

# Management of Nonfunctioning Pancreatic Endocrine Tumors in the Context of Multiple Endocrine Neoplasia Type 1 Syndrome

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## Abstract

The **aim** of our study is to present our experience in the surgical treatment of nonfunctioning pancreatic endocrine tumors (NFPETs) in patients with multiple endocrine neoplasia type 1 (MEN-1). **Patients and method.** Between 1996 and 2006 a total of 11 patients with clinically confirmed MEN 1 syndrome were monitored in an annual screening program that included evaluation of the pancreas. Our policy was to use Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Endoscopic Ultrasound (EUS) in combination with biochemical screening in an effort to early diagnose and categorize the pancreatic involvement in MEN-1. **Results.** NFPETs were identified in 4 female patients (36.4%). Diagnosis of NFPET was established 4.2 years later than that of MEN 1. The median tumor diameter at diagnosis was 2.2 cm (range 1.8-2.6 cm). All patients were treated by distal pancreatectomy. Diagnosis of NFPET was established in histological sections by staining with neuroendocrine tumor markers. Adjuvant therapy with streptozocin in combination with 5-fluorouracil was applied in two patients. After surgery the patients were followed up annually with clinical evaluation, biochemical tests and imaging studies. **Conclusions.** Early detection of NFPETs in patients with MEN-1 syndrome can be accomplished by biochemical and radiological screening program. NFPETs should be removed when diagnosed, in order to achieve a timely and efficient prophylaxis against further tumor growth and malignant development.

## Key words

Multiple endocrine neoplasia type 1 - nonfunctional pancreatic endocrine tumors (NFPETs) - pancreatectomy

## Introduction

Multiple endocrine neoplasia type 1 (MEN-1) syndrome, also known as Wermer's syndrome is a rare disease, inherited as an autosomal dominant trait with an estimated prevalence of 0.01-2.5/100000 (1). MEN-1 syndrome is characterized by parathyroid hyperplasia, neuroendocrine pancreatoduodenal tumors, and pituitary adenomas. Less commonly, MEN-1 patients can develop bronchial, gastrointestinal and thymic carcinoids, benign thyroid and adrenocortical tumors, lipomas, angiofibromas, skin collagenomas and ependymomas of the central nervous system (2).

Multiple neuroendocrine tumors are the dominating feature of pancreatic MEN 1. Among these the third most common lesions are the nonfunctioning pancreatic endocrine tumors (NFPETs). The multifocality of NFPETs is known as typical, although not exclusive phenomenon in MEN 1 syndrome (3). Concerning the diagnosis and treatment of NFPETs, substantial progress during recent years resulted from subtle immunohistochemical analysis of surgically removed duodenopancreatic MEN 1 specimens. NFPETs may occur together with functioning tumors, although many patients harbor multiple NFPETs alone (3,4). At present, the role of surgery is to prevent malignant spread while minimizing the mortality and morbidity associated with pancreatic resection.

The aim of our study is to present our experience in the diagnosis and surgical treatment of nonfunctioning pancreatic endocrine tumors (PETs) in patients with MEN-1 syndrome.

## Patients and methods

Between 1996 and 2006, a total of 11 patients with clinically confirmed MEN 1 syndrome (typical manifestation in two organ systems and/or affected first-degree relative with at least one of the three major components of the syndrome - in our Institution genetic testing has been available since 2002) were monitored in a regular screening program that included clinical, biochemical and radiological

**Table I** The clinical features of patients with MEN 1

N	Gender	Age at diagnosis of MEN 1	Para-thyroid	Pancreas	Anterior pituitary	Adrenals	Other
1	F	40	PHPT	NFT	Prolactinoma		Lung carcinoid
2*	F	19	PHPT	NFT	NFT		
3*	F	46	PHPT	NFT	ACTH- secreting adenoma	NFT	
4	F	38	PHPT		Prolactinoma		
5*	F	18	PHPT		NFT	NFT	
6	F	44	PHPT		NFT		
7*	M	28	PHPT				
8*	M	57	PHPT	Gastrinoma		NFT	
9	M	32	PHPT	Insulinoma			
10*	M	40	PHPT		Prolactinoma	Cushing syndrome	
11	F	33	PHPT	NFT	Nelson syndrome		

\* Affected first-degree relative with at least one of the three major components of MEN 1; PHPT: primary hyperparathyroidism; NFT: non-functioning tumor

pancreatic evaluation. All patients gave informed consent to participate in the study, which was approved by the local Ethical Committee.

Our policy was to use annually Computed Tomography (CT), Magnetic Resonance Imaging (MRI) or both, and since 2001, Endoscopic Ultrasound (EUS) to reveal metastatic disease, nodal involvement or further intra- or extrapancreatic lesions. In parallel, measurements on a yearly basis of serum chromogranin A (CgA) levels, basal serum pancreatic polypeptide (PP), proinsulin, human chorionic gonadotropin alpha subunit (HCGa), and basal serum gastrin levels were performed.

NFPETs were surgically removed immediately after their radiological diagnosis, when their diameter exceeded 1 cm. The rationale for surgical intervention was to achieve a timely and efficient prophylaxis against further tumor growth and malignant development. An expectancy approach was favored in cases of a preoperatively unlocalized asymptomatic tumor with positive biochemistry (abnormal raise of at least two independent tumor markers). Surgery depended primarily on radiology, despite a clear-cut biochemical diagnosis. The procedure included bidigital pancreatic palpation and intraoperative ultrasonography. Routine duodenotomy was not performed in the absence of an elevated gastrin level. The procedure included also careful lymph node dissection along the hepatic ligament and celiac tract. NFPETs were confirmed in histological sections by staining with neuroendocrine tumor markers such as chromogranin A, neuron-specific enolase (NSE), and synapto-physine. The malignant nature of the lesion was determined by the size, the presence of distant metastasis, local invasion, the number of mitoses per 10 high power fields (HPF) and immunohistochemical expression of Ki-67 according to WHO classification (5). After surgery, the patients were followed up annually for identifying recurrent and/or metastasizing pancreatic neoplasms.

## Results

The mean age at the diagnosis of MEN 1 was 35.9 years

(range 18-57 years). Table I provides an overview of the clinical features of MEN 1 patients.

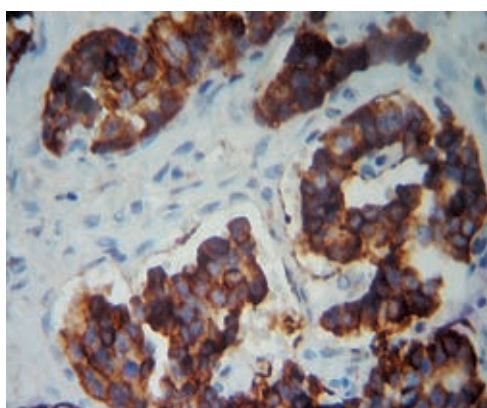
Nonfunctioning PETs were identified in 4 female patients (36.4%). Diagnosis was established 4.2 years later than that of MEN 1. The median tumor diameter at diagnosis was 2.2 cm (range 1.8-2.6 cm).

The first patient was a 42-year-old woman, who underwent in 1990 unilateral adrenalectomy for a cortisone-secreting adenoma of the left adrenal and six years later, in subtotal parathyroidectomy (3 and 1/2 glands, multiglandular parathyroid hyperplasia) for primary hyperparathyroidism. The patient was ever since followed up at regular intervals, in an effort to diagnose early the pancreatic involvement. In 2001, EUS detected a 2 cm in diameter tumor of the tail of the gland, whereas 16 months before a CT screening scan had failed to depict the lesion. Biochemical screening revealed abnormal basal serum PP levels. Preoperative CT and MRI excluded liver metastasis or other extrapancreatic tumors. The patient underwent a distal pancreatectomy, while intraoperative ultrasonography (IOUS) revealed four microscopic lesions in the head of the gland measuring <1 cm in diameter, which were enucleated ("Ann Arbor" or "N. Thompson" procedure). No postoperative complications were encountered, and she was discharged from Hospital on the 12<sup>th</sup> postoperative day. However, diabetes ensued one year following surgery. The tumor was benign showing 2 mitoses/10 HPF and Ki-67 1-2%. Furthermore, the tumor cells were immunohistochemically positive for NSE, CgA, and negative for somatostatin. The enucleated lesions proved to be adenomas. The patient was followed up five years postoperatively and remained free of pancreatic recurrent disease, while PP levels returned to normal values.

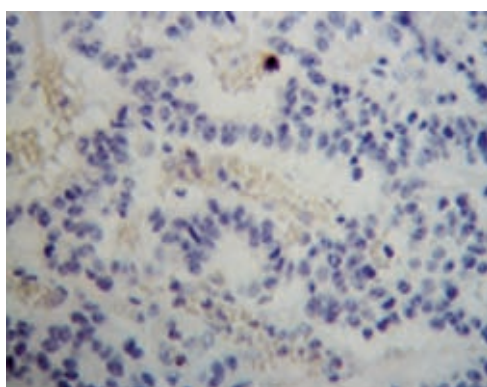
The second patient was a woman who underwent in 1993 subtotal parathyroidectomy for primary hyperparathyroidism. In 1997, at 45 years of age she developed prolactinoma, which was successfully managed conservatively with bromocriptine. In 2001, EUS detected a 1.8 cm in diameter NFPET of the tail of the gland, while 14 months before, screening CT scan had failed to detect the lesion. Biochemical screening revealed no abnormal tumor markers

and preoperative imaging excluded liver metastases or other extrapancreatic tumor burden. The patient underwent distal pancreatectomy. IOUS revealed three microscopic lesions of the pancreatic remnant which were enucleated and proved to be adenomas. She made a very satisfactory recovery and was discharged on the 10<sup>th</sup> postoperative day. According to the pathology report the tumor was benign showing <1 mitosis/10HPF and Ki-67 1%. No long-term complications related to the procedure were encountered. Immunohistochemically, the tumor cells were positive for NSE and CgA (Fig. 1). In 2003, she died from small-cell lung cancer while at that time follow up examinations regarding pancreatic involvement were negative for recurrent disease.

The third patient underwent in 1996 transsphenoidal excision of a nonfunctional microadenoma of the anterior pituitary and five years later a subtotal parathyroidectomy for primary hyperparathyroidism. In 2002, MRI detected a 2.6 cm in diameter NFPET of the tail of the gland. The patient had refused to participate for the last two years before diagnosis in our annual screening program. Last examination, 64 months before diagnosis, by CT scan did not detect abnormal findings. Biochemical screening revealed no abnormal tumor markers. The patient underwent spleen-preserving distal pancreatectomy. Intraoperative



**Fig.1** Neoplastic cells of the tumor proved immunohistochemically positive for CgA confirming the diagnosis of PET in patient 2.



**Fig.2** Immunohistochemical-staining assay for Ki-67 (10% Ki-67-positive cells) indicating the malignancy of the tumor in patient 3.

ultrasonography displayed a single pancreatic tumor. She made an uneventful recovery and was discharged on the 12<sup>th</sup> postoperative day. Histopathologically, the tumor was a low-grade malignant endocrine tumor, confined to pancreas with 6 mitoses/10 HPF, 10% Ki-67-positive cells (Fig.2), and perineural invasion. As in the first two patients, the tumor cells of the surgical specimen were found immunohistochemically positive for NSE, CgA, and negative for somatostatin confirming the diagnosis of PET. Adjuvant therapy with streptozocin in combination with 5-fluorouracil has been applied postoperatively. The patient was followed up four years postoperatively and remained free of pancreatic recurrent disease. However, she developed endocrine and exocrine insufficiency 6 and 14 months after pancreatic resection, respectively.

The fourth patient underwent bilateral adrenalectomy in 1994 for Cushing's syndrome for a non-detectable microadenoma of the anterior pituitary (Cushing's disease). Two years later at the age of 40 she developed Nelson's syndrome and was treated by external irradiation of the pituitary gland. In 1998, primary hyperparathyroidism was diagnosed establishing the diagnosis of MEN-1, and was treated by subtotal parathyroidectomy. In 2003, during the follow up investigations, a nonfunctional, 2.4 cm in diameter tumor of the tail of the pancreas was diagnosed. Twenty months before, a screening CT scan had not detected the lesion. Biochemical screening revealed elevated plasma CgA and basal PP levels. CT and MRI excluded liver metastases however peri-pancreatic nodal involvement was documented. The patient was treated by distal pancreatectomy, although IOUS revealed multiple microscopic (<0.5 cm in diameter) lesions in the pancreatic remnant. Total pancreatectomy was the only way for cure. However, considering the metabolic problems, which ensue postoperatively and reduce quality of life, we decided not to perform this type of operation. She made an uncomplicated recovery and was discharged on the 11<sup>th</sup> postoperative day. According to the pathology report, the tumor was poorly differentiated endocrine carcinoma showing 15 mitoses/10HPF, Ki-67 30% with metastases in peripancreatic lymph nodes. The neoplastic cells of the tumor were positive for NSE, CgA, and negative for somatostatin confirming the diagnosis of PET. One month after surgery, adjuvant therapy was applied with streptozocin in combination with 5-fluorouracil. The patient was followed up two years postoperatively and remained free of pancreatic recurrent disease while pp and CgA levels returned to normal values. No long-term complications related to the procedure occurred.

## Discussion

Tumors of the pancreatic islet cells (PETs) occur in as many as 30% to 80% of patients with MEN 1. They can be either functional (>80%, usually gastrinomas or insulinomas), or rarely nonfunctional (10%) and mostly benign (90%) (2). PETs are the second most frequently expressed manifestation

of MEN-1. The most common functional pancreatic neoplasm is gastrinoma followed by insulinoma and although other islet tumor types such as glucagonoma, somatostatinoma, and VIPoma can arise in MEN-1, the third most common pancreatic lesion is nonfunctional (clinically silent) PET. Although not exclusively diffuse islet hyperplasia is characteristically present throughout the gland in MEN 1 NFPETs. Each islet can develop into a microadenoma, macroadenoma, or malignant adenocarcinoma (2). Patients previously operated on for MEN-1 pancreaticoduodenal tumors, generally have a clinical syndrome of hormone excess, commonly Zollinger-Ellison syndrome (ZES). Fewer patients develop hyperinsulinism and hypoglycemia. Patients with VIPoma are rare and glucagonoma exceptional (6).

As most endocrine tumors, PETs are histologically bland without useful histologic criteria to predict malignant potential. However, considering cancer prevention programmes, recent studies report that MEN-1 patients with NFPETs should be considered for surgery (7,8). Skogseid et al (7) reported in 1996 that NFPETs, often PP producing, are an entity requiring surgery. Specifically, they stated that these tumors should be removed when their diameter exceeds 1 cm. As reported in other relevant studies this approach is considered a timely and accurate prophylaxis against further tumor growth and malignant development (9-11). Additionally, Lairmore et al reported that these tumors should be surgically removed because of their malignant potential (12). On the other hand some authors claimed recently that the mortality and morbidity of pancreatic resection outweigh the low risk of metastasis and death in MEN 1 patients with NFPETs <2 cm, and therefore recommended a conservative approach for these patients. We tend to agree with this approach, however we strongly suggest that patients with rapidly growing tumors or tumors > 2 cm should be offered surgical resection (13,14).

A pancreatic endocrine lesion may stain immunohistochemically for several peptide hormones, or none, but generally one hormonal syndrome predominates clinically in MEN-1. However, one third of PETs are clinically nonfunctioning, as happened in our patients. By immunohistochemistry, the most commonly expressed hormones are PP, glucagon and insulin, followed by somatostatin, gastrin, vasoactive intestinal peptide and neurotensin (15). Additionally, PETs in MEN-1 can be identified in histological sections by staining with neuroendocrine tumor markers such as CgA, NSE, and synaptophysin (8). However, non-functioning PETs may fail to express CgA, while immunohistochemical expression of synaptophysin and NSE is usually preserved. Importantly, the clinical syndrome of hormone hypersecretion in functioning PETs is not necessarily associated with the same pattern of immunohistochemical expression. Non-functioning PETs and PPomas may also stain positive for insulin-like peptide, pp, glucagon, or somatostatin. As with functioning PETs, the intensity of immunohistochemical staining for these peptides does not directly correspond to

serum levels of the hormone or to the severity of any clinical symptoms. Thus, a PET that stains positively for one or more neuroendocrine hormones should still be considered non-functioning in the absence of elevated serum levels of specific pancreatic peptides (5).

The potential malignancy and the rate at which a tumor grows, spreads to distant sites, and finally leads to death is not clearly defined in patients with NFPETs (13,14). Furthermore, malignancy cannot be reliably predicted based on tumor histology. Invasion of adjacent organs or distant metastases confirm the diagnosis of malignant neuroendocrine carcinoma. Therefore all PETs, possibly with the exception of small insulinomas, should be considered potentially malignant. Tumor size greater than 2 cm, proliferative activity (Ki-67) of more than 2%, and the presence of mitotic activity, aneuploidy, and angioinvasion are all associated with an increased risk for malignant behaviour (5,15). In our study, the malignant nature of the lesion was determined by the presence of metastasis, local invasion in addition to the number of mitoses and the immunohistochemical-staining assay for Ki-67.

Metastases from MEN-1 PETs occur in regional lymph nodes or the liver. Extraabdominal spread is rare but may occur to lungs and skeleton (16). However, with the routine of treating patients by surgery when a syndrome of hormone excess or radiologically visible, large pancreatic tumor has been present, as many as 25-50% of patients already have metastases (17). On the other hand, a biochemical and radiological screening program seems to achieve earlier diagnosis and the possibility of surgical treatment apparently before metastases have developed (9). Our patients were under a biochemical and radiological screening program that allowed early diagnosis and surgical intervention before the development of metastatic disease.

Sensitive biochemical markers may reveal NFPETs at early stages often during the third decade (8,18). These tumors secrete hormones in low amounts or without clinical effects and may grow conspicuously large without notable symptoms. Markers for biochemical diagnosis are chromogranin A, serum PP response to a meal test, basal serum PP, glucagon, proinsulin, insulin, gastrin and calcitonin (8,19). Our patients were annually under biochemical screening program which indicated pancreatic involvement (two abnormally raised tumor markers) in one.

Spiral CT with contrast enhancement, MRI at high resolution, positron emission tomography (PET), and somatostatin receptor scintigraphy (SRS) have all been used to identify and evaluate preoperatively MEN-1 PETs (11). However, they are generally unable to reveal the smallest lesion and are therefore inefficient for early diagnosis (20). The recently introduced endoscopic ultrasound (EUS) has proven particularly sensitive for early detection of MEN-1 PETs. EUS had sensitivity of 70-90% and has been shown to reveal lesions as small as 5 mm in diameter (21,22). Our policy concerning the imaging screening program of our patients was to use annually EUS (since 2001), and CT or

MRI or both, to reveal metastatic disease, nodal involvement or further intra- or extrapancreatic lesions.

PETs may be recognized decades before a syndrome of hormone excess develops. The most common lesion is multiple or rarely single nonfunctioning tumors. With the intent of cancer prevention, MEN-1 patients with NFPETs should undergo surgical treatment when the diagnosis is established (8,23). Some authors claim that NFPETs should be principally removed when diagnosed by biochemistry or their diameter exceeds 1cm (9,24). Resection of such a tumor concomitantly with removal of the distal part of the pancreas and enucleation of microscopic lesions of the pancreatic remnant is considered a timely and efficient prophylaxis against further tumor growth and malignant development (9,10,13,16).

After surgery, patients should be followed up annually with biochemical markers and imaging studies. Reoperation may be required with resection or enucleation of new tumors. Total pancreatectomy may theoretically be required for recurrent or unusual large tumors (25). Nevertheless, total pancreatectomy should be avoided or delayed as far as possible because the diabetes that will ensue is often difficult to manage medically. Indeed, in a significant number of patients having NFPETs complete resection may be impossible. This is because NFPETs are often multiple in patients with MEN 1 syndrome, and therefore total pancreatectomy would be the only way to cure. Nevertheless, as mentioned above, this procedure is rarely attempted owing to considerable metabolic problems, which reduce the quality of life. In such cases, additional therapies include chemotherapy, embolization, biotherapy, and radiotherapy. Among these, streptozocin in combination with 5-FU or doxorubicin chemotherapy has been applied for treating various non-resectable or residual tumors (26). In our patients, we applied streptozocin in combination with 5-FU adjuvant therapy in cases of malignant disease and in cases of peripancreatic nodal involvement and/or involvement of pancreatic nerves and capsule.

In conclusion, early detection of clinically silent (non-functioning) PETs in patients with MEN-1 syndrome can be accomplished by biochemical and radiological screening program. NPETs should be principally removed when diagnosed in order to achieve a timely and efficient prophylaxis against further tumor growth and malignant development.

### Conflicts of interest

None to declare.

### References

- Schussheim DH, Skarulis MC, Agarwal SK et al. Multiple endocrine neoplasia type 1: a new clinical and basic findings. *Trends Endocrinol Metab* 2001; 12: 173-178
- Glascok MJ, Carty SE: Multiple endocrine neoplasia type 1: fresh perspective on clinical features and penetrance. *Surg Oncol* 2002; 11: 143-150
- Kent RB, van Heerden JA, Weiland LH et al. Nonfunctioning islet cell tumors. *Ann Surg* 1981; 193:185-190.
- Bartsch DK, Langer P, Wild A, et al. Pancreaticoduodenal endocrine tumors in multiple endocrine neoplasia type 1: surgery or surveillance? *Surgery* 2000; 128:958-966
- Heitz P, Komminoth P, Perren A, Kloppel. Tumours of the endocrine pancreas in WHO classification of tumours. Pathology and genetics of tumours of endocrine organs. IARC Press: Lyon, 2004
- Ballard HS, Frame B, Hartosock RJ. Familial multiple endocrine adenoma-peptic ulcer complex. *Medicine (Baltimore)*1991; 70: 281-283
- Skogseid B, Oberg K, Eriksson B et al. Surgery for asymptomatic pancreatic lesion in multiple endocrine neoplasia type 1. *World J Surg* 1996; 20: 872-877
- Akerstrom G, Hessman O, Skogseid B. Timing and extent of surgery in symptomatic and asymptomatic neuroendocrine tumors of the pancreas in MEN 1. *Langenbeck's Arch Surg* 2002; 386: 558-569
- Skogseid B, Rastad J, Akerstrom G. Pancreas endocrine tumors in multiple neoplasia type 1. In: Doherty GM, Skogseid B (eds) *Surgical endocrinology*. Lippincott Williams & Wilkins, Philadelphia, 511-525
- Lowney JK, Frisella MM, Lairmore TC, Doherty GM. Pancreatic islet cell tumor metastasis in multiple endocrine neoplasia type 1: a correlation with primary tumor size. *Surgery* 1998; 124: 1043-1048
- Dralle H, Krohn SL, Karges W, Boehm BO, Brauckhoff M, Gimm O. Surgery of resectable nonfunctioning neuroendocrine pancreatic tumors. *World J Surg* 2004; 28:1248-60
- Lairmore TC, Chen VY, De Benedetti MK, Gillanders WE, Norton JA, Doherty GM. Duodenopancreatic resections in patients with multiple endocrine neoplasia type 1. *Ann Surg* 2000; 231: 909-918
- Triponez F, Dosseh D, Coudet P, et al. Epidemiology data on 108 MEN 1 patients from the GTE with isolated nonfunctioning tumors of the pancreas. *Ann Surg* 2006; 243: 265-272
- Falconi M, Plockinger U, Kwekkeboom DJ, et al. Frescati Consensus Conference. European Neuroendocrine Tumor Society. Well-differentiated pancreatic nonfunctioning tumors/ carcinoma. *Neuroendocrinology* 2006; 84:196-211.
- Kloppel G, Willemer S, Stamm B et al. Pancreatic lesions and hormonal profile of pancreatic tumors in multiple endocrine neoplasia type 1: an immunocytochemical study of nine patients. *Cancer* 1986; 57: 1824-32
- Ramage JK, Davies AH, Ardill J, et al. UKNETwork for Neuroendocrine Tumours. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. *Gut* 2005; 54 Suppl 4:iv1-16
- Doherty GM, Olson JA, Frisella MM, Lairmore TC, Wells SAJr, Norton JA. Lethality of multiple endocrine neoplasia type 1. *World J Surg* 1998; 22: 581-586
- Ruszniewski P, Podevin P, Cadiot G et al. Clinical, anatomical, and evolutive features of patients with the Zollinger-Ellison syndrome combined with type 1 multiple endocrine neoplasia. *Pancreas* 1993; 8: 295-304
- Granberg D, Stridsberg M, Seensalu R et al. Plasma chromogranin A in patients with multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab* 1999; 84: 2712-2717
- Skogseid B, Grama D, Rastad J et al. Operative tumour yield obviates preoperative pancreatic tumour localization in

- multiple endocrine neoplasia type 1. *J Intern Med* 1995; 238: 281-288
21. Zimmer T, Stolzel U, Bader M et al. Endoscopic ultrasonography and somatostatin receptor scintigraphy in preoperative localization of insulinomas and gastrinomas. *Gut* 1996; 39: 562-568
  22. Proye C, Malvaux P, Pattou F et al. Noninvasive imaging of insulinomas and gastrinomas with endoscopic ultrasonography and somatostatin receptor scintigraphy. *Surgery* 1998; 124: 1134-1143
  23. Skogseid B, Eriksson B, Lundqvist G et al. Multiple endocrine neoplasia type 1: a 10 year prospective screening study in four kindreds. *J Clin Endocrinol Metab* 1991; 73: 281-287
  24. Grama D, Skogseid B, Wilander E et al. Pancreatic tumors in multiple endocrine neoplasia type 1: clinical presentation and surgical treatment. *World J Surg* 1992; 16: 611-618
  25. Tisell LE, Ahlman H, Jansson S, Grimelius L. Total pancreatectomy in the MEN 1 syndrome. *Br J Surg* 1988; 75: 154-157
  26. Wiedenmann B, Jensen RT, Mignon M, et al. Preoperative diagnosis and surgical management of neuroendocrine gastroentero-pancreatic tumors: general recommendations by a consensus workshop. *World J Surg* 1998; 22:309-318