World J Surg (2009) 33:1208–1218
DOI 10.1007/s00268-009-9983-8

World Journal of Surgery

Screening of Patients with Multiple Endocrine Neoplasia Type 1 (MEN-1): A Critical Analysis of Its Value

Jens Waldmann · Volker Fendrich · Nils Habbe · Detlef K. Bartsch · Emily P. Slater · Peter H. Kann · Matthias Rothmund · Peter Langer

Published online: 7 April 2009

Abstract
Background Screening of multiple endocrine neoplasia type 1 (MEN-1) patients is widely recommended because one-fifth succumb to malignant neoplasms. However, recommendations for screening modalities and intervals are based mostly on nonprospective data.
Methods Thirty-five of 48 MEN-1 patients were evaluated at least twice by an annual screening program in a single-center, prospective, nonrandomized study between 1997 and 2006. The screening program comprised anamnesis, clinical examination, imaging procedures, and extensive biochemical evaluations. Prospectively diagnosed lesions were evaluated separately from nonprospectively diagnosed lesions at first evaluation.
Results The median age of the patients was 45 years (range = 15–70) at initial assessment. They were followed for a median of 72 months (range = 24–108) by a median of 6 (range = 2–10) evaluations. The vast majority of lesions were nonprospectively diagnosed at initial evaluation: 13 of 17 patients had primary hyperparathyroidism (pHPT), 24 of 29 had pancreatic endocrine tumors (PETs), and 4 of 4 had carcinoids. Vice versa adrenal lesions were mostly prospectively detected (18/23). Malignancy was observed in 10 patients (28%) in the initial assessment and without symptoms in 5 patients (9 PETs, 3 carcinoids). Endoscopic ultrasound (EUS) of 29 patients detected 88 PETs which were followed for 157 patient years. The mean annual growing rate was 13.28 ± 28.23 mm with respect to the baseline tumor diameter of 9 mm. In 35 patients the mean incidence of newly diagnosed PETs was 0.52/year. Adrenal lesions were invariably nonfunctional. A mean change in diameter of 6.7 ± 23.44% was monitored and malignant transformation was absent.
Conclusions Most lesions are detected at initial screening, particularly malignant tumors. Computed tomography of the abdomen and chest did not identify additional lesions. The interval between screenings could be extended to 3 years based on annually calculated growth rates and the incidence of MEN-1-associated lesions. The assessment of calcium, gastrin, and prolactin is sufficient for biochemical screening in MEN-1.

J. Waldmann · V. Fendrich · N. Habbe · D. K. Bartsch · E. P. Slater · M. Rothmund · P. Langer (✉)
Department of General Surgery, Philipps-University Marburg, Baldingerstrasse, 35033 Marburg, Germany
e-mail: langerp@mailer.uni-marburg.de

J. Waldmann
e-mail: jwaldman@med.uni-marburg.de

P. H. Kann
Department of Internal Medicine, Division of Endocrinology, Philipps-University Marburg, Baldingerstrasse, 35033 Marburg, Germany

Introduction

Multiple endocrine neoplasia type 1 (MEN-1) is a hereditary cancer syndrome characterized by primary hyperparathyroidism (pHPT), pancreaticoduodenal endocrine tumors (PETs), and pituitary neoplasms. In addition to these most common findings, adrenal tumors, thymic and bronchial carcinoids, lipoma, and angiofibromatous tumors may occur [1–9].

Since the identification of the MEN-1 gene in 1997, about 600 different germline mutations that cause the syndrome have been reported [10]. Predictive genetic screening is recommended because it provides the basis for genetic counseling and identification of asymptomatic

mutation carriers. Secondary unaffected family members could be spared from unnecessary examinations [5]. The penetrance of the MEN-1 syndrome is approximately 100%. About one-fifth of deaths of MEN-1 patients are caused by malignant neoplasms [6, 11, 12]. The presence of PETs, rare carcinoids of the thymus, and adrenocortical carcinoma have apparently become determinants of long-term survival [13, 14]. Zollinger-Ellison syndrome (ZES) is the most frequently observed malignant functional PET and occurs in 20–70% of the patients. The management of PETs in MEN-1 patients is controversial, especially in the case of ZES. The therapeutic recommendations for patients with ZES range from conservative treatment by the use of proton pump inhibitors to aggressive surgery [15, 16]. To date a phenotype-genotype correlation is lacking, although carriers of truncated mutations in exons 2, 9, and 10 of the MEN-1 gene seem to have a higher incidence of malignant tumors as previously published by our group [17].

The NIH consensus conference in 2001 emphasized a widespread, extensive screening strategy to reduce morbidity and mortality by early detection of tumor manifestations. According to the NIH recommendations, periodic screening should include anamnesis, with special attention paid to symptoms caused by functional tumors, and biochemical and imaging tests. Biochemical screening should be performed annually and imaging tests are recommended every 3–5 years [5]. Biochemical tests should include levels of calcium concentrations, parathormone (PTH), gastric output, fasting glucose, insulin, proinsulin, chromogranin A, glucagon, prolactin, and insulin-like growth factor 1 (IGF-1). There are no special recommendations for patients after pancreatic or other surgery. Little is known about the impact of psychological adverse effects of regular screening. Only a few prospective screening studies that focused on distinct diseases associated with MEN-1 have been published [3, 18–20]. Based on the results of these studies, biochemical and clinical features that contribute to earlier diagnosis and consequently improve short and long-term management were identified. The findings of these studies resulted in modified recommendations for surveillance and therapy. The most favorable strategy to clarify whether regular screening improves long-term survival is a multicenter study which is difficult to perform because of the low incidence of the MEN-1 disease: it occurs in 30 of 100,000 people.

It still remains to be determined whether periodic screening is capable of improving long-term survival of MEN-1. The costs to the healthcare system are high and the psychological effects on patients are often underscored. The goals of this single-center study were to evaluate which screening modalities are most efficient for early detection of gland involvement of MEN-1 disease and to recommend an interval of screening based on tumor growth rates and incidences of propectively diagnosed lesions.

Methods

Patients

A total of 48 consecutive MEN-1 patients evaluated between 1997 and 2006 were considered for this study. Eligibility requirements included a germline mutation within the MEN-1 gene, at least two evaluations during this period, and informed consent. Thirty-five patients (8 asymptomatic mutation carriers and 27 MEN-1 patients) were included. These 35 patients were from 25 unrelated kindreds from 10 different states in Germany. The remaining 13 patients were excluded because of negative genetic testing (3) or incomplete assessments (10).

Clinical data were prospectively recorded and analyzed with special regard to symptoms related to hormone excess in endocrine diseases. To determine the extent of gland involvement patients' blood samples underwent extensive biochemical screening for endocrinologic laboratory tests (Table 1). Urine was sampled for 24 h to screen for adrenal tumors (pheochromocytoma, Cushing's syndrome) as well as neuroendocrine tumors (5-HIAA). Pathologic endocrine tests were followed by stimulating tests (Table 1). In addition, patients were routinely assessed by thin-sliced computed tomography (CT) of chest and abdomen, magnetic resonance imaging (MRI) of the pituitary, somatostatin-receptor-scintigraphy (SRS), and endoscopic ultrasound (EUS) of the pancreas and adrenal glands. Patients were evaluated annually. Upon discovery of pathologic findings, the interval between two evaluations was adapted to between 3 to 12 months depending on the patient.

Screening for gland involvement and therapeutic strategies

Parathyroid glands

Parathyroid function was monitored by assessing intact parathormone level (normal range [NR] < 65 pg/ml), total serum (NR < 2.6 mmol/L), and ionized calcium (NR < 1.6 mmol/L). We recorded first clinical symptoms, time of surgery and surgical procedure, postoperative hypocalcemia, and reoperations. In general, a bilateral exploration of the neck with total parathyroidectomy, thymectomy, and autotransplantation in the forearm was performed as the initial operation. In case of recurrence we used sestamibi scintigraphy and ultrasound to localize the remnant parathormone source.

Pituitary

To assess pituitary disease, ACTH (normal range [NR] < 60 pg/ml), GH (< 15 ng/ml), TSH (NR $= 0.34$-5.6

Table 1 Clinical screening in asymptomatic menin mutation carriers and MEN-1 patients

Comprehensive interview and physical examination (particular attention paid to symptoms compatible to endocrine diseases)
Biochemical tests
Basic parameters in blood (sodium chloride, potassium, creatinine, urea, serum albumin, hemoglobin level)
Specific parameters in blood (PTH, calcitonin, PP, CgA, gastrin, insulin, C-peptide, somatomedin, glucagon, VIP, serotonin, cortisol, aldosterone, renin, DHEAS, prolactin, hCG, ACTH)
Specific parameters in 24-h urine (adrenalin, noradrenalin, metanephrine, normetanephrine, 5-HIAA, VMA, cortisol)
Standardized endocrinologic tests (secretin provocation test, dexamethasone suppression test, ACTH test, pituitary tests)
Imaging modalities
CT of chest and abdomen
SRS/SPECT
MRI of pituitary gland
Endoscopic ultrasound of adrenal glands and pancreas

mU/ml), LH (NR = 1.9-12.5 U/L), and FSH (NR = 35-52 ng/L) and prolactin levels (NR = 2.1-17.7 μg/ml) in serum were measured and MRI of the pituitary was performed.

Pancreas

PETs were visualized by CT scan, octreotide scan, and endoscopic ultrasound. The tumor diameters were assessed by EUS initially and in the follow-up; the incidence of new tumors was recorded. The diagnosis of a functional tumor was established if there was excess hormone, except for an isolated elevation of pancreatic polypeptide (PP). We assessed PP (NR < 400 pg/ml), gastrin (NR < 125 pg/ml), serotonin (NR = 40-400 ng/ml), chromogranin A (NR = 0-50 U/L), insulin (NR = 2.5-24 mU/L), C-peptide (NR = 0.8-3.9 μg/L), glucose (NR = 60-110 mg/dl), glucagon (NR = 59-177 pg/ml), vasoactive intestinal peptide (VIP) (NR = 0-150 pg/ml), ACTH (NR < 60 pg/ml), and urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) (NR = 10.5-47.1 μnol/day).

Zollinger-Ellison syndrome (ZES) was diagnosed in the presence of clinical symptoms, an elevated fasting serum gastrin level (norm < 125 pg/ml), a positive secretin stimulation test (increase > 200 pg/ml), and a low pH (<2) of the stomach. Preoperatively we regionalized the gastrin source using selective arterial secretin injection angiography (SASI) in a few cases [21]. If symptomatic hypoglycemia (<40 mg/ml) was combined with hyperinsulinism (>20 μU/ml), insulinoma was confirmed by a supervised fasting test. A vipoma was defined in case of watery diarrhea (>6 L/day) and elevated VIP serum levels (>130 pg/ml). Pancreatic tumors were considered nonfunctional if neither hormone levels were elevated nor symptoms associated with hormone excess were evident except PP. Tumors were classified as malignant when they demonstrated infiltrating growth, angioinvasion, lymph node involvement, or distant metastases.

MEN-1 patients with ZES or hyperinsulinism underwent laparotomy after diffuse metastases were excluded by preoperative imaging. In case of nonfunctional PETs, patients underwent laparotomy if the tumor size exceeded 10 mm. An intraoperative ultrasound and bidigital palpation of the pancreas were performed in all patients. For ZES we routinely performed a distal pancreas resection to the level of the portal vein, enucleation of pancreatic head tumors, a duodenotomy with removal of tumors in the first to the fourth portion complemented by lymph node dissection as implemented by Thompson [22] until 1997. The spleen was preserved except when malignancy was considered. Since 1997 we have preferred a pylorus-preserving pancreaticoduodenectomy because of the high incidence of duodenal gastrinomas in MEN-1 patients [23]. In the presence of nondisseminated liver metastases, we aimed for resection or radiofrequency ablation. At the diagnosis of nonfunctional (nf) PETs exceeding 10 mm, we admitted patients for surgery to prevent further growth and the development of metastases. The standard procedure for nf PETs was distal pancreatic resection up to the level of the portal vein. If malignancy was macroscopically suspected, the resection was followed by lymphadenectomy and splenectomy.

Adrenal gland

Biochemical screening for adrenal tumors included assessment of plasma concentrations of adrenalin (A) (NR < 150 pg/ml), noradrenalin (NA) (NR < 400 pg/ml), CgA (NR = 0-50 U/L), cortisol (NR = 43-224 μg/L at 8 and 12 a.m. and 20 p.m.), ACTH (NR < 60 pg/ml),

DHEAS (NR = 80-560 μg/dl), aldosterone (NR = 0.7-15 ng/dl), and renin (NR = 5.2-33.4 pg/ml) and daily urinary secretion of A (NR = 22-109 nmol/day), NA (NR = 135-620 nmol/day), metanephrine (MN) (NR = 375-1506 nmol/day), normetanephrine (NMN) (NR = 573-1932 nmol/day), and cortisol (NR = 28.5-214 μg/day). Adrenal lesions were followed by thin-cut computed tomography and endoscopic ultrasound. Nonfunctional lesions were diagnosed if enlargement or nodular changes of the adrenal gland were present in imaging tests without causing symptoms or abnormal hormone levels. Adrenal Cushing's syndrome was diagnosed if the dexamethasone (2 mg) suppression test (cutoff < 30 μg/L) was positive and ACTH levels were suppressed. Elevated cortisol levels were assessed in 24-h urine and also in serum to detect the loss of the diurnal rhythm. Surgery was performed on nonfunctioning lesions larger than 50 mm as well as on functioning tumors. After 2001 we followed a more aggressive strategy because we found that 6% of 66 patients with small nonfunctioning adrenal lesions larger than 30 mm went on to develop ACC [24]. Therefore, we reset our limit for resection to 30 mm. Nonfunctional adrenal lesions smaller than 30 mm were followed by imaging every 3-6 months if newly diagnosed and longer intervals if they did not change in growth or appearance.

Thymus and lung

Intrathoracic organs were assessed radiologically by thin-cut CT scan and SRS. Serum levels of 5-HIAA, serotonin, and CgA were obtained. Thymic carcinoid was treated by transsternal resection; lung/bronchus carcinoids were confirmed by thoracotomy and treated by resection and lymphadenectomy at limited stage. Lesions that were diagnosed before the first screening are referred to as nonprospectively diagnosed and data are included in the section "Patients and methods." We defined prospectively diagnosed lesions as lesions that were newly detected during the 8-year period of prospective screening.

All resected specimens were assessed histologically at the Department of Pathology of the University of Giessen and Marburg. Clinical data were recorded in access data files, with special regard to the onset and the diagnosis of the MEN-1 syndrome. Additional data were collected to characterize the phenotype, including affected organs, number and type of tumor, and incidence of malignant tumors. MEN-1 gene analysis was provided by Taq cycle sequencing using an automated sequencer (ABI Prism 310, Applied Biosystems, Foster City, CA) as described previously by our group [25].

Patients were admitted to our hospital by the general practitioner and discharged after 2-3 days. In general, all investigations were scheduled within this period.

The study's protocol was approved by the local ethics committee.

Nonprospectively diagnosed lesions in 35 patients (Table 2)

Parathyroid glands

Thirteen patients were diagnosed by a median age of 29 years (range = 15–70). Median calcium concentration was 2.9 mmol/L (range = 2.7–3.2), with a median level of intact parathormone of 109 pg/ml (range = 69–273). It is of note that 8 of 13 patients were asymptomatic at the time of diagnosis. Four of 13 patients presented recurrent pHPT after a median period of 10 years (range = 6–26) after the initial operation. Patients were followed for a median of 46 months (range = 11–71) after the last parathyroid surgery. Three of six asymptomatic mutation carriers were diagnosed at the initial screening by a median age of 18.5 years (range = 15–46).

Pancreaticoduodenal tumors (PETs)

PETs were diagnosed in 29 of 35 (85%) patients in this study. The median age was 45 years (range = 15–70) at the initial evaluation. Eighteen patients (59%) displayed the feature of nf PETs, 11 patients had functioning tumors (9 gastrinomas, 2 insulinomas). In nine patients (26%) the diagnosis of a malignant PET was established. Twenty-four patients were nonprospectively diagnosed as they presented with PETs at the initial assessment.

Median age at diagnosis was 41 years (range = 20–54). Twenty patients have undergone surgery so far. Malignant PETs occurred in 9 patients (7 gastrinomas [Gas], 2 neuroendocrine carcinomas [NECA]), benign PETs in 12 patients (3 Gas, 2 insulinomas [Ins], 7 nf PETs); five of nine were asymptomatic. Malignancy was established due to lymph

Table 2 Nonprospectively diagnosed lesions in 35 MEN-1 patients

Lesions	No. of patients	Asymptomatic	Surgery	Malignant disease (MD)	Age MD (years)
Parathyroid	13	8/13	13	0	ND
Pituitary	17	10/17	5	0	ND
Adrenal	5	5/5	1	0	ND
Pancreas	24	17/24	20[a, b]	9	39 (32-49)
Thymus	1	1	1	1	46
Bronchus	2	2	2	2	32.51

[a] WHO classification of 20 patients: 12 WHO I, 8 WHO II

[b] TNM classification of 20 patients: 8 T1N0, 3 T2N0, 1 T3N0, 5 T1N1, 1 T2N1, 1 T4N0, T4N1

MD = malignant disease

node metastases in six patients, liver metastases in two patients, and invasion of the pancreatic capsule in one patient. Six of nine patients with malignant PETs immediately underwent surgery after the diagnosis of PETs was established. Three patients were followed for 6, 12, and 60 months before they were scheduled for surgery. Seventeen of 24 (71%) patients were asymptomatic. EUS identified PETs in 20 of 20 patients (not done in 4 patients preoperatively), whereas CT scan and SRS were nondiagnostic in 9 of 24 (38%) and 11 of 24 (46%) of the cases, respectively.

In 24 patients we detected 62 PETs by EUS and followed them for 124 patient years. The annual growth rate was 11.7 ± 24.1% with respect to the baseline tumor diameter of 9.0 mm. In these patients the incidence of newly diagnosed PETs was 0.49/year. All patients who previously underwent pancreatic surgery (19/24) developed nf PETs with a median number of two tumors (range = 1–10) after a follow-up of 6 years (range = 1–37).

In four patients with distant (2) or lymph node metastases (2), CT found three of four and SRS four of four lesions, but EUS was nondiagnostic in three of four. No other distant or lymph node metastases were detected by CT scan. As a consequence of these findings, all four patients underwent surgery.

Hormone levels

Patients with ZES (9) often presented with more than one elevated biochemical parameter (9 gastrin, 6 CgA, 4 Sero, 3 Glu, 1 PP). Ten of 18 patients with nf PETs showed biochemical evidence for PETs (7 PP, 4 Pro-Ins, 3 Gas).

Adrenal lesions

Twenty-three of 35 patients (66%) revealed adrenal lesions within the screening period. Only 5 of 23 patients demonstrated adrenal lesions within the first screening. The median age at diagnosis was 45 years (range = 19-49) with a median tumor diameter of 9 mm (range = 7–50). Three patients showed bilateral disease and 2 unilateral disease. All patients were asymptomatic and exclusively nonfunctioning tumors were observed. Two patients with functioning tumors (1 pheochromocytoma, 1 bilateral Cushing's syndrome) were scheduled for surgery before 1997 as previously mentioned. Endoscopic ultrasound visualized all adrenal lesions, whereas CT was nondiagnostic in one of five patients (20%). One patient underwent laparoscopic adrenalectomy because of an incidentaloma of 50 mm, revealing an adenoma at histology. One patient with adrenocortical cancer, who had been reported on previously, did not match the criteria for this study [24, 26].

Pituitary tumors

Pituitary lesions were nonprospectively diagnosed in 17 of 35 (49%) patients, with 7 (41%) patients being symptomatic. The median age at the initial screening was 37 years (range = 18–70). Prolactinoma was the tumor entity observed most frequently (11/17 patients, 65%). Only two of the eight asymptomatic mutation carriers showed microprolactinoma by the age of 18 and 19 years, respectively. Five patients underwent transsphenoidal resection. Eight patients with prolactinoma were treated by the administration of Cabergoline® (Pfizer, NY). No progression or invasive growth was detected after a median follow-up of 6 years (range = 2–9), and none of the patients without pituitary tumors at the initial assessment developed a pituitary lesion during further follow-up. In the majority of patients (14/17), hormone levels were elevated.

Bronchial, foregut, and thymic carcinoids

We nonprospectively identified one patient with a thymic carcinoid, two patients with a bronchial carcinoid, and one patient with a recurrent gastric carcinoid. They all were diagnosed at the first assessment.

The thymic carcinoid was detected by CT scan and SMS in an asymptomatic patient. No elevated hormone levels were observed. This patient underwent sternotomy and complete resection of the tumor at the age of 46 years and was without evidence of recurrence after 7 years of annual screening.

The bronchial carcinoids were diagnosed in a 32-year-old asymptomatic female and in a 51-year-old male by CT scan and SRS. We performed a lower-left lobectomy and lymphadenectomy. Histology revealed neuroendocrine carcinoma with a peribronchic lymph node metastasis. After a follow-up of 6 years the patient revealed enlarged mediastinal lymph nodes above the aortic arc, which were stable since 12 months. The male patient had disseminated disease and a diagnostic biopsy was performed. Stable disease was observed for 9 years, but he also showed an enlarged lymph node above the aortic arc 7 years after the diagnostic biopsy.

One patient with a gastric carcinoid was treated by gastrotomy and excision at the age of 47 years.

Results

The median age at first evaluation was 45 years (range = 15–70) and patients were followed for a median of 72 months (range = 24–108). Seventeen females and 18 males were evaluated by a median of 6 assessments (range = 2–10). Median age at diagnosis of MEN 1 was

35 years (range = 18–57); median age of eight asymptomatic mutation carriers at the first evaluation was 24 years (range = 15–47).

A total of 155 CT scans of chest and abdomen, 145 EUS, 149 SRS, and 86 MRI of the pituitary gland were performed. In general, about 40 different laboratory tests were performed for each patient annually, encompassing approximately 8000 biochemical parameters. The annual costs were about 2,100€ with respect to the DRG, the real costs were about 1,600€.

Below we discuss only prospectively diagnosed lesions (Table 3) to clearly separate them from nonprospective diagnosed lesions discussed in "Patients and methods" (Table 2).

Primary hyperparathyroidism

Four patients were prospectively diagnosed by a median age of 20 years (range = 18–22). Median calcium concentration was 2.8 mmol/L (range = 2.7–2.9), with a median level of intact parathormone of 86 pg/ml (range = 78–112). Patients were followed for a median of 74 months (range = 60–108) after parathyroid surgery. Three of six asymptomatic mutation carriers were prospectively diagnosed.

Pancreaticoduodenal tumors

The median age at diagnosis of five patients with PETs was 32 years (range = 18–52). All patients had nonfunctioning PETs and were asymptomatic. Three patients underwent surgery. Histology revealed well-differentiated neuroendocrine tumors. CT scan missed three of five PETs and SRS missed two of five PETs. Four of five patients demonstrated biochemical evidence for PETs (1 gastrin, 1 proinsulin, 2 PP) before lesions could be imaged by EUS. The patient with the moderately elevated gastrin level did not match the criteria for ZES because the secretin provocation test was within the normal range.

Table 3 Prospectively diagnosed lesions in 35 MEN-1 patients

Lesions	No. of patients	Asymptomatic	Surgery	Malignant disease (MD)	Age MD (years)
Parathyroid	4	4/4	4	0	ND
Pituitary	0	0	0	0	ND
Adrenal	18	18/18	1	0	ND
Pancreas	5	5/5	3[a, b]	0	ND
Thymus	0	0	0	0	ND
Bronchus	0	0	0	0	ND

[a] WHO classification of 3 patients: 3 WHO I

[b] TNM classification of 3 patients: 2 T1N0, 1 T2N0

MD = malignant disease

Imaging and hormone levels in 29 patients with PETs

In five prospectively diagnosed patients we detected 21 PETs by EUS and followed them for 33 patient years. The annual growth rate was 19.4 ± 41.4% with respect to the baseline tumor diameter of 6.6 mm. In all patients the incidence of newly diagnosed PETs was 0.64/year. Two of three patients who previously underwent pancreatic surgery developed two nf PETs, each after a follow-up of 1 and 2 years .

Hormone levels in further follow-up

In six of eight patients with nf PETs but without initially elevated hormone levels, biochemical evidence for PETs was observed in the additional follow-up (4 PP, 2 Sero, 1 Gas). In 13 patients with a negative EUS, we found elevated hormone levels in six patients who developed PETs, which were visualized by EUS, after a median interval of 1 year (range = 1–2). Two of 13 patients were without evidence of PETs after 3 and 8 years, and 5 developed PETs without any hormone secretion after a median of 4 years (range = 2–6). Unequivocally, the most frequent elevated parameters indicating PETs were gastrin, pancreatic polypeptide, and chromogranin A.

Adrenal lesions

The majority of patients (18) were prospectively diagnosed after a median of 2.5 years (range = 1–6) after an initially negative evaluation. The median age of the patients at diagnosis was 48 years (range = 19–54), with a median tumor diameter of 10 mm (range = 7–39). Eight patients showed bilateral disease and 10 unilateral disease. All patients were asymptomatic and exclusively nonfunctioning tumors were observed. EUS visualized all adrenal lesions, whereas CT was nondiagnostic in nine patients (50%). One patient was scheduled for laparoscopic adrenalectomy who showed an annual tumor progression of 10 mm at EUS in a cystic tumor of 42 mm. Histologic analysis identified an adrenal pseudocyst.

Extensive biochemical screening for functional adrenal lesions did not provide any additional information as only nonfunctioning lesions were observed during the prospective screening program.

Thirty-seven adrenal lesions were followed in 23 patients for a median of 36 months (range = 12–48), with an average size of 11.51 ± 9.49 mm at baseline. The average annual growth rate was 6.7 + 23.44%. Lesions were followed during a total of 119 patient years. The incidence of additional lesions in patients with previously detected adrenal lesions was very low: only three new lesions were additionally diagnosed which means 0.03 per patient year.

Pituitary tumors

Only in one 27-year-old female did we observe sublinical Cushing disease with elevated ACTH and an elevated cortisol level in 24-h urine. She was followed for 6 years before these findings with a microprolactinoma treated with Dostinex.

Bronchial, foregut, and thymic carcinoids

After follow-up of 6 and 9 years, both patients with bronchial carcinoids developed enlarged mediastinal lymph nodes that were highly suspicious for LNM above the aortic arc. We performed endoscopic resection by esophagoduodenoscopy in the patient with the gastric carcinoid after follow-up of 42, 73, and 95 months since the initial operation. A total of four neuroendocrine tumors were excised. Gastroscopy was unremarkable 24 months after removal of the last tumor.

Genetics

Mutations of the MEN-1 gene were identified in all patients included in this study and they were found to be distributed throughout the gene. In 35 patients from 26 nonrelated families, a total of 19 different mutations were observed (Table 4): six nonsense mutations (E116X, P529X, F448X, Y90X, E530X, K119X), two frameshift (K120X, Q554X), six missense mutations (R171Q, L168P, E26 K, W126 K, R436Y, T193I), one splice site mutation nt894-1 G→A, one out-of-frame deletion nt1390 del6, one nt1507 del14, one in-frame-insertion nt1651 InsC, and one nt302 Ins5. We could not confirm that MEN-1 patients with truncating mutations have a higher risk for malignant tumors, as previously reported by our group [27] in this subset of patients: Eleven of 23 patients with truncating mutations developed malignant tumors, whereas only 2 of 12 patients with nontruncated mutations ($p = 0.13$) did (Table 5). There were no statistical differences regarding adrenal lesions, age at initial diagnosis, or family history.

Discussion

About 20% of MEN-1 patients succumb to malignant tumors. Malignant PETs are unequivocally the most frequent cause of death [11] since diagnosis and management of pHPT and ZES have improved. The mortality in older studies was caused mainly by complications of peptic ulcer disease [1, 28]. Before 1997 clinical and biochemial screenings served to both identify putative MEN-1 carriers and detect distinct lesions in MEN-1-affected patients. Since the identification of the *Menin* gene in 1997 by Chandrasekharappa, predictive genetic screening allows surveillance of mutation carriers by prospective screening and to keep patients without germline mutation and typical gland involvement from further unnecessary investigations [25, 29].

There are several potential benefits of a screening program for MEN-1-affected patients or asymptomatic germline mutation carriers: The first screening may lead to earlier diagnosis of distinct organ manifestations. It could help to avoid endocrine morbidity and malignant transformation. However, it is still a matter of debate whether screening actually increases the survival rate. First experiences with prospective screening in MEN-1 patients were reported by Skogseid et al. [18]. They had earlier detection of affected organs and emphasized less morbidity but could not confirm or deny reduced mortality. Since then, we and other groups assessed the prevalence and clinical characteristics of MEN 1-associated diseases such as ZES and thymic carcinoids in the special setting of a prospective screening program [3, 20, 30, 31]. Some retrospective studies indicated that reduced mortality from a screening strategy for MEN-1 is likely because of prevention of development and progression of malignancies [32–34].

The aim of this study was to evaluate annual screening in MEN-1 patients with respect to tumor detection by different diagnostic modalities and the impact on therapeutic implications.

First, one should compare the expression of the MEN-1 syndrome in our cohort with that in the literature to underline that our results are not caused by an extraordinary subset of patients. If we analyzed the expression pattern of organ involvement in our 35 patients that were assessed by our screening program at the end of the study period, 32 of 35 (91%) revealed pHPT, 34 (97%) PETs, 25 (71%) adrenal lesions, and 18 (51%) pituitary tumors. Less frequently, we observed one thymic (3%), two bronchial (6%) and one gastric (3%) carcinoid. Prevalence of pHPT (82-97%), PT (18-65%), and carcinoids (0-14%) was consistent with the literature. PETs (38-84%) and adrenal lesions (5-45%) were detected more frequently than previously reported by other groups [1, 2, 14, 35–43]. However, it has been proposed that extensive screening strategies and long-term follow-up with regular imaging procedures may lead to a higher prevalence of the different tumor entities.

The NIH consensus conference of 2001 recommends regular screening in MEN-1 patients by biochemical assessments every year and by imaging every 3-5 years. The biochemical markers proposed for use are calcium, PTH, prolactin, IGF-1, gastrin, glucagon, chromogranin A, fasting glucose, and insulin [5]. In addition to these hormones, we introduced to our screening program biochemical markers that are known to be elevated in neuroendocrine tumors (Table 1) and shortened the intervals of imaging to 6-12 months. Costs for this screening were about 2,100€/ year per patient.

Table 4 Mutations and endocrine organ involvement in 35 MEN-1 patients

Patient	Gender	Mutation	pHPT age	PET age	PT age	Carc age
F1lll3	F	P529X Ex10	y 28	y 32	n	n
F2lll8	F	E116X Ex2	y 40	y 41	y 40	n
F3 lll2	M	Q554X Ex10	y 46	y 45 MD	n	n
F4 ll 4	F	R171Q Ex3	n	n	y 41	n
F5 ll1	F	L168P Ex3	y 33	y 32 MD	y 37	n
F5 ll2	M	L168P Ex3	n	y 35	n	n
F5 ll4	F	L168P Ex3	n	y 36	n	n
F5 ll7	M	L168P Ex3	y 47	y 49	y 44	n
F5lll1	M	L168P Ex3	y 22	n	n	n
F5lll9	F	L168P Ex3	y 18	y 19	n	n
F6ll3	F	E26 K Ex2	y 32	y 32	n	n
F6 lll1	F	E26 K Ex2	y 23	y 23	y 31	n
F8IV23	F	F448X Ex9	y 32	y 32 MD	y 32	n
F9ll1	F	nt894-1 G- > A	y 37	y 37 MD	n	n
F11ll3	M	K 119 X Ex2	y 40	y 48	y 48	n
F11lll5	F	K 119 X Ex2	y 18	y 18	y 18	n
F12ll3	F	nt1390 del6 Ex9	y 45	y 45 MD	n	n
F15lll3	M	E116XEx2	y 44	Lipoma 45	n	yL 51
F15lll4	M	E116XEx2	y 48	y 52	y 43	n
F16ll1	F	Y90X Ex2	y 58	n	y 59	yG 47
F17lll4	F	K120XEx2	y 32	y 32 MD	y 32	yL 32
F18ll1	M	E 530XEx10	y 70	y 32	y 70	n
F20ll1	M	W 126 K Ex2	y 33	y 33 MD	y 33	n
F22lll1	M	E530X Ex10	y 49	y 49 MD	n	n
F23ll1	F	R436YEx9	y 44	y 45	y 45	n
F24lll2	F	nt894 G- > A	y 51	y 51	y 44	n
F24IV1	M	nt894 G- > A	y 19	y 19	y 19	n
F25lll1	M	E 116 X Ex2	y 19	y 23	n	n
F26lll2	F	T1931	y 23	y 32	n	n
F28	M	nt1507 del14	y 36	y 35 MD	n	yT 46
F29lll1	F	E530X Ex10	y 32	y 58	n	n
F31ll1	M	nt302 lns5	y 45	y 45	n	n
F31 IV1	M	nt302 lns5	y 19	y 20	n	n
F33ll1	M	E 116 X Ex2	y 27	y 37	y 37	n
F34ll1	M	lnsC 514 Ex10	y 31	y 38	n	n

F = female; M = male; y = yes; n = no; MD = malignant disease; L = lung; S = stomach; T = thymus

Table 5 Truncated and nontruncated mutations and malignant tumors

Mutations	No. of patients with malignant tumors/total ($n = 35$)	p (χ^2 test)
Truncated	11/23	0.13 NS
Nontruncated	2/12	

NS = not significant

Prospective versus nonprospective lesions

Our results show that the majority of lesions were detected in the first screening: 14/17 pHPT, 24/29 PETs, 4/4 carcinoids, and for 5/23 adrenal lesions. Patients with newly diagnosed lesions underwent surgery for pHPT and PETs in most cases. However, eight patients with PETs were followed for a median of 3 years (range = 0.5–5) prior to pancreatic resection. Bronchial and thymic carcinoids were rarely observed (9%) and, surprisingly, were identified at

the initial screening. Consequently, we do not recommend a CT scan of the chest and abdomen. PETs in MEN-1 patients are often small and therefore superiorly visualized by EUS, followed by SRS, as previously published by our group [48]. However, in patients with a previous pancreatic resection, SRS and CT should be applied, as lymph node and distant metastases occurred in 17% (4/23) in our cohort. However malignant tumors were confirmed in 12 patients with nonprospectively diagnosed lesions within the first screening (30%).

Malignancy

Whereas 6 of 9 (66%) gastrinomas were malignant, only 3 of 13 (23%) nf PETs were classified as NECA. This is consistent with the reported malignancy rate for gastrinomas of 40-60%, but lower than that so far reported in nf PETs (27%) [20, 44]. This might be explained by the low diameter of nf PETs, which is a result of our aggressive strategy to schedule patients for surgery when PETs exceed 10 mm. Patients with malignant PETs tend to be older than patients with benign PETs, with the former having a median age of 39 years (range = 32–49) versus 32 years (range = 20–55) for the latter. Both the lower incidence of malignant PETs and smaller tumors in younger patients emphasizes the benefit of early and aggressive surgery to prevent and to detect metastases.

Growth rates of PETs and adrenal lesions

In the debate on the intervals of screening in MEN-1 patients, growth rate plays a pivotal role in providing recommendations that should be based on prospective data. PETs in MEN-1 patients usually grow slowly (13.3%/year) and a mean of 0.52 tumor develops annually. This is consistent with the literature, which is very limited. We previously reported a growth rate of 1.3%/month and an annual tumor incidence of 0.62/patient [45]. Thomas-Marquez et al. [46] observed stable disease, without an increase in the number and diameter in 62.5%, while the number increased in 25% and diameter in 12.5%, respectively. This provides important evidence for the definition of screening intervals; thus, fast-growing tumors are rare (1/35). In patients younger than 40 years of age, PETs grew more slowly with a mean annual change in size of $4.7 \pm 17.8\%$ compared with patients older than 40 years with mean annual change in size of $19 \pm 31\%$, although the tumor diameters at baseline were similiar at 8.4 and 9.4 mm, respectively. Therefore, EUS should be performed every 3 years if rapid growth is not detected in the first two annual evaluations. The incidence and the different entities of PETs are consistent with our previously published data [27, 47, 48].

Sixty-six percent of the 35 assessed MEN-1 patients had adrenal lesions, which was in the line with the results of previous publications by our group [24, 26, 49] but higher than that reported in the literature [50–52]. Eight of 23 patients with adrenal lesions showed no evidence of growth, whereas 15 of 23 demonstrated a mean annual change of tumor diameter of $6.7 \pm 23.44\%$ during a median follow-up of 3 years by EUS. CT missed adrenal lesions in 10 of 23 patients. All lesions were nonfunctional and malignant disease was not observed in any of these patients. In a recent study Kann et al. [49] reported no significant growth in 27 patients followed for 24 months. An overlap of 13 of 23 patients compared in both studies shows that our results support the finding that adrenal lesions in MEN-1 patients are commonly small, nonfunctional, and stable in follow-up. We therefore suggest a follow-up every 5 years, except for lesions larger than 30 mm, as malignant disease is reported in the literature [24, 51].

Biochemical markers

Various biochemical markers such as insulin, proinsulin, PP, and glucagon were reported to be helpful in the diagnosis and management of PETs in MEN-1 patients [19]. However, EUS allows a superior detection of PETs. The only parameter that was of clinical value in our study was the gastrin level as was the secretin provocation test because it has tremendous impact on the surgical procedure. About half of the patients with nonfunctional PETs had elevated hormone levels, most often PP and proinsulin, but it had no effect on the management of these patients because the pivotal parameter in nf PETs was the size. Therefore, hormone levels for glucagon, proinsulin, and insulin could be excluded from the NIH recommendations without loss of infromation.

Hormone levels for carcinoids, pituitary, and adrenal lesions are not essential because flush was not observed, all adrenal lesions were nonfunctional, and most patients with functioning tumors displayed prolactinomas. Therefore, prolactin is sufficient and other hormones should be assessed only in cases of clinical symptoms.

Nonfunctioning PETs after pancreatic resections were observed in 17 of 20 patients after a median follow-up of 6 years. This may pose difficulties in further management because it will lead to further operations with a high risk of a pancreoprivic diabetes in patients in their mid-40 s. On the other hand, this situation has to be taken into consideration because we know that the mean age of premature death in up to 17% of MEN-1 patients ranges from 45 to 55 years [11, 14, 53] and insulin treatment offers an adequate care for diabetes.

There is an ongoing discussion about the benefit of regular screening for MEN-1 patients: All 35 patients were alive at the end of this study with a median age of 49 years (range = 22–76). However, in retrospective studies, 17%

Table 6 Recommendation for screening modalities and intervals in MEN-1 patients

Modalities	Interval (years)
EUS	3
Biochemical screening (Ca, gastrin, PP, prolactin)	3
CT chest and abdomen (exclusively in patients with previous pancreatic resections or with bronchic or thymic carcinoids)	3
SRS (only in patients with malignant PETs)	3
Exceptions	**Interval (year)**
(1) After pancreatic resection	
CT abdomen	1
EUS and SRS	1
Biochemical screening	1
(2) New diagnosed lesion	
EUS	1
Biochemical screening	1

of MEN-1 patients succumbed to the disease at a mean age of 47 years due to malignant PETs and carcinoids [11, 14, 53]. None of the eight patients who entered our study as asymptomatic mutation carriers had a malignant PET, whereas 10 of 27 MEN-1 patients had malignant tumors ($p = 0.07$ NS). In total, 10 of 35 patients revealed 12 malignant tumors and none had diffuse metastatic spread. The penetrance of the MEN-1 syndrome was 100%. Altogether these findings emphasize the benefit of regular screening in these patients from our point of view.

The cost of annual screening in MEN-1 patients was 2,100€ per patient per year and was accepted by health insurance. The costs decreased to approximately 700€ per year if intervals were extended to 3 years. Indeed, we identified malignant tumors in 30% of patients, and we have to assume that these patients will have a survival benefit due to early diagnosis and therapy. Long-term follow-up will clarify the uncertainty with respect to an evident survival benefit.

From our our findings we provide an algorithm for screening MEN-1 patients; it is given in Table 6.

Conclusions

Generally, most lesions, and in this cohort all malignant lesions, are detected at initial screening. Therefore, CT scan of the chest and abdomen has to be part of the initial screening. In further follow-up, CT scan of the chest and abdomen did not contribute to the identification of additional lesions and therefore should not be routinely performed. EUS and SMS should be used in the follow-up after pancreatic resections, as 17% revealed LNM or DM. Based on our data on growth rates, intervals could be extended to 3 years in small PETs and adrenal tumors as rapid growth is rare. The assessment of calcium, gastrin, pancreatic polypeptide, prolactin, and ACTH is sufficient for biochemical screening in MEN-1.

Acknowledgment This study was supported by a grant of the Else-Kröner-Fresenius Stiftung.

References

1. FB Ballard HS, Hartstock RJ (1964) Familial endocrine adenoma-peptic ulcer complex. Medicine (Baltimore) 43:481–516
2. AE Croisier JC, Lubetzki J (1971) L'adenomatose polyendocrinienne (syndrome de Wermer). Semin Hop Paris 47:494–525
3. Gibril F, Chen YJ, Schrump DS et al (2003) Prospective study of thymic carcinoids in patients with multiple endocrine neoplasia type 1. J Clin Endocrinol Metab 88(3):1066–1081
4. Marx S, Spiegel AM, Skarulis MC et al (1998) Multiple endocrine neoplasia type 1: clinical and genetic topics. Ann Intern Med 129(6):484–494
5. Brandi ML, Gagel RF, Angeli A et al (2001) Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 86(12):5658–5671
6. Burgess JR, Greenaway TM, Shepherd JJ (1998) Expression of the MEN-1 gene in a large kindred with multiple endocrine neoplasia type 1. J Intern Med 243(6):465–470
7. Darling TN, Skarulis MC, Steinberg SM et al (1997) Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. Arch Dermatol 133(7):853–857
8. Duh QY, Hybarger CP, Geist R et al (1987) Carcinoids associated with multiple endocrine neoplasia syndromes. Am J Surg 154(1):142–148
9. Metz DC (1995) Multiple endocrine neoplasia type I. Semin Gastrointest Dis 6(2):56–66
10. Guo SS, Sawicki MP (2001) Molecular and genetic mechanisms of tumorigenesis in multiple endocrine neoplasia type-1. Mol Endocrinol 15(10):1653–1664
11. Doherty GM, Olson JA, Frisella MM et al (1998) Lethality of multiple endocrine neoplasia type I. World J Surg 22(6):581-586; discussion 586–587
12. Dean PG, van Heerden JA, Farley DR et al (2000) Are patients with multiple endocrine neoplasia type I prone to premature death? World J Surg 24(11):1437–1441
13. Oberg K, Skogseid B, Eriksson B (1989) Multiple endocrine neoplasia type 1 (MEN-1). Clinical, biochemical and genetical investigations. Acta Oncol 28(3):383–387
14. Lips CJ, Vasen HF, Lamers CB (1984) Multiple endocrine neoplasia syndromes. Crit Rev Oncol Hematol 2(2):117–184
15. Mignon M, Cadiot G (1998) Diagnostic and therapeutic criteria in patients with Zollinger-Ellison syndrome and multiple endocrine neoplasia type 1. J Intern Med 243(6):489–494
16. Norton JA, Alexander HR, Fraker DL et al (2001) Comparison of surgical results in patients with advanced and limited disease with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome. Ann Surg 234(4):495–505; discussion 505–506
17. Bartsch D, Kopp I, Bergenfelz A et al (1998) Germline mutations in the MEN1 gene: basis for predictive genetic screening and clinical management of multiple endocrine neoplasia type 1 (MEN1) families. Dtsch Med Wochenschr 123(51–52):1535–1540

18. Skogseid B, Eriksson B, Lundqvist G et al (1991) Multiple endocrine neoplasia type 1: a 10-year prospective screening study in four kindreds. J Clin Endocrinol Metab 73(2):281–287
19. Skogseid B, Oberg K (1992) Prospective screening in multiple endocrine neoplasia type 1. Henry Ford Hosp Med J 40(3–4): 167–170
20. Gibril F, Venzon DJ, Ojeaburu JV et al (2001) Prospective study of the natural history of gastrinoma in patients with MEN1: definition of an aggressive and a nonaggressive form. J Clin Endocrinol Metab 86(11):5282–5293
21. Imamura M, Komoto I, Doi R (2005) Recent trend of diagnosis and treatment for Zollinger-Ellison syndrome. Gan To Kagaku Ryoho 32(2):147–151
22. Thompson NW (1998) Management of pancreatic endocrine tumors in patients with multiple endocrine neoplasia type 1. Surg Oncol Clin N Am 7(4):881–891
23. Thompson NW (1998) Current concepts in the surgical management of multiple endocrine neoplasia type 1 pancreatic-duodenal disease. Results in the treatment of 40 patients with Zollinger-Ellison syndrome, hypoglycaemia or both. J Intern Med 243(6):495–500
24. Langer P, Cupisti K, Bartsch DK et al (2002) Adrenal involvement in multiple endocrine neoplasia type 1. World J Surg 26(8): 891–896
25. Kopp I, Bartsch D, Wild A et al (2001) Predictive genetic screening and clinical findings in multiple endocrine neoplasia type I families. World J Surg 25(5):610–616
26. Waldmann J, Bartsch DK, Kann PH et al (2007) Adrenal involvement in multiple endocrine neoplasia type 1: results of 7 years prospective screening. Langenbecks Arch Surg 392(4): 437–443
27. Bartsch DK, Langer P, Wild A et al (2000) Pancreaticoduodenal endocrine tumors in multiple endocrine neoplasia type 1: surgery or surveillance? Surgery 128(6):958–966
28. Vasen HF, Lamers CB, Lips CJ (1989) Screening for the multiple endocrine neoplasia syndrome type I. A study of 11 kindreds in The Netherlands. Arch Intern Med 149(12):2717–2722
29. Chandrasekharappa SC, Guru SC, Manickam P et al (1997) Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science 276(5311):404–407
30. Ferolla P, Falchetti A, Filosso P et al (2005) Thymic neuroendocrine carcinoma (carcinoid) in MEN1 syndrome: the Italian series. J Clin Endocrinol Metab 90(5):2603–2609
31. Waterlot C, Porchet N, Bauters C et al (1999) Type 1 multiple endocrine neoplasia (MEN1): contribution of genetic analysis to the screening and follow-up of a large French kindred. Clin Endocrinol (Oxf) 51(1):101–107
32. Teh BT, McArdle J, Chan SP et al (1997) Clinicopathologic studies of thymic carcinoids in multiple endocrine neoplasia type 1. Medicine (Baltimore) 76(1):21–29
33. Skogseid B, Oberg K, Eriksson B et al (1996) Surgery for asymptomatic pancreatic lesion in multiple endocrine neoplasia type I. World J Surg 20(7):872–876; discussion 877
34. Teh BT, Zedenius J, Kytola S et al (1998) Thymic carcinoids in multiple endocrine neoplasia type 1. Ann Surg 228(1):99–105
35. Eberle F, Grun R (1981) Multiple endocrine neoplasia, type I (MEN I). Ergeb Inn Med Kinderheilkd 46:76–149
36. Marx SJ, Agarwal SK, Kester MB et al (1999) Multiple endocrine neoplasia type 1: clinical and genetic features of the hereditary endocrine neoplasias. Recent Prog Horm Res 54:397–438; discussion 438–439
37. Thakker RV (2000) Multiple endocrine neoplasia type 1. Endocrinol Metab Clin North Am 29(3):541–567
38. Trump D, Farren B, Wooding C et al (1996) Clinical studies of multiple endocrine neoplasia type 1 (MEN1). QJM 89(9):653–669
39. Burgess JR, Shepherd JJ, Parameswaran V et al (1996) Spectrum of pituitary disease in multiple endocrine neoplasia type 1 (MEN 1): clinical, biochemical, and radiological features of pituitary disease in a large MEN 1 kindred. J Clin Endocrinol Metab 81(7):2642–2646
40. Chanson P, Cadiot G, Murat A (1997) Management of patients and subjects at risk for multiple endocrine neoplasia type 1: MEN 1. GENEM 1. Groupe d'Etude des Neoplasies Endocriniennes Multiples de type 1. Horm Res 47(4–6):211–220
41. Karges W, Schaaf L, Dralle H et al (2000) Concepts for screening and diagnostic follow-up in multiple endocrine neoplasia type 1 (MEN1). Exp Clin Endocrinol Diabetes 108(5):334–340
42. Verges B, Boureille F, Goudet P et al (2002) Pituitary disease in MEN type 1 (MEN1): data from the France-Belgium MEN1 multicenter study. J Clin Endocrinol Metab 87(2):457–465
43. Gibril F, Schumann M, Pace A et al (2004) Multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome: a prospective study of 107 cases and comparison with 1009 cases from the literature. Medicine (Baltimore) 83(1):43–83
44. Triponez F, Dosseh D, Goudet P et al (2006) Epidemiology data on 108 MEN 1 patients from the GTE with isolated nonfunctioning tumors of the pancreas. Ann Surg 243(2):265–272
45. Kann PH, Balakina E, Ivan D et al (2006) Natural course of small, asymptomatic neuroendocrine pancreatic tumours in multiple endocrine neoplasia type 1: an endoscopic ultrasound imaging study. Endocr Relat Cancer 13(4):1195–1202
46. Thomas-Marques L, Murat A, Delemer B et al (2006) Prospective endoscopic ultrasonographic evaluation of the frequency of nonfunctioning pancreaticoduodenal endocrine tumors in patients with multiple endocrine neoplasia type 1. Am J Gastroenterol 101(2):266–273
47. Bartsch DK, Fendrich V, Langer P et al (2005) Outcome of duodenopancreatic resections in patients with multiple endocrine neoplasia type 1. Ann Surg 242(6):757–764; discussion 764–766
48. Langer P, Kann PH, Fendrich V et al (2004) Prospective evaluation of imaging procedures for the detection of pancreaticoduodenal endocrine tumors in patients with multiple endocrine neoplasia type 1. World J Surg 28(12):1317–1322
49. Schaefer S, Shipotko M, Meyer S et al (2008) Natural course of small adrenal lesions in multiple endocrine neoplasia type 1: an endoscopic ultrasound imaging study. Eur J Endocrinol 158(5): 699–704
50. Barzon L, Pasquali C, Grigoletto C et al (2001) Multiple endocrine neoplasia type 1 and adrenal lesions. J Urol 166(1):24–27
51. Skogseid B, Larsson C, Lindgren PG et al (1992) Clinical and genetic features of adrenocortical lesions in multiple endocrine neoplasia type 1. J Clin Endocrinol Metab 75(1):76–81
52. Skogseid B, Rastad J, Gobl A et al (1995) Adrenal lesion in multiple endocrine neoplasia type 1. Surgery 118(6):1077–1082
53. Geerdink EA, Van der Luijt RB, Lips CJ (2003) Do patients with multiple endocrine neoplasia syndrome type 1 benefit from periodical screening? Eur J Endocrinol 149(6):577–582