

NEN: Advancement in Diagnosis and Minimally Invasive Therapy

NET: Neue Entwicklungen in Diagnostik und minimalinvasiver Therapie

Authors

Daniel Putzer, Peter Schullian, Werner Jaschke, Reto Bale

Affiliation

Radiology, Interventional Oncology – Microinvasive Therapy (SIP), Medical University of Innsbruck, Austria

Key words

neuroendocrine tumor imaging, locoregional treatment, percutaneous ablation, stereotactic radiofrequency ablation (SRFA), minimally invasive therapy

received 04.04.2019

accepted 09.10.2019

Bibliography

DOI <https://doi.org/10.1055/a-1030-4631>

Published online: 20.11.2019

Fortschr Röntgenstr 2020; 192: 422–430

© Georg Thieme Verlag KG, Stuttgart · New York

ISSN 1438-9029

Correspondence

Prof. Reto Bale

Radiology, Interventional Oncology – Microinvasive Therapy (SIP), Medical University of Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria

Tel.: ++ 43/5 12/50 48 05 40

reto.bale@i-med.ac.at

ZUSAMMENFASSUNG

Neuroendokrine Tumoren (NET) bilden eine heterogene Entität maligner Erkrankungen und werden häufig durch Symptome manifest, die durch die Ausscheidung metabolisch aktiver Substanzen oder durch Fernmetastasen hervorgerufen werden, wobei Metastasen der Leber häufig auftreten. Die frühzeitige Diagnose einer metastasierten Erkrankung gilt als der wichtigste Prognosefaktor für NET-Patienten. Eine vollständige chirurgische Resektion ist nur in ausgewählten Fällen möglich. Für Patienten mit nicht resezierbaren Lebermetastasen stehen verschiedene lokoregionäre Behandlungsansätze zur Verfügung. In den letzten zehn Jahren wurden therapeutische Verfahren einschließlich lokoregionärer und systemischer Behandlungen für gastroenteropankreatische NET (GEP-NET), insbesondere für Lebermetastasen, untersucht. Nur wenige prospektive klinische Studien zielen darauf ab, diese Ansätze zu vergleichen, und das Management einzelner Patienten unterliegt weiterhin klinischem Fachwissen und Urteilsvermögen. Lokal ablative Verfahren stellen ein effektives therapeutisches Verfahren für Patienten dar, die einem

kurativen Therapieansatz zugänglich sind, und können ebenso zur Tumorreduktion und Symptomkontrolle bei Patienten mit multifokaler Metastasierung der Leber verwendet werden.

Kernaussagen:

- Neuroendokrine Neoplasien (NENs) sind eine heterogene Gruppe von seltenen Malignomen.
- Bei primären nicht metastasierten NENs gilt die chirurgische Resektion als Therapie der ersten Wahl.
- Metastasen von neuroendokrinen Tumoren befallen am häufigsten die Leber.
- Eine limitierte Lebermetastasierung kann mittels chirurgischer Resektion oder thermischer Ablation mit kurativer Zielsetzung behandelt werden.
- Die stereotaktische thermische Ablation mit multiplen Nadeln und Bildfusion zur intraoperativen Kontrolle eines ausreichenden Sicherheitssaums erlaubt eine sichere und effektive Behandlung von großen Lebermetastasen.

ABSTRACT

Neuroendocrine neoplasms (NEN) are a heterogeneous type of malignant disease and frequently present with symptoms caused by the secretion of metabolically active substances or the manifestation of distant metastases, with the liver being the most frequent site of spreading. Early diagnosis of metastatic disease is recognized as the major prognostic factor in NEN patients. Complete surgical resection is feasible in only selected cases. For patients with unresectable liver metastases, various locoregional treatment approaches are available. Over the last decade, therapeutic procedures including locoregional and systemic treatments have been investigated for gastroenteropancreatic NEN (GEP-NEN), especially for metastatic disease to the liver. Only a few prospective clinical trials have compared these approaches, and the management of individual patients remains subject to clinical expertise and judgement. Locoregional treatments are applicable in patients with limited metastatic involvement of the liver, and may be used for tumor debulking and symptom control in patients with diffuse liver involvement.

Key Points:

- Neuroendocrine Neoplasms (NENs) represent a heterogeneous class of rare malignancies.
- Surgery is the treatment of choice for primary non-metastatic NEN.
- The liver is the most frequently affected site by neuroendocrine metastases.

- In limited metastatic liver disease local curative treatment may be accomplished by surgical resection or percutaneous thermal ablation.
- Multi-probe stereotactic thermal ablation with image fusion for intraoperative evaluation of a sufficient safety margin allows for safe and effective treatment of large liver metastases.

Citation Format

- Putzer D, Schullian P, Jaschke W et al. NET: Neue Entwicklungen in Diagnostik und minimalinvasiver Therapie. *Fortschr Röntgenstr* 2020; 192: 422–430

Introduction

Neuroendocrine Neoplasms (NENs) are a heterogeneous class of rare malignancies with variable tumor biology and characteristics. Only a minor percentage of NENs are metabolically active. The worldwide incidence has steadily increased over the past decades. In the literature from Northern Europe an incidence of 3.24/100 000 is reported, while the incidence in the USA has reached 5.25/100 000 [1].

The clinical studies on tumor detection and treatment mainly focus on gastroenteropancreatic NENs (GEP-NENs), which include subgroups of tumors with or without hormone secretion capacity. Functionally active tumors release different peptide hormones. In intestinal and pancreatic neuroendocrine tumors (NETs), metastatic disease is highly prevalent. Metastases are present in 65–95 % of patients suffering from GEP-NEN when initially diagnosed [2, 3]. The lungs, liver and bone are the sites that are frequently affected by metastatic spreading [4, 5]. The liver is the site most frequently affected by metastases, and the prevalence depends on the primary location of the tumor, the tumor spread, which is characterized by the T-stage, histological differentiation and the proliferation index. The tumor biology and the presence of distant metastases are key prognostic factors. In comparison to patients with non-metastatic NEN, these two tumor characteristics correlate with a significant reduction in overall survival (OS) [6]. Patients suffering from metastatic NEN have reached a 5-year OS of 56–83 %, while patients with metastatic pancreatic NEN have a 5-year OS of 40–60 % [7]. For GEP-NEN, the aggressive treatment of hepatic metastases has proven to be beneficial for the quality of life and OS [8], despite the fact that liver surgery is generally not a curative option. Even if R0 resection is confirmed histopathologically, the recurrence rate 5 years after surgery reaches 94 % [9].

The clinical treatment decision has to be made on an individual basis, relying on histopathological and immunohistochemical findings, and many patients are not amenable to complete resection because of multifocal metastatic disease.

According to consensus guidelines from national NET databases, the prognosis for metastatic midgut NET has improved over the last decades. The 5-year OS is reported to reach 50 % to 60–80 %, according to different patient cohorts. The 5-year OS in metastatic pancreatic NET has reached up to 60 % in patients undergoing multidisciplinary treatment. These strategies include surgery as well as locoregional and systemic treatment such as SSA or PRRT [10]. Debulking procedures in non-resectable metastatic disease have shown to be beneficial, resulting in an improvement of the 5-year OS rate, reaching 75 % [9]. The combi-

nation of hepatic debulking and local ablative treatments showed comparable results without further improvement [11].

The consensus guidelines are based on the clinical benefit from the differentiation of 3 patterns that have been observed in NEN patients regarding the presence of liver metastases, influencing the therapeutic outcome according to the consensus guidelines: The first group of liver metastases (20 % to 25 % of patients) affects only one lobe of the liver or is restricted to 2 adjacent segments, which can be effectively treated by anatomical resection of the liver segments. The group showing a complex pattern (10 % to 15 % of patients) is characterized by metastases in one liver lobe, while the other lobe shows only small satellite metastases. These lesions are accessible to locoregional treatments. 60 % to 70 % of patients already present with diffuse metastases or metastases of the liver, requiring systemic treatment.

For patients who are not eligible for local treatment, systemic therapeutic options are available. Somatostatin analogs (SSAs) have shown an antiproliferative effect in prospective randomized controlled trials, including the PROMID and CLARINET study [12, 13]. SSAs are the established first-line therapy in functionally active NEN [14, 15]. Interferone-alpha (INF-alpha) is approved for midgut NET treatment, when other drugs are not available. A randomized trial including 400 patients under SSA therapy evaluated INF-alpha compared to bevacizumab (SWOG trial) [16]. For patients with pancreatic NET and metastatic foregut NET grade 2 and NEN grade 3 who cannot be treated surgically, chemotherapeutic agents have proven to have an impact on treatment outcome [17, 18]. In pancreatic NEN, the chemotherapeutic regimen using streptozotocin is combined with doxorubicin and/or fluorouracil, and reaches response rates of 30 % to 40 % [19]. A high rate of partial remission of 70 %, and progression free survival (PFS) of 18 months and an OS of 92 % at the 2-year follow-up in metastatic pancreatic NEN were reported after combined treatment using temozolomide and capecitabine [20]. In metastatic neuroendocrine carcinoma (NEC) grade 3, the combination of cisplatin and etoposide is recommended [21].

New treatment approaches in pancreatic NEN involve targeted therapies such as Everolimus and Sunitinib. Everolimus has an inhibitory effect on the mammalian target of the rapamycin (mTOR) pathway, while Sunitinib inhibits the tyrosine kinase pathway. The RADIANT 3 study is a randomized, placebo-controlled trial, which has shown an improvement of the median PFS from 4.6 months to 11 months for Everolimus, while only 5 % of the patients had an objective response [22]. Sunitinib treatment resulted in a higher PFS of 11.4 months vs. 5.5 months in a placebo-controlled, multicenter phase 3 study, with a rate of objective response of 9.3 % [23].

In retrospective trials, peptide receptor radionuclide therapy (PRRT) has shown efficacy in non-operable, low grade NETs, which are defined as G1 or G2 tumors, showing high expression of Somatostatin receptor (SSTR) subtype 2. SSTR expression is demonstrated by In-111 octreotide scintigraphy (Octreoscan) or Ga-68 labeled peptides for PET/CT imaging [24, 25]. PRRT has been performed with Yttrium-90 or Lutetium-177 and has demonstrated disease control rates of up to 68 % and response rates of up to 30 % in pretreated and advanced stage patients [26, 27]. The first multicenter randomized controlled phase 3 study evaluating Lu-177 Octreotate for the treatment of inoperable midgut NEN (NETTER-1 trial) reported an increase in PFS of 65.2 % vs. 10.8 % for patients treated with long acting SSA. In the PRRT treatment arm, objective response was observed in 18 % vs. 3 % in the SSA treatment arm [28].

Considering the vast armamentarium of therapeutic regimens that are available for NEN patients, treatment options facilitating the sequential use of different therapeutic agents to implement a high success rate and a low rate of adverse events are an integral component for improving survival and maintaining good clinical status. The role of locoregional treatment approaches is evolving in this field.

Imaging and Staging

Staging procedures are essential for accurate initial diagnosis in NEN, for tumor detection, assessment of the tumor stage and for treatment planning [10]. In highly differentiated NEN (grade 1 and grade 2 tumor), computed tomography (CT) can be combined with SSTR imaging, including scintigraphy or positron-emission-tomography (PET) imaging. In poorly differentiated NEN (NET G3), CT of the thoracic, abdominal and pelvic region is regularly performed [29]. In cancer of unknown primary (CUP), a scintigraphic procedure including single photon emission computed tomography (SPECT) or PET using Ga-68 for SSR imaging should be combined with triphasic CT [29].

Triphasic CT is the established standard diagnostic procedure in primary NET for initial tumor staging, as well as follow-up and treatment monitoring. However, metastatic involvement of lymph nodes and bone may be missed in the early stage due to low sensitivity [30]. The sensitivity and specificity in CT imaging for the detection of primary NET in different studies range from 61–93 % and 71–100 % on a patient basis, and from 77–89 % and 71–89 % on a lesion basis, respectively [31]. Corresponding values for the detection of liver metastasis range from 75–100 % and 83–100 % [32–35]. For lymph node detection, the reported sensitivity ranges from 60–70 % and the specificity from 87–100 % [36].

Magnetic resonance imaging (MRI) including dynamic gadolinium (Gd) contrast-enhanced sequences and diffusion-weighted imaging (DWI) can overcome these limitations, with available standardized protocols used for restricted body areas. 60 % to 70 % of liver metastases in NET show an increased uptake of contrast media in liver metastases during arterial phase imaging [37], and ring enhancement has been described in up to 72 % of cases [38].

If planar SSTR scintigraphy fails to detect NEN, hybrid imaging as a complementary procedure with PET/CT using Ga-68 labeled SSA may be considered, leading to a higher rate of detection of the primary neuroendocrine tumor and early detection of metastatic spreading [31]. Four meta-analyses of SSA PET/CT reported sensitivities of 88–93 % and specificities of 88–95 % [39–42].

Conventional bone scintigraphy and CT are less accurate [30]. F-18 DOPA PET/CT has shown favorable results in functionally active NEN and may be considered if SSR imaging results are negative [43]. F-18-FDG PET/CT has shown prognostic relevance in well-differentiated NEN and functionally active NEN, as tumor cell clones with more aggressive potential show higher FDG uptake. Endoscopic ultrasound (EUS) is preferentially used to diagnose small pancreatic NET, including MEN 1 patients [44]. Contrast-enhanced ultrasonography (CEUS) can be useful to correlate equivocal findings in CT and MRI and can be used to guide biopsy. Colonoscopy should be considered for the workup of CUP syndrome. Virtual endoscopy may be an attractive alternative to investigate disease in the small intestine.

Next to diagnostic imaging, a detailed characterization of the tumor biology is part of the diagnostic workup in NEN therapy guidelines. After histopathologic confirmation of NEN, the tumor has to be characterized according to the differentiation grade and the proliferative index. The WHO classification differentiates well and poorly differentiated NENs using immunostaining. Ki-67 (MIB1) antigen is a marker that depends on the cell cycle and is expressed in the cell nucleus [45]. The Ki-67 proliferation index is the basis for tumor grading. G1 is defined by an index < 2 %, G2 is characterized by an index of 2–20 %, and G3 shows an index > 20 %. Optionally the immunostaining of somatostatin receptor 2 (SSTR 2) can be performed. GEP-NENs that are positive for SSTR 2 show increased tracer uptake upon SSA nuclear medicine imaging [46].

TNM staging includes information about the primary tumor site, the tumor diameter and the presence of necrosis or cysts. The location of the tumor is characterized according to anatomical landmarks, taking into consideration the resection margin after surgery. The TNM staging procedure also includes information regarding the extent of lymph node metastases and distant metastases [47, 48].

When the comprehensive diagnostic workup has been completed, follow-up visits include biochemical parameters in addition to conventional imaging. In patients with surgically resected grade 1 or grade 2 NET, it is recommended to perform imaging with an interval of 3–6 months, while the interval is shortened to 2–3 months in NEC grade 3 [29]. In patients with liver disease that cannot be treated surgically, the follow-up interval is 3 months from initial diagnosis and then every 6–12 months in stable disease. SSTR imaging comprises Octreoscan or PET using a ⁶⁸Ga-SSA. These nuclear medicine procedures are recommended at a follow-up of 18–24 months if positive upon initial diagnosis, or to rule out extrahepatic tumor manifestation if tumor markers are on the rise.

Surgical treatment

Surgery is the treatment of choice for primary non-metastatic GEP-NEN [49]. Surgery is performed in a curative approach in primary NEN or NEN with well-differentiated metastases, regardless of whether the primary tumor is located in the foregut, midgut or hindgut. It has been proven that the main factor influencing OS after surgery is radical excision, assuring tumor-free surgical margins [50]. Complete resection resulting in tumor-free resection margins (R0) has resulted in an improved long-term survival in midgut and hindgut tumors [51–54]. The survival rate in these patient cohorts in a 5-year follow-up has been reported to reach 60–80%, while the survival rate in patients with liver metastases that cannot be treated surgically is low (up to 30%) [55].

In gastric NEN, three subtypes can be differentiated that need to be considered before deciding on surgical resectability [56]. The most prevalent type is type 1 tumors, which are characterized by a low malignant potential. The structure of these tumors is polypoid. They are mainly found in the gastric body during endoscopy. Tumors are usually resected endoscopically, and endoscopic mucosal resection is the treatment of choice if the tumor diameter is 5 mm or larger [57]. Gastrectomy is an option in metastatic disease or poor differentiation. The survival rate is nearly 100%. The follow-up is usually performed endoscopically [58]. Type 2 gastric NENs are small polyps. Patients are frequently diagnosed because of hypergastrinemia and peptic ulcers as part of MEN 1 syndrome. About 10% to 30% of manifestations are in a metastatic state, and the mortality is below 10%, so surgical resection is recommended [59]. Type 3 gastric NENs are usually larger sporadic tumors with an infiltrative and metastatic tendency. Surgery is the standard treatment, with mortality rates of 30% and post-operative tumor spreading in 50–100% of cases [60].

Duodenal NENs are rare tumors that manifest mostly in the upper part of the duodenum, mostly confined to the mucosa and submucosa. Lymph node metastases are present in up to 40% of patients, and also liver metastases in 10%. Treatment includes endoscopic or surgical resection [61].

Small intestine NENs often present as small tumors with a high rate of metastatic disease, 80–90% presenting with liver metastases at initial diagnosis. Due to the histopathologic rating as G1 tumors, all patients should be considered for surgery or locoregional ablative treatment [62].

Pancreatic NENs are non-functioning tumors in 60–90% of cases, while 10% are part of inherited syndromes, such as insulinomas, VIPomas or glucagonomas, or as part of MEN 1 syndrome [63]. 60–70% of patients suffer from liver metastases upon initial staging [64]. Surgical exploration and tumor resection with regional lymph node extirpation can be performed with curative intent, especially in sporadic disease, but also in syndromic disease. Surgery is controversial only in MEN 1 disease due to a high rate of metastatic disease. EUS and SSA PET/CT can be performed pre-surgically to evaluate resectability in functioning tumors.

Colonic NENs are frequently aggressive and metastatic at diagnosis [65]. Treatment of patients suffering from NENs of the colon is comparable to treatment strategies for adenocarcinomas. Regional colectomy including oncological resection of lymph nodes is state-of-the-art. Tumors with a diameter of less than 2 cm can

be treated endoscopically or using EMR. Surgical resection of the primary tumor is also considered in patients with distant metastases, especially if intestinal obstruction can be avoided.

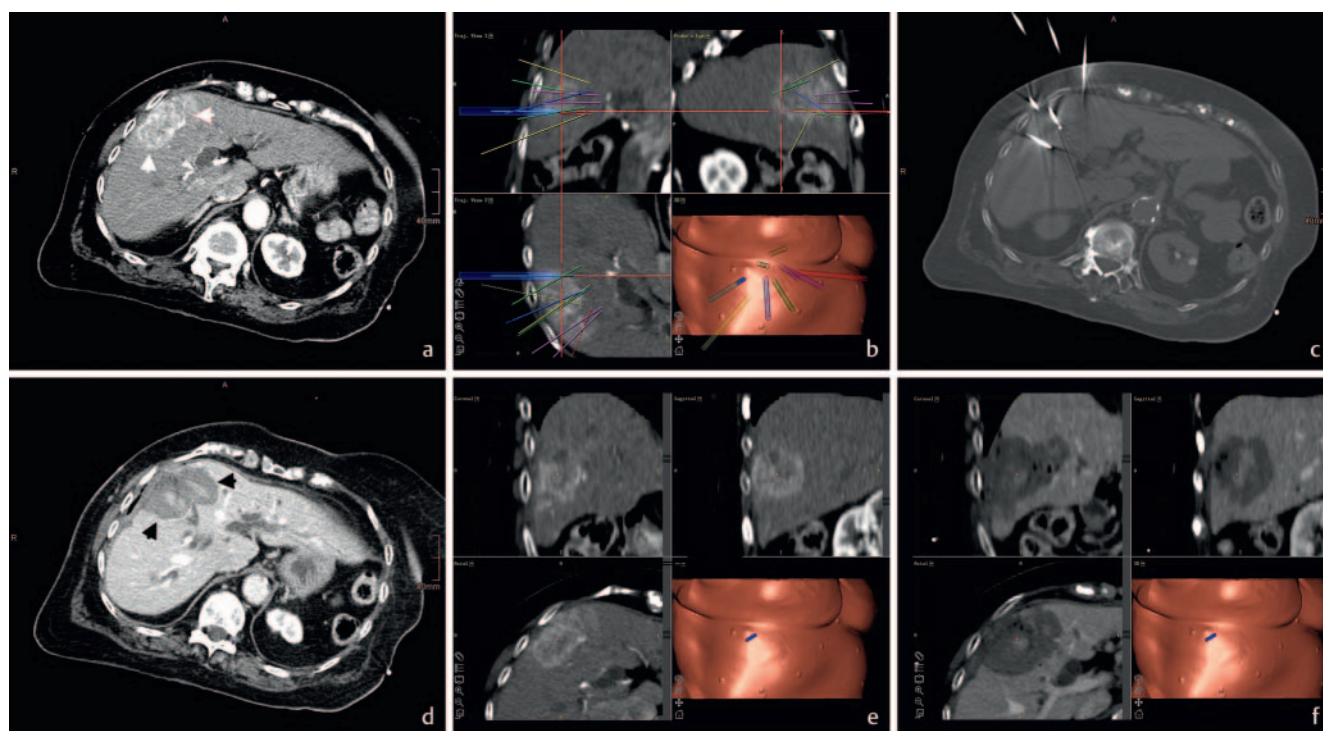
NENs of the lung are rare neoplasms with a heterogeneous tumor biology. Well and poorly differentiated NENs of the lung have to be differentiated. These tumors are frequently diagnosed incidentally on chest X-ray screening or chest CT. Surgical resection is the only curative approach, and resection of the primary tumor resulting in R0 margins in combination with lymph node resection is considered the gold standard in peripheral tumors [66].

In metastatic disease, surgery is part of the treatment protocol, is subject to debate in a multidisciplinary treatment approach, and is performed either on a curative or cytoreductive basis [67]. Further locoregional treatment approaches include ablative procedures, such as radiofrequency ablation or microwave ablation, mechanical embolization (TAME) and chemoembolization (TACE) and radioembolization (TARE) using either biological or cytotoxic or targeted agents, which are applied either locally or systemically, and will be discussed later.

Curative surgery is applicable according to the tumor biology and the presence of metastases, considering the location, size and number of tumors and the patients' general health status [68, 69]. In a curative setting, the absence of extrahepatic disease is a prerequisite [70]. The 5-year OS for patients undergoing surgery with curative intent is reported to reach 60–80% as compared to 30% for patients with GEP-NEN with liver metastases not treated by surgery [9]. A study evaluating the debulking of unresectable NEN metastases reported improved survival in this cohort [71]. In pancreatic NET, patients who underwent a cytoreduction of more than 70% showed improved PFS and OS. In small bowel NET, only the PFS was improved. However, the role of debulking surgery and a possible benefit in asymptomatic patients is not yet clear, and comparative trials to systemic therapy are not available. The low incidence and differences in surgical approach for various subtypes of NEN impede randomized controlled trials in this setting.

Ablative treatment

In radiofrequency ablation (RFA), alternating current (in the range of 350–500 kHz) is used to generate heat within the tumor tissue [72]. The target tissue is heated up to 100 °C leading to coagulation necrosis. Microwave ablation uses an electromagnetic field which is created by a needle-like antenna to induce heat. The electromagnetic energy causes a heating effect in the tissue, resulting in coagulation necrosis at a larger radius compared to RFA. In cryoablation, a well-defined ice ball is created using probes with argon or helium gas, resulting in irreversible tumor cell damage. The ice ball can be monitored under image guidance in real time during ablation. Irreversible electroporation (IRE) is a non-thermal procedure using short electric high-frequency pulses of high voltage between two electrodes in order to induce apoptosis, causing irreversible damage to the cell membrane. This procedure requires general anesthesia, muscular blockade and cardiac triggering in order to prevent cardiac arrhythmia. The parameters that impact the effectiveness and clinical feasibility of RFA are



► **Fig. 1** **a** A 78-year-old woman underwent resection of a well-differentiated neuroendocrine carcinoma of the pancreatic cauda, initially staged as pT3 N1 M0 G1 L1. In the follow-up computed tomography examination, a solitary liver metastasis with a diameter of 6 cm was detected in segment VIII, showing intense contrast enhancement in the arterial phase CT (white arrowheads). **b** The lesion was treated by stereotactic radiofrequency ablation (SRFA) in one session. Path planning and needle placement were performed using a stereotactic navigation system. The needle trajectories were defined in the three-dimensional reconstructed planning-CT dataset. **c** Control CT scan confirmed accurate needle placement. **d** Intraoperative contrast-enhanced CT at the end of the procedure did not yield any major complications (black arrowhead). **e** Registration of the contrast-enhanced planning CT scan (E) and the contrast-enhanced control CT scan (F) confirmed complete tumor ablation with a sufficient ablation margin in axial, sagittal and coronal planes. **f** Registration of the contrast-enhanced planning CT scan (E) and the contrast-enhanced control CT scan (F) confirmed complete tumor ablation with a sufficient ablation margin in axial, sagittal and coronal planes.

the diameter and location of the liver metastases. Conventional single-needle in-plane techniques using US or CT have shown limitations regarding accessibility, while recent multi-needle approaches based on CT imaging and 3D treatment planning and stereotactic needle guidance (SRFA) have overcome these restrictions [73, 74].

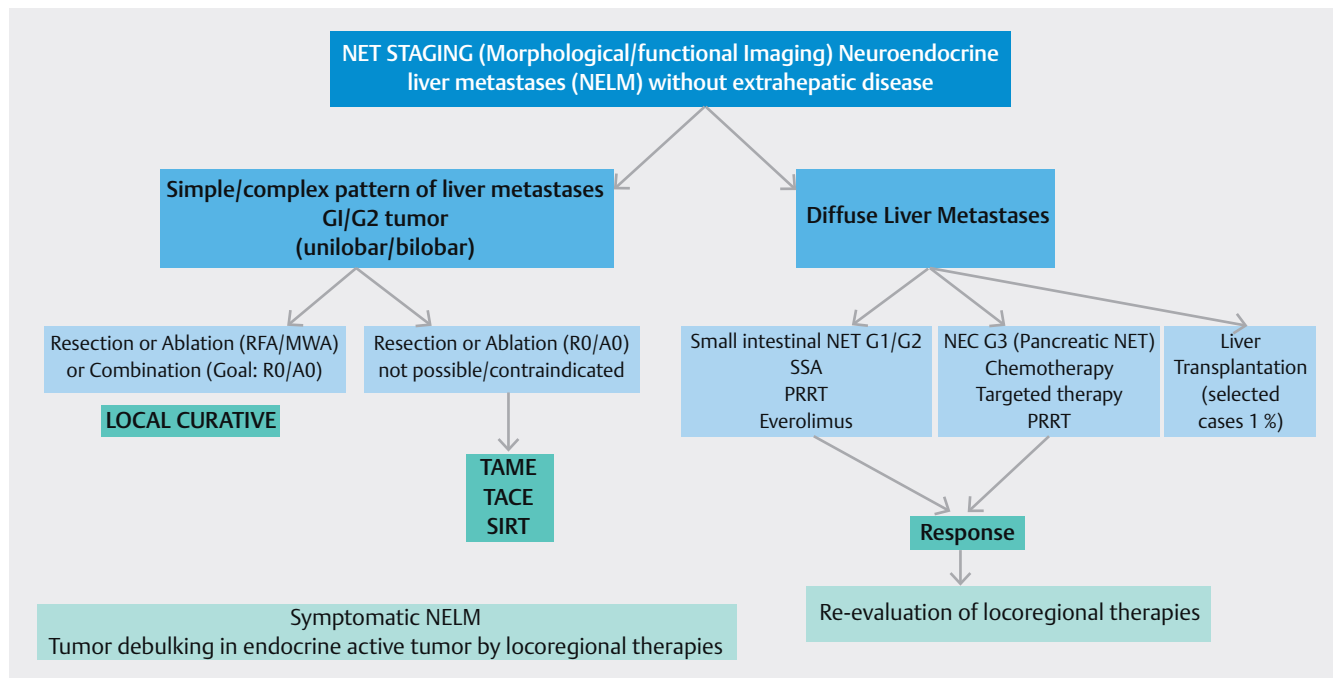
In multifocal, bilobar liver metastases of NEN, parenchyma-sparing debulking procedures such as enucleation or wedge resections have been associated with an improvement in the clinical status and survival rate, despite significant morbidity being associated with the intervention [11]. Locoregional ablative procedures have the potential to achieve local curative treatment comparable to surgery, while reducing morbidity and minimizing the loss of healthy liver tissue. The efficacy of locoregional therapies and palliative liver surgery or systemic therapy has not yet been compared in a randomized controlled trial. The therapeutic technique, such as RFA, hepatic transcatheter arterial embolization (TAE), chemoembolization (TACE) or selective internal radiotherapy (SIRT), is chosen based on the clinical expertise and individual patient features including the tumor size and location [75].

Locally ablative procedures are performed using a percutaneous or laparoscopic approach in NEN patients that are potentially resectable, but also in patients not eligible for major surgical procedures [76]. The ablative techniques have shown high effec-

tiveness in patients with a low tumor volume. This group includes patients with a lesion size between 1 and 5 cm and a low number of metastases (less than 6) [77]. RFA has proven to deliver symptom relief in 97 % of patients affected by liver metastases. In the follow-up, a high recurrence rate was observed, with 22 % of the patients showing local recurrence in the liver and 63 % suffering from new liver metastases [78], resulting in a median disease-free survival and OS of 1.3 years and 6 years, respectively. Taking into consideration the slow tumor progression and the inhomogeneous clinical presentation of NENs, RFA presents an attractive treatment alternative to surgery, due to the favorable safety profile with a morbidity of less than 5 % and a very low mortality [79].

A systematic review on RFA in NEN liver metastases reported results from 8 studies including 301 patients [80]. 92 % had post-operative improvement in tumor-associated symptoms, lasting for 14–27 months. 63–87 % of patients had local recurrence, and the mortality rate was reported as 0.7 %. The combination of surgical resection and RFA in hepatic metastases from NEN led to comparable results in 172 patients [81, 82].

SRFA is effective and safe in the treatment of large tumors [83]. A0 ablation is defined as an ablation resulting in a 3D safety margin of at least 5 mm. Intraoperative imaging can be performed to verify and document this margin, using image registration (► **Fig. 1**). Multimodal image interpretation of PET-CT during



► **Fig. 2** This flowchart summarizes a proposal for treatment allocation in neuroendocrine liver metastases without extrahepatic disease, according to tumor characteristics and clinical status, based on the ENETS consensus guidelines [10]. Since NETs represent a rare and heterogeneous disease, the key prognostic factors are tumor biology and the metastatic spread. Randomized controlled trials are still missing so that general treatment recommendations cannot be given. Therefore, the treatment decision has to be made on an individual basis, relying on histopathological findings and the clinical presentation. The local expertise and clinical environment of the treating facility will influence individually chosen treatment algorithms. In limited disease, local curative treatment can be accomplished, either by surgery (R0 resection) or ablation (A0 ablation). Locoregional ablation procedures yield comparable results to surgery with less morbidity. If surgery or ablation are contraindicated, TAME, TACE or SIRT are an alternative. Diffuse metastatic spread is not subject to curative treatment. Systemic treatment is indicated in extensive metastatic spread and G3 tumors. A multidisciplinary treatment approach favors sequential use of available therapeutic options. Up to now, no randomized controlled trial has evaluated the role of locoregional therapies in NEC G3. However, these treatment options can be considered in NEC G3, depending on the liver tumor burden, the extent of extrahepatic metastatic spread and the tumor proliferative activity [91].

SRFA allows selective targeting of active metastases recognized by 68-Ga DOTA-TOC uptake.

In treatment guidelines, RFA is considered a locoregional treatment approach that should be considered as one of the first treatment strategies in the multidisciplinary treatment algorithm, following SSA therapy [84]. RFA is applicable to prevent carcinoid crisis in patients with metabolically active tumors and has shown good results in comparison to systemic treatment in non-functioning NETs restricted to the liver and for downstaging in bulky disease [85]. The treatment can be performed repeatedly during the course of the disease.

Transarterial treatment

NEN metastases generally show a high grade of vascularization. The tumors are fed by the hepatic artery. The healthy liver parenchyma is usually supplied by the portal vein. The selective catheterization of vessels supplying the tumor allows for administration of therapeutic substances into target vessels, in order to induce tumor ischemia and to apply chemotherapeutic substances locally.

Transarterial mechanical embolization (TAME) is based on the administration of particular embolization materials into branches

of the hepatic artery. Conventional TACE (cTACE) uses Lipiodol as the carrier for chemotherapeutic agents and is often combined with particulate embolization. Further transarterial approaches include the application of drug-eluting beads (DEB-TACE), which are impregnated using chemotherapeutic agents including doxorubicin or irinotecan. The use of TACE for NEN patients has been described in small retrospective cohort studies for non-resectable liver metastases [81, 83].

TACE resulted in 5-year OS rates of 50–83%. These results are comparable to TAME trials, reporting a 5-year OS rate of 40% to 67% [86]. The overall response of symptoms and the response on imaging were described in 73–100% and 33–50% of the patients, respectively. TACE and TAME are effective with respect to symptom control in 73–100%, with a duration of 14 to 22 months [87].

Limiting factors regarding the application of these procedures include portal vein thrombosis, hepatic failure and comorbidities. Previously performed Whipple procedures are a contraindication, leading to a significantly higher risk of a perioperative inflammatory process and a higher rate of hepato-pulmonary shunts.

Transarterial radioembolization (TARE) using yttrium-90 (Y-90) microspheres is another novel treatment strategy for combined radiation and embolization therapy of liver metastases. TARE is a

promising new therapeutic approach that can overcome limiting factors such as portal vein thrombosis.

High radiation doses can be delivered directly to the tumor taking advantage of the fact that 80–100% of the blood supply of liver metastases originates from the arterial rather than the portal circulation of the liver. Patients with hepatic primary or metastatic cancer that is not resectable are considered for TARE if the tumor is mainly restricted to the liver. Before deciding on TARE treatment, the arterial blood supply is evaluated on imaging, and relevant hepatic-pulmonary shunts (> 10%) have to be excluded. TARE response rates have been reported to reach 70–90% [88]. However, TARE is still considered to be investigational, and a trial comparing results from TARE to bland embolization is required. In addition, long term safety data on the tolerability of TARE need to be acquired before considering this therapeutic approach within the treatment algorithm, as these therapies are safe and seem to assure tumor stabilization for prolonged periods [89]. In particular, no difference in long-term outcomes has been reported when comparing surgery to intra-arterial therapies being applied in asymptomatic patients with large liver tumors, suggesting that intraarterial therapies may be an attractive alternative to surgery [90].

Conclusion

The heterogeneity of NENs in combination with the vast armamentarium of available treatment approaches result in the need for highly individualized treatment and diligent scheduling of therapeutic approaches (► Fig. 2) depending on clinical expertise, tumor characteristics, tumor burden and extrahepatic spreading, since randomized controlled clinical trials have not yet been published.

Minimally invasive radiologic procedures are an appealing treatment solution for liver metastases in NEN, in the case of disease progression or in symptomatic NEN, offering a well-tolerated alternative to surgery and systemic treatment. They can be performed repeatedly and generally show low rates of adverse events.

Locoregional treatment of NET metastases is feasible and safe, making it possible to effectively control disease in patients with limited liver involvement. In patients with multifocal liver metastases, these procedures make it possible to control tumor-associated symptoms effectively.

Conflict of Interest

Reto Bale is a paid consultant of Cascination.

References

- [1] Niederle MB, Hackl M, Kaserer K et al. Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. *Endocr Relat Cancer* 2010; 17: 909–918
- [2] Modlin IM, Lye KD, Kidd M. A 5decade analysis of 13715 carcinoid tumors. *Cancer* 2003; 97: 934–959
- [3] Yao JC, Hassan M, Phan A et al. One hundred years after “carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in 35825 cases in the United States. *J Clin Oncol* 2008; 26: 3063–3072
- [4] Stump R, Haueis S, Kalt N et al. Transplantation and surgical strategies in patients with neuroendocrine liver metastases: protocol of four systematic reviews. *JMIR Res Protoc* 2013; 2: e58
- [5] Rindi G, Arnold R, Bosman F et al. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, et al., editor WHO Classification of Tumours of the Digestive System. Lyon: IARC Press; 2010: 1314
- [6] Saxena A, Chua TC, Sarkar A et al. Progression and survival results after radical hepatic metastasectomy of indolent advanced neuroendocrine neoplasms (NENs) supports an aggressive surgical approach. *Surgery* 2011; 149: 209–220
- [7] Pape UF, Berndt U, Müller-Nordhorn J et al. Prognostic factors of long-term outcome in gastroenteropancreatic neuroendocrine tumours. *Endocr Relat Cancer* 2008; 15: 1083–1097
- [8] Norton JA, Warren RS, Kelly MG et al. Aggressive surgery for metastatic liver neuroendocrine tumors. *Surgery* 2003; 134: 1057–1063
- [9] Mayo SC, de Jong MC, Pulitano C et al. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. *Annals of Surgical Oncology* 2010; 17: 3129–3136
- [10] Pavel M, Baudin E, Couvelard E et al. ENETS Consensus Guidelines for the Management of Patients with Liver and Other Distant Metastases from Neuroendocrine Neoplasms of Foregut, Midgut, Hindgut, and Unknown Primary. *Neuroendocrinology* 2012; 95: 157–176
- [11] Glazer ES, Tseng JF, Al-Refaie W et al. Long-term survival after surgical management of neuroendocrine hepatic metastases. *HPB* 2010; 12: 427–433
- [12] Rinke A, Wittenberg M, Schade-Brittinger C et al. Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors (PROMID): Results of Long-Term Survival. *Neuroendocrinology* 2017; 104: 26–32
- [13] Michael M, Garcia-Carbonero R, Weber MM et al. The Antiproliferative Role of Lanreotide in Controlling Growth of Neuroendocrine Tumors: A Systematic Review. *Oncologist* 2017; 22: 272–285
- [14] Eriksson B, Klöppel G, Krenning E et al. Consensus guidelines for the management of patients with digestive neuroendocrine tumors – well-differentiated jejunal-ileal tumor/carcinoma. *Neuroendocrinology* 2008; 87: 8–19
- [15] Ruzsiewicz P, Ish-Shalom S, Wymenga M et al. Rapid and sustained relief from the symptoms of carcinoid syndrome: results from an open 6-month study of the 28-day prolonged-release formulation of lanreotide. *Neuroendocrinology* 2004; 80: 244–251
- [16] Yao J, Guthrie K, Moran C et al. SWOG S0518: phase III prospective randomized comparison of depot octreotide plus interferon alpha-2b versus depot octreotide plus bevacizumab (NSC #704865) in advanced, poor prognosis carcinoid patients (NCT00569127). *J Clin Oncol* 2015; 33(suppl):abstr 4004
- [17] Walter T, Brixi-Benmansour H, Lombard-Bohas C et al. New treatment strategies in advanced neuroendocrine tumours. *Dig Liver Dis* 2012; 44: 95–105
- [18] Kouvaraki MA, Ajani JA, Hoff P et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol* 2004; 22: 4762–4771
- [19] Delaunoy T, Ducreux M, Boige V et al. The doxorubicin-streptozocin combination for the treatment of advanced well-differentiated pancreatic endocrine carcinoma: a judicious option? *Eur J Cancer* 2004; 40: 515–520

- [20] Strosberg JR, Cheema A, Kvols LK. A review of systemic and liverdirected therapies for metastatic neuroendocrine tumors of the gastroenteropancreatic tract. *Cancer Control* 2011; 18: 127–137
- [21] Moertel CG, Kvols LK, O'Connell MJ et al. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer* 1991; 68: 227–232
- [22] Yao JC, Pavel M, Lombard-Bohas C et al. Everolimus for the Treatment of Advanced Pancreatic Neuroendocrine Tumors: Overall Survival and Circulating Biomarkers From the Randomized, Phase III RADIANT-3 Study. *J Clin Oncol* 2016; 34: 3906–3913
- [23] Raymond E, Dahan L, Raoul JL et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011; 364: 501–513
- [24] Bodei L, Ferone D, Grana CM et al. Peptide receptor therapies in neuroendocrine tumors. *J Endocrinol Invest* 2009; 32: 360–369
- [25] Kwekkeboom DJ, Kam BL, van Essen M et al. Somatostatinreceptorbased imaging and therapy of gastroenteropancreatic neuroendocrine tumors. *Endocr Relat Cancer* 2010; 17: R53–R73
- [26] Bodei L, Kwekkeboom DJ, Kidd M et al. Radiolabeled Somatostatin Analogue Therapy Of Gastroenteropancreatic Cancer. *Semin Nucl Med* 2016; 46: 225–238
- [27] van Essen M, Krenning EP, Bakker WH et al. Peptide receptor radionuclide therapy with ¹⁷⁷Luoctreotate in patients with foregut carcinoid tumours of bronchial, gastric and thymic origin. *Eur J Nucl Med Mol Imaging* 2007; 34: 1219–1227
- [28] Strosberg J, El-Haddad G, Wolin E et al. Phase 3 Trial of (¹⁷⁷)LuDotatate for Midgut Neuroendocrine Tumors. *N Engl J Med* 2017; 376: 125–135
- [29] Sundin A, Arnold R, Baudin E et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Radiological, Nuclear Medicine & Hybrid Imaging. *Neuroendocrinology* 2017; 105: 212–244
- [30] Putzer D, Gabriel M, Henninger B et al. Bone metastases in patients with neuroendocrine tumor: ⁶⁸Ga-DOTA-Tyr3-octreotide PET in comparison to CT and bone scintigraphy. *J Nucl Med* 2009; 50: 1214–1221
- [31] Gabriel M, Decristoforo C, Kendler D et al. ⁶⁸Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. *J Nucl Med* 2007; 48: 508–518
- [32] Klöppel G, Couvelard A, Perren A et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Towards a Standardized Approach to the Diagnosis of Gastroenteropancreatic Neuroendocrine Tumors and Their Prognostic Stratification. *Neuroendocrinology* 2009; 90: 162–166
- [33] Chiti A, Fanti S, Savelli G et al. Comparison of somatostatin receptor imaging, computed tomography and ultrasound in the clinical management of neuroendocrine gastro-entero-pancreatic tumours. *Eur J Nucl Med* 1998; 25: 1396–1403
- [34] Dahdaleh FS, Lorenzen A, Rajput M et al. The value of preoperative imaging in small bowel neuroendocrine tumors. *Ann Surg Oncol* 2013; 20: 1912–1917
- [35] Kumbasar B, Kamel IR, Tekes A et al. Imaging of neuroendocrine tumors: accuracy of helical CT versus SRS. *Abdom Imaging* 2004; 29: 696–702
- [36] Hubalewska-Dydejczyk A, Fröss-Baron K, Mikołajczak R et al. ^{99m}Tc-EDDA/HYNIC-octreotate scintigraphy, an efficient method for the detection and staging of carcinoid tumours: results of 3 years' experience. *Eur J Nucl Med Mol Imaging* 2006; 33: 1123–1133
- [37] Duran R, Ronot M, Kerbaol A et al. Hepatic hemangiomas: factors associated with T2 shine-through effect on diffusion-weighted MR sequences. *Eur J Radiol* 2014; 83: 468–478
- [38] Dromain C, de Baere T, Baudin E et al. MR imaging of hepatic metastases caused by neuroendocrine tumors: comparing four techniques. *Am J Roentgenol* 2003; 180: 121–128. Reubi JC: Peptide receptor expression in GEP-NET. *Virchows Arch* 2007;451(suppl 1): S47–S50
- [39] Yang J, Kan Y, Ge BH et al. Diagnostic role of Gallium-68 DOTATOC and Gallium-68 DOTATATE PET in patients with neuroendocrine tumors: a meta-analysis. *Acta Radiol* 2014; 55: 389–398
- [40] Johnbeck CB, Knigge U, Kjær A. PET tracers for somatostatin receptor imaging of neuroendocrine tumors: current status and review of the literature. *Future Oncol* 2014; 10: 2259–2277
- [41] Geijer H, Breimer LH. Somatostatin receptor PET/CT in neuroendocrine tumours: update on systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging* 2013; 40: 1770–1180
- [42] Treglia G, Castaldi P, Rindi G et al. Diagnostic performance of Gallium-68 somatostatin receptor PET and PET/CT in patients with thoracic and gastroenteropancreatic neuroendocrine tumours: a meta-analysis. *Endocrine* 2012; 42: 80–87
- [43] Putzer D, Gabriel M, Kendler D et al. Comparison of (⁶⁸)Ga-DOTA-Tyr(3)-octreotide and (¹⁸)F-fluoro-L-dihydroxyphenylalanine positron emission tomography in neuroendocrine tumor patients. *Q J Nucl Med Mol Imaging* 2010; 54: 68–75
- [44] Dromain C, Déandréis D, Scoazec JY et al. Diagn Interv Imaging. Imaging of neuroendocrine tumors of the pancreas 2016; 97: 1241–1257
- [45] Rindi G, Klöppel G, Ahlman H et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2006; 449: 395–401
- [46] Rindi G, Klöppel G, Couvelard A et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2007; 451: 757–762
- [47] Scigliano S, Lebtahi R, Maire F et al. Clinical and imaging followup after exhaustive liver resection of endocrine metastases: a 15-year monocentric experience. *Endocr Relat Cancer* 2009; 16: 977–990
- [48] Grandhi MS, Lafaro KJ, Pawlik TM. Role of Locoregional and Systemic Approaches for the Treatment of Patients with Metastatic Neuroendocrine Tumors. *J Gastrointest Surg* 2015; 19: 2273–2282
- [49] Sarmiento JM, Heywood G, Rubin J et al. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *J Am Coll Surg* 2003; 197: 29–37
- [50] Elias D, Lasser P, Ducreux M et al. Liver resection (and associated extrahepatic resections) for metastatic well differentiated endocrine tumors: a 15-year single-center prospective study. *Surgery* 2003; 133: 375–382
- [51] Chamberlain R, Canes D, Brown K et al. Hepatic neuroendocrine metastases: does intervention alter outcomes? *J Am Coll Surg* 2000; 190: 432–445
- [52] Chen H, Hardacre J, Uzar A et al. Isolated liver metastases from neuroendocrine tumors: does resection prolong survival? *J Am Coll Surg* 1998; 187: 88–92
- [53] Kianmanesh R, O'Toole D, Sauvanet A et al. Surgical treatment of gastric, enteric, and pancreatic endocrine tumors. Part 2. Treatment of hepatic metastases. *J Chir (Paris)* 2005; 142: 208–219
- [54] Frilling A, Li J, Malamutmann E et al. Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. *Br J Surg* 2009; 96: 175–184
- [55] Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? *J Hepatol* 2007; 47: 460–466
- [56] Delle Fave G, O'Toole D, Sundin A et al. ENETS Consensus Guidelines update for gastroduodenal neuroendocrine neoplasms. *Neuroendocrinology* 2016; 103: 119–124
- [57] Gibril F, Schumann M, Pace A et al. 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)* 2004; 83: 43–48

- [58] Sato Y, Hashimoto S, Mizuno K et al. Management of gastric and duodenal neuroendocrine tumors. *World J Gastroenterol* 2016; 22: 6817–6828
- [59] Hoffmann KM, Furukawa M, Jensen RT. Duodenal neuroendocrine tumors: classification, functional syndromes, diagnosis and medical treatment. *Best Pract Res Clin Gastroenterol* 2005; 19: 675–697
- [60] Niederle B, Pape UF, Costa F et al. ENETS Consensus Guidelines update for neuroendocrine neoplasms of the jejunum and ileum. *Neuroendocrinology* 2016; 103: 125–138
- [61] Halfdanarson TR, Rabe KG, Rubin J et al. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol* 2008; 19: 1727–1733
- [62] Jensen RT, Cadiot G, Brandi ML et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. *Neuroendocrinology* 2012; 95: 98–119
- [63] Ramage JK, De Herder WW, Delle Fave G et al. ENETS Consensus Guidelines update for colorectal neuroendocrine neoplasms. *Neuroendocrinology* 2016; 103: 139–143
- [64] Caplin ME, Baudin E, Ferolla P et al. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. *Ann Oncol* 2015; 26: 1604–1620
- [65] de Baere T, Deschamps F, Tselikas L et al. GEP-NETS update: interventional radiology: role in the treatment of liver metastases from GEP-NETS. *Eur J Endocrinol* 2015; 172: R151–R166
- [66] Pavel M, O'Toole D, Costa F et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. *Neuroendocrinology* 2016; 103: 172–185
- [67] Reddy SK, Clary BM. Neuroendocrine liver metastases. *Surg Clin North Am* 2010; 90: 853–861
- [68] Bacchetti S, Bertozzi S, Londero AP et al. Surgical treatment and survival in patients with liver metastases from neuroendocrine tumors: a meta-analysis of observational studies. *Int J Hepatol* 2013; 2013: 235040
- [69] Maxwell JE, Sherman SK, O'Dorisio TM et al. Liver-Directed Surgery of Neuroendocrine Metastases: What is the Optimal Strategy? *Surgery* 2016; 159: 320–335
- [70] Tsoi M, Chatzellis E, Koumariou A et al. Current best practice in the management of neuroendocrine tumors. *Ther Adv Endocrinol Metab* 2018; 10: 1–18
- [71] Grozinsky-Glasberg S, Thomas D, Strosberg JR et al. Metastatic type 1 gastric carcinoid: a real threat or just a myth? *World J Gastroenterol* 2013; 19: 8687–8695
- [72] Steinmüller T, Kianmanesh R, Falconi M et al. Consensus guidelines for the management of patients with liver metastases from digestive (neuro)endocrine tumors: foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* 2008; 87: 47–62
- [73] Bale R, Widmann G, Stoffner DI. Stereotaxy: breaking the limits of current radiofrequency ablation techniques. *European journal of radiology* 2010; 75: 32–36
- [74] Bale R, Schullian P, Eberle G et al. Stereotactic Radiofrequency Ablation of Hepatocellular Carcinoma: a Histopathological Study in Explanted Livers. *Hepatology* 2019; 70: 840–850
- [75] Grandhi MS, Lafaro KJ, Pawlik TM. Role of Locoregional and Systemic Approaches for the Treatment of Patients with Metastatic Neuroendocrine Tumors. *J Gastrointest Surg* 2015; 19: 2273–2282
- [76] Akyildiz HY, Mitchell J, Milas M et al. Laparoscopic radiofrequency thermal ablation of neuroendocrine hepatic metastases: longterm followup. *Surgery* 2010; 148: 1288–1293
- [77] Lewis MA, Hubbard J. Multimodal liverdirected management of neuroendocrine hepatic metastases. *Int J Hepatol* 2011; 2011: 452343
- [78] Mohan H, Nicholson P, Winter DC et al. Radiofrequency Ablation for Neuroendocrine Liver Metastases: A Systematic Review. *J Vasc Interv Radiol* 2015; 26: 935–942
- [79] Pawlik T, Izzo F, Cohen D et al. Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. *Ann Surg Oncol* 2003; 10: 1059–1069
- [80] Evard S, Becouarn Y, Fonck M et al. Surgical treatment of liver metastases by radiofrequency ablation, resection, or in combination. *Eur J Surg Oncol* 2004; 30: 399–406
- [81] Vogl TJ, Naguib NN, Zangos S et al. Liver metastases of neuroendocrine carcinomas: interventional treatment via transarterial embolization, chemoembolization and thermal ablation. *Eur J Radiol* 2009; 72: 517–528
- [82] Memon K, Lewandowski RJ, Riaz A et al. Chemoembolization and radioembolization for metastatic disease to the liver: available data and future studies. *Curr Treat Options Oncol* 2012; 13: 403–415
- [83] Widmann G, Schullian P, Haidu M et al. Stereotactic Radiofrequency Ablation (SRFA) of Liver Lesions: Technique Effectiveness, Safety, and Interoperator Performance. *Cardiovascular and interventional radiology* 2012; 35: 570–580
- [84] Mohan H, Nicholson P, Winter DC et al. Radiofrequency ablation for neuroendocrine liver metastases: a systematic review. *J Vasc Interv Radiol* 2015; 26: 935–942
- [85] Cazzato RL, Garnon J, Ramamurthy N et al. 18FFDOPA PET/CT Guided Radiofrequency Ablation of Liver Metastases from Neuroendocrine Tumours: Technical Note on a Preliminary Experience. *Cardiovasc Intervent Radiol* 2016; 39: 1315–1321
- [86] Landry CS, Scoggins CR, McMasters KM et al. Management of hepatic metastasis of gastrointestinal carcinoid tumors. *J Surg Oncol* 2008; 97: 253–258
- [87] Memon K, Lewandowski RJ, Riaz A et al. Chemoembolization and radioembolization for metastatic disease to the liver: available data and future studies. *Curr Treat Options Oncol* 2012; 13: 403–415
- [88] Ejaz A, Reames BN, Maithel S et al. The impact of extrahepatic disease among patients undergoing liver-directed therapy for neuroendocrine liver metastasis. *J Surg Oncol* 2017; 116: 841–847
- [89] Grozinsky-Glasberg S, Kaltsas G, Kaltsatou M et al. Hepatic intraarterial therapies in metastatic neuroendocrine tumors: lessons from clinical practice. *Endocrine* 2018; 60: 499–509
- [90] Mayo SC, de Jong MC, Bloomston M et al. Surgery versus intraarterial therapy for neuroendocrine liver metastasis: a multicenter international analysis. *Ann Surg Oncol* 2011; 18: 3657–3665
- [91] Coriat R, Walter T, Terris B et al. Gastroenteropancreatic well-differentiated Grade 3 Neuroendocrine Tumors: Review and position statement. *Oncologist* 2016; 21: 1191–1199