REVIEW

Surgical management of pancreatico-duodenal tumors in multiple endocrine neoplasia syndrome type 1

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Pancreatico-duodenal tumors are the second most common endocrinopathy in multiple endocrine neoplasia syndrome type 1, and have a pronounced effect on life expectancy as the principal cause of disease-related death. Previous discussions about surgical management have focused mainly on syndromes of hormone excess and, in particular, the management of multiple endocrine neoplasia syndrome type 1-related Zollinger–Ellison syndrome. Since hormonal syndromes tend to occur late and indicate the presence of metastases, screening with biochemical markers and endoscopic ultrasound is recommended for early detection of pancreatico-duodenal tumors, and with early surgery before metastases have developed. Surgery is recommended in patients with or without hormonal syndromes in the absence of disseminated liver metastases. The suggested operation includes distal 80% subtotal pancreatic resection together with enucleation of tumors in the head of the pancreas, and in cases with Zollinger–Ellison syndrome, excision of duodenal gastrinomas together with clearance of regional lymph node metastases. This strategy, with early and aggressive surgery before metastases have developed, is believed to reduce the risks for tumor recurrence and malignant progression.

KEYWORDS: Multiple Endocrine Neoplasia Type 1; Neuroendocrine Pancreatico-Duodenal Tumors; Surgical Treatment.

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INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant hereditary syndrome with high penetrance, where 50% of children of an affected parent inherit the trait, and virtually all gene carriers develop features of the syndrome (1–3). The syndrome is rare, with a prevalence of two or three cases per 100,000 population, being equally common in males and females (2,3). MEN1 patients classically present with tumors of the parathyroid, the endocrine pancreas/duodenum and the anterior pituitary. The trait also implies increased risk of adrenocortical lesions (with hyperplasia, adenoma, rarely carcinoma in up to 30% of patients), increased incidence of foregut carcinoids (occurring in 7%, in the thymus, bronchial tree, and the stomach), and lower incidence of multiple lipoma, ependymoma, leiomyoma, meningeoma, facial angiofibroma, and collagenoma (2–5).

Genetic diagnosis

MEN1 is caused by inactivating mutations of the *MEN1* tumor suppressor gene on chromosome 11q13, germline mutation has inactivated one allele, and tumors occur when the second allele is silenced by somatic mutation. The gene encodes for Menin, with an important role for DNA replication and transcriptional regulation (6). The gene is complex, with more than 1,000 identified mutations, without strong genotype–phenotype correlations and also with variable disease expression within families (7). Genetic diagnosis is obtained by complete *MEN1* gene sequencing, which can reveal mutations in 70–90% of typical MEN1 cases, and a recently introduced multiplex ligation-dependent assay (MLPA), which can detect large deletions in another 4% (8). If mutation is unknown in the family, the genetic diagnosis can be difficult and negative genetic testing cannot exclude the syndrome. Without positive genetic diagnosis, MEN1 is clinically diagnosed if a patient has tumors in two of the three classical endocrine organs (parathyroid, pancreas/duodenum, or pituitary), or has family history of MEN1 and one such tumor (2).

Genetic family screening is important since unaffected family members may be spared unnecessary investigations and anxiety (3). Screening for MEN1 endocrine tumors is recommended in gene carriers, since biochemical abnormalities can often be revealed decades before clinical symptoms appear (2,9). If screening is delayed until clinical symptoms develop, morbidity and mortality may be encountered, especially from neuroendocrine pancreatico-duodenal (NEN-PET) and thymic tumors (2,3,9–11). Screening to reveal any of the three classical endocrinopathies should begin in children during the first decade of life (Table 1) (11,12).

No potential conflict of interest was reported.

Table 1 - MEN1 screening. Revised from Brandi et al (12).

Tumor	Age that screening began (years)	Biochemical tests (annually)	Imaging (every 3 years)
Parathyroid	10	Serum calcium (PTH)	None
Gastrinoma	20	Serum gastrin	None
Insulinoma	5	Fasting serum glucose/insulin/proinsulin	None
Non-functioning PETs	20	PP, proinsulin, insulin, glucagon, VIP, chromogranin A	Endoscopic US (OctreoScan, CT)
Anterior pituitary	5	Prolactin, IGF-1	Brain MRI
Foregut carcinoid	20	None	CT

It is most important to emphasize that primary hyperparathyroidism (pHPT) has been the most common and generally the first detected endocrinopathy in MEN1, often diagnosed at ~20 years of age, and affecting more than 95% of patients at 40 years of age (2,3,9–12). MEN1-pHPT is typically associated with hyperplasia/multiglandular parathyroid disease, and should be suspected in all cases with multiglandular involvement or recurrent HPT (13). Younger HPT patients (<40 years) may often (~10%) be index cases for MEN1 kindreds, and are liberally subjected to parathyroid surgery due to long-term risk for osteoporosis and renal complications (2,9–16). The presence of the MEN1 syndrome may be revealed by screening with serum calcium or careful penetration of the family history in patients with pancreatico-duodenal tumors, pituitary tumors, or foregut carcinoids (2,3,9,11). Hypercalcemia caused by HPT stimulates gastrin, and early parathyroid surgery is recommended in patients with MEN1-associated Zollinger–Ellison syndrome (ZES), together with liberal use of proton pump inhibitors (PPIs) (16,17).

Pancreatico-duodenal neuroendocrine tumors (PETs)

PETs are the second most common endocrinopathy in MEN1, with a prevalence of 35–40% at the age of 50 years, with higher figures if patients are subjected to more careful screening programs (2,3,11,18,19). Rarely, patients will have PETs as the first endocrinopathy recognized in childhood. The MEN1 endocrinopathy consists of numerous microadenomas typically spread throughout the entire pancreas, which vary in size from slightly larger than a normal islet to a few millimeters in diameter, and with generally only few concomitant larger tumors (2,3,8,9,11,20,21). Pancreatic islets of normal size, cell morphology, and arrangement invariably surround the microtumors and often occur together with areas of nesidioblastosis with exocrine duct proliferations, and clusters of endocrine cells, which has been claimed to support the origin of microadenomas from pancreatic duct precursor cells rather than the pancreatic islets (2,11,21). Microtumors lack the normal islet cell organization, and frequently show immunoreactivity for multiple hormones, most commonly pancreatic polypeptide (PP), but there may also be reactivity for glucagon, insulin, proinsulin, somatostatin, or sometimes only chromogranin A (21,22). Duodenal microtumors, which have been identified in 50% of patients with the endocrinopathy, stain for serotonin, gastrin, and somatostatin (23). Gastrin immunoreactivity has generally been absent in pancreatic microadenomas, and only occasionally demonstrated in larger pancreatic tumors (21), in which PP or only chromogranin A reactivity has been most common (2,21). The presence of endocrinopathy can be diagnosed by serum measurements of pancreatic hormones even in the absence of a syndrome of hormone excess, most commonly showing raised serum values of PP and chromogranin A, sometimes gastrin, insulin and proinsulin, occasionally glucagon, vasoactive intestinal peptide (VIP) or calcitonin (2,4,11). Only a minority of the microtumors acquire the potential to grow to clinically relevant lesions, since each patient will during their lifetime experience only few large tumors (2,4,11,18). Cure requires total pancreatico-duodenectomy, which is rarely considered as initial procedure because of significant morbidity and mortality associated with resulting severe diabetes and exocrine pancreatic insufficiency (2,3,11).

Extended survival has been reported in MEN1 patients with PETs, even in the presence of metastases, suggesting that the disease may often have an overall indolent course. However, disease progression varies widely between and within families, and individual patients have PETs with exceedingly more malignant behavior (2,4,19). Although suggested by some authors, no convincing and confirmed genotype–phenotype relationships have yet been demonstrated (2,4,9,19,24). The MEN1 PETs have been claimed to have favorable prognosis compared with sporadic tumors, though earlier diagnosis of MEN1 tumors, or in case of ZES, disparate survival for patients with duodenal and pancreatic gastrinomas, appear to explain this difference (11,21,25). With adjustment for younger age due to screening detection in MEN1, similar survival expectancy has been revealed for MEN1-associated and sporadic PETs (11,21,25).

Malignant progression of PETs and thymic carcinoids has been the principal cause of premature disease-related death in MEN1, and the pancreatic malignancy has been identified as the major cause of death, with nearly half of affected patients dying before 50 years of age, mainly with liver metastases (2,9,11,26–29). When first recognized in 1989 that duodenal gastrinomas was the most common cause of MEN1 ZES, Norman Thompson introduced the procedure for distal, subtotal (80–85%) pancreatic resection, together with enucleation of pancreatic head tumors, duodenotomy for excision of duodenal gastrinomas and careful dissection of lymph gland metastases around the pancreatic head (11,30,31). In our experience, PETs could be detected by biochemical screening decades before development of a clinical syndrome of hormone excess (such as ZES), and we have suggested earlier surgery for malignancy prevention, not only in the MEN1 ZES patients, but also in patients with non-functioning MEN1 lesions (2,3,9,11,18,32). Screening studies revealed that 30–50% of patients already had metastases when a clinical syndrome of hormone excess, most often ZES, had developed, and for two decades we have therefore recommended timely repeated biochemical screening for PETs in MEN1 carriers to achieve early diagnosis, and early surgery for malignancy prevention

(2,3,9,11,18,20,21,29,32). Consequently, in our center, the non-functioning PETs have become the most common tumor entity requiring surgery in ~50% of MEN1 patents (19,29,32).

Surgery for non-functioning PETs

Raised biochemical markers, especially serum PP values, have together with raised values of chromogranin A become increasingly important for early detection of non-functioning PETs (2,3,9,11,29,32). Patients may also have raised insulin/proinsulin, glucagon, VIP or calcitonin values, without a hormone excess syndrome. Most authors agree that patients with non-functioning tumors larger than 2–3 cm should undergo surgery, but the size limit has been the subject of controversy (19). Studies of non-functioning MEN1 PETs in the French GTE register revealed a low (4%) metastases rate for tumors ≤10 mm, and notably higher metastases rate (15–52%) for larger tumors (33–35). However, reporting a 15% mortality risk from pancreatic surgery, the authors recommended surgery for non-functioning PETs greater than or equal to 2 cm (33–35). We and other authors recommend surgery for non-functioning MEN1 PETs around or greater than 10 mm, since the metastases rate is unacceptably high for larger tumors, and surgery has been carried in rather large series without mortality (11,19,36,37).

Before surgery, contrast-enhanced computed tomography (CT) is routinely performed to clarify the anatomy and possible presence of liver metastases (11). C-5-hydroxytryptophane (5HTP)-positron emission tomography (PET) has been efficiently used in our department to reveal small PETs and lymph node metastases (38). Endoscopic ultrasound (EUS) has become the most important method for early detection of PETs, with the ability to show the relation to the pancreatic and the bile ducts, and is now used for routine screening follow-up of MEN1 patients (11,19,36,37,39).

The surgical procedure generally consists of distal 80% subtotal pancreatic resection with the pancreas divided to the left of the portal vein, and enucleation of possible pancreatic head tumors. Occasionally patients present with larger or multiple tumors, and more extensive procedures may be required. Smaller tumors (<5 mm) deep in the pancreatic head, or close to the bile or pancreatic ducts, are left if enucleation is considered hazardous. Duodenotomy is not done in patients without a rise in serum gastrin.

Surgery for PETs with syndromes of hormone excess

ZES has been the most common hormone syndrome in MEN1, which ultimately may be present in 30–50% of patients, and implies that 30% or more of ZES patients have the MEN1 syndrome (2,3,11,19,36). Insulinoma causing the hypoglycemia syndrome has been revealed in 4–10%, vipoma in 3–5% and symptomatic glucagonoma has been exceptionally rare (<1%) (2,3,11,19,36).

Surgery for insulinomas, vipomas and glucagonomas

There is general consensus to submit MEN1 patients with insulinoma and a hypoglycaemia syndrome to surgery after biochemical diagnosis and fasting test verification, more or less irrespective of tumor size, since no efficient medical treatment option is available (2,11,18,19,39–43).

In patients with hypoglycaemia, a single tumor ≥5 mm is expected to cause hyperinsulinism, and the tumor can often be revealed by EUS. Non-functioning tumors may, however, occur concomitantly and the source of insulin (or proinsulin) excess may occasionally have to be determined by selective intra-arterial calcium-injection test (SAS test), which can regionalize the hypersecretion and identify rare multifocal insulinomas (11,41). Favorable cure rate after surgery has been reported in patients with MEN1 insulinomas, but concomitant distal (80%) pancreatic resection is recommended to remove concomitant non-functioning tumors and minimize risk of recurrence (11,19,40–42). Tumor enucleation has only been reported with increased risk for recurrence of non-functioning tumors or new insulinoma (2,11,19,40–42). The most important is to emphasize that the malignancy rate is higher with MEN1 associated than with sporadic insulinoma, and may be recognized by metastases with also moderately large MEN1 insulinomas (11).

Rare MEN1 patients with vipoma or glucagonoma syndromes usually present with large PETs with high risk of malignancy, and should be treated with radical surgery (11,19,44,45). Due to severe hormone symptoms, patients with these tumors may require liver resection, treatment with repeated radiofrequency (RF) ablation or even resection of lung metastases (46).

Surgery for ZES

For MEN1 ZES patients surgery remains controversial because persistent normalization of raised gastrin levels is rarely achieved, and long survival can also be expected without operation (2,3,11,19,47,48). Some surgeons have advocated surgery when gastrin excess could be regionalized by the SAS (Imamura) test, others only when tumors >2–3 cm have been visualized (30,31,48–50).

We have also proposed surgery in the absence of liver metastases without pre-operative tumor localization or regionalization, since the vast majority (~90%) of MEN1 ZES patients have single, or multiple, small duodenal tumors as the cause of gastrin excess, and smaller tumors generally require duodenotomy for visualization (2,11, 21,23,30,31). Also, the smaller duodenal tumors are often associated with conspicuously larger regional lymph node metastases which may easily be mistaken for the primary tumor when occurring within the peripancreatic fasciae capsule (11,51). Ultimately, there is often delay before liver metastases develop in ~10–20% of patients, which may provide a favorable interval for intervention, where lymph node metastases may be excised together with the primary lesion (11,52). Gastrin-secreting pancreatic tumors are uncommon in MEN1, but have been reported to be large and they may be associated with earlier liver metastases, as reported for patients with sporadic pancreatic gastrinoma (19,50). Survival is favorable in patients with small duodenal gastrinomas, even in the presence of lymph node metastases, but is worse for patients with larger duodenal or pancreatic gastrinomas (19). Surgical excision of gastrinoma and lymph gland metastases may normalize gastrin excess, but the effect is time-limited, since virtually all patients will recur with hypergastrinemia, sometimes after several years' delay (3,11,19,47,48,53,54). Since ZES patients with liver metastases have significantly shorter survival, and liver metastases possibly develop less frequently in operated patients, we perform surgery to reduce the risk of further

progression (3,11,19,50,53). Milder recurrent hypergastrinemia in ZES can be efficiently controlled by PPI, and surgery has in our opinion the additional important goal to delay malignant development, also by removal of concomitant non-functioning tumors (2,3,11,18). Non-functioning tumors of conspicuous size have in our experience been almost invariably present when MEN1 patients have been subjected to surgery with ZES, and may be a more likely cause of spread with liver metastases.

Our general policy is to subject MEN1 patients with raised serum gastrin and ZES verified by gastric acid hypersecretion (pH<2 in gastric aspirate) to exploration with duodenotomy for visualization (palpation is essential) of single or multiple duodenal gastrinomas. Distal (80%) pancreatic resection is carried out for removal of concomitant non-functioning tumors together with careful dissection of regional metastases, and enucleation of possible tumors in the head of the pancreas (3,11,18).

Pancreatico-duodenectomy (PD) has been performed in limited series of MEN1 patients and shown to offer better possibilities for cure of ZES in selected patients than excision of duodenal gastrinomas combined with subtotal pancreatic resection (3,11,19,37,43). However, in our experience concomitant non-functioning tumors have virtually always necessitated distal pancreatic resection in the ZES patients (3,11,18) Moreover, if reoperation is required for recurrent pancreatic tumor this may be exceedingly difficult after previous pancreatico-jejunostomy as part of PD. After PD, treatment of liver metastases with embolization or RF ablation may be hazardous and should be avoided due to risk for serious ascending infection via the hepatico-jejunostomy (46). Still PD is occasionally required as the primary procedure in MEN1 patients with a large pancreatic head or duodenal tumors, and sometimes also required at reoperation for recurrent duodenal or pancreatic head tumors (55). In our experience such recurrences have been treated with re-resection of the pancreatic neck or new enucleations rather than total pancreatectomy, but this may ultimately be required (55). Pancreas-preserving duodenectomy has been reported as an elegant technique to remove multiple duodenal gastrinomas entirely, but it is a difficult procedure suggested to benefit selected patients with multifocal duodenal gastrinomas, with the problem of leaving behind the possible common concomitant non-functioning pancreatic tumors (56–58).

High gastrin and long-standing gastrin excess may, in 5–30% of MEN1-ZES patients, result in development of type 2 gastric carcinoids in the gastric body and fundus and occasionally in the antrum (51). These tumors are generally multiple and often larger than 1.5 cm, and may occupy virtually the entire fundic mucosa. Occasional tumors are larger (>4 cm). Lymph node metastases occur in ~30%, and liver metastases in 10–20%. Smaller lesions may sometimes regress if eugastrinemia is achieved, and the remaining tumors should be locally excised (59). Some MEN1 patients have died from such malignant gastric carcinoids with metastases, and therefore gastrectomy may sometimes be required for the large gastric carcinoids (59,60).

Technical aspects of MEN1 pancreatico-duodenal exploration

In MEN1 patients the entire pancreas is explored by bilateral subcostal incision. The duodenum and the pancreatic head are mobilized with ventral and dorsal surfaces dissected to the aorta. The pancreatic tail and body are explored via the lesser sack, with retroperitoneum incised below the pancreas, to allow blunt dissection of the distal parts. The entire pancreas is bidigitally palpated and scanned with intraoperative ultrasonography (IOUS), revealing lesions larger than 3-4 mm, and facilitating safe enucleation by showing relations between tumors and ductal structures (2,3,11). Metastatic lymph glands are searched for around the splenic and celiac vessels, in the hepatoduodenal ligament, and especially within the dorsal fasciae capsule of the pancreatic head.

A pancreatic head tumor is generally enucleated by cautious dissection with careful ligation/clipping of vessels and any pancreatic duct tributaries. A distal 80% body and tail resection is undertaken by transecting the pancreatic neck to the left of the porto-mesenteric vein. Any enucleated area in the pancreatic head is left open, with drainage carefully applied.

Since the majority of MEN1 patients require prophylactic cancer operation, and efficient removal of lymph node metastases, with predilection in the hilus of the spleen, splenectomy rather than spleen preservation is generally recommended.

Duodenotomy is more efficient than duodenoscopy or EUS to visualize gastrinomas in MEN1-ZES, which can be multiple in ~50% of patients (58). Routine duodenal exploration is performed in patients with the ZES syndrome via longitudinal duodenotomy in the descending part of the duodenum. Even small tumors can be identified by palpation after digital inversion of the proximal and distal parts of the duodenum. Duodenal tumors smaller than 5 mm can be enucleated with the mucosa; larger tumors require limited excision of the duodenal wall.

Postoperative follow-up/reoperation. Surgery for the MEN1 pancreatico-duodenal endocrinopathy rarely results in lifelong cure, and recurrence should be expected (2,3,11,19,53,54). The patients should be subjected to, in general, yearly follow-up with biochemical markers and radiological investigations, including EUS. Reoperation is considered when a lesion of arbitrarily ~10 mm is visualized concomitant with a rise in biochemical markers, or a patient develops a clinical syndrome of hormone excess. Reoperations have in our experience been mainly performed as resections or enucleations of new tumors, and have been uncomplicated and compatible with long survival and generally preserved pancreatic function. We have experienced no mortality, or pancreatic fistulas requiring reoperation, after primary or reoperative surgery in our MEN1 PETs patients. Total pancreatectomy may be required for recurrent, rapidly growing, or unusually large tumors, and is even considered when there is a strong history of markedly malignant pancreatic tumors in the family (2,3,11,55). We have with few exceptions avoided this, due to the resulting generally severe diabetes that ensues, and complete removal of the pancreatic head and duodenum to achieve total pancreatectomy, after previous subtotal pancreatic resection, has, according to reports from other groups, sometimes been difficult or complicated (19,54). Liver metastases are treated with liver resection when possible, and RF ablation. In patients with unresectable liver spread or other distant metastases, oncologic treatment is given, with a common response to combinations of streptozotocin and 5-fluorouracil or doxorubicin;

recently radioreceptor therapy with Luthetium has also been considered.

Several patient series support the active management strategy for MEN1 PETs by reporting reduced death risk in operated patients (19,24,37,43,54,56–58,61–63). However, strong evidence for an improvement in survival is lacking. It is crucial to emphasize that liberal indications for pancreatico-duodenal surgery, and aggressive resection surgery, have to be undertaken cautiously with low morbidity and virtually absent mortality, since extended survival can often be expected without surgery (11,55,61,64).

AUTHOR CONTRIBUTIONS

Åkerström G was responsible for the manuscript writing, layout and references. Stålberg P provided assistance to the manuscript writing and permission requests. Hellman P provided assistance to the manuscript writing.

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