The future: diagnostic and imaging advances in MEN1 therapeutic approaches and management strategies

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Abstract

Prospective randomized data are lacking, but current clinical expert guidelines recommend annual screening examinations, including laboratory assessments and various imaging modalities (e.g. CT, MRI, scintigraphy and EUS) for patients with multiple endocrine neoplasia type 1 (MEN1). Routine screening is proposed to detect and localize neuroendocrine manifestations as early as possible. The goal is timely intervention to improve quality of life and to increase life expectancy by preventing the development of life-threatening hormonal syndromes and/or metastatic disease. In recent years, some studies compared different and new imaging methods regarding their sensitivity and utility in MEN1 patients. This present article reviews the proposed diagnostic tools for MEN1 screening as well as potential future perspectives.

Introduction

Since the discovery of the causative gene of the MEN1 syndrome (Chandrasekharappa et al. 1997), a much better insight was gathered in this rare disease. For the first time, it was possible to verify the disease in affected and suspected patients by a simple gene test (Marini 2015, Falchetti 2017) and exclude unaffected patients from unnecessary screening examinations. Up to date more than 1300 mutations were described throughout the MEN1 gene (Marini 2015, Falchetti 2017). However, in up to 10% of patients with typical organ manifestations, no MEN1 mutation can be identified (Lemos & Thakker 2008). The life expectancy in MEN1 patients is reduced compared to the general population. A recent study reported that the mean age at death in MEN1 patients is about 55 years, which is 20 years younger than expected for the general population (Ito 2012). Duodenopancreatic neuroendocrine neoplasias (dpNEN) and thymic NEN are the most common causes of death in MEN1 patients (Goudet et al. 2010, Ito et al. 2013). The prognosis and the quality of life for MEN1 patients can be improved by presymptomatic tumor detection in routine screening programs and consequent specific treatment of the affected organ manifestations (Ramundo et al. 2011). Thus, expert guidelines (Thakker et al. 2012) recommended that all MEN1 mutation carriers should undergo regular screening, ideally in prospective controlled screening programs. In the present article, current screening strategies, its controversies as well as new diagnostic tools are reviewed.

Genetic testing

Since the discovery of the MEN1 gene in 1997, it is possible to offer genetic testing to prove MEN1 mutation in suspected patients and exclude unaffected patients from
unnecessary screening examination. If a MEN1 germline mutation is present, the penetrance of the disease is almost 100% by the age of 50 years (Machens et al. 2007).

Prior to genetic testing, genetic counseling is mandatory and informed consent should be obtained for every individual to be tested. Mutational analysis of the MEN1 gene should be offered to:

- asymptomatic first-degree relatives of a positive tested MEN1 patient;
- patients with at least two typical MEN1 lesions or one MEN1 lesion and a positive family history for MEN1;
- individuals with early age onset (<30 years) of a typical MEN1 manifestation (e.g. primary hyperparathyroidism, Zollinger-Ellison syndrome).

Currently, prenatal testing is not recommended and it is a controversial topic in the scientific world (Giusti et al. 2008). According to the current expert practice guidelines, genetic testing is recommended at the age of 5 years (Thakker et al. 2012). This recommendation, however, is still a matter of debate, as some experts claim that genetic testing should be postponed until the second decade of life to prevent psychological distress associated with a positive gene test and unnecessary examinations in asymptomatic children (Gonçalves et al. 2014, Goroshi et al. 2016, Manoharan et al. 2017). This holds especially true, since there is yet no role for prophylactic medical treatment or surgery in asymptomatic young MEN1 patients.

So far, no reliable genotype and phenotype correlation could be identified. In literature, some yet not confirmed correlations were recently postulated. The MEN1 cohort of the GTE (Groupe d'étude des Tumeurs Endocrines) group reported that MEN1 patients harboring a MEN1 mutation in the JunD interacting domain have a higher risk of death (Thevenon et al. 2013). A higher risk of malignant pancreatic neuroendocrine neoplasms (pNENs) with an aggressive course of disease was found in MEN1 patients with MEN1 mutations leading to loss of interaction with the checkpoint kinase 1 (CHES1) (Bartsch et al. 2014).

**Begin and intervals of screening**

All MEN1 gene mutation carriers and even negative tested patients with a high clinical suspicion for MEN1 should be kept under regular surveillance, ideally in prospective controlled screening programs (Brandi et al. 2001, Thakker et al. 2012), since such surveillance with a consecutive timely intervention resulted in reduced hormone hypersecretion associated mortality over the last decade (Norton et al. 2015, Casey et al. 2017).

However, the time point to begin screening and screening intervals are still matter of debate among experts, especially given the prerequisite that the goal of every screening program for inherited tumor syndromes should be effectiveness with regard to diagnostic yield, costs and psychological burden of the screened individuals. Current clinical practice guidelines recommend to start routine screening already at the age of five years (Thakker et al. 2012). These expert recommendation are based on the fact that severe organ manifestations (insulinoma, malignant thymic or bronchial carcinoids, gastrinoma, adrenal lesions) can occur in children, although they are rare (Kontogeorgos et al. 2001, Gatta-Cherifi et al. 2012, Goudet et al. 2015, Manoharan et al. 2017). Recently, two prospective databases were retrospectively analyzed regarding the incidence of typical MEN1 lesions in children (Goudet et al. 2015, Manoharan et al. 2017). In a German cohort (Manoharan et al. 2017), 20 of 166 MEN1 (12%) patients under the age of 19 years and 8 of 166 patients (4.8%) below the age of 16 years revealed at least one organ manifestation. Only 5 of the 20 (25%) young patients (<19 years) and 3% of the whole cohort (n=166) of patients had symptomatic or significant manifestations before the age of 16 years, including 4 symptomatic insulinomas and one bronchial carcinoid. The authors concluded that symptomatic or severe manifestations in MEN1 patients rarely occur below the age of 16 years. With regard to psychological burden and cost-effectiveness, routine screening of asymptomatic MEN1 patients should thus be postponed at least until the age of 16 years, since screening in asymptomatic MEN1 patients before the age of 16 years seems not to be effective (Manoharan et al. 2017). The GTE study (Groupe d’étude des Tumeurs Endocrines) reported at least one organ manifestation below the age of 21 years in 160 (17%) and below the age of 16 years in 76 (8.2%) of 924 MEN1 patients (Goudet et al. 2015). Four (5.2%) of the patients below 16 years had symptomatic and malignant lesions (one gastrinoma with liver metastases, two 7-cm adrenal carcinomas, and one multietatatic thymic carcinoid). These authors concluded that MEN1 lesions might occur during the first two decades of life. As insulinomas imply a potential life-threatening risk and pHPT is the most prevalent manifestation, the authors suggest that regarding these tumors, young MEN1 patients should be already screened at the age of five years. According to the GTE study, screening of further MEN1 lesions should be postponed until the age of 10 years (Goudet et al. 2015).

The length of screening intervals are also still under debate. Current expert practice guidelines
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(Thakker et al. 2012) and the majority of groups (Karges et al. 2000, Waldmann et al. 2009, Goudet et al. 2015, Giusti et al. 2017, Manoharan et al. 2017) recommend annual routine screening of MEN1 patients. Some observational studies, however, suggest an extension of screening intervals up to 2 or 3 years, if no serious organ manifestations were detected at the initial screening visit, since rapid progression of organ manifestations is rarely observed (Kann et al. 2006a, Waldmann et al. 2009). The Dutch MEN1 group, for example, explored in 34 patients the growth rate of small pNENs (median size 5 mm). The overall growth rate was about 0.1 mm/year, and therefore, the authors suggest that surveillance might be prolonged without missing any serious manifestation (Kappelle et al. 2016). As a matter of fact, in a significant proportion of MEN1 patients, the screening intervals have to be adapted to the existing organ manifestations and thus individualized, especially if a malignant tumor is or was present.

Ideally MEN1 screening should be performed under standardized prospective protocols at expert centers who work in multidisciplinary teams. The responsible physicians should have detailed knowledge about the syndrome, the varying phenotypes and its treatment options.

Screening modalities

MEN1 screening is determined by local resources, clinician’s expertise and patient’s preferences. Since screening is a life-long program, psychological burden, cost-effectiveness and side effects have to be considered (Stromsvik et al. 2007, Waldmann et al. 2009, Thakker et al. 2012, Manoharan et al. 2017).

Recent clinical practice guidelines (Thakker et al. 2012) recommend certain examinations for MEN1 screening based on expert experiences and mostly retrospective data (evidence levels 3–5). Although these recommendations are promoted by several groups, no generally accepted screening protocol yet exists. In Table 1, the recommendation of current clinical practice guidelines (Thakker et al. 2012) is summarized and are compared to the screening protocol of the authors group. Table 2 provides an overview of the sensitivity and specificity of the different imaging modalities in MEN1-associated NENs (Table 2).

The annual screening examination, including baseline laboratory testing and imaging, should ideally cover all potential affected organs, even in asymptomatic patients. Over the last decades, the value of imaging compared to laboratory testing has emerged. In older practice guidelines (Brandi et al. 2001), there was strong recommendation to perform imaging only every 3 years, if there was no clinical or biochemical suspicion of a distinct organ manifestation. Nowadays, clinical practice guidelines recommend annual cross-sectional imaging (e.g. MRI, CT) (Thakker et al. 2012). In the following sections, the current screening modalities are reviewed with regard to the potentially affected organ.

Tumor markers

Despite the annual assessment of typical hormones of functioning NENs (as insulin, gastrin, etc.) the current guidelines recommend to measure chromogranin A, pancreatic polypeptide (PP) and glucagon serum levels as tumor markers (Thakker et al. 2012). An Italian study of 68 patients with sporadic pNENs has postulated that the combined examination of chromogranin A and PP leads to a significant increase of sensitivity in the diagnosis of pNENs, especially in detecting non-functioning tumors (Panzuto et al. 2004). In MEN1 patients, however, this finding could not be confirmed. de Laat et al. (2013), for example, determined for the markers chromogranin A, PP and glucagon, a sensitivity of 45% and specificity of 75% for MEN1-associated pNENs. In their study, the diagnostic accuracy of these tumor markers was low compared to imaging (de Laat et al. 2013). These results were supported by several other studies (Granberg et al. 1999, Walter et al. 2012, Rehfeld et al. 2014, Qiu et al. 2016). In the authors’ opinion, the tumor markers PP, chromogranin A and glucagon can be omitted from MEN1 screening.

Previously, Modlin and coworkers introduced a new PCR-based blood-based multianalyte neuroendocrine gene transcript assay (NETest) for the diagnosis of gastroenteropancreatic neuroendocrine neoplasia (GEP-NEN) (Modlin et al. 2015). The NETest comprises 51 multigene transcripts (Modlin et al. 2014a). The results of this test were compared to expression of chromogranin A in sporadic GEP-NEN. The NETest was more sensitive compared to the common tumor marker. The sensitivity/specificity rate was about 92.8%/92.8% (Modlin et al. 2014b). This NETest was than examined pre- and postoperatively in 27 patients with GEP-NEN to monitor the therapeutic effect (Modlin et al. 2016). In 23 of 27 patients, the NETest result was significantly reduced (preoperative: 80±5%, postoperative: 29±5%, P<0.0001) after curative resection of the GEP-NEN. There are yet no data published regarding the value of the NETest in MEN1 patients. However, if initial results

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can be confirmed in large prospective MEN1 cohorts, the NETest might be a valuable screening modality for MEN1 patients.

In the future, distinct micro-RNAs (miRNA) also might become potential tumor or biomarkers for MEN1 screening. Micro-RNAs (miRNA) are important genetic regulators and upregulation or downregulation of specific miRNAs lead to tumor initiation and progression in several malignancies (Saini et al. 2007). miRNA levels can be measured in serum, especially if they are upregulated.

<table>
<thead>
<tr>
<th>Clinical practice guidelines (Thakker et al. 2012)</th>
<th>Marburg MEN1 screening protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical test (plasma or serum) annually</td>
<td>Biochemical test (plasma or serum) annually</td>
</tr>
<tr>
<td>Imaging method</td>
<td>Imaging method</td>
</tr>
<tr>
<td><strong>Start 8 years</strong></td>
<td><strong>Start 16 years</strong></td>
</tr>
<tr>
<td>Calcium, PTH</td>
<td>Calcium, PTH</td>
</tr>
<tr>
<td><strong>Start 20 years</strong></td>
<td><strong>Start 16 years</strong></td>
</tr>
<tr>
<td>Gastrin, gastric pH</td>
<td>Gastrin, gastric pH, secretin test</td>
</tr>
<tr>
<td>Annual pancreatic and duodenal imaging with MRI, CT, or EUS</td>
<td>EUS and esophagogastroduodenoscopy (annually)</td>
</tr>
<tr>
<td><strong>Start 5 years</strong></td>
<td><strong>Start 16 years</strong></td>
</tr>
<tr>
<td>72h-fasting glucose, insulin</td>
<td>48h-fasting glucose test, insulin</td>
</tr>
<tr>
<td>Annual pancreatic and duodenal imaging with MRI, CT, or EUS</td>
<td>EUS and MRI (annually)</td>
</tr>
<tr>
<td><strong>Start &lt;10 years</strong></td>
<td><strong>Start 16 years</strong></td>
</tr>
<tr>
<td>Chromogranin A, pancreatic polypeptide, glucagon, VIP</td>
<td>Chromogranin A; pancreatic polypeptide, glucagon, VIP</td>
</tr>
<tr>
<td>Annual pancreatic and duodenal imaging with MRI, CT, or EUS</td>
<td>EUS and MRI (annually)</td>
</tr>
<tr>
<td><strong>Start 5 years</strong></td>
<td><strong>Start 16 years</strong></td>
</tr>
<tr>
<td>Prolactin, IGF1</td>
<td>Prolactin, IGF1</td>
</tr>
<tr>
<td>MRI (every 3 year)</td>
<td>MRI (every 3 years)</td>
</tr>
<tr>
<td><strong>Start &lt;10 years</strong></td>
<td><strong>Start 16 years</strong></td>
</tr>
<tr>
<td>None unless symptoms or signs of functioning tumor and/or tumor &gt;1cm</td>
<td>Lesions &gt; 1 cm or functioning lesion:</td>
</tr>
<tr>
<td></td>
<td>– Plasma renin</td>
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<td></td>
<td>– Plasma aldosterone</td>
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<td></td>
<td>– Low-dose dexamethasone</td>
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<td></td>
<td>– Suppression test</td>
</tr>
<tr>
<td></td>
<td>– Urinary catecholamines and/or metanephrines</td>
</tr>
<tr>
<td><strong>Start 15 years</strong></td>
<td><strong>Start 20 years</strong></td>
</tr>
<tr>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>CT or MRI (every 1–2 year)</td>
<td>CT of the thorax (every 2 years)</td>
</tr>
<tr>
<td><strong>Not evaluated</strong></td>
<td><strong>Start 40 years</strong></td>
</tr>
<tr>
<td>Not evaluated</td>
<td>Recommendation for female patients to undergo breast cancer screening, e.g. mammography (every 2 years)</td>
</tr>
</tbody>
</table>
Table 2  Sensitivity and specificity of preoperative imaging modalities in MEN1-associated NENs.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary tumor</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Parathyroid hyperplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>⁹⁹mTc-MIBI scintigraphy</td>
<td>69–98</td>
<td>63–97</td>
<td></td>
</tr>
<tr>
<td>C-11 Met-PET/CT</td>
<td>74–91</td>
<td>–100</td>
<td></td>
</tr>
<tr>
<td>Duodenal gastrinoma and gastric NEN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>43–73</td>
<td>–96</td>
<td></td>
</tr>
<tr>
<td>EUS</td>
<td>40–72</td>
<td>–100</td>
<td></td>
</tr>
<tr>
<td>Gastro-duodenoscopy</td>
<td>40–100</td>
<td>80–100</td>
<td></td>
</tr>
<tr>
<td>SRS scintigraphy</td>
<td>66–80</td>
<td>86–100</td>
<td></td>
</tr>
<tr>
<td>Ga-68-DOTATOC-PET/CT</td>
<td>37–85</td>
<td>83–100</td>
<td></td>
</tr>
<tr>
<td>Pancreatic NEN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>74–94</td>
<td>80–100</td>
<td>Baumann et al. (2016), Binderup et al. (2010), Christ et al. (2013), Garcia-Carbonero et al. (2015), Maxwell et al. (2016), Kornaczelewski et al. (2017), Partelli et al. (2014)</td>
</tr>
<tr>
<td>CT</td>
<td>69–94</td>
<td>80–89</td>
<td></td>
</tr>
<tr>
<td>EUS</td>
<td>88–100</td>
<td>40–95</td>
<td></td>
</tr>
<tr>
<td>SRS scintigraphy</td>
<td>52–96</td>
<td>&gt;95</td>
<td></td>
</tr>
<tr>
<td>Ga-68-DOTATOC-PET/CT (low sensitivity for insulinoma)</td>
<td>37–93</td>
<td>85–100</td>
<td></td>
</tr>
<tr>
<td>¹⁸F-FDG PET/CT (only for G2/G3 pNEN)</td>
<td>73–92</td>
<td>&gt;95</td>
<td></td>
</tr>
<tr>
<td>GLP-1 scintigraphy (only in insulinoma)</td>
<td>–95</td>
<td>20–25</td>
<td></td>
</tr>
<tr>
<td>Adrenal lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>81–100</td>
<td>94–100</td>
<td>Kann (2016), Langer et al. (2002), Park et al. (2016), Waldmann et al. (2007)</td>
</tr>
<tr>
<td>CT</td>
<td>66–79</td>
<td>98–100</td>
<td></td>
</tr>
<tr>
<td>EUS</td>
<td>85–100</td>
<td>96–100</td>
<td></td>
</tr>
<tr>
<td>Bronchial and thymic carcinoid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>95–100</td>
<td>95–100</td>
<td>Gibril et al. (2003), Goudet et al. (2009), Lococo &amp; Treglia (2014), Lococo et al. (2014)</td>
</tr>
<tr>
<td>CT</td>
<td>95–100</td>
<td>95–100</td>
<td></td>
</tr>
<tr>
<td>Ga-68-DOTATOC-PET/CT</td>
<td>86–100</td>
<td>–99</td>
<td></td>
</tr>
<tr>
<td>F-¹⁸-FDG PET/CT</td>
<td>14–96</td>
<td>–11</td>
<td></td>
</tr>
</tbody>
</table>

CT, computed tomography; EUS, endoscopic ultrasonography; MRI, magnet resonance imaging; SRS scintigraphy, somatostatin receptor scintigraphy.

So far, miRNA has only been analyzed in MEN1-associated primary hyperparathyroidism (Luzi et al. 2017). The authors found three miRNAs (miR-4258, miR-664 and miR-1301), which were involved in the MEN1-associated parathyroid neoplasia.

Lee and coworkers reported a high expression of miRNA-196a in pNEN compared to normal controls (Lee et al. 2015), which was not confirmed in another study (Slater et al. 2014). In recent small scale studies, miRNAs such as miR-7-5p and miR-96-5p have been evaluated and were clearly upregulated in the preoperative sera of patients with GEP-NEN (Heverhagen et al. 2017). Li and coworkers characterized miRNA levels in well-differentiated small intestinal neuroendocrine tumors. The authors detected nine miRNAs: five (miR-96, -182, -183, -196a and -200a) were upregulated during tumor progression and the rest (miR-31, -129-5p, -133a and -215) were downregulated (Li et al. 2013).

Much more research is necessary to determine whether a distinct miRNAs or miRNA profiles might be valuable diagnostic biomarkers.

Primary hyperparathyroidism (pHPT)

Nearly all MEN1 patients develop pHPT until the age of 50 years, which is the first organ manifestation in the majority of patients (Thakker et al. 2012, Lassen et al. 2014). The typical age of onset of pHPT is 20–30 years (Giusti et al. 2013, Romero Arenas et al. 2014). PHPT is caused by an asymmetric 4-gland hyperplasia. The majority of affected patients are asymptomatic and the diagnosis is established by repeated measurement of elevated serum calcium levels (>2.65 mmol/L) and inadequate elevated intact parathyroid hormone levels (PTH). Thus, these parameters should be obtained during every screening visit. If calcium and PTH levels are not elevated, no imaging of the neck is needed. In the presence of a pHPT, the current practice guidelines do also not recommend any special imaging of the neck, since the standard surgical treatment for MEN1-pHPT is either subtotal parathyroidectomy (3.5 resection) or total parathyroidectomy with autotransplantation with transcervical thymectomy to cure the multiple gland disease (Brandi et al. 2001,
Before surgery, however, several groups recommend an ultrasonography of the neck to clarify concomitant thyroid pathology that might influence the operative strategy. Since 2015, the authors‘ group performs ultrasonography of the neck and \(^{99m}\)Tc-MIBI scintigraphy in patients with MEN1-pHPT to clarify preoperatively the presence of unilateral enlarged glands. If this is the case, a unilateral exploration with resection of two glands and thymectomy will be performed to avoid postoperative hypocalcemia. In case of recurrence (which can last up to 20 years or even longer), only the remaining previously untouched side has to be explored.

In case of persistent or recurrent pHPT, screening should include at least ultrasonography of the neck and \(^{99m}\)Tc-MIBI scintigraphy, which have a sensitivity and specificity of 69% to 98% and 63% to 97% (Shepherd et al. 2000, Keutgen et al. 2016). MRI (magnetic resonance imaging) or CT (computed tomography) of the neck and upper mediastinum can be added, if the latter examinations are negative. It should be the goal to identify the enlarged gland preoperatively to provide the ability for a focused operative approach. However, in some cases, imaging fails to visualize the proliferated hyperplastic gland(s). In these cases, a selective venous sampling with PTH measurement can be performed to regionalize the source of PTH hypersecretion. In addition, PET (positron emission tomography) imaging has been previously reported as a very sensitive and noninvasive imaging tool, which might be more sensitive than \(^{99m}\)Tc-MIBI scintigraphy. Weber and coworkers evaluated the value of C-11 Met-PET/CT in 50 patients with sporadic pHPT and negative localization procedures such as ultrasound and \(^{99m}\)Tc-MIBI scintigraphy. In these cases, the sensitivity of C-11 Met-PET/CT was still 76% and the new imaging method was able to detect parathyroid tissue in 37 of 50 cases (Weber et al. 2017). Moreover, in a small Dutch study, abnormal parathyroid glands could be identified with fluorine-18 fluorocholine PET-CT (F-FCH PET-CT) (Kluifjouth et al. 2016). In 33 patients, F-FCH PET-CT could successfully localize 33 of 35 abnormal glands (94.3%). Further studies are required in MEN1 patients to determine the value of these new imaging methods for the detection of hyperplastic parathyroid tissue.

**Duodenopancreatic neuroendocrine neoplasia (dpNEN)**

Duodenopancreatic neuroendocrine neoplasias (dpNEN) are the second most common manifestation and the leading cause of death in MEN1. Tumors include gastrinomas (~20–30%), insulinomas (~10%), vipomas (<5%), glucagonomas (<3%) and non-functioning pancreatic neuroendocrine neoplasias (NF-pNEN, 50–80% until 50 years). Nowadays, NF-pNENs are the most frequently detected tumors of the pancreaticoduodenal region in adult MEN1 patients. Most tumors are small (<10 mm) and develop multiple throughout the duodenum and pancreas (Anlauf et al. 2007). Therefore, laboratory screening should include measurement of gastrin, insulin, proinsulin, vasoactive polypeptide, glucagon and PP in the serum (Waldmann et al. 2009, Thakker et al. 2012, Goudet et al. 2015). A standardized meal test for the early detection of pNENs, as proposed in former times, has no more clinical impact (Langer et al. 2001).

If the serum gastrin is elevated and/or specific symptoms of a Zollinger-Ellison syndrome (ZES) are present, a secretin provocation test should be performed. In cases of gastrin serum levels of <10 fold greater than normal an assessment of gastric pH (pH typically <4 in ZES) is required (Ito 2012). If the secretin provocation test is performed properly, it is highly sensitive and specific for ZES (Berna et al. 2006). However, it has to be considered that there are also some limiting factors such as achlorhydric, hypochlorhydric, hyperparathyroidism or PPI treatment, leading to misinterpretation of the test (Norton et al. 2001, Berna et al. 2006). Before performing the secretin test, a primary hyperparathyroidism should be excluded or corrected by surgery to prevent a false-positive secretin test (Norton et al. 2008). Proton pump inhibitor treatment should be paused 48 h before initiating the test. Pausing the PPI treatment might be a challenging event in some patients by causing acid-peptic-induced complications (Poitras et al. 2012).

An insulinoma is suspected based on hypoglycemia symptoms, plasma glucose levels <2.2 mmol/L (40 mg/dL), concomitant elevated serum insulin levels and relief of symptoms by administration of glucose (Falconi et al. 2012, Thakker et al. 2012), and current clinical practice guidelines recommend that the biochemical diagnosis should be established by a supervised positive 72-h fasting test, defined by a pathological Insulin Glucose Index and symptomatic hypoglycemia (Sakurai et al. 2012, Thakker et al. 2012). Nowadays, some groups advocate that a 48-h supervised fasting test is sufficient (Hirschberg et al. 2000, Ueda et al. 2017). Previously, it was reported that the 48-h fasting test combined with a glucagon stimulatory test provides the best results (Ueda et al. 2017).

Current clinical practice guidelines also recommend the use of imaging methods to visualize dpNENs in addition to measurement of serum hormone levels during a screening visit (Thakker et al. 2012). There is, however,
no general recommendation for the type of imaging in routine screening of MEN1 patients, as clinical data are limited and imaging techniques depend on local conditions and preferences as well as on local resources. In most centers, modern imaging methods such as MRI, multi-slice contrast-enhanced CT, endoscopic ultrasound (EUS) and functional receptor imaging such as positron emission tomography with CT (PET/CT) using Gallium-68 radiolabeled somatostatin analogs are used.

Several studies on EUS have shown that it is the most sensitive imaging modality for the detection of dpNEN, especially of those smaller than 1 cm in size (van Asselt et al. 2015, Kann et al. 2006b). Kann and coworkers demonstrated that EUS is capable to identify MEN1 associated pNEN as small as 2 mm and in diameter and is more sensitive than CT or MRI (Kann et al. 2006a). EUS detected 82 pNENs <15 mm in 20 MEN1 patients, whereas only 4 of 82 (6.3%) and 4 of 39 (10.3%) of these lesions were detected by CT or MRI. In another prospective study on 41 MEN1 patients, EUS detected 101 pNEN in 34 patients, whereas CT/MRI plus somatostatin receptor scintigraphy identified only 32 lesions in 18 patients (P<0.001). These data are confirmed by the data of the authors’ group (Albers et al. 2017). In 33 MEN1 patients, EUS detected 116 pNEN compared to 30 detected by MRI (Albers et al. 2017). Given these data, EUS should be an integral part of MEN1 screening (Fig. 1).

Despite its high sensitivity for small pNEN, another advantage of EUS is that changes in size or growth over time can be reliably determined. The Dutch MEN1 group used EUS in 38 MEN1 patients and could identify 226 pNENs (Kappelle et al. 2016). Overall growth rate was 0.10 mm/year (95% CI 0.02–0.19; P=0.01). PNENs <10 mm (n=198) did not grow (P=0.23), whereas...
pNENs ≥10 mm (n=28) grew 0.44 mm/year (95% CI 0.10–0.78; \( P=0.01 \)). Kann and coworkers prospectively studied 20 MEN1 patients with pNENs over a period of 20±12 months (33.8 patient years, 106.7 tumor years) by EUS (Kann et al. 2006a). Increase of the largest tumor diameter was found to be 1.3±3.2% per month, and annual tumor incidence rate was 0.62 in new tumors per patient year.

EUS offers also the possibility of fine-needle aspiration (FNA) of pancreatic lesions. In the current practice guidelines, there is no special recommendation regarding the use of EUS-guided FNA (Thakker et al. 2012). It can be used to confirm the existence of a pNEN and to provide prognostic information by the determination of the Ki67 index and tissue grading (Larghi et al. 2012, Rindi et al. 2012, 2014, Farrell et al. 2014). In two previous meta-analyses, a pooled sensitivity up to 86% and a specificity of 95% for the correct pathology in solid pancreatic lesions in non-MEN1 patients was reported (Chen et al. 2013, Puli et al. 2013). In the setting of MEN1, however, there is no role for routine use of EUS-FNA, since it is obvious that any lesion in the pancreas will be most likely a pNEN. The histopathological proof of a pNEN does not change the further management in MEN1 patients in general. In selected cases with rapidly growing small pNENs, an EUS-FNA with determination of the Ki67 index (>2%) and grading (G2/G3) might be a useful adjunct, which might indicate an operation in tumors <2 cm in size. Although EUS is currently the most sensitive imaging method for MEN1-pNENs, there is still need for cross-sectional imaging modalities, such as MRI or CT. EUS is an investigator-dependent and invasive procedure which can miss some pNENs, especially in the pancreatic tail. Cross-sectional imaging also provides an overview of the whole abdomen, including liver, adrenals, lymph nodes and so forth. In a recent prospective study of the GTE on 90 MEN1 patients, EUS and MRI missed 11/24 and 4/24 lesions ≥20 mm, respectively (Barbe et al. 2012). EUS failed to identify 9/57 (15.7%) patients with pancreatic tumors ≥10 mm, and MRI failed to identify 11/57 (19.3%) patients with pancreatic tumors ≥10 mm. The authors concluded that EUS and MRI should be used complementary in the pancreas work-up for patients with MEN1, which is supported by our group (Albers et al. 2017). Compared to other cross-sectional imaging modalities such as CT or PET/CT, there is no risk of radiation in MRI, which is an advantage of this imaging tool.

CT is still the most often used cross-sectional imaging method for pancreatic tumor localization. In literature, there are several studies comparing CT, MRI and EUS for sporadic pNENs. In summary, the sensitivities of modern CT and MRI imaging modalities are comparable and most authors suggest that EUS is superior to CT for diagnosing small pNENs (Gouya et al. 2003, Khashab et al. 2011). However, as MEN1 patients undergo regular surveillance, the radiation exposure of CT has to be taken into consideration. Casey et al. (2017), for example, retrospectively analyzed the cumulative radiation exposure of 43 MEN1 patients due to screening and calculated an estimated mean lifetime risk of secondary cancer of 0.49% (Casey et al. 2017). Therefore, these authors and several other groups (Ito & Jensen 2016, Albers et al. 2017, Casey et al. 2017) prefer MRI over CT for the screening/imaging of dpNENs in MEN1 patients.

A further imaging modality for the detection of dpNEN and other extrapancreatic organ manifestations in the sense of a whole-body scan is somatostatin receptor imaging. It was developed as somatostatin receptor scintigraphy with 111 In-pentetretotide (SRS) in the 1990s and presented the standard imaging for GEP-NENs for more than two decades in most countries. The technique is based on the fact that GEP-NENs express somatostatin receptors (Shi et al. 1998, van Essen et al. 2013), especially the subtypes sst2 and sst5, which allow to visualize these tumors with radiolabeled somatostatin analogs. Several studies in the past have shown that the SRS scintigraphy is a useful imaging modality to detect pNEN and is even more sensitive than cross-sectional imaging (Gibril et al. 1996, Langer et al. 2004, Sundin 2012, van Essen et al. 2013). One exception is the insulinoma, which is positive in SRS imaging in only 30–60% of cases (de Herder et al. 2005, Zhang et al. 2009).

However, in the last years in most centers, SRS scintigraphy has been replaced by PET with somatostatin analogs (e.g. Ga-68-DOTATOC-PET) combined with CT for anatomical correlation of lesions. Ga-68-DOTATOC-PET/CT has proven to be a highly sensitive and specific technique for imaging of well-differentiated NENs. The technique showed high sensitivity of 93–96% and specificity of 85–100% for sporadic pNEN (Yang et al. 2014). Superior spatial resolution, faster imaging, lower radiation exposure and lower costs are reasons for the replacement (Öberg & Sundin 2016). Ga-68-DOTATOC-PET/CT has also been found to be superior to conventional imaging (CT, MRI and endoscopic ultrasonography) in the diagnosis and staging of sporadic neuroendocrine tumors. Hofman et al. (2012) could demonstrate that Ga-68-DOTATOC-PET/CT was superior to somatostatin receptor scintigraphy and conventional cross-sectional imaging in sporadic pNEN (Hofman et al. 2012). In 40 of 59 (68%) patients, Ga-68-DOTATOC-PET/CT provided additional information.
compared to conventional imaging. Disadvantages of this technique are the high costs and radiation exposure, if applied annually. In MEN1 screening, especially for the detection of dpNENs and other extrapancreatic NENs, the role of Ga-68-DOTATOC-PET/CT has yet not been clarified. Its use was not discussed in the current clinical practice guidelines (Thakker et al. 2012) due to lack of experience with this technique in the setting of MEN1 at that time. Since then, only few case series with 18–33 patients reported on the use of Ga-68-DOTATOC-PET/CT in MEN1 patients (Froeling et al. 2012, Sadowski et al. 2015, Lastoria et al. 2016, Morgat et al. 2016, Albers et al. 2017). Most studies compared Ga-68-DOTATOC-PET/CT to CT and/or SRS/SPECT. In one prospective observational study of Sadowski and coworkers, Ga-68-DOTATOC-PET/CT detected 107 lesions compared to detection of 33 and 48 lesions with 111In-pentetreotide SPECT/CT and CT scan in 26 MEN1 patients, respectively. These findings of the Ga-68-DOTATOC-PET/CT led to a change of further management in 8 of 26 patients (Sadowski et al. 2015). Another series presenting data from 18 MEN1 patients compared Ga-68-DOTATOC-PET/CT to EUS, CT of the trunk and MRI of the pituitary, and found no benefit of PET/CT compared to conventional imaging (Lastoria et al. 2016). Our group was the first to compare prospectively Ga-68-DOTATOC-PET/CT with conventional techniques for complete screening in 33 MEN1 patients, including MRI of the abdomen, EUS, esophagogastroduodenoscopy, CT of the thorax and MRI of the pituitary. In this study, PET/CT failed to visualize 92 of 145 NENs detected by other imaging modalities resulting in an overall sensitivity of only 37% (Albers et al. 2017). Ninety (62%) pNENs detected by conventional imaging were missed by Ga-68-DOTATOC-PET/CT. However, Ga-68-DOTATOC-PET/CT detected more liver and lymph node metastases in patients with known metastatic disease, which was already reported for sporadic metastatic pNENs (Versari et al. 2010). Based on the available data, somatostatin PET/CT imaging cannot be recommended for routine screening of MEN1 patients, but it probably provides important additional information in patients with suspected or known metastatic disease.

Besides Ga-68-DOTATOC-PET/CT, there are also some other tracers, that might be useful for the diagnosis of MEN1 dpNENs. Earlier studies have claimed a limited value of 18F-FDG PET/CT for the diagnosis of sporadic dpNEN due to a low expression of glucose receptors in well-differentiated tumors (Adams et al. 1998, Eriksson et al. 2005). Another study reported that 18F-FDG PET/CT is helpful for the detection of malignant sporadic pNEN, especially in smaller tumors (Binderup et al. 2010). Kornaczewski Jackson and coworkers recently performed structural and functional imaging (magnetic resonance imaging, CT, ultrasonography and 18F-FDG PET/CT) in 49 MEN1 patients. Twenty-five (51.0%) had pancreatic lesions on structural imaging and five (25%) of these had 18F-FDG PET/CT-positive lesions. Eight patients with pNENs underwent surgery (three 18F-FDG-positive and five -negative pNENs). The Ki-67 index was ≥5% in 18F-FDG-positive pNENs and <2% in 18F-FDG-negative pNENs. Overall, six of the eight (75%) patients with 18F-FDG-positive hepatopancreatic lesions harbored aggressive or metastatic pNENs compared with one of 41 patients (2.4%) without hepatopancreatic 18F-FDG positivity (P<0.001). Thus, the authors concluded, that 18F-FDG PET/CT is an effective screening modality in MEN1 for identifying pNENs of increased malignant potential (Kornaczewski Jackson et al. 2017). This has to be confirmed in a large prospective observational study.

Recent data suggest that glucagon-like peptide-1 receptor scintigraphy (GLP-1 scintigraphy) might be a sensitive and specific imaging modality for the detection of insulinoma. Glucagon-like peptide-1 (GLP-1) is a well-known pancreatic beta-cell receptor. GLP-1 scintigraphy was used in 40 patients with hypoglycemia (Sowa-Staszczyk et al. 2016). Positive results of GLP-1 scintigraphy were observed in 28 patients. Out of these 28 patients, 18 patients underwent surgery and the histopathological examination of the tissue proved the diagnosis of an insulinoma. The authors conclude that GLP-1 scintigraphy might be a helpful diagnostic tool (Sowa-Staszczyk et al. 2016). Besides scintigraphy, GLP-1 receptor is used in PET/CT. Recently, Luo and coworkers investigated in 43 insulinoma patients the value of GLP-1 PET/CT compared to conventional imaging as CT, EUS and MRI. In 42 out of 43 patients a positive tracer uptake could be revealed with GLP1- PET/CT. The authors reported about a sensitivity of 97.7%. Furthermore, the authors claim that the sensitivity of EUS in their study was only 84% (21/25) (Luo et al. 2016). The preoperative reliable detection of an insulinoma in MEN1 by GLP1-PET/CT would be a substantial progress, since parenchyma-sparing enucleation of insulinoma is nowadays even an option for MEN1 associated insulinomas. It provides long-term cure, spares parenchyma and reduces the rate of postoperative diabetes mellitus compared to formal pancreatic resections (Bartsch et al. 2013). In addition, it can be also performed minimally invasive in MEN1 patients (Lopez et al. 2016, Nell et al. 2016).
If a gastrinoma could not be detected preoperatively or in case of multiple lesions, some authors recommend to perform the selective arterial secretin injection (SASI) angiography to regionalize the source of gastrin hypersecretion (Imamura et al. 1986, 2011, Wada et al. 2000, Okada et al. 2016). Since it is now well established that more than 95% of gastrinomas are located in the duodenum (Pipeleers-Marichal et al. 1993, Anlauf et al. 2006) and that concomitant pNENs are most likely non-functioning (Bartsch & Albers 2015), the value of this invasive test in MEN1 patients has to be questioned. The authors do not recommend SASI angiography for the regionalization of MEN1-ZES anymore, it was not used once in the last 7 years.

If an insulinoma cannot be detected by EUS, cross-sectional or PET imaging, especially in the presence of multiple pNENs >1 cm, a selective arterial calcium injection (SACI) angiography can be performed to regionalize the source of insulin excess with high sensitivity and specificity of >85% (Haji et al. 2000, Gimm et al. 2007, Thakker et al. 2012).

In conclusion, the authors recommend annual EUS and MRI of the abdomen for the work-up of dpNEN (Tables 1 and 2). Ga-68-DOTATOC-PET/CT should only be performed in patients with suspected or known metastatic pNEN disease. This holds true especially for MEN1-ZES to detect lymph node or liver metastases, since up to 80% of these tumors are malignant. Although 18F-FDG PET/CT might be another effective screening modality for the identification of malignant pNENs, its routine use can yet not be recommended due to the lack of convincing data. In case of organic hyperinsulism with multiple pNENs ≥ 1 cm, it seems worthwhile to perform a GLP1-PET/CT to identify the insulinoma(s) in order to plan the operative strategy. If GLP1-PET/CT is not available or negative, a selective angiography with calcium stimulation (SACI angiography) can be performed to regionalize the source of insulin excess.

Gastric NEN

Patients with MEN1-ZES develop gastric NEN type 2. The prevalence of type 2 gastric NEN varies between 5 and 50% (Rindi et al. 1993, Tomassetti et al. 2000, Bartsch & Albers 2015, Li et al. 2016). Therefore, the authors recommend annual esophagogastroduodenoscopy (EGD) for these patients to detect and treat gastric NEN type 2.

Pituitary tumors

The incidence of MEN1-associated pituitary lesions vary from 15 to 50% (Vergès et al. 2002). These tumors are divided into micro (<1 cm) and macroadensomas (>1 cm) depending on their size. Symptoms of MEN1-associated pituitary lesions are similar to their sporadic counterpart and depend on size and hormone secretion. In about 60%, the tumors secrete secretin (Thakker et al. 2012). Current clinical guidelines recommend performing annual monitoring of serum prolactin and IGF1 (insulin-like growth factor 1). MRI is the imaging modality of choice to visualize potential tumors and is recommended every three years or earlier, if symptoms are present (Scarsbrook et al. 2006, Waldmann et al. 2007, Thakker et al. 2012).

Adrenal neoplasias

The prevalence of adrenal lesions in MEN1 patients is up to 45% in cohorts that were investigated with new cross-sectional imaging and EUS (Skogseid et al. 1992, 1995, Langer et al. 2002, Gibril et al. 2004, Waldmann et al. 2007). In most cases, the tumors are small and non-functioning lesions of the adrenal cortex. Primary hyperaldosteronism and ACTH-independent Cushing’s disease are the most common functioning lesions and occur in less than 10% of MEN1 patients (Gatta-Cherifi et al. 2012). Only about 2% of MEN1 patients develop an adrenocortical carcinoma (ACC), but this is a life-threatening malignant tumor (Skogseid et al. 1995, Gibril et al. 2004, Waldmann et al. 2007). Biochemical investigation, including plasma renin, aldosterone and cortisol concentrations and low-dose dexamethasone suppression test, is recommended in MEN1 patients with adrenal lesions with a size > 1 cm. Additionally, cross-sectional imaging should be offered (Thakker et al. 2012). Current clinical expert guidelines recommend using MRI or CT to detect adrenal lesions (Thakker et al. 2012). In several studies, adrenal lesions were more likely detected with EUS than with MRI or CT. Waldmann and coworkers reported that EUS was the most sensitive imaging procedure in adrenal lesions (Waldmann et al. 2007). EUS was capable to detect adrenal enlargement in 21/21(100%) cases, whereas CT failed in 7 cases. Kann confirmed these results (Kann 2016). The authors prefer EUS and MRI for adrenal imaging, which is already covered by imaging for dpNEN.

Bronchial and thymic carcinoid

Bronchial and thymic carcinoids occur only in about 5–8% of MEN1 patients (Sachithanandan et al. 2005, Christakis et al. 2016). Thymic carcinoids develop almost exclusively in man (Singh Ospina et al. 2015, Christakis et al. 2016). The fast majority of these tumors...
are asymptomatic for a long time and do not secrete any special hormones. Therefore, current practice guidelines do not recommend specific laboratory examinations for screening, but imaging with CT or MRI of the chest is recommended every 2 years (Thakker et al. 2012). This also holds true after prophylactic thymectomy during a previous parathyroidectomy, since transcervical thymectomy does not prevent the development of thymic carcinoids (Burgess et al. 2001, Recuero Díaz et al. 2013, Singh Ospina et al. 2015). Gibril and coworkers reported about 7 cases of thymic carcinoids of 128 MEN1 patients. In this study, MRI and CT of the chest, both, were able to identify all tumors (Gibril et al. 2003). Recently, some authors reported about the use of somatostatin receptor imaging, Ga-68-DOTATOC-PET/CT and 18F-FDG PET/CT in bronchial and thymic carcinoid patients (Groves et al. 2004, Ito & Jensen 2016). Regarding PET/CT as an imaging method in bronchial and thymic carcinoid, controversial results were obtained (Perez-Monte et al. 1997, Lococo & Treglia 2014, Lococo et al. 2014). In 2014, Lococo and coworkers reviewed the literature regarding the assessment of Ga-68-DOTATOC-PET/CT and F-18-FDG PET/CT in bronchial carcinoids of non-MEN1 patients. Ga-68-DOTATOC-PET/CT provided the best results in initial evaluation of patients with clinical suspicion of bronchial carcinoid (Lococo et al. 2014). The detection rate of positive bronchial carcinoids with Ga-68-DOTATOC-PET/CT varied from 95 to 100%. In F-18-FDG PET/CT the detection rate ranged from 14 to 96%. F-18-FDG PET/CT might offer additional information, if Ga-68-DOTATOC-PET/CT present negative results (Lococo et al. 2014). Abe and coworkers presented a case of simultaneous occurrence of thymic and bronchial carcinoid of a MEN1 patient. In this patient, 18F-FDG PET/CT visualized the thymic carcinoid, but did not detect the bronchial carcinoid (Abe et al. 2008).

There have been only a few reports concerning the use of 18F-FDG PET/CT in thymic carcinoid. Groves and coworkers described the usage of 18F-FDG PET/CT in a 35-year-old man with thymic carcinoid. In this case, 18F-FDG PET/CT could reveal the primary tumor, but missed the skeletal lesions, which were identified with MRI (Groves et al. 2004). Further results are required to evaluate the value of PET/CT as a screening modality for bronchial and thymic carcinoids in MEN1 patients. So far, it cannot be recommended for routine use. The authors prefer chest CT every 2 years. If the lesion exceeds 1 cm in size, a Ga-68-DOTATOC-PET/CT will be added to clarify the diagnosis of a NEN.

Breast cancer

Recently, Seigne and coworkers reported a high frequency of mammary intraepithelial neoplasias in the transgenic Men1 mouse model WapCre-Men1F/F compared to controls (51% vs 7%) (Seigne et al. 2013). Afterward, the Dutch MEN1 group explored the incidence of breast cancer in 190 female MEN1 patients and calculated an increased relative risk of 2.83 for the development of invasive breast cancer. In this cohort, 12 out of 190 patients (6.3%) developed breast cancer with a mean age at diagnosis of 48.0±8.8 years. Compared to the general Dutch population, the breast cancer was diagnosed about 12 years earlier (Dreijerink et al. 2014). The same group performed a cross-sectional case-control study using the Dutch MEN1 cohort (van Leeuwaarde et al. 2017). In 138 MEN1 female patients, a questionnaire regarding breast cancer was carried out. Eleven of the 138 MEN1-affected females had breast cancer at a median age of 45 years. In addition, 34 female relatives (among those 11 known mutation carriers) with breast cancer were identified. The increased breast cancer risk in MEN1 carriers was not related to other known breast cancer risk factors or familial cancer history. Therefore, the authors concluded that breast cancer surveillance from the age of 40 years for all women with MEN1 is justifiable. Although above mentioned data are quite convincing, the prevalence in other large MEN1 cohorts should be assessed before a recommendation for an annual routine breast cancer screening beginning at age 40 years can be given for female MEN1 patients.

Conclusion

The goal of every screening program for inherited tumor syndromes should be effectiveness with regard to diagnostic yield, costs and psychological burden of the screened individuals. Unfortunately, screening of MEN1 mutation carriers is complex and a variety of questions, especially with regard to begin of screening, screening intervals and most effective imaging modalities and interventional consequences of screening results (surveillance, medical treatment, surgery) are yet not resolved. In many patients, the screening has to be individualized according to their personal medical history. Therefore, screening should be ideally performed in specialized centers with multidisciplinary teams and standardized screening protocols. Current evidence favors annual screening with well-established laboratory parameters. The diagnostic value of the NETest and/or
other new biomarkers such as distinct miRNAs should be validated in the future for their use as additional tools for the early detection of NENs. Currently, annual EUS and complementary MRI seem the best imaging modalities for screening of dpNENs and adrenal lesions. For pituitary lesions MRI, every 3 years appears to be optimal. For detecting bronchial or thymic NENs, CT of the chest every 2 years is an effective screening strategy. In certain clinical scenarios (e.g. ZES; insulinoma gastrinoma, bronchial or thymic NE, suspicious of metastases), PET/CT imaging with specific tracers (e.g. Ga68, 18F-FDG or GLP 1) are useful additional modalities that can be used.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Thematic Review

Diagnostic and imaging in MEN

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