, by showing bleeding after transection (**Fig. 2**). When preparing the remnant cell seeding should be avoided to reduce risk for recurrence by implantation.

Total parathyroidectomy with forearm autotransplantation (or autotransplantation to subcutaneous fat on the thorax or abdomen) is less commonly performed. This procedure has higher risk for hypoparathyroidism, but may be required in presence of four markedly enlarged glands, or often at reoperation.[14,21] It is important to select tissue

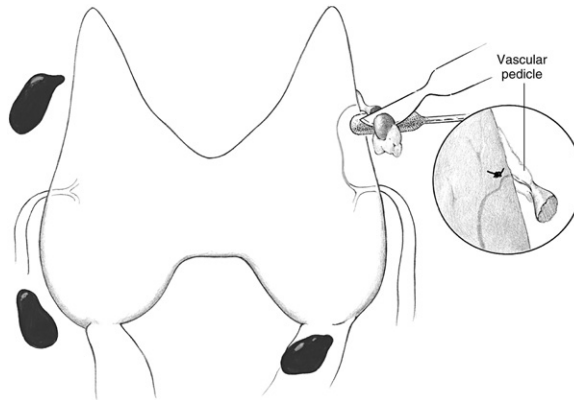

Fig. 2. Subtotal parathyroidectomy. After all four parathyroid glands have been visualized, the smallest gland is selected as remnant and resected to approximately 50 mg. When viability of the remnant is ensured (by verifying that it is bleeding after transection), the other glands are removed. The remnant location is marked with suture or clip. (*From* Åkerström G, Juhlin C. Surgical management of multiglandular parathyroid disease. In: Randolph GW, editor. Surgery of the thyroid and parathyroid glands. Philadelphia: WB Saunders; 2003. p. 529–48; with permission.)

for grafting from the smallest, least diseased gland. The patients experience long periods of postoperative hypocalcemia, and in contrast to what was initially thought, this procedure has not simplified treatment of recurrence.[22]

Intraoperative PTH determination is of reported value in MEN-1 patients, but requires special criteria to avoid false results, implying evaluation 20 minutes after glandular removal and that an end point value within the assay limits is reached.[14,23–25]

Because of risk for remnant ischemia and permanent hypoparathyroidism, cryopreservation of parathyroid tissue is recommended if facilities are available.[14] Needle biopsy aspiration with rapid PTH determination has more or less replaced the use of frozen sections for parathyroid tissue verification in resected specimens.

Series of reoperative pHPT patients have emphasized that MEN-1 HPT is a common cause of failed parathyroid surgery.[12,22,23,25–27] Persistent HPT is common if the syndrome is not recognized at the primary operation and all glands have not been visualized, or if one has not searched for ectopic glands. Recurrence is encountered in MEN-1 patients because it is genetically determined, but can with appropriate surgery be minimized to around 30% during 10 years, but with markedly higher rate (>50%), and earlier recurrence with less than subtotal parathyroidectomy.[16,20,23,27]

Reoperation in MEN-1 is undertaken only after careful localization studies, comprising percutaneous ultrasound, sestamibi scintigraphy, CT with contrast enhancement, occasionally positron emission tomography with methionine tracer, ultrasound-guided fine-needle biopsy with PTH measurement, and in selected cases selective venous sampling with rapid PTH determination.[26,27] Concordant results of two investigations are generally required. Four-dimensional contrast-enhanced dynamic CT scan seems to provide improved parathyroid localization, but is not yet generally available.[28] The reoperative surgery is often done as focused operation with guidance from results of the preoperative localization diagnosis, and with results approaching that of primary operations, but to markedly higher costs and with increased complication risks.[25–27]

Endocrine Pancreatic and Duodenal Tumors

Like the other MEN-1 endocrinopathies pancreatic involvement is multicentric. Minute, numerous microadenomas, with possible origin in pancreatic duct precursor cells, are typically spread in the entire pancreas, and sometimes in the duodenum.[4,29] The microtumors express immunoreactivity for pancreatic polypeptide, glucagon, insulin, proinsulin, somatostatin, or only chromogranin A.[30] Duodenal microtumors, identified in 50% of patients with MEN-1 pancreaticoduodenal tumors (PETs), stain for serotonin, gastrin, and somatostatin.[31] Presence of the endocrinopathy can be demonstrated by serum measurements, most often showing raised values of pancreatic polypeptide and chromogranin A, sometimes gastrin, insulin, and proinsulin.[4,5] A minority of the microtumors grow to clinically relevant lesions, because each patient during lifetime experiences rather few large tumors. Total pancreaticoduodenectomy is only rarely considered because of the risks associated with resulting severe diabetes. MEN-1 PETs have been claimed to have favorable prognosis compared with the corresponding sporadic tumors. Earlier diagnosis of MEN-1 tumors, or disparate survival for patients with pancreatic and duodenal gastrinomas, however, may explain this difference. Recent review of 324 patients with PETs treated in Uppsala, Sweden, revealed no survival difference for MEN-1 PETs compared with sporadic tumors.[32] Survival was related to TNM stage and Ki67 proliferation index. Nonfunctioning tumors (57%) had worse survival than functioning tumors, and outcome was markedly better in operated patients.

Malignant progression of PETs has been identified as the most important cause of premature disease-related death in MEN-1.[4,5,33–36] Screening studies have revealed that endocrine symptoms of PETs occur late in MEN-1, and when a clinical syndrome of hormone excess is awaited up to 50% of patients already have metastases.[4,5,36] High prevalence of malignancy is also seen with PETs larger than 3 cm. The authors have proposed screening for PETs in MEN-1 carriers to achieve early diagnosis, and surgery before metastases occur, and suggested that this may limit the risk for progressive metastatic disease, although randomized evaluation is lacking.[4,36–39]

Surgery for Nonfunctioning Pancreaticoduodenal Tumors

Raised serum pancreatic polypeptide values in 75% of patients with nonfunctioning tumors are important for early detection of the endocrinopathy. The patients may also have raised insulin, proinsulin, or glucagon values without a syndrome of hormone excess. The policy is to admit MEN-1 patients to surgery when the diagnosis is established by biochemical markers and radiologic studies detect tumors of appreciable size. From studies of nonfunctioning MEN-1 PETs in the French GTE register Triponez and coworkers[40,41] recommended surgery for nonfunctioning MEN-1 tumors greater than or equal to 2 cm, but revealed 4% metastases for tumors less than or equal to 10 mm and markedly higher metastases rate (15%–52%) for larger tumors. The present authors recommend surgery for nonfunctioning tumors around or greater than 10 mm, because they consider that the metastases rate is otherwise unacceptably high, and in their experience larger tumors may have distinct malignant features (**Fig. 3**).[42,43]

Contrast-enhanced CT is used to provide anatomy and reveal liver metastases, and is often used together with ^{11}C-5-hydroxytryptophane positron emission tomography, which may efficiently reveal smaller tumors. Endoscopic ultrasound has become the most important method for early detection of MEN-1 PETs and is now used for routine follow-up.[42–44]

The generally applied operative procedure consists of tumor enucleation in the pancreatic head, and concomitant distal 80% subtotal pancreatic resection. Few

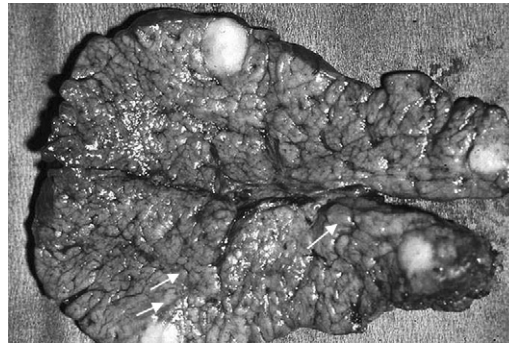

Fig. 3. Transected distal pancreatic specimen with two larger (*whitish*) and three smaller (*arrows*) tumors. All tumors in this case were clinically nonfunctioning. The larger tumors often have apparent malignant features and often occur in patients with syndromes of hormone excess, such as ZES (where the functioning tumor is commonly in the duodenum), and may easily be mistaken to represent the functional lesion. (*From* Åkerström G, Hessman O, Hellman P, et al. Pancreatic tumors as part of the MEN-I syndrome. Best Pract Res Clin Gastroenterol 2005;19:819–30; with permission.)

patients develop diabetes with this resection (**Fig. 4**). Larger or multiple tumors may require more extensive procedures (**Fig. 5**). Minimal tumors (<5 mm) deep in the pancreatic head may be left if enucleation is risky. Duodenotomy is not done unless the patient has a rise in gastrin.

Surgery for Pancreaticoduodenal Tumors with Syndromes of Hormone Excess

ZES has been the most common hormone syndrome in MEN-1, ultimately present in 50% of patients; the hypoglycemia syndrome has been revealed in less than 10%, vipoma in 3% to 5%, and symptomatic glucagonoma has occurred exceptionally (<1%).[4,42]

Surgery for Insulinomas, Vipomas, and Glucagonomas

It is generally agreed that MEN-1 patients with hypoglycemia syndrome and patients with vipoma and glucagonoma should be subjected to surgery after biochemical diagnosis irrespective of tumor size.[42,43,45,46]

Malignancy rate is higher with MEN-1 associated than with sporadic insulinoma. A single tumor greater than or equal to 5 mm in size is expected to cause the hyperinsulinism, and can often be revealed by endoscopic ultrasound. Concomitant nonfunctioning tumors are common, however, and if multiple tumors are revealed by radiology, source of insulin (or proinsulin) excess may be determined by selective intra-arterial calcium-injection test, which may regionalize the hypersecretion and identify unusual multifocal insulinoma.[46–48] Cure rate after surgery has been favorable in MEN-1 insulinomas, but concomitant distal (80%) pancreatic resection is recommended to minimize the risk for recurrence.[45,46] Tumor enucleation has also been done, but with higher risk for recurrence of nonfunctioning tumors or new insulinoma.

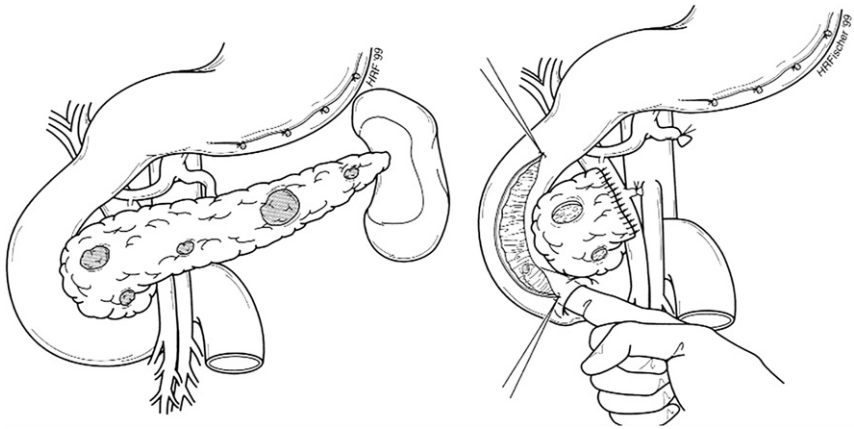

Fig. 4. The commonly applied surgical procedure in MEN-1 patients (depicted by N. Thompson). The pancreas is scanned with intraoperative ultrasound; identified lesions in the pancreatic head are enucleated, and distal tumors are removed with approximately 80% distal pancreatic resection. Duodenotomy is performed in patients with raised gastrin levels, allowing palpation of the entire duodenal mucosa, to identify duodenal gastrinomas, which in 90% is the cause of gastrin excess in MEN-1 patients. (*From* Skogseid B, Rastad J, Åkerström G. Pancreatic endocrine tumors in multiple endocrine neoplasia type I. In: Doherty GM, Skogseid B, editors. Surgical endocrinology. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 511–24; with permission.)

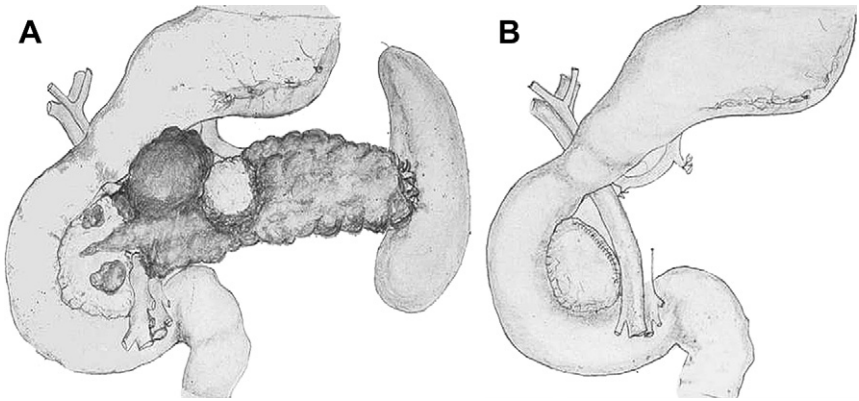

Fig. 5. (*A*) Operation for a large nonfunctioning PET, with dissection of deep extension into the pancreatic head, and enucleation of additional tumors within the opened pancreas. (*B*) Limited part of the pancreatic head remained without development of diabetes. (*From* Åkerström G, Hessman O, Hellman P, et al. Pancreatic tumors as part of the MEN-I syndrome. Best Pract Res Clin Gastroenterol 2005;19:819–30; with permission.)

MEN-1–associated vipoma, glucagonoma, or somatostatinoma syndromes are rare. Tumors causing these syndromes are usually large with high risk of malignancy, and should be treated with radical surgery.[49,50] Liver metastases from the pancreatic tumors should be considered for liver resection or radiofrequency ablation to alleviate severe hormone symptoms.[51]

Surgery for ZES

Surgery has been controversial for MEN-1 ZES patients because cure is rarely achieved. Some surgeons have advocated surgery if a tumor greater than 2 to 3 cm has been visualized, others when gastrin excess could be regionalized.[52–55] The authors have proposed surgery in absence of liver metastases also without preoperative tumor localization or regionalization, because most (90%) MEN-1 ZES patients have solitary, or typically multiple, small duodenal tumors causing the gastrin excess.[31,37,38,52,53] Despite sometimes inconspicuous size the duodenal tumors are frequently associated with conspicuously larger regional lymph gland metastases often mistaken to represent the primary tumor (**Fig. 6**).[56] Because of delay before liver metastases develop, there may be a favorable interval for surgical intervention where lymph gland metastases may be excised together with the primary lesion to prevent further spread.[57] Gastrin-secreting pancreatic tumors have been uncommon in MEN-1, but reported to be large and associated with early liver metastases.

Normalization of gastrin excess may be achieved by surgical excision of gastrinoma and lymph gland metastases, but most patients recur with hypergastrinemia, and surgery is done to reduce the risk for further progression.[53–55,58] ZES patients with liver metastases have significantly shorter survival, and liver metastases develop less frequently in operated patients.[55,58] The hypergastrinemia in ZES can be efficiently controlled by proton pump inhibitors, and surgery has the additional goal to delay malignant development also by removal of concomitant nonfunctioning tumors.[4,29]

MEN-1 patients with raised serum gastrin are subjected to duodenotomy, with excision of duodenal gastrinomas; enucleation of possible tumors in the head of the

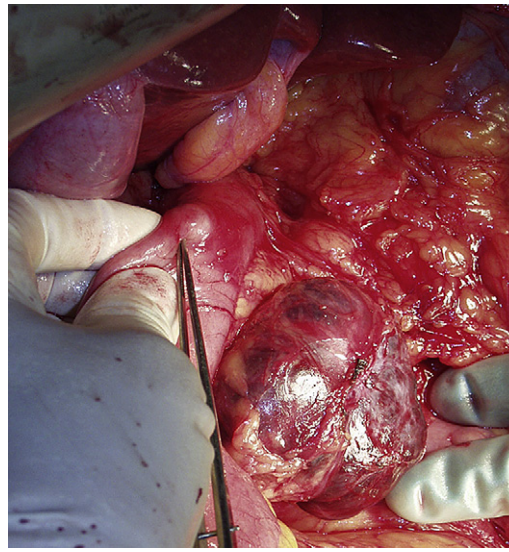

Fig. 6. Operation photo of small duodenal gastrinoma with large lymph gland metastases in a patient with MEN-1 ZES. (*From* Åkerström G, Hellman P, Stålberg P. Carcinoid: presentation and diagnosis, surgical management. In: Hubbard JGH, Inabnet WB, Lo C-Y, editors. Endocrine surgery (Springer Specialist Surgery Series). London: Springer-Verlag; 2008. Chapter 44; with permission.)

pancreas; dissection of regional metastases; and as in other MEN-1 patients, concomitant distal (80%) pancreatic resection (see **Fig. 4**).

Pancreaticoduodenectomy may offer prolonged postoperative eugastrinemia, perhaps even better than the excision of duodenal gastrinomas combined with subtotal pancreatic resection.[43,59] Common concomitant nonfunctioning tumors in ZES patients have, in the authors' experience, virtually always necessitated distal pancreatic resection (see **Fig. 3**).[38] Moreover, frequently required reoperation for recurrent tumor may be exceedingly difficult if pancreaticojejunostomy has been performed. After pancreaticoduodenectomy there is also a risk for ascending infection by the hepaticojejunostomy, making treatment of liver metastases with embolization or radiofrequency ablation hazardous.[51] Pancreaticoduodenectomy is still required in MEN-1 patients with large or recurrent pancreatic head or duodenal tumors. Pancreas-preserving duodenectomy has been reported to remove all duodenal gastrinomas, although this is a difficult procedure with the possible drawback to leave concomitant pancreatic tumors remaining.[60]

Patients with MEN-1 ZES may develop multiple gastric type 2 carcinoids, which may sometimes regress if eugastrinemia is achieved.[61] Remaining tumors should be locally excised. Some MEN-1 patients have died of malignant gastric carcinoids with spread metastases, and large gastric carcinoids may require gastrectomy.[61,62]

Operation

Pancreaticoduodenal exploration in MEN-1 patients is performed by bilateral subcostal incision. The head of the pancreas and the duodenum are mobilized to the aorta, and the ventral and dorsal surfaces of the pancreatic head are dissected. The pancreatic body and tail are explored by way of the lesser sack, with the retroperitoneum

incised below the pancreas, allowing blunt dissection of the body and tail. The entire pancreas is bidigitally palpated and scanned with intraoperative ultrasonography, from anterior and posterior surfaces.[4,29] Intraoperative ultrasonography can reveal most lesions larger than 3 to 4 mm and also visualizes relations between tumors and pancreatic and bile ducts, facilitating safe enucleation. Metastatic lymph glands are mainly searched for by exploration and palpation around the splenic and celiac vessels, in the hepatoduodenal ligament, and at the posterior surface of the pancreatic head.

Any tumor in the head of the pancreas is enucleated by dissection from the surrounding pancreatic tissue, with careful ligation of vessels and pancreatic duct tributaries. A distal 80% body and tail resection is performed, transecting the neck of the pancreas just to the left of the superior mesenteric vein (see **Fig. 4**). An enucleated area in the pancreatic head is left open with carefully applied drainage.

Because most MEN-1 patients require prophylactic cancer operation with efficient removal of lymph node metastases, which have predilection site in the splenic hilum, splenectomy is recommended generally as part of the procedure rather than spleen preservation.

Duodenotomy

In patients with ZES routine duodenal exploration is undertaken by longitudinal duodenotomy in the descending part of the duodenum (see **Fig. 4**). Small tumors can be identified by palpation after digital inversion of proximal and distal parts of the duodenum. Duodenal tumors smaller than 5 mm can be enucleated with the overlying mucosa; larger tumors require excision of the duodenal wall.

Postoperative Follow-up and Reoperation

After primary surgery lifelong cure is uncommon with the MEN-1 pancreaticoduodenal endocrinopathy and recurrence should be anticipated.[58] The patients are followed with biochemical markers and radiologic investigations, including endoscopic ultrasonography. Reoperation is considered when a lesion of arbitrarily approximately 10 mm or larger is visualized concomitant with rise of biochemical markers. Reoperations have been performed with resection or enucleation of new tumors, and have been uncomplicated and compatible with long survival and preserved pancreatic function. Total pancreatectomy may be required for recurrent, rapidly growing, or unusually large tumors, and perhaps even initially in patients with a family history of especially malignant pancreatic tumors.[63] This is avoided or delayed as much as possible because of the generally severe diabetes that ensues. In patients with metastatic disease oncologic treatment is given, with common response to combinations of streptozotocin and 5-fluorouracil or doxorubicin in patients with low-proliferative lesions as determined with the Ki67 index. In addition, liver metastases is liberally treated with liver resection and radiofrequency ablation.

The active management strategy for MEN-1 PETs is supported by several patient series revealing apparently reduced death risk in operated patients.[64–67] Strong evidence for effects on survival is still lacking. Liberally applied pancreatic surgery has to be performed with minimal morbidity and virtually absent mortality, because long survival may be obtained also without surgery.[68,69]

MEN TYPE 2

MEN-2 is an autosomal-dominant hereditary syndrome caused by germline activating mutations of the *RET* proto-oncogene on chromosome 10q11.2, affecting 1 per

30,000 individuals.[70–74] MEN-2 comprises MEN-2A, MEN-2B, and familial MTC (FMTC). Uncommon variants include MEN-2A with cutaneous lichen amyloidosis (a pruritic lichenoid skin lesion usually on the upper back) and MEN-2A with Hirschsprung disease.[71,72,74]

In MEN-2A, originally described by Sipple in 1961, virtually all patients (more than 90%) have MTC, in combination with pheochromocytoma (in 40%–50%), and pHPT (in approximately 20%). This is the most common of MEN-2 syndromes (accounting for approximately 50%–60% of patients with hereditary MTC). MTC is generally the first manifestation of MEN-2A, developing most often between 5 and 25 years of age.

MEN-2B is the rarest subtype (approximately 5%–10% of MEN-2 cases), consisting of MTC in all cases; pheochromocytoma (50% of patients); ganglioneuromatosis; and typical features with marfanoid habitus, enlarged lips, and mucosal neuromas in the tongue, lips, and eyelids.[72,75,76] pHPT is not part of the MEN-2B syndrome. Ganglioneuromatosis of the gastrointestinal tract may frequently cause abdominal complaints, megacolon, obstipation, or diarrhea. Patients with MEN-2B have early disease onset and aggressive MTC, developing during the first year of life and associated with early dissemination and mortality. Most patients have spontaneous new RET mutations, as index cases without positive family history.[72] The patients often experience delay in diagnosis until mucosal neuromas or palpable thyroid tumors are obvious. The syndrome may be recognized in early childhood by characteristic neuromas and typical features (patients look different than other family members).[72,75,76]

FMTC (approximately 35%–40% of MEN-2 cases) is a generally milder variant of MEN-2, more frequently diagnosed in recent years.[72–74,77] MTC may have later onset, with better prognosis. Many cases have initially been thought to have sporadic MTC, but revealed by genetic screening. Identical germline mutations have been reported in MEN-2A and FMTC families, and some FMTC patients belong to MEN-2A kindreds, where pheochromocytoma or HPT have not been detected. Strict criteria are required to exclude MEN-2 with need of screening and follow-up of multiple members in a kindred.[72,73,78] Unclassified cases have few family members with too limited follow-up to exclude MEN-2A.[72]

MTC

MTC is a rare carcinoma developing from thyroid calcitonin-producing parafollicular C-cells, occurring most frequent in-between the upper and middle thirds of both thyroid lobes.[72,78] Hereditary MTC occurs at younger age than sporadic MTC; is associated with C-cell hyperplasia (CCH); and has multifocal, frequently bilateral tumors in contrast to solitary sporadic MTC tumors. Tumor cells have granulated cytoplasm and stain for calcitonin and amyloid (with Congo red reactive with calcitonin prohormone). CCH consists of C-cell clusters dispersed in-between the thyroid follicles, and is considered a premalignant condition preceding hereditary MTC, but occurs also in 20% to 30% of normal individuals. Time required for progression from CCH to microscopic carcinoma is variable.[72] Frequency of lymph node metastases relates to tumor size, being 20% and 30% for tumors greater than or equal to 1 cm, 50% for tumors measuring 1 to 4 cm, and up to 90% for tumors greater than 4 cm.[78] Distant metastases occur to liver, bone, and lung. Liver metastases are often initially small (1–3 mm) and easily missed by imaging with CT, MRI, or contrast-enhanced ultrasound, and may require visualization by laparoscopy.

Approximately 50% of index patients with MEN-2 present with palpable tumor and locally advanced disease, with regional lymph gland metastases.[78] Diagnosis of MTC is made by fine-needle aspiration and calcitonin staining. Basal serum calcitonin is

virtually always high in patients with palpable MTC, and correlates with tumor burden. Raised calcitonin levels following surgical tumor removal indicate persistent or recurrent disease. Previously, family screening for hereditary MTC used pentagastrin (or calcium) to stimulate calcitonin secretion from malignant or hyperplastic C cells. Raised stimulated, but normal basal calcitonin occurs with CCH, but the stimulation test cannot distinguish between CCH and minimal MTC.[72] Occasionally, calcitonin release from nonfunctioning PETs may give suspicion of MTC, but values then fail to rise after stimulation as expected with MTC. Carcinoembryonic antigen can be used as additional tumor marker together with calcitonin, but is not specific for MTC.

Genetic Diagnosis

The *RET* proto-oncogene on chromosome 10q11.2 was identified by genetic linkage analysis in 1987, and the MEN-2 syndrome was demonstrated to result from missense germline mutations in this gene.[70–74,79–81] The *RET* proto-oncogene with 21 exons, encodes a tyrosine kinase receptor, with an extracellular domain containing a ligand-binding site; a cysteine-rich region (exons 10 and 11); a transmembrane domain; an intracellular part with two tyrosine kinase domains (exons 13–15); and an intracellular catalytic core (exon 16) (**Fig. 7**).[72,82,83] *RET* is expressed mainly in neuronal and neuroepithelial cells of neural crest origin, as thyroid C-cells, adrenomedullary chromaffin cells, and parathyroid cells. Gain-of-function mutations activate the *RET* receptor kinase causing thyroid CCH, adrenomedullary hyperplasia, and parathyroid hyperplasia. Alteration in the intracellular catalytic core (mutations in codon 918, classical MEN-2B genotype) has the highest transforming capacity; ligand-independent dimerization and cross-phosphorylation (mutations in codon 609, 611,

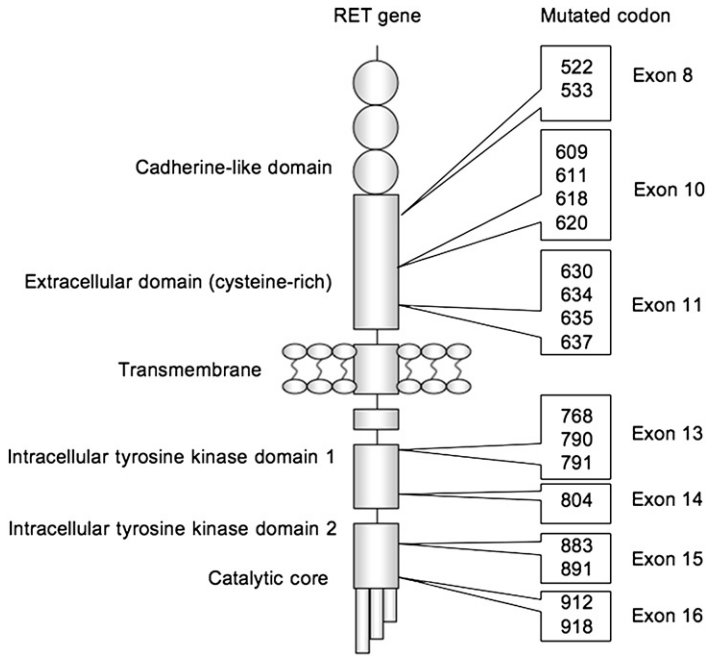

Fig. 7. The schematic structure of the *RET* tyrosine kinase receptor. (*Adapted from* Machens A, Dralle H. Genotype-phenotype based surgical concept of hereditary medullary thyroid carcinoma. World J Surg 2007;31:957–68; with permission.)

618, 630, and 634) has intermediate activity; and interference with ATP binding (mutations in codons 768, 790, 791, 804, and 891) has lower transforming activity.[82,83] Age-related progression from CCH to MTC, and development of pheochromocytoma and parathyroid nodular hyperplasia, correlates with transforming capacity of the *RET* mutations, but require also additional somatic second hits.[83] MTC is generally the first neoplastic manifestation because of higher susceptibility of C cells to the oncogenic *RET* activation.[73]

Somatic RET mutations are found in approximately 25% of patients with sporadic MTC. The most frequent mutations in codon 918 are associated with aggressive MTC.[72,84–87] Somatic *RET* mutations also occur in sporadic pheochromocytoma.[72,85] Somatic *RET* rearrangements are seen in papillary thyroid carcinoma.

MEN-2 accounts for approximately 25% of MTC cases and 7% to 25% of patients with ''apparently sporadic'' MTC.[74,88] Mutation testing has identified over 50 different missense *RET* gene mutations in MEN-2 families, and genetic testing detects approximately 98% of mutation carriers.[73] Only family members with germline missense mutations have the disease. *RET* gene testing should be performed before surgical intervention in all patients with diagnosed MTC, to provide risk assessment for family members, determine risk for associated endocrinopathies, and guide surgical management of MTC.[72,73] All members of MEN-2 and FMTC kindreds should undergo genetic testing and gene carriers should be offered prophylactic thyroidectomy during childhood. *RET* gene testing is recommended also as screening of patients with pheochromocytoma.

Genotype-phenotype Correlation

MEN-2A is most often caused by RET mutations in codons of exons 10 and 11, but also by more rare intracellular mutations (**Fig. 8**).[70–74,89] Codon 634 mutations (exon 11) are reported in approximately 40% of MEN-2A patients,[73] and also seen with MEN-2A and cutaneous lichen amyloidosis (in 12% of codon 634 mutations).[71,72,74] With codon 634 mutation MTC develops during the first decade of life, not influenced by the type of amino acid substitute at codon 634. Mutations in codons 609, 611, 618, and 620 (exon 10) cause 10% to 15% of MEN-2A and MEN-2A associated with

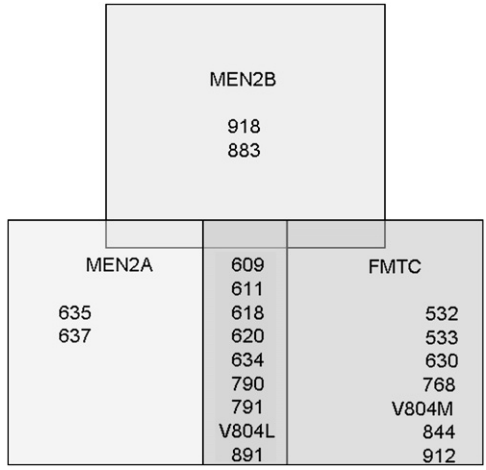

Fig. 8. Correlation of specific RET codon mutations with the phenotypic expression of hereditary MTC.

Hirschsprung disease.[72] Pheochromocytoma is less prevalent in these families, and MTC rarely presents before the age of 10 years. MEN-2A mutations also include codons 635 and 637 (exon 11); 790 and 791 (exon 13); 804 L (exon 14); and 891 (exon 15).[72] Mutations at codon 804 were initially believed to be associated with FMTC, although subsequent studies identified patients with late-onset pheochromocytoma, and HPT (associated with 804 L but not 804 M mutations).[90,91]

FMTC mutations are distributed throughout the *RET* gene including the codons causing MEN-2A at exons 10, 11, 13, 14, and 15.[72] Mutations at codon 532, 533, 768, 844, and 912 have only been identified in families with FMTC. FMTC rarely develops before the age of 20 years.

Codon 918 mutations (exon 16), revealed in 95% of MEN-2B cases, have aggressive MTC with metastases reported before the age of 12 months.[71,92] Few MEN-2B patients have mutations in codon 883 (exon 15).[93]

Risk Levels

A three-level risk stratification has been adopted by an international consensus panel, suggesting time for prophylactic thyroidectomy generally as close as possible to the earliest reported age of onset for each genotype.[7,72,94–97] For the highest-risk group, including MEN-2B carriers (mutations of codons 918 and 883), prophylactic thyroidectomy should be done within the first year of life, preferably by the age of 6 months. For the high-risk group (mutations of codons 609, 611, 618, 620, and 634), where most patients have MEN-2A, prophylactic thyroidectomy is recommended before the age of 5 years. For the least high-risk group, (mutations of codons 768, 790, 791, 804, and 891), the recommended age for thyroidectomy remains controversial, suggested at 5 to 10 years, or when a calcitonin stimulation test becomes abnormal.[7,72–74,91,94–97] Codon 609 was subsequently reclassified to the high-risk group, and codon 630 previously not classified was included as high-risk group.[74,95] Evidence-based evaluation has supported DNA-based evaluation as superior to calcitonin-based screening in asymptomatic *RET* carriers, and some centers consider this to have limited value because of poor specificity and tolerance.[95] If basal calcitonin values are raised thyroidectomy should be performed.[95] The outlined recommendations can result in undertreatment of codon 634 mutation carriers, where MTC has developed between 1 and 2 years of age, and some surgeons recommend testing during first year of life and thyroidectomy by age 2.[78,96] MTC in codon 634 mutation carriers younger than 5 years has been so rare, however, that thyroidectomy before age 5 is often accepted.[96] There is also risk for overtreatment of least high-risk mutation carriers, with variable disease penetration, but with MTC reported from the second to third decade. The exception is codon 804 mutation carriers with variable disease onset, and reported ultimately fatal MTC in a 6-year-old proband.[95,97,98] Codon 791 mutation carriers have low disease penetrance, and may as alternative to the age-related thyroidectomy be followed with repeated basal and stimulated calcitonin screening.[73]

Lymph Node Dissection

MEN-2 patients with clinically detected MTC should be subjected to total thyroidectomy with bilateral central and lateral neck compartment dissection, removing lymph nodes in-between the jugular veins from the hyoid bone to the innominate vein.

For the highest-risk mutation carriers bilateral central and lateral cervical lymph node dissection is advocated at time of thyroidectomy.[96] It is recommended for high-risk mutations from age 5 years (codon 634) and 10 years (codons 609, 611, 618, 620, and 630). Lymph node dissection is recommended from the age of 20 years for the least high-risk mutations, but data are inconclusive.[96]

Prophylactic thyroidectomy based on DNA testing in the MEN-2 syndrome is considered as one of the greater achievements in cancer treatment, because it may be performed before thyroid carcinoma development, and provides cure for the patient. The association between disease phenotype and *RET* mutation genotype also has important implications for the clinical management of MEN-2 patients and families. A patient's genotype can be used to decide intensity of screening for pheochromocytoma and HPT, which always need to be excluded before thyroidectomy for MTC.

Pheochromocytomas

Pheochromocytomas are most frequent with mutations in codons 634 and 918, but occur with germline mutations in all MEN-2–associated codons except 768.[7,72,89,90,98–100] The MEN-2 tumors are generally diagnosed at younger age than sporadic tumors, with mean age of diagnosis in MEN-2A approximately 35 years, MEN-2B approximately 25 years, and as early as age 5 years in codon 634 mutation carriers.[7,72,98,100–102] Screening for pheochromocytoma is recommended from age of 5 to 7 years, especially for codon 634 mutation carriers. Pheochromocytomas are rarely (approximately 15%) the initial manifestation of MEN-2, occur concomitant with MTC in 25%, but most often after MTC, with mean approximately 10 years delay.[70,72,99–101] The pheochromocytomas are often bilateral, but often develop asynchronously, with a contralateral new pheochromocytoma occurring after 4 years in approximately 30% of patients.[99,100,103]

The histologic pattern is similar in MEN-2A and -B, with single or multiple tumors in a background of micronodular or diffuse medullary hyperplasia.[104] Pheochromocytomas in MEN-2 are rarely extra-adrenal (<1%) or malignant (3%–4%).[99–102] Malignant pheochromocytomas are more likely with tumor size exceeding 5 cm. Histologic features are uncertain, and malignant diagnosis generally requires demonstration of metastases, or is sometimes evident after long follow-up.[99,104]

Diagnosis

MEN-2 pheochromocytomas have an adrenergic biochemical phenotype, with diagnosis based on measurements of plasma or 24-hour urinary fractionated metanephrine. Annual biochemical screening and CT is done to exclude development of pheochromocytoma in patients with MEN-2. Because of increased detection by screening approximately 50% or more of MEN-2 patients with pheochromocytoma have been asymptomatic at time of diagnosis.[99]

Surgical Management

A unilateral pheochromocytoma in MEN-2 patients is generally removed by total removal of this adrenal, most often by laparoscopy, and this leaves a macroscopically normal gland for follow-up.[99,100] Only few large or suspect malignant tumors require open surgery. The risk for recurrent contralateral pheochromocytoma has been approximately 30% during 5 years, and 50% during 11 years of follow-up.[99–101,103] Bilateral pheochromocytomas in MEN-2 patients may require bilateral adrenalectomy, and the patient needs lifelong substitution with glucocorticoid and mineralocorticoid replacement, with risk for development of Addison crisis.[99] To avoid adrenal insufficiency efforts have been made to preserve adrenal function by partial, cortical-sparing adrenalectomy in MEN-2A. This can be done as an open, laparoscopic, or retroperitoneoscopic operation, aided by intraoperative ultrasound.[99,105–107] For bilateral pheochromocytomas or subsequent operation of the contralateral gland after prior adrenalectomy, an adrenal cortical-sparing operation is generally recommended,

unless a large tumor or unfavorable location precludes sparing of a significant amount of the adrenal. Recurrence has been reported in 10% to 20% of patients, subjected to long-term follow-up.[105,108] Also for recurrence in the remnant gland an additional subtotal adrenalectomy has been performed without morbidity.[107–109]

Hyperparathyroidism

pHPT occurs in 20% of patients with MEN-2A, most commonly associated with codon 634 mutations, less frequently with mutations in codons 609, 611, 618, 620, 790, and 791, and is not part of the MEN-2B syndrome.[11,70,72,74,110,111] Parathyroid disease in MEN-2A is generally mild, with only slight elevation of serum calcium.[11,110] Most patients (85%) have been asymptomatic, few patients have had renal stone disease or evident neuropsychiatric symptoms.[110,111] Most patients have presented with slight parathyroid enlargement discovered during prophylactic or therapeutic thyroidectomy, with normal serum calcium and PTH levels, and with diagnosis based on morphology.[11,110,111] Histologically, the predominant finding has been nodular parathyroid chief-cell hyperplasia, affecting more than one gland, but asymmetrically, implying that enlarged glands coexist with normal-sized ones.[111] Single and multiple adenomas have been described and it is suggested that adenomas may evolve from the nodular hyperplasia. The principal problem in patients with the MEN-2A syndrome has been to avoid hypoparathyroidism during thyroidectomy combined with extensive lymph node dissections, and the surgical management of pHPT should aim to preserve parathyroid function.[11,111] All parathyroids should be identified, but only enlarged glands should be removed, although this is recommended even if the patient is eucalcemic. In cases with four-gland enlargement subtotal parathyroidectomy is preferred to total parathyroidectomy with autotransplantation. The strategy during thyroidectomy is generally to leave normal parathyroids in situ, and perform autotransplantation of devascularized glands. If normal parathyroids are inadvertently removed or are at risk during lymph node dissection, they should be liberally autotransplanted to the forearm in MEN-2A cases (and to the sternocleidomastoid muscle in MEN-2B cases).[74]

Many cases of HPT develop several years after thyroidectomy, resulting from single adenoma or multiglandular disease, and can then be managed with conservative strategy, removing only enlarged parathyroid glands.[74,110]

Cure rate after a depicted conservative approach of parathyroid surgery in MEN-2A patients has been 97% and 100%, and recurrence rate low (3%–5%).[11,110,111]

REFERENCES

1. Chandrasekharappa SC, Guru SC, Manickam P, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science 1997;276:404–7.
2. Lemos MC, Thakker RV. Multiple endocrine neoplasia type 1 (MEN 1): analysis of 1336 mutations reported in the first decade following identification of the gene. Hum Mutat 2008;29:22–32.
3. Tham E, Grandell U, Lindgren E, et al. Clinical testing for mutations in the MEN 1 gene in Sweden: a report on 200 unrelated cases. J Clin Endocrinol Metab 2007; 92:3389–95.
4. Skogseid B, Rastad J, Åkerström G. Pancreatic endocrine tumors in multiple endocrine neoplasia type I. In: Doherty GM, Skogseid B, editors. Surgical endocrinology. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 511–24.

5. Skogseid B, Eriksson B, Lundquist G, et al. Multiple endocrine neoplasia type I: a 10-year prospective screening study in four kindreds. J Clin Endocrinol Metab 1991;73:281–7.
6. 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;239:637–45.
7. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type1 and type2. J Clin Endocrinol Metab 2001;86:5658–71.
8. Uchino S, Noguchi S, Sato M, et al. Screening of the MEN 1 gene and discovery of germ-line and somatic mutations in apparently sporadic parathyroid tumors. Cancer Res 2000;60:5553–7.
9. Langer P, Wild A, Hall A, et al. Prevalence of multiple endocrine neoplasia type 1 in young patients with apparently sporadic primary hyperparathyroidism or pancreaticoduodenal endocrine tumors. Br J Surg 2003;90:1599–603.
10. Burgess JR, David R, Greenway TM, et al. Osteoporosis in multiple endocrine neoplasia type 1: severity, clinical significance, relationship to primary hyperparathyroidism, and response to parathyroidectomy. Arch Surg 1999;134:1119–23.
11. Åkerström G, Juhlin C. Surgical management of multiglandular parathyroid disease. In: Randolph GW, editor. Surgery of the thyroid and parathyroid glands. Philadelphia: Saunders; 2003. p. 529–48.
12. 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;247:501–10.
13. Harach HR, Jasani B. Parathyroid hyperplasia in multiple endocrine neoplasia type 1: a pathological and immunohistochemical reappraisal. Histopathology 1992;21:513–9.
14. Stålberg P, Carling T. Familial parathyroid tumors. In: Evidence Based Symposium on Hyperparathyroidism, World J Surg 2009 [epub ahead of print].
15. Åkerström G, Malmaeus J, Bergström R. Surgical anatomy of human parathyroid glands. Surgery 1984;95:14–21.
16. Hellman P, Skogseid B, Öberg K, et al. Primary and reoperative parathyroid operations in hyperparathyroidism of multiple endocrine neoplasia type 1. Surgery 1998;124:993–9.
17. O'Riordain DS, O'Brien T, Grant CS, et al. Surgical management of primary hyperparathyroidism in multiple endocrine neoplasia types 1 and 2. Surgery 1993;114:1031–7 [discussion: 1037–9].
18. Goudet P, Cougard P, Verges B, et al. Hyperparathyroidism in multiple endocrine neoplasia type I: surgical trends and results of a 256-patient series from Groupe D'etude des Neoplasies Endoccriniennes Multiples Study Group. World J Surg 2001;25:886–90.
19. Elaraj DM, Skarulis MC, Libutti SK, et al. Results of initial operation for hyperparathyroidism in patients with multiple endocrine neoplasia type 1. Surgery 2003;134:858–64 [discussion: 864–5].
20. Kraimps JL, Denizot A, Carnaille B, 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; 20:808–12 [discussion: 812–3].
21. Wells SA, Farndon JR, Dale JK, et al. Long-term evaluation of patients with primary parathyroid hyperplasia managed by total parathyroidectomy and heterotopic autotransplantation. Ann Surg 1980;192:451–8.

22. Hubbard JGH, Sebag F, Maweja S, et al. Subtotal parathyroidectomy as an adequate treatment for primary hyperparathyroidism in multiple endocrine neoplasia type 1. Arch Surg 2006;141:235–9.
23. Kivlen M, Bartlett DL, Libutti SK, et al. Reoperation for hyperparathyroidism in multiple endocrine neoplasia type 1. Surgery 2001;130:991–8.
24. Clerici T, Brandle M, Lange J, et al. Impact of intraoperative parathyroid hormone monitoring on the prediction of multiglandular parathyroid disease. World J Surg 2004;28:187–92.
25. Thompson GB, Grant CS, Perrier ND, et al. Reoperative parathyroid surgery in the era of sestamibi scanning and intraoperative parathyroid hormone monitoring. Arch Surg 1999;134:699–705.
26. Udelsman R, Donovan PI. Remedial parathyroid surgery: changing trends in 130 consecutive cases. Ann Surg 2006;244:471–9.
27. Hessman O, Stålberg P, Sundin A, et al. High success rate of parathyroid reoperation may be achieved with improved localization diagnosis. World J Surg 2008;32:774–81 [discussion: 782–3].
28. Rodgers SE, Hunter GJ, Hamberg LM, et al. Improved preoperative planning for directed parathyroidectomy with 4-dimensional computed tomography. Surgery 2006;140:932–40.
29. Åkerström G, Hessman O, Hellman P, et al. Pancreatic tumours as part of the MEN-I syndrome. Best Pract Res Clin Gastroenterol 2005;19:819–30.
30. Klöppel G, Willemer S, Stamm B, et al. Pancreatic lesions and hormonal profile of pancreatic tumors in multiple endocrine neoplasia type I: an immunocytochemical study of nine patients. Cancer 1986;57:1824–32.
31. Pipellers-Marichal M, Somers G, Willems E, et al. Gastrinomas in the duodenums of patients with multiple endocrine neoplasia type I and the Zollinger-Ellison syndrome. N Engl J Med 1990;322:723–7.
32. Ekeblad S, Skogseid B, Dunder K, et al. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. Clin Cancer Res 2008;14:7798–803.
33. Doherty GM, Olson JA, Frisella MM, et al. Lethality of multiple endocrine neoplasia type I. World J Surg 1998;22:581–7.
34. Dean PG, van Heerden JA, Farley DR, et al. Are patients with multiple endocrine neoplasia type I prone to premature death? World J Surg 2000;24:1437–41.
35. Lowney J, Frisella MM, Lairmore TC, et al. Islet cell tumor metastasis in multiple endocrine neoplasia type I: correlation with primary tumor size. Surgery 1998;124:1043–9.
36. Skogseid B, Öberg K, Eriksson B, et al. Surgery for asymptomatic pancreatic lesion in multiple endocrine neoplasia type I. World J Surg 1996;20:872–7.
37. Åkerström G, Johansson H, Grama G. Surgical treatment of endocrine pancreatic lesions in MEN-I. Acta Oncol 1991;30:541–5.
38. Grama D, Skogseid B, Wilander E, et al. Pancreatic tumors in multiple endocrine neoplasia type I: clinical presentation and surgical treatment. World J Surg 1992;16:611–9.
39. Skogseid B, Öberg K, Åkerström G. Limited tumor involvement found at multiple endocrine neoplasia type I pancreatic exploration: can it be predicted by preoperative tumor localization? World J Surg 1998;22:673–8.
40. Triponez F, Goudet P, Dosseh D, et al. Is surgery beneficial for MEN 1 patients with small ($\leq$2 cm), nonfunctioning pancreaticoduodenal endocrine tumor? An analysis of 65 patients from the GTE. World J Surg 2006;30:654–62.

41. Triponez F, Dosseh D, Goudet P, et al. Epidemiology data on 108 MEN 1 patients from the GTE with isolated nonfunctioning tumors of the pancreas. Ann Surg 2006;243:265–72.
42. Doherty GM, Thompson NW. Multiple endocrine neoplasia type 1: duodenopancreatic tumours. J Intern Med 2003;253:590–8.
43. Bartsch DK, Fendrich V, Langer P, et al. Outcome of duodenopancreatic resections in patients with multiple endocrine neoplasia type 1. Ann Surg 2005;242: 757–66.
44. Hellman P, Hennings J, Åkerström G, et al. Endoscopic ultrasound for evaluation of pancreatic tumors in multiple endocrine neoplasia type 1. Br J Surg 2005;92:1508–12.
45. O'Riordian DS, O'Brian T, van Heerden JA, et al. Surgical management of insulinoma associated with multiple endocrine neoplasia type 1. World J Surg 1994; 18:488–94.
46. Demeure MJ, Klonoff CC, Karam JH, et al. Insulinomas associated with multiple endocrine neoplasia type 1: the need for a different surgical approach. Surgery 1991;110:998–1005.
47. Grant CS. Insulinoma. Best Pract Res Clin Gastroenterol 2005;19:783–98.
48. Kato M, Imamura M, Hosotani R, et al. Curative resection of microgastrinomas based on the intraoperative secretin test. World J Surg 2000;24:1425–30.
49. Levy-Bohbot N, Merie C, Goudet P, et al. Prevalence, characteristics and prognosis of MEN 1-associated glucagonomas, VIPomas, and somatostatinomas. Gastroenterol Clin Biol 2004;28:1075–81.
50. Bartsch D, Langer P, Wild A, et al. Pancreaticoduodenal endocrine tumors in multiple endocrine neoplasia type 1: surgery or surveillance? Surgery 2000; 128:958–66.
51. Hellman P, Ladjevardi S, Skogseid B, et al. Radiofrequency tissue ablation using coiled tip for liver metastases of endocrine tumors. World J Surg 2002;26: 1052–6.
52. Thompson NW, Vinik AI, Eckhauser F. Microgastrinomas of the duodenum: a cause of failed operations for the Zollinger-Ellison syndrome. Ann Surg 1989;168:396–404.
53. Thompson NW. Current concept in the surgical management of multiple endocrine neoplasia type 1 pancreaticoduodenal disease: results in the treatment of 40 patients with Zollinger-Ellison syndrome, hypoglycaemia or both. J Intern Med 1998;243:495–500.
54. Norton JA, Fraker DL, Alexander HR, et al. Surgery to cure the Zollinger-Ellison syndrome. N Engl J Med 1999;341:635–44.
55. Norton J, Jensen RT. Role of surgery in Zollinger-Ellison syndrome. J Am Coll Surg 2007;205(Suppl 4):S34–7.
56. Åkerström G, Hellman P, Stålberg P. Carcinoid: presentation and diagnosis, surgical management. In: Hubbard JGH, Inabnet WB, Lo C-Y, editors. Endocrine surgery (Springer Specialist Surgery Series). London: Springer-Verlag; 2008. Chapter 44.
57. Modlin IM, Lawton GP. Duodenal gastrinoma: the solution to the pancreatic paradox. J Clin Gastroenterol 1994;19:184–8.
58. Hausman MS Jr, Thompson NW, Gauger PG, et al. The surgical management of MEN-1 pancreatoduodenal neuroendocrine disease. Surgery 2004;136: 1205–11.
59. Tonelli F, Fratini G, Falchetti A, et al. Surgery for gastroenteropancreatic tumors in multiple endocrine neoplasia type 1: review and personal experience. J Intern Med 2005;257:38–49.

60. Imamura M, Komoto I, Doi R, et al. New pancreas-preserving total duodenectomy technique. World J Surg 2005;29:203–7.
61. Richards ML, Gauger P, Thompson NW, et al. Regression of type II gastric carcinoids. World J Surg 2004;28:652–8.
62. Norton JA, Melcher ML, Gibril F, et al. 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; 136:1267–74.
63. Tisell LE, Ahlman H, Jansson S, et al. Total pancreatectomy in the MEN 1 syndrome. Br J Surg 1988;75:154–7.
64. You YN, Thompson GB, Young WF, et al. Pancreatoduodenal surgery in patients with multiple endocrine neoplasia type 1: operative outcomes, long-term function, and quality of life. Surgery 2007;142:829–36.
65. Kouvaraki MA, Shapiro SE, Cote GJ, et al. Management of pancreatic endocrine tumors in multiple endocrine neoplasia type 1. World J Surg 2006;30:643–53.
66. Tonelli F, Fratini G, Nesi G, et al. Pancreatectomy in multiple endocrine neoplasia type 1-related gastrinomas and pancreatic endocrine neoplasias. Ann Surg 2006;244:61–70.
67. Wilson SD, Krzywda EA, Zhu Y-r, et al. The influence of surgery in MEN-1 syndrome: observations over 150 years. Surgery 2008;144:695–702.
68. Norton JA, Jensen RT. Resolved and unresolved controversies in the surgical management of patients with Zollinger-Ellison syndrome. Ann Surg 2004;240: 757–73.
69. Lairmore TC, Chen VY, DeBenedetti MK, et al. Duodenopancreatic resections in patients with multiple endocrine neoplasia type I. Ann Surg 2000;231:909–18.
70. Mulligan LM, Eng C, Healey CS, et al. Specific mutations of the RET proto-oncogene are related to disease phenotype in MEN 2A and FMTC. Nat Genet 1994;6: 70–4.
71. Eng C, Clayton D, Schuffenecker I, et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET Mutation Consortium Analysis. JAMA 1996;276:1575–9.
72. Kouvaraki MA, Shapiro SE, Perrier ND, et al. *RET* proto-oncogene: a review and update of genotype-phenotype correlations in hereditary medullary thyroid cancer and associated endocrine tumors. Thyroid 2005;15:531–44.
73. Raue F, Frank-Raue K. Multiple endocrine neoplasia type 2: 2007 update. Horm Res 2007;68(Suppl 5):101–4.
74. Callender GG, Rich TA, Perrier ND. Multiple endocrine neoplasia syndromes. Surg Clin North Am 2008;88:863–95.
75. Schimke RN, Hartmann WH, Prout TE, et al. Syndrome of bilateral pheochromocytoma, medullary thyroid carcinoma and multiple neuromas: a possible regulatory defect in the differentiation of chromaffin tissue. N Engl J Med 1968;279:1–7.
76. Wray CJ, Rich TA, Waguespack SG, et al. Failure to recognize multiple endocrine neoplasia 2B: more common than we think? Ann Surg Oncol 2008;15: 293–301.
77. Farndon JR, Leight GS, Dilley WG, et al. Familial medullary thyroid carcinoma without associated endocrinopathies: a distinct clinical entity. Br J Surg 1986; 73:278–81.
78. Grant CS. Medullary thyroid carcinoma and associated multiple endocrine neoplasia type 2. In: Hay ID, Wass JAH, editors. Clinical endocrine oncology. 2nd edition. Singapore: Blackwell Publishing; 2008. p. 515–22.

79. Mulligan LM, Kwok JB, Healey CS, et al. Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. Nature 1993;363:458–60.
80. Donis-Keller H, Dou S, Chi D, et al. Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. Hum Mol Genet 1993;2:851–6.
81. Mulligan LM, Marsh DJ, Robinson BG, et al. Genotype-phenotype correlation in multiple endocrine neoplasia type 2: report of the International RET Mutation Consortium. J Intern Med 1995;238:343–6.
82. Eng C. Seminars in medicine of the Beth Israel Hospital, Boston. The RET proto-oncogene in multiple endocrine neoplasia type 2 and Hirschsprung's disease. N Engl J Med 1996;335:943–51.
83. Machens A, Dralle H. DNA-based window of opportunity for curative pre-emptive therapy of hereditary medullary thyroid cancer. Surgery 2006;139:279–82.
84. Hofstra RM, Landsvater RM, Ceccherini I, et al. A mutation in the RET proto-oncogene associated with multiple endocrine neoplasia type 2B and sporadic medullary thyroid carcinoma. Nature 1994;367:375–6.
85. Eng C, Smith DP, Mulligan LM, et al. Point mutation within the tyrosine kinase domain of the RET proto-oncogene in multiple endocrine neoplasia type 2B and related sporadic tumours. Hum Mol Genet 1994;3:237–41.
86. Zedenius J, Larsson C, Bergholm U, et al. Mutations of codon 918 in the RET proto-oncogene correlate to poor prognosis in sporadic medullary thyroid carcinomas. J Clin Endocrinol Metab 1995;80:3088–90.
87. Alemi M, Lucas SD, Sallstrom JF, et al. A complex nine base pair deletion in RET exon 11 common in sporadic medullary thyroid carcinoma. Oncogene 1997;14: 2041–5.
88. Elisei R, Romei C, Cosci B, et al. RET genetic screening in patients with medullary thyroid cancer and their relatives: experience with 807 individuals at one center. J Clin Endocrinol Metab 2007;92:4725–9.
89. Yip L, Cote GL, Shapiro SE, et al. Multiple endocrine neoplasia type 2: evaluation of the genotype-phenotype relationship. Arch Surg 2003;138:409–16.
90. Nilsson O, Tisell LE, Jansson S, et al. Adrenal and extra-adrenal pheochromocytomas in a family with germline RET V804L mutation. JAMA 1999;281: 1587–8.
91. Learoyd DL, Gosnell J, Elston MS, et al. Experience of prophylactic thyroidectomy in multiple endocrine neoplasia type 2A kindreds with *RET* codon 804 mutations. Clin Endocrinol (Oxf) 2005;63:636–41.
92. Vasen HF, van der Feltz M, Raue F, et al. The natural course of multiple endocrine neoplasia type 2b. Arch Intern Med 1992;152:1250–2.
93. Smith DP, Houghton C, Ponder BA. Germline mutation of RET codon 883 in two cases of de novo MEN 2B. Oncogene 1995;15:1213–7.
94. Gimm O, Ukkat J, Niederle BE, et al. Timing and extent of surgery in patients with familial medullary thyroid carcinoma/multiple endocrine neoplasia type 2A-related *RET* mutations not affecting codon 634. World J Surg 2004;28: 1312–6.
95. Learoyd DL, Robinson BG. Do all patients with *RET* mutations associated with multiple endocrine neoplasia type 2 require surgery? Nat Clin Pract Endocrinol Metab 2005;1:60–1.
96. Machens A, Dralle H. Genotype-phenotype based surgical concept of hereditary medullary thyroid carcinoma. World J Surg 2007;31:957–68.
97. Frohnauer MK, Decker RA. Update on the MEN 2A c804 RET mutation: is prophylactic thyroidectomy indicated? Surgery 2000;128:1052–7 [discussion: 1057–8].

98. Webb TA, Sheps SG, Carney JA. Differences between sporadic pheochromocytoma and pheochromocytoma in multiple endocrine neoplasia, type 2. Am J Surg Pathol 1980;4:121–6.
99. Yip L, Lee JE, Shapiro SE, et al. Surgical management of hereditary pheochromocytoma. J Am Coll Surg 2004;198:525–34 [discussion: 534–5].
100. Åkerström G, Hellman P. Genetic syndromes associated with adrenal tumors. In: Linos D, van Heerden JA, editors. Adrenal surgery. Heidelberg, Germany: Springer; 2005. p. 251–4.
101. Modigliani E, Vasen HM, Raue K, et al. Pheochromocytoma in multiple endocrine neoplasia type 2: European study. J Intern Med 1995;238:363–7.
102. Casanova S, Rosenberg-Bourgin M, Farkas D, et al. Phaeochromocytoma in multiple endocrine neoplasia type 2A: survey of 100 cases. Clin Endocrinol 1993;38:531–7.
103. Lairmore TC, Ball DW, Baylin SB, et al. Management of pheochromocytomas in patients with multiple endocrine neoplasia type 2 syndromes. Ann Surg 1993; 217:595–603.
104. Pomares FJ, Canas R, Rodriguez JM, et al. Differences between sporadic and multiple endocrine neoplasia type 2A phaeochromocytoma. Clin Endocrinol 1998;48:195–200.
105. Lee JE, Curley SA, Gagel RF, et al. Cortical-sparing adrenalectomy for patients with bilateral pheochromocytoma. Surgery 1996;120:1064–71.
106. Inabnet WB, Caragliano P, Pertsemlidis D. Pheochromocytoma, inherited associations, bilaterality, and cortex preservation. Surgery 2000;128:1007–12.
107. Walz MK, Peitgen K, Diesing D, et al. Partial versus total adrenalectomy by the posterior retroperitoneoscopic approach: early and long-term results of 325 consecutive procedures in primary adrenal neoplasia. World J Surg 2004;28: 1323–9.
108. Asari R, Scheuba C, Kaczirek K, et al. Estimated risk of pheochromocytoma recurrence after adrenal-sparing surgery in patients with multiple endocrine neoplasia type 2A. Arch Surg 2006;141:1199–205.
109. Brauckhoff M, Gimm O, Brauckhoff K, et al. Repeated adrenocortical-sparing adrenalectomy for recurrent hereditary pheochromocytoma. Surg Today 2004; 34:251–5.
110. Raue F, Kraimps JL, Dralle H, et al. Primary hyperparathyroidism in multiple endocrine neoplasia type 2A. J Intern Med 1995;238:369–73.
111. Snow KJ, Boyd AE. Management of individual tumor syndromes: medullary thyroid carcinoma and hyperparathyroidism. Endocrinol Metab Clin North Am 1994;23:157–66.