ENETS Consensus Guidelines

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ENETS Consensus Guidelines for the Management of Patients with Liver and Other Distant Metastases from Neuroendocrine Neoplasms of Foregut, Midgut, Hindgut, and Unknown Primary

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Introduction

Neuroendocrine neoplasms (NEN), especially those of the intestine and pancreas, are frequently metastatic at the time of initial diagnosis. The identification of metastatic disease represents the most important prognostic factor after tumor grading [1–3]. Advances in modern histopathological and imaging techniques for the diagnosis and staging of NEN have improved not only in terms of sensitivity and specificity but also in terms of greater availability. This diagnostic amplification has proceeded with substantial broadening of the spectrum of therapeutic options available for the management of metastatic disease. The new WHO classification incorporates grading and staging, and provides a basis for prognostic prediction. However, it provides limited information for patients with distant metastatic (stage IV) disease. This limitation is apparent even in the subgroup of patients with well-differentiated metastatic neuroendocrine tumors (NET G1/G2) since the disease is heterogeneous, and there is a paucity of data on therapeutic outcome correlated with histopathological data. The terminology of the new WHO classification (NET G1/G2; neuroendocrine carcinoma (NEC) G3) [4] is utilized in this article in concert with the former appellation (well-differentiated endocrine tumor/carcinoma; poorly differentiated endocrine carcinoma). Of note, this does not imply that grading has been assessed in the cited studies. This reflects the difficulty that until recently grading was neither routine method nor a requirement for clinical studies, and both, differentiation status and grading, are not necessarily the same.

Therapeutic approaches for management of metastatic disease include surgical, medical, radiological and nuclear medicine strategies. More recently, novel molecular targeted drugs have been introduced into the NET treatment armamentarium. Each of the management strategies exhibit potential therapeutic benefits and the indications for their usage as well as the outcomes are discussed in detail.

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Recommendations are mainly based on retrospective studies but where available prospective studies are used although they are limited in number. Given the limited ability to biologically characterize individual tumors and the wide array of palliative therapy available, optimization of diverse management strategies is best achieved by multidisciplinary assessment and consensus-based therapy.

Epidemiology

In the largest US epidemiological database (SEER), of all cases with available information, 49% of NEN were localized, 24% showed regional metastases, and 27% were associated with distant metastases [3]. In contrast, in European databases distant metastases of gastroenteropancreatic (GEP) NEN at initial diagnosis are more frequent, and reported in 44 [5] to 73% [6, 7] in specialized centers. This may reflect a preselection of patients with advanced disease based upon referral to specialized centers rather than a real disease difference. The distribution of primary tumor sites varies depending on the entry criteria of the database (e.g. including lung or GEP neoplasms only). In addition, the disease stage is also reflective of the location of the primary tumor site at initial diagnosis. In the SEER database, distant metastases are present in 64% of pancreatic NEN, followed by cecal, colonic and small intestinal NEN in 44, 32 and 30%, respectively [3]. In European and US referral centers, up to 77% of patients with pancreatic and up to 91% of patients with intestinal NEN [6, 8–10] present with distant metastases at initial diagnosis, whereas rectal NEN in ~40%, gastric in 20–30% and appendiceal in less than 5% [5, 6]. Furthermore, the occurrence of liver metastases depends on tumor extent (T-stage), differentiation, and proliferative activity (grading: G1-G3). As might be expected in the SEER database histologic differentiation and proliferative activity were strongly associated with disease stage; 50% of patients with poorly differentiated neuroendocrine carcinomas (NEC G3) exhibited distant metastasis at initial diagnosis, whereas only 21 and 30% of patients with well-differentiated and moderately differentiated neuroendocrine tumors (NET G1 and G2) displayed distant metastasis at initial diagnosis, respectively [3]. European databases confirmed these findings. In the Spanish registry, 67% of patients with poorly differentiated endocrine carcinoma (NEC G3) had distant metastases compared to 38% of the patients with well-differentiated NET [5]. Functionality is associated with metastatic disease depending on the tumor cell type. In patients with carcinoid syndrome, metastatic disease is present in all cases. In contrast, insulinomas are benign in more than 90% of cases. In the future a more robust epidemiological database derived from a European registry that is currently under construction will be available.

Minimal Consensus Statement on Epidemiology

Presence of liver metastases is dependent on the primary tumor site, tumor extent (T-stage), histologic differentiation, and proliferative activity (grading; G1-G3). Pancreas, right hemicolon and small intestine are the most frequent primary tumor sites associated with distant metastases at initial diagnosis. The frequency of metastases varies depending on the structure of the database/registry. In specialized centers, 80–90% of patients who present with small intestinal and 60–70% of patients with pancreatic NEN show liver metastases. While the carcinoid syndrome is regularly associated with distant metastases, insulinoma are localized in ~90% of patients. Patients with poorly differentiated endocrine carcinoma/NEC G3 have more frequently distant metastases compared to patients with well-differentiated neuroendocrine tumors/NET G1-G2.

Prognosis

Histologic differentiation and proliferative activity are the strongest predictors of survival. In the most recent SEER database analysis, median survival in distant metastatic disease was 33 months in patients with NET G1-G2, but only 5 months in patients with poorly differentiated carcinomas/NEC G3. Survival at 5 years was 35% in well-differentiated to moderately differentiated NET but less than 5% in poorly differentiated NEC [3]. In specialized centers for the treatment of NET, 5-year overall survival rates in stage IV pancreatic and small intestinal NET are much higher than those published in the SEER database. This may be related to an improved overall management of NEN in specialized centers with a multidisciplinary approach having access to a broader spectrum of therapeutics. The 5-year survival rate of G1-G2 small intestinal and pancreatic NET in the SEER database is 54 and 27%, respectively [3]. In specialized centers, 5-year survival rates in metastatic midgut NET exceed 50% (e.g. 56% UKI NET study, 68% Spanish registry, 75% Tampa Single Center or even 83% Berlin/Paris centers) [5, 9–11]. In metastatic pancreatic NET, 5-year survival rates are around 40–60% [5, 8, 12]. In a multivariate analysis of patients with well-differentiated to moderately differentiated NET/NET G1-2 from the SEER database disease stage, primary tumor site, histologic differentiation, sex, race, age, and year of diagnosis were predictors of outcome ($p < 0.001$) [3]. Advanced stage, low histologic differentiation, and age were strongest predictors of worse survival in an analysis

of 1,483 cases of pancreatic NET at the Mayo Clinic [13]. In a center-based multivariate analysis of 324 patients with pancreatic NET, prognostic factors were the recently established TNM classification, the histologic classification according to the WHO, proliferative activity (measured by Ki67) and radical surgery [8]. In midgut NET, age at initial diagnosis, proliferative activity (measured by Ki67) and surgery of primary tumor [10, 14] were of prognostic impact. With respect to Ki67, cut-off values as proposed by the WHO classification (G1: ≤2%; G2: 3–20; G3: >20%) have been validated in a limited number of studies [1, 2, 8], but not in a prospective study and specifically for stage IV disease. Based on the new WHO classification, slightly corrected cut-off values depending on primary tumor site may allow a more precise prognostic stratification for pancreatic NET (e.g. <5%, 5–20% and >20%) [15, 16]. However, comparative analyses on proliferative activity of primary tumors and their metastases are still lacking, and the prognostic and predictive value of Ki67 in stage IV disease still needs to be validated. Univariate analysis revealed the influence of systemic therapy with either somatostatin analogues (SSA) or peptide receptor radionuclide therapy (PRRT) on the outcome [10, 17]. Early primary tumor resection including oncological lymph node dissection and/or debulking surgery or locoregional therapies were associated with a better prognosis [14, 18–21] but are exclusively derived from retrospective trials and may be biased by preselection of patients for surgery who might have had a more favorable prognosis. The presence of carcinoid heart disease or bone metastases are negative prognostic factors [9, 22, 23]. In a series of 146 patients including midgut NET with distant metastases, median survival decreased from overall 8.5 to 4.4 years from the time of diagnosis of carcinoid heart disease and 2.7 years with bone metastases [9]. Liver tumor burden or number of metastases, rate of tumor growth, extrahepatic distant metastases, comorbidities and performance status represent additional prognostic parameters [6, 14, 21, 24, 25]. Retrospective data indicate that circulating chromogranin A (CgA) is of prognostic value [26, 27]; highly elevated levels were associated with limited survival [27–29]. Other prognostic tissue markers are available (e.g. CK19, PTEN, TSC-2 in situ expression) but have to be validated in the future [30, 31].

Minimal Consensus Statement on Prognosis

The presence of liver metastases largely influences prognosis in all types of NEN and is dependent on primary tumor site, tumor extent (T-stage), histological differentiation (NET vs. NEC) and proliferative activity (grading; G1-G3). In addition, progressive liver metastases, liver tumor burden, presence of extrahepatic disease and carcinoid heart disease are negative prognostic factors. According to national databases and NET registries it appears that prognosis has improved with 5-year overall survival increasing from ≤50 to 60–80% in metastatic midgut NET and up to 60% in metastatic pancreatic NET in patients undergoing multidisciplinary treatment. The latter includes hepatobiliary surgery, locoregional and/or medical therapies such as SSA or PRRT. Metastatic NEC G3 have an overall poor prognosis whether presenting with or without liver metastases.

Clinical and Pathological Presentation

The clinical presentation of liver metastases from NEN depends on the excessive hypersecretion of hormones and/or monoamines from the tumor cells with corresponding syndromes (e.g. gastrin/Zollinger-Ellison syndrome or serotonin/carcinoid syndrome). In patients with non-functional tumors, symptoms depend on tumor load and the location of the metastases (i.e. non-specific abdominal pain, weight loss, etc.). Due to these non-specific clinical features, initial diagnosis of liver metastases from non-functioning NET may be an incidental finding (e.g. on ultrasound study).

Macroscopically, three different patterns of liver infiltration by metastases have to be differentiated, since they have an impact on the therapeutic approach [32] (fig. 1).

(A) Liver metastases confined to one liver lobe or limited to two adjacent segments can be resected by a standard anatomical resection. This 'simple pattern' can be found in 20–25% of the cases.

(B) Liver metastases with a 'complex pattern', i.e. with one lobe primarily affected but with smaller satellites contralaterally occur in 10–15% of the cases and can still be handled surgically, including ablative approaches.

(C) Diffuse, multifocal liver metastases are found in 60–70% of the cases and should not be treated surgically.

Liver metastases may be associated with or without extrahepatic metastases including lymph nodes, peritoneal cavity, lung, bone and rare other metastatic disease sites (e.g. brain, heart, ovaries) [33–35]. Patients may be asymptomatic or present with leading symptoms such as bone pain when bone metastases are present or with headaches in case of brain metastases. For management of distant metastases, see Consensus Guidelines on rare metastases.

Diagnostic Work-Up

The initial diagnostic approach in patients with liver metastases includes histological examination of the me-

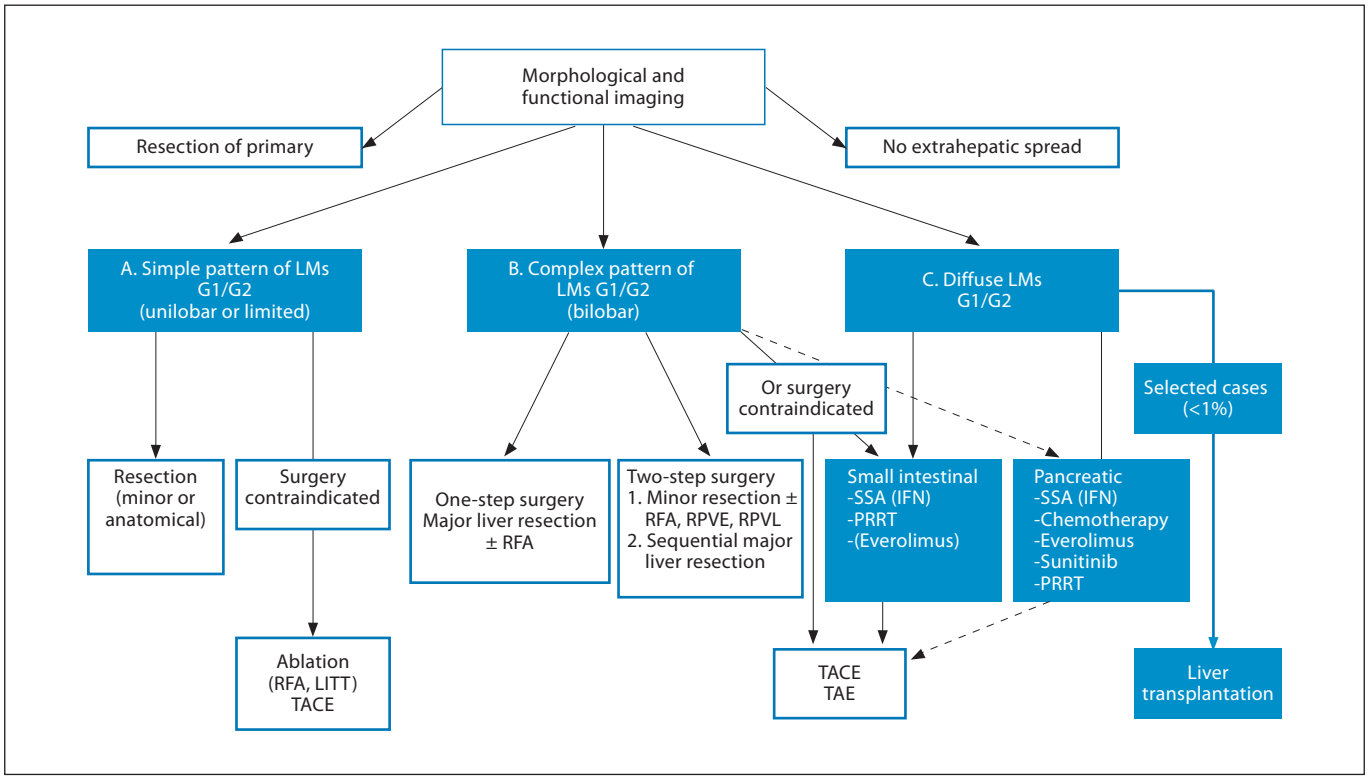

Fig. 1. Treatment approach to liver metastases without extrahepatic spread. The first line of therapy in limited unilobar and complex liver disease without extrahepatic spread is surgical resection with or without local ablative techniques in the absence of progression assessed by reliable imaging in tumor follow-up before surgery. Patients with diffuse liver disease, Ki67 >10–15% (G2) (there is no clearly defined Ki67 cutoff value) and those who are poor surgical candidates, may be treated with somatostatin analogs/IFN-α, or chemotherapy, molecular targeted therapy (sunitinib or everolimus), PRRT or TACE/TAE depending on primary tumor site and individual conditions. In highly selected candidates with diffuse metastases, liver transplantation may be an option. LMs = Liver metastasis; RFA = radiofrequency ablation; RPVE = right portal vein embolization; RPVL = right portal vein ligation; LITT = laser-induced thermotherapy; TACE = transcatheter arterial chemoembolization; TAE = transcatheter arterial embolization.

tastases, which is always required prior to planning therapeutic decision unless there is a histological report available from the primary tumor. It can also be considered to perform repetitive liver biopsies to reassess the prognosis if the disease course changes significantly.

The following investigations are required: (a) pathology analysis by conventional histology and immunohistochemistry; (b) assessment of the primary tumor and the extent of extrahepatic spread by imaging according to the above-mentioned patterns of hepatic metastases, and (c) biochemical assessment of functionality and general tumor markers including the search for inherited syndromes when appropriate.

(a) Pathology analysis should include conventional histology, immunohistochemistry for general neuroendocrine markers (i.e. synaptophysin and CgA and determination of the proliferative activity by using Ki67 (MIB-1) antibodies and/or counting mitoses per 10 high-power fields [36, 37]. The Ki67 (MIB-1) index serves as the basis for grading of the tumors as G1 (≤2%), G2 (3–20%) or G3 (>20%) [4]. In the pathology report, information has to be provided on differentiation, number, size, grading and resection margins of liver metastases. *For known primaries*, immunohistochemical analysis of specific hormones and/or monoamines are optional to verify the production of a hormone/monoamine at the cellular level [37]. Where somatostatin receptor scintigraphy (SRS) is not available, assessment of SSTR-2A may be considered and optionally in small SRS-negative tumors. In patients with *multiple endocrine neoplasia type 1* (MEN-1), analysis of primary specific hormones may verify the site of the primary tumor and the functional activity (e.g. gastrin, insulin,

glucagon) [38–40]. *For NEN with unknown primary (CUP syndrome),* analysis of hormones, monoamines and transcription factors may provide clues to the site of the primary tumor (i.e. TTF-1 – lung or medullary thyroid carcinoma, CDX2 – intestinal, serotonin – ileum, islet-1 – pancreas, PP/glucagon – pancreas, gastrin/somatostatin – duodenum or pancreas) [41–43].

(b) Tumor staging in poorly differentiated neuroendocrine carcinomas (NEC G3) should include computed tomography (CT) of the chest-abdomen-pelvis. In well-differentiated neuroendocrine tumors (NET G1/G2), an additional SRS is required. In case of CUP syndrome, a single photon emission computed tomography (SPECT)-SRS and triphasic CT of the chest, abdomen and pelvis (CT/SPECT) should be performed [44, 45] or, if available, a high-resolution three-phase CT with positron emission tomography (PET) using a ^{68}Ga-SSA (^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE or ^{68}Ga-DOTANOC) (PET/CT-SRS). If SRS was used first-line and failed to detect the primary tumor, it may be considered to perform PET/CT using a ^{68}Ga-SSA in addition if it is expected to be of consequence for the choice of therapy or the overall disease management (e.g. curative resection, liver transplantation). PET/CT using a ^{68}Ga-SSA, such as DOTATOC, may help to identify the primary tumor [46] and is a reliable method for the early detection of bone metastases in patients with NET. In contrast, conventional bone scintigraphy and CT are less accurate [47]. For detection of small pancreatic NET (including MEN-1), endoscopic ultrasonography (EUS) seems superior to PET/CT-SRS [48]. In general, PET should be replaced by PET/CT, and depending on availability and local legislation and reimbursement, conventional SRS may be replaced by PET/CT using a ^{68}Ga-SSA, such as DOTATOC [49–51]. ^{18}F-DOPA PET/CT or 5-HTP-PET/CT are promising diagnostic tools [52, 53], and may be considered if available and if SRS is negative. However, its use in the standard work-up cannot be suggested at this time. Although recent studies indicate a prognostic value of FDG-PET in well-differentiated NET (NET G2) [54], it is not recommended as a routine imaging method either and further studies are needed to support its role as a prognostic tool. In special situations, however, e.g. if liver transplantation is considered an FDG-PET/CT can be considered in NET G2.

Investigation of the large bowel may be useful by means of colonoscopy, including ileoscopy, especially in case of CUP syndrome. In a retrospective analysis of 123 metastatic NET patients, colonoscopy revealed the primary in almost half of the cases in the small or large intestine [55]. If the primary tumor is suspected in the small intestine, double balloon enteroscopy or video capsule endoscopy may be performed if available and if considered of impact on the therapeutic management. If the CT study of liver metastases is inconclusive, T_2-weighted thin-slice dynamic Gd-enhanced magnetic resonance imaging (MRI), or, if available, a contrast-enhanced ultrasonography should be performed. MRI is considered superior to CT in the detection and follow-up of liver metastases (see Consensus Guidelines on standards of care) [56] and is a preferable choice in clinical trials. The imaging report should include segmental information on the distribution of liver metastases. Although there are no standardized imaging techniques to reliably measure liver tumor burden, it can be considered to estimate the percentage of liver tumor involvement by an experienced radiologist in comparable manner to the PROMID trial [14].

(c) The minimal biochemical work-up for metastases from NET includes circulating CgA and determination of a specific marker to assess functionality, such as urinary 5-HIAA in case of carcinoid syndrome. Additional assessment of insulin, C-peptide (proinsulin), gastrin, pancreatic polypeptide, vasoactive intestinal polypeptide, glucagon and calcitonin should depend on the tumor functional status, clinical symptoms, and histological features and has been dealt with elsewhere [38, 39, 57, 58].

Minimal Consensus Statement on Clinical Presentation and Diagnosis

The clinical presentation depends on the functionality of the tumor. The majority of NEN are non-functioning and discovered incidentally or due to unspecific symptoms. In the pathology report, information has to be provided on differentiation, number, size, proliferative activity and resection margins of liver metastases. Histological examination (including Ki67 and mitotic index determination) of the metastases is essential for planning the course of treatment. Immunohistochemistry with CgA and synaptophysin should be performed. The minimal biochemical work-up includes circulating CgA and in the case of suspected clinical syndrome determination of a specific marker to assess functionality, such as urinary 5-HIAA in case of carcinoid syndrome. Tumor staging in NEC G3 requires a chest-abdomen-pelvis CT and occasionally SRS. In NET G1-G2, a SPECT/CT-SRS or PET/CT using a ^{68}Ga-SSA or MRI and somatostatin receptor imaging (SRI) is recommended for staging. Resectability of liver metastases may be evaluated by MRI and/or CT imaging.

Surgical Therapy

Resection

A prerequisite prior to undergoing surgery in patients with liver metastases is the assurance that they are in fact well-differentiated (NET G1/G2) lesions. Surgery is generally proposed in curative intent to all patients with operable well-differentiated metastases from NET regardless of the site of origin (foregut, midgut, hindgut) although resection of metastases with hindgut origin is rare since these tumors are in general non-functional and extrahepatic metastases are frequent. The benefits of surgical resection of liver metastases have been demonstrated in terms of overall survival and quality of life. Complete resection (R0/R1) for both mid- and hindgut tumors is associated with better long-term survival in all series [59–62], survival rates of 60–80% at 5 years may be achieved. In comparison, in patients whose liver metastases are not resected a survival rate of only 30% is reported [19, 63]. However, preselection of patients with a better performance status or less advanced disease seems likely to affect the outcome of surgery, and prospective trials are lacking. Resection is associated with a low mortality rate (0–5%) and an acceptable morbidity (close to 30%). It can be of particular benefit in alleviation of symptoms related to hypersecretion of serotonin or of other mediators of functioning tumors. In a study of 170 patients, 95% of patients with specific symptoms at the time of surgery experienced improvement afterward [64]. If palliative surgery of liver metastases is attempted, the presence of functionality is a major component for decision-making. In NET associated with endocrine syndromes debulking surgery is attempted whenever feasible. Incomplete debulking surgery (R2) has limited indications, but it may improve the quality of life in selected patients for whom medical treatment has failed, especially in functioning tumors. Improvement of specific symptoms after surgery may be long-lasting with a median duration of 19.3–45.5 months [62, 64]. Debulking procedures include resection of liver metastases, primary tumor and lymph nodes, but also ablative therapies that remove >90% of the tumor volume [18, 64, 65]. It is still a matter of debate, which percentage of tumor burden should be resectable to achieve a benefit with respect to syndrome control and improvement of outcome. Prospective clinical trials are necessary to better define requirements and benefits of debulking surgery. The additional use of locoregional procedures may be useful to achieve better syndrome control.

One of the crucial factors after resection is the high rate of recurrence after a median time of 16–20 months, and the majority will have recurrent disease at 5 years [59, 66]. Recurrence can be either hepatic and/or extrahepatic. Time of recurrence depends mainly on the initial completeness of liver resection and requires pre- and intraoperative assessment of small liver metastases using the most sensitive available imaging techniques (e.g. MRI with Gd-EOB-DTPA). If liver surgery with 'curative intent' is intended, liver metastases should be highly differentiated (NET G1-G2) and absence of extrahepatic metastases and/or diffuse or unresectable peritoneal carcinomatosis should be confirmed by high-resolution CT and SPECT/CT-SRS or PET/CT using a ^{68}Ga-SSA. In patients at risk for development of carcinoid heart disease, it is of importance to exclude right heart insufficiency. If heart surgery is also required, it should be undertaken 3 months prior to liver surgery due to the need for anticoagulants after valvular replacement [67] and to avoid cardiovascular comorbidity during abdominal surgery. Mortality related to surgery should be less than 5%. The primary tumor, if not resected previously, is usually also deemed resectable. The type of surgical resection is related to the patient's general condition, the number and location of liver metastases, the complexity of the liver resection, and the estimation of the future remnant liver parenchyma volume. In this regard, specialized surgery can safely remove 65–70% of the whole liver volume (in patients with non-injured liver parenchyma) [68, 69]. In all cases in which the patients have carcinoid syndrome, specific perioperative treatment with SSA is indicated to prevent intra- and postoperative carcinoid crisis [57, 70].

The effectiveness of the resection of liver metastases depends on the operative techniques employed as well as the expertise and skills of the hepatobiliary surgeon. Intraoperative ultrasonography is essential in defining the extent of any known lesions and to detect smaller lesions occulted at preoperative diagnosis. The presence and extent of steatosis must also be assessed in order to correctly estimate the amount of liver that may be removed without compromising liver function. Several techniques of liver surgery, either lobectomy with prior ligation/embolization of the portal vein to induce hypertrophy of the remaining liver lobe or combination of surgical resection and the use of local ablative therapies or repetitive hepatic surgery, are applied in synchronous and metachronous liver metastases and described in detail elsewhere [32].

In selected patients, liver resection can be proposed after down-staging of liver disease in a predefined multi-

disciplinary strategy [71]. For non-resectable liver metastases, if growth is controlled, the resection of the primary tumor may be recommended to avoid local complications such as intestinal occlusion, mesenteric retraction, and hemorrhage. If surgery is indicated, a cholecystectomy may be considered to prevent ischemic complications of the gallbladder subsequent to (chemo)embolization. Gallstones are less frequently observed with SSA therapy than formerly expected, thus preventive cholecystectomy may not necessarily be required.

The use of adjuvant medical therapy after either R0 or R1 resection cannot be recommended in the absence of clinical data supporting its use. In a single small trial of well-differentiated digestive NET, the use of streptozotocin-based chemotherapy in an adjuvant setting in comparison to observation was not associated with a survival benefit [72].

Minimal Consensus Statement on Surgical Resection

Surgical resection in curative intent remains the gold standard in the treatment of liver metastases, achieving a survival rate of 60–80% at 5 years with low mortality (0–5%) and acceptable morbidity (close to 30%). The minimal requirements for resection with 'curative intent' are the following: (1) resectable G1-G2 liver disease with acceptable morbidity and <5% mortality, (2) absence of right heart insufficiency, (3) absence of unresectable lymph node and extra-abdominal metastases, and (4) absence of diffuse or unresectable peritoneal carcinomatosis. Resection of metastases of NEC G3 is in general not recommended, but may be considered in individual cases with isolated resectable metastases. In planning the operation, care should be taken to assess the amount and quality of the postoperative remnant liver parenchyma using the most sensitive imaging methods available. In both synchronous and metachronous tumors, one- and two-step procedures may be undertaken, depending upon whether the liver disease is unilobar or complex. Debulking resections, with or without other locoregional or ablative procedures, can exceptionally be justified in palliative situations; however, removal of approximately 90% of the tumor volume is recommended (lower percentage particularly in refractory functioning NET may be considered). Prospective clinical trials are necessary to define this indication. If the primary tumor is still present, removal of the primary is recommended when feasible, in a one- or two-step surgical approach. In the absence of data, adjuvant therapy is not recommended in R0/R1 resection.

Liver Transplantation

Liver transplantation in patients with liver metastases of NET has proved effective for selected patients for whom standard surgical and medical therapies have failed. With the exception of hepatocellular carcinoma, NET liver metastases are almost the only indication that justifies liver transplantation as a viable therapy in malignant disease [73–75]. The potential benefit of liver transplantation in patients with malignant NET needs to be weighed, however, against issues of perioperative morbidity and the ethical distribution of donor organs. While the main indication for liver transplantation in NET patients is hormonal symptoms refractory to surgical or any other therapy, patients with non-functioning tumors and widespread liver disease may occasionally also be liver transplant candidates. Patients with NET G1 seem to be the best candidates for liver transplantation [76]. There is, however, no clear cut-off value for Ki67/MIB-1 for recommendation of liver transplantation. Based on the results of the French multicenter trial and on expert opinion, a Ki67 of 10% is probably a cut-off value that should not be exceeded [77, 78]. Worse prognostic factors are hepatomegaly, and primary tumors of the pancreas compared to small intestinal (carcinoid) tumors [78]. It has been proposed that a patient age of less than 50 years is of favorable prognostic value. The importance of high postoperative mortality in patients with extended abdominal surgery in addition to the liver transplant has also been noted. Patients who underwent Whipple's operation had a 5-year survival rate of only 31% [79]. There is no consensus reached to adhere to the criteria published by Mazzaferro et al. [77] for selection of patients with NET for liver transplantation. Therefore, judgments regarding transplant therapy remain based on limited evidence. Nonetheless, the very small percentage of tumor-free patients after 5 years reinforces the impression that liver transplant is undertaken with palliation as the realistic goal. Liver transplantation with intent to cure remains the exception.

At least 6 months of prior observation of tumor growth behavior are required to rule out aggressive behavior or microscopic extrahepatic disease before transplantation. The exclusion of extrahepatic metastases needs to be guaranteed prior to transplantation, and should be accomplished by an extensive work-up, including SPECT/CT-SRS and preferentially, but also if SPECT/CT-SRS does not show any extrahepatic disease, PET/CT using a ^{68}Ga-SSA, and in special situations FDG-PET/CT (e.g. in NET G2) or alternative tracers (5-HTP, ^{18}F-DOPA) may be required. Even staging laparotomy or intraoperative staging is recommended in some cases [75, 80].

Minimal Consensus Statement on Liver Transplantation

In patients who suffer from life-threatening hormonal disturbances refractory to medical therapy or patients with non-func-

tioning tumors with diffuse unresectable liver metastases refractory to all other available treatments, liver transplantation may be a possible therapy option. Minimal requirements for consideration of liver transplantation are the following criteria: mortality should be <10%, absence of extrahepatic disease as determined by PET/CT, primary tumor removed prior to transplantation, well-differentiated NET (NET G1, G2). Patients less than 50 years old who are free of extrahepatic tumor and have low Ki67 are those who are most likely to benefit from liver transplantation. However, a long-term disease-free survival by transplantation will be an exceptional event even in this highly selected subgroup.

Local Ablative and Locoregional Techniques

There are no randomized clinical trials comparing efficacy of locoregional therapies and palliative liver surgery or medical treatment [81]. The choice of the ablative or locoregional procedure (such as radiofrequency ablation, laser-induced thermotherapy or selective hepatic transcatheter arterial embolization (TAE) or chemoembolization (TACE), selective internal radiotherapy) depends on the local expertise, extension (number and size of lesions) and location of liver involvement. These methods are used in functioning and non-functioning tumors to reduce liver tumor burden. Locoregional therapies may be used early to prolong time to medical treatment (e.g. with SSA), but most frequently are used in combination with SSA, particularly in functioning NET. If bulky disease is present, locoregional therapy is indicated early also in non-functioning tumors, and is useful for downstaging. There are currently no data favoring early use of locoregional therapies depending on tumor grading (G1/G2). Locoregional therapies are more frequently used in midgut NET compared to other sites, since alternative treatment options are limited in this type of tumor. In patients with functioning tumors, locoregional therapies may be considered in the presence of extrahepatic disease if the liver is major site of the disease. In some conditions, systemic medical therapies or PRRT are used preferentially compared to locoregional approaches, e.g., if extrahepatic tumor load is higher than hepatic tumor burden, and if pancreas is the primary tumor site.

Radiofrequency Ablation

The use of radiofrequency ablation (RFA) has been shown to be effective in both relieving the symptoms of NET liver metastases and in achieving local control of the metastases. RFA has become the preferred local ablative therapy in most centers, achieving reduction of tumor mass in functioning and non-functioning metastases. Both percutaneous and laparoscopic applications of RFA are available, depending upon the location and extent of metastatic spread [82, 83]. The combination of resection and RFA provides the opportunity to achieve complete tumor removal [84, 85]. The number of studies investigating RFA treatment of NET liver metastases is still limited. In the largest study to date, 73 patients with foregut (n = 6) or midgut carcinoids (n = 37), endocrine pancreatic tumors (n = 28), and with NET of unknown origin (n = 2) were studied. Symptom improvement was noted in 12 of 17 (70.6%) patients with carcinoid syndrome, and this was associated in 75% of the patients with a reduction of 5-HIAA and CgA by at least 50%. Significant decrease of biochemical markers was also achieved in 4 of 8 patients with functioning pancreatic NET [86]. In another study including 34 patients with a total number of 234 NET metastases, 80% of the patients had complete or significant relief from their symptoms, lasting for an average of 10 months, and 41% of the treated patients showed no evidence of progression [83]. In a prospective study of 63 patients, 70% had significant or complete symptom relief, and duration of symptom control was 11 $\pm$ 2.3 months [87]. The procedure was safe with a perioperative morbidity of 5% and no 30-day mortality.

The probability of full eradication of a lesion decreases with its size and a tumor >5 cm is considered unsuitable for RFA. Preferably tumors <3 cm should be treated with RFA in combination with resection [88], and the number of tumor lesions should be limited.

Laser-Induced Thermotherapy and Other Techniques

Laser-induced thermotherapy (LITT) has been used to a limited extent to eradicate liver metastases from endocrine tumors. The range of effect can be more precisely controlled than with RFA [89], and larger tumors may be successfully treated up to 7 cm in size with multiple fibers [90], but its widespread use is limited and it has been abandoned in favor of RFA in most centers. Similarly, cryotherapy and ethanol injection have been abandoned in favor of other techniques. For details on further studies and techniques, see ENETS Consensus Guidelines 2008 [32].

Embolization and Chemoembolization

Selective hepatic TAE or TACE with hepatic artery occlusion can be applied in the treatment of liver metastases from all types of NET G1/G2. More data are available using this method for liver metastases of midgut origin than in foregut or hindgut tumors. Selective embolization of peripheral arteries induces temporary, but com-

plete ischemia. The procedure can be performed repeatedly. For TACE, the cytotoxic agent most often used is doxorubicin or streptozotocin [91–93]. The latter should be used under general anesthesia due to pain induced at injection. TACE or TAE alone can be used if surgery is not feasible for tumor reduction in functioning and nonfunctioning NET. Complete or partial responses for symptoms, tumor markers and imaging occurred in 73–100, 57–91 and 33–50% of the patients, respectively. The duration of symptomatic response varied between 14 and 22 months [91, 93–96]. The 5-year survival rates from several studies using TACE were 50–83%, and similar outcomes were reported for TAE with 5-year survival rates between 40 and 67% [96]. Whether survival is prolonged following TACE/TAE has yet to be demonstrated. Mortality (0–3.3%) of the procedure is low in experienced hands [91, 93–95]. As significant morbidity may result from this procedure, TACE should be performed only in experienced centers. Minor side effects such as nausea and vomiting (50–70%), right upper quadrant pain (50–60%), fever (30–60%), and elevation of transaminases (100%) are common [97]. The postembolization syndrome is often observed. Major side effects include: gallbladder necrosis, hepatorenal syndrome, pancreatitis, liver abscess, and formation of aneurysms. The procedure is contraindicated in patients with complete portal vein thrombosis and poor liver function [65, 91, 93, 95, 98]. Whipple procedure is contraindication for TACE/TAE since it increases the risk of morbidity (e.g. liver abscess) and mortality. Other contraindications for TACE/TAE include hepatopulmonary shunt and severe comorbidities (renal, cardiac, etc.). In patients in whom liver transplantation may subsequently be considered, multiple TAE or TACE may render the vascular reconstruction at transplantation more difficult due to arterial thrombosis.

In the absence of comparative trials [81] it remains unclear whether TACE is preferable to TAE alone; also the timing of sequential (chemo)embolizations and choice of cytotoxic agents is still unclear (e.g. doxorubicin vs. streptozotocin).

Selective Internal Radiation Therapy

Selective internal radiation therapy (SIRT) is still considered investigational. Recent studies with ^{90}Y microspheres in altogether ~200 patients indicate objective response rates of 50–60% in patients with liver metastases from NET. Most data, however, are retrospective and derived from small phase II trials [23, 99, 100]. Only one prospective study (n = 34) addresses syndrome control (55% response). One death from liver failure is reported in this series when used with concomitant infusional 5-fluorouracil (5-FU) [101]. For all locoregional therapies, randomized clinical trials comparing efficacy and outcome of different procedures with each other or with liver resection are needed.

Minimal Consensus Statement on Local Ablative and Locoregional Techniques

Ablative Techniques

Ablative techniques such as RFA can be used effectively as anti-tumor treatment and in relieving symptoms in patients with NET liver metastases, either as a sole therapy or in combination with surgery. While surgery remains the therapy of choice in limited tumor disease, RFA may be employed for palliation in order to avoid a major surgical procedure and it can also effectively supplement a surgical resection. In patients with tumors >5 cm in diameter or near vital structures, RFA or other ablative techniques are not a suitable single therapy.

Embolization and Chemoembolization

Selective hepatic TAE or TACE may be used to treat liver metastases in patients where surgery is not feasible regardless of the origin of the primary tumor. These modalities are effective in the control of symptoms and tumor growth and result in significant decrease in biochemical markers with objective tumor responses in about half of the patients. No current evidence exists that TACE is superior to TAE. Cytotoxics used include either doxorubicin or streptozotocin in mixtures with Lipiodol. Because of its potential morbidity, TAE or TACE should be performed in experienced centers; a common side effect is postembolization syndrome. Major side effects are rare and the procedure is contraindicated in case of complete portal vein thrombosis, hepatic insufficiency and Whipple procedure. Selective internal radiotherapy is still an investigational method in the treatment of liver metastases of NET.

Medical Therapy

Antisecretory Treatment

The use of SSA is standard therapy in functioning NET of any site. Interferon-α (IFN) may also be considered for symptom control in some patients, e.g. if SSA are not well tolerated. IFN is frequently used as second-line therapy due to its less favorable toxicity profile, but has additional value as add-on therapy in patients with carcinoid syndrome that is not controlled with SSA alone [57, 70]. Careful control of symptoms in relation to hormonal hypersecretion should be ensured prior to specific anti-tumoral treatment measures (surgical or locoregional) in patients with liver and/or other distant metastases. In 70–90%, SSA (octreotide, lanreotide) are efficacious in the treatment of the carcinoid syndrome (e.g. in liver me-

tastases from serotonin-secreting small intestinal NET (midgut carcinoids)) or other clinical syndromes related to hypersecretion of rare pancreatic NET such as VIPoma or glucagonoma. Octreotide and lanreotide are considered equally effective for syndrome control [57, 102] and are approved for antisecretory treatment in Europe. A standard dose of long-acting formulations is octreotide 20–30 mg/4 weeks i.m. and lanreotide autogel 90–120 mg/4 weeks s.c. Doses are adapted to the individual needs and depend on tumor burden. Specific details related to the use of these analogues have been dealt with in a consensus manner elsewhere [57]. Preventive SSA therapy prior to surgery or use of locoregional therapies (delivered as either s.c. bolus and/or an i.v. 50–100 μg/h perfusion) is usually effective [70]. IFN-α is used at a dose of 3–5 million units subcutaneously three times per week [103]. Long-acting pegylated IFN is an alternative formulation, administered in doses from 80–150 μg once weekly. There are no comparative data of both regimens, and pegylated IFN is not approved for its use in NET yet. The use of pegylated IFN may, however, be considered for better tolerability [104].

Other specific therapies are required according to the primary and related hypersecretion [38, 39, 58]. In gastrinoma, the use of high dosages of proton pump inhibitors (standard dose × 2–10 per day) is standard and first-line therapy (see the chapter on gastrinoma). In the treatment of metastatic insulinoma, a recent advance is the use of the mTOR inhibitor, everolimus. Current medical treatment includes SSA and diazoxide. However, only 50% of the patients respond to SSA and efficacy of diazoxide is transient and associated with side effects, particularly in the elderly patients (renal dysfunction, edema) [105]. Although the number of reported patients is still low, symptom control was achieved in patients with heavily pretreated and refractory hypoglycemia syndrome [106, 107]. In a report of 4 patients, everolimus treatment lead to normalization of blood glucose and withdrawal of glucose infusion/tablets or enteral feeding. Treatment was associated with partial tumor remissions in 2 patients lasting for 16 and 29 months, and stable disease for at least 6 months in the other 2 patients. Everolimus is recommended in metastatic insulinoma when resistant to the standard medical management.

The use of PRRT is considered an alternative therapeutic option for syndrome control. In 3 of 5 patients treated with ^{177}Lu-DOTATATE, partial tumor remissions were achieved [108]. Individual cases were successfully treated with SIRT [109, 110].

Minimal Consensus Statement on Antisecretory Treatment

Symptoms from hormonal hypersecretion are frequent in functional tumors with liver metastases. Control of these symptoms is often urgent and SSA (with or without IFN) are highly effective. Locoregional therapies may be required to achieve symptomatic relief. Prophylaxis against carcinoid crisis should be performed prior to surgical or locoregional interventions using adequate doses of SSA (usually with bolus subcutaneous therapy *and* intravenously). Everolimus and PRRT are effective in treatment of hypoglycemia in metastatic insulinoma and are recommended after failure to standard treatment.

Antiproliferative Treatment

Somatostatin Analogues

The anti-tumor efficacy of SSA appears weak with respect to objective tumor responses that occur in <10%, even if used at high dosages [102, 111–113]. However, disease stabilization of up to 50–60% has been reported. In a prospective randomized placebo-controlled trial of octreotide LAR in midgut NET (PROMID trial) the antiproliferative efficacy of octreotide LAR has been confirmed. Median time to tumor progression was 14.3 months with octreotide LAR and 6.0 months with placebo [14]. Based on these results, the use of SSA, especially octreotide LAR, is recommended for antiproliferative purposes in functioning and non-functioning midgut tumors. SSA are the recommended first-line therapy in non-functioning, progressive, small intestinal G1 NET. Therapy may be considered in therapy-naive, metastatic patients without a prior observation period of spontaneous tumor growth. However, it remains unclear if there is an individual benefit with respect to improved prognosis and increased survival if treatment is started early after initial diagnosis compared to a 'watch-and-wait' strategy until tumor progression occurs. There are no evidence-based data with respect to survival that support the early use of SSA. In addition, the extent of the disease (liver tumor burden) and in the case of prior observation of tumor growth, the tumor growth rate should be taken into account for the choice of the appropriate therapy. A higher tumor burden may require early additional or alternative therapies, and more aggressive tumor growth may necessitate an alternative treatment approach. Grading is mostly G1 in midgut NET, and there are not sufficient data on the efficacy of SSA in NET G2. The determination of a cut-off value for recommendation of SSA is still controversially discussed. In individual cases of midgut NET G2, alternative therapies to SSA may be considered. The recommended dosage for antiproliferative pur-

poses is octreotide LAR 30 mg i.m. per month as it was used in the PROMID trial. There is a higher level of evidence for the use of octreotide compared to lanreotide in midgut NET, since placebo-controlled data for lanreotide are not yet available and dose selection is not validated for lanreotide either. A placebo-controlled trial of lanreotide autogel 120 mg/month in non-functioning enteropancreatic NET is ongoing and will provide more evidence on the antiproliferative efficacy of lanreotide, especially in pancreatic NET in the future.

Octreotide and lanreotide may be of value also in other subgroups of patients with slowly progressive low proliferative NET (G1) of pancreatic and gastroduodenal origin and its use is supported by literature data on retrospective and non-randomized prospective trials in more than 500 patients [102, 111, 112, 114]. In patients with gastric NET, SSA have been shown to exert antiproliferative effects in man [115, 116], however, data is not available in cases of liver metastases (see chapter gastric NET). There are no data on the use of SSA in NET with primary tumor origin of the colon and rectum. Nevertheless, according to expert opinion, SSA may be considered a therapeutic option in these cases, if tumors are classified as NET G1.

SSA can also be considered if SRI is negative (<10% of the cases) or is not available based on the experience of some centers with beneficial effects in these subgroups of patients. However, in patients with high tumor load a positive SRS is required to choose SSA for antiproliferative purposes. The role of immunohistochemical determination of SSTR2A in SRS-negative cases needs to be further explored, especially if the tumor lesion size does not reach the threshold for detection by SRS.

In contrast, in metastatic NEC G3, regardless of the site of origin, SSA treatment is not recommended. There is also no indication for adjuvant therapy with SSA in NET G1/G2 irrespective of primary tumor origin and potential microscopic metastases in up to 50% of the cases. It is also not recommended to use SSA instead of resection of liver metastases and/or locoregional therapies if curative treatment seems feasible.

Interferon-α

Tumor remissions occur rarely with IFN (~11%) [103], however disease stabilization is observed in 40–50% of the patients. IFN-α is equally effective in functioning and non-functioning tumors with respect to tumor growth control. Two prospective randomized trials in metastatic gastroenteropancreatic NET have shown that SSA, IFN or the combination of both have comparable antiproliferative effects when used after prior disease progression [111, 112]. Although the number of patients included in these trials is limited, based on these results, the early combination use of SSA and IFN for antiproliferative purposes is not recommended. Data from a recent French multicenter trial in advanced NET provide a progression-free survival (PFS) of 14.1 months in a cohort of 32 patients where prior disease progression was documented [117]. However, this trial has some limitations: a heterogeneous patient population (53% midgut, 15% foregut, 3% hindgut NET, 22% CUP), an underpowered trial and a non-significant p value in comparison to chemotherapy arm (PFS 5.5 months). Patients with low proliferating (G1), slowly progressive NET or patients with SRS-negative tumors are considered candidates for IFN therapy. IFN should be used with caution if hepatic tumor burden is high. The treatment is associated with more frequent side effects compared to SSA [103, 104, 111, 112, 117]. The IFN dose should be titrated individually by side effects and leukocyte count (~3,000/μl).

Systemic Chemotherapy

Chemotherapy is recommended in pancreatic NET, metastatic foregut NET G2, and in NEC G3 of any site. So far, results with systemic chemotherapy are poor in patients with well-differentiated metastatic midgut NET with response rates of ~15% in the largest published study [118]. Therefore, these patients (G1/G2 NET) should in general not receive current cytotoxic regimens. Chemotherapy might be an option exclusively in advanced intestinal NET after failure to previous treatment lines. Results from recent phase II and non-randomized trials with either metronomic 5-FU in combination with octreotide, or capecitabine and oxaliplatin in well-differentiated NET including those of midgut origin [119, 120] are promising, but limited, and still considered investigational. Their value in the management of advanced midgut NET remains unclear since mixed patient populations were investigated in these studies. Limited data are available in relation to systemic chemotherapy in patients with liver metastases from hindgut NET G2. Such treatment can be proposed in progressive disease although the choice of agents needs to be defined in clinical trials.

Systemic cytotoxics are indicated in patients with inoperable progressive liver metastases from G1-G2 pancreatic NET using combinations of streptozotocin and 5-FU and/or doxorubicin with objective response rates in the order of 35–40% [24, 121, 122]. These response rates are considerably lower than the 69% reported by Moertel et al. [123] in 1992. There is long-standing experience

with streptozotocin-based chemotherapy since the 1980s [124]. With respect to response rates, three drug regimens including either cisplatin [125] or doxorubicin [24] seem not to be superior to two drug regimens with streptozotocin and 5-FU or streptozotocin and doxorubicin [121–123]. From a single retrospective trial (n = 30 patients), temozolomide-based chemotherapy is promising in pancreatic NET if combined with capecitabine [126]. Given the high partial remission rate of 70% reported for this drug combination as a first-line chemotherapy together with a favorable median PFS of 18 months, further investigation of this chemotherapy in prospective comparative trials is warranted. Efficacy is supported by other trials [127, 128]. Despite these limited data on temozolomide, based on its effectiveness in daily clinical use, however, the use of temozolomide is recommended by the experts. Temozolomide may be used with or without capecitabine.

Chemotherapy may be the first-line therapy in pancreatic NET, if there are tumor-related local symptoms, in the case of high liver tumor burden, or tumor progression, in foregut NET G2 and always in NEC G3. Although retrospective data indicate increasing sensitivity to chemotherapy with increasing proliferation index [125], these data are still limited due to retrospective assessment in mixed patient populations. There is currently no clear cut-off value for Ki67 for recommendation of chemotherapy, and bias by sampling times and techniques may exist. Chemotherapy may also be considered in pancreatic NET G1 in the case of tumor progression. The treatment is in general well tolerated [117, 118]. Nausea, well controlled by antiemetics, and renal toxicity may occur, but is mostly mild to moderate with creatinine elevation in ~20% and proteinuria in 40% as recently reported in a prospective trial [117].

In cases of liver metastases involving high-grade NEC G3, regardless of the site of the primary tumor, combination chemotherapy using cisplatin/etoposide (Moertel regimen) [129] is recommended early (provided that the patient has adequate organ function and performance status). There is no established second-line therapy for poorly differentiated endocrine carcinoma. A recent retrospective study with temozolomide alone or in combination with capecitabine (± bevacizumab) in 25 patients reports a partial tumor response rate of 33% [130]. Further investigation in a prospective trial is warranted with this combination therapy. Encouraging results using either 5-FU i.v. or capecitabine orally combined with oxaliplatin or irinotecan may also be an option in the future [120, 131, 132].

In the adjuvant setting, there is only one study with streptozotocin and 5-FU after resection of liver metastases from digestive endocrine tumors compared to observation. Relapse-free survival in patients with adjuvant therapy was similar to that of the observation group or historical controls [72]. Although this was a small trial (n = 52) and patient population heterogeneous streptozotocin-based chemotherapy cannot be recommended in this indication.

Peptide Receptor Targeted Radiotherapy

Promising data evolved with regard to PRRT in the treatment of NET with liver metastases using ^{90}Y- and ^{177}Lu-labelled DOTATOC, or DOTATATE [133–136]. PRRT can be considered in both functioning and nonfunctioning NET with positive SRS, irrespective of the primary tumor site. Based upon phase II trials of various, mostly small sizes and mainly retrospective data, partial remission rates range between 0 and 37% [135–138] and are higher in pancreatic compared to midgut NET. In the prospective multicenter phase II PRRT trial using ^{90}Y-edotreotide/DOTATOC, a highly selected group of patients with refractory carcinoid syndrome developed a partial remission rate of 4% and disease stabilization rate of 70%. PFS was favorable with 16.3 months [137]. Prospective randomized trials are still lacking, but in progress. Different SSA and radionuclides are used, and their use depends on national law and local permissions.

Radionuclide therapy with either ^{90}Y- and/or ^{177}Lu-labeled SSA is most frequently used in NET. However, so far, no registrational trial exists. There are no randomized clinical studies on efficacy of both radionuclides, but ^{177}Lu-labeled SSA are considered less nephrotoxic, also applied with simultaneous renal protection by e.g. amino acids. In general, the use of PRRT is after failing first-line medical therapy. The presence of expression of sstr2 as visualized by SRI is a prerequisite for the use of PRRT; a better anti-tumor effect is reported with increasing sstr2 expression according to SRS [136]. The minimum requirements for PRRT are reported in a separate consensus guideline [138]. There are different research PRRT protocols in use with either standard dose or individualized therapy with a variable number of cycles. General practice is to use a standard dose. The distance between two cycles should at least reach 6 weeks. Tolerability is in general good, serious side effects including severe bone marrow disease (acute myelogenous leukemia, myelodysplastic syndrome; both in patients with and without prior chemotherapy), kidney failure and liver failure occur in ~3–5% of the patients [135, 136].

New Molecular Targeted Therapies

New molecular targeted therapies have been investigated in phase II and III clinical trials and include angiogenesis inhibitors, single and multiple tyrosine kinase inhibitors and novel SSA (e.g. pasireotide). The multiple tyrosine kinase inhibitor sunitinib and the mammalian target of rapamycin (mTOR) inhibitor everolimus advanced most in the field of NET and were evaluated in phase III placebo-controlled trials. Whereas tumor remissions are rare with these small molecules, disease stabilization is observed in a high proportion of patients (60–80%). Since a slow progression rate may also occur in the natural course of the disease, placebo-controlled trials are required. The primary endpoint of these trials was PFS given the low remission rates known from phase II trials.

Neuroendocrine Tumors of the Pancreas

Everolimus and sunitinib are novel treatment options in advanced pancreatic NET. The use of everolimus in pancreatic NET is supported by a large phase II trial with 160 patients and a placebo-controlled phase III trial with 410 patients. In the phase II trial, failure to at least one line of chemotherapy was required as inclusion criteria. One subgroup of the patients received prior octreotide and continued the treatment while starting everolimus therapy. A high rate of disease stabilization after prior tumor progression was accompanied by favorable PFS times of 9.7 and 16.7 months without or with concomitant octreotide, respectively [139]. In the placebo-controlled trial, a prolongation of PFS of 6.4 months was reached with everolimus compared to placebo (11.0 vs. 4.6 months). There was a consistent benefit among subgroups (including age, gender, region of origin, tumor grade, WHO performance status, prior use of either long-acting SSA or chemotherapy). The rate of tumor remissions was, however, low (5%). Everolimus had an acceptable safety profile. Most frequent side effects included stomatits (64%), rash (49%) and diarrhea (34%), and the most frequent grade 3/4 side effects were stomatitis (7%), anemia (6%) and hyperglycemia (5%) [140]. Everolimus represents a treatment option after failure of chemotherapy in pancreatic NET, but can be considered as first-line therapy in selected cases as an alternative treatment to locoregional therapies or chemotherapy. Indeed, the RADIANT-3 study included 40% therapy-naive patients, and efficacy was equally good in therapy-naive patients as in patients with previous therapies [140]. Its general, early use cannot be recommended based on the lack of long-term toxicity data in this tumor entity. In May 2011, the FDA approved everolimus (Afinitor®) for the treatment of progressive neuroendocrine tumors of pancreatic origin in patients with unresectable, locally advanced or metastatic disease. Accordingly, the European Medicines Agency adopted a positive opinion for everolimus recently.

Results from a phase III placebo-controlled trial support the efficacy of sunitinib, a multiple tyrosine kinase inhibitor that targets PDGF-R, VEGF-R, c-kit, RET and FLT-3, in progressive pancreatic NET. Sunitinib was first studied in a phase II study in 107 patients including 66 patients with pancreatic NET. The objective response rate was 16.7% in pancreatic NET and the rate of stable disease was 68% [141]. The placebo-controlled phase III study of sunitinib (37.5 mg/day on a continuous basis) in patients with progressive well-differentiated pancreatic NET recruited 171 out of 340 planned patients. The primary endpoint of the study, PFS, was superior in the sunitinib arm with 11.1 months compared to 5.5 months in the placebo arm [142]. Objective remission rate was less than 10%. The most frequent side effects included diarrhea (59%), nausea (45%), vomiting (33%), asthenia (33%) and fatigue (32%). Adverse events were rarely grade 3 or 4 and included hypertension (10%) and neutropenia (12%) as the most frequent serious side effects [142]. Sunitinib (Sutent®) has recently been approved by the FDA and EMA for the treatment of advanced and progressive well-differentiated pancreatic NET. The majority of the patients had undergone prior systemic therapy, especially systemic chemotherapy. The main indication of sunitinib is its use as a second- or third-line therapy. Similarly to everolimus, based on the lack of long-term data of this drug in NET, sunitinib should be considered as first-line therapy only in selected cases as an alternative treatment option if SSA, chemotherapy and/or locoregional therapies are not feasible or promising.

In general, small molecules, such as sunitinib or everolimus should be used after occurrence of tumor progression. In exceptional cases, such as symptomatic, bulky disease or intolerance of ongoing therapy, or if the patient is not amenable to chemotherapy or locoregional therapies, everolimus or sunitinib might be considered a first-line therapeutic option (table 1). There is no preference of grading (G1 or G2) with respect to therapeutic consideration of targeted drugs in NET. So far, most patients in clinical trials treated with everolimus or sunitinib had advanced disease. Until now, it is unclear if patients will benefit from earlier treatment. Predictors of response are expected to rationalize the therapeutic approach in the future.

Table 1. Therapeutic options and conditions for preferential use as first-line therapy

Drug	Functionality	Grading	Primary site	SSTR status	Special considerations
Octreotide	+	G1	midgut	+	low tumor burden
Lanreotide	+	G1		+	placebo-controlled data on antiproliferative activity pending
STZ+5-FU	+/–	G1-G2	pancreas		progressive in short-term[1] or high tumor burden or symptomatic
TEM/CAP	+/–	G2	pancreas		progressive in short-term[1] or high tumor burden or symptomatic; contraindication for STZ-based regimen
Everolimus	+/–	G1-G2	pancreas		insulinoma; contraindication for CTX
Sunitinib	+/–	G1-G2	pancreas		contraindication for CTX
PRRT	+/–	G1-G2	any	+	extended disease; extrahepatic disease, e.g. bone metastases (if tumor burden not too high); high uptake of tumor lesions on Octreoscan and limited disease amenable to surgery after down-staging
Cisplatin + etoposide	+/–	G3	any	+/–	all poorly differentiated NEC

CTX = Chemotherapy; STZ = streptozotocin; SSTR = somatostatin receptor.
[1] 3–6 months.

Neuroendocrine Tumors of Extrapancreatic Primaries (Carcinoids)

In the largest clinical trial available in NET of different sites (carcinoids), especially intestinal NET with a history of carcinoid syndrome (RADIANT-2), everolimus (10 mg/day orally) or placebo was administered along with octreotide LAR 30 mg every 4 weeks i.m. in both treatment arms. In this trial, 429 patients with progressive disease within 12 months prior to study entry were included. The patient population was unexpectedly heterogeneous, whereby the initially aimed study group, i.e. the midgut subgroup, represented only ~50% of the total patient population. Other primary tumor sites included lung, colon and pancreas among others but also unknown primaries. The primary endpoint of the trial, PFS, as per adjudicated central radiological review was 16.4 months with everolimus/octreotide and 11.3 months with placebo/octreotide. However, the result narrowly missed statistical significance [143] and the drug is not approved for extrapancreatic NET. The local radiological analysis, however, supports some efficacy of the drug. Given the limited treatment options for antiproliferative therapy in NET of midgut and other non-pancreatic sites, everolimus, if available, may be considered as a treatment option in progressive, functioning and non-functioning NET when other therapeutic options failed, such as SSA, IFN, PRRT and locoregional therapies. Everolimus may be used with or without concomitant SSA. There is no clear evidence that the combination therapy of everolimus and octreotide LAR is superior to monotherapy with everolimus, and therefore the combination therapy cannot be recommended in non-functioning tumors. Although side effects are in general mild and include most frequently stomatitis (62%), rash (37%) and fatigue (31%), everolimus should be used with caution since long-standing immunosuppression may represent a potential risk for the patient, and infections are reported in ~20% of the patients. Another potential side effect are pulmonary events (e.g. lung infiltrates, interstitial pneumonitis) that occurred in ~12% of the patients. Careful surveillance of the patient is required.

The multiple tyrosine kinase inhibitor sunitinib, however, cannot be recommended in NET outside of the pancreas in the absence of any trials supporting its efficacy. So far, only 41 patients with extrapancreatic NET of different sites have been treated with sunitinib within a phase II trial, more than half received concomitant octreotide. Partial tumor remissions were observed in 2% of the patients. The time to tumor progression was 10 months without required disease progression prior to sunitinib [141].

Minimal Consensus Statement on Medical Therapy

SSA and/or IFN have weak antiproliferative effects. Octreotide should be considered as first-line systemic antiproliferative treatment of patients with advanced unresectable midgut NET.

Systemic chemotherapy using combinations of streptozotocin and doxorubicin or 5-FU should be considered in patients with advanced unresectable progressive G1-G2 pancreatic NET. Cytotoxics are not considered when the primary location is in the midgut. Combinations of etoposide and cisplatin are indicated in metastatic NEC G3 regardless of the origin of the primary. PRRT may be used to treat metastases of NET G1/G2, with ^{90}Y- and/or ^{177}Lu-DOTATOC or -DOTATATE showing particular promise, but prospective randomized clinical trial results are warranted. Everolimus and sunitinib represent novel therapeutic options in patients with surgically non-resectable, pancreatic NET after progression following chemotherapy. These small molecules can only be considered as first-line therapy in selected cases. If available, everolimus may be a therapeutic option after failure of other treatments in extrapancreatic NET.

Differential Indication

Several parameters, including functionality, primary tumor site, grading, uptake on SRI, extent of liver metastases and extrahepatic disease including the presence of bone metastases have an impact on therapeutic decision-making. Therapeutic options and conditions for preferential use as first-line therapy are summarized in table 1.

SSA are first-line therapy in functioning and non-functioning NET G1 of midgut origin with diffuse liver metastases. In patients with complex bilobar pattern of liver metastases, if the disease is limited to the liver, treatment with SSA represents an alternative approach to surgery in midgut tumors. Second-line therapies in functioning NET after failure of SSA include locoregional and ablative therapies, IFN-α and PRRT. In non-functioning NET, PRRT is frequently used as a second-line therapy in the absence of any other approved antiproliferative agents. Everolimus may be a therapeutic option if available (see above). If extrahepatic disease is present, additional therapies may be required (e.g. bisphosphonates) and PRRT may be considered earlier in the therapeutic algorithm (see Consensus Guidelines for the management of rare metastases) [33, 34].

In pancreatic NET G1/G2, several therapeutic options are available. Comparative clinical trials are lacking, thus currently different therapies cannot be placed in a specific order. In pancreatic NET SSA, chemotherapy, novel molecular targeted agents (sunitinib and everolimus), and PRRT are therapeutic options. If extrahepatic spread is present in pancreatic NET, locoregional therapies are in general not indicated unless required for better syndrome control. In poorly differentiated metastatic NEC G3 of any sites, etoposide/cisplatin regimen is used.

Minimal Consensus Statement on Differential Indication

If metastases are limited to the liver, stable or slowly progressive and resectable, surgical resection is preferable to ablative therapies if the patient is amenable to surgery with low risk. Even complex patterns of metastases can often be eliminated through a combination of resection and ablation, as well as sequential intervention. If extrahepatic metastases are present as well, systemic therapies are first choice of treatment. However, interventional therapies may have significant palliative value, especially for hormone-secreting tumors. Differentiation, including grading, and localization of the primary tumor have an impact on therapeutic decision-making in distant metastatic disease with or without extrahepatic spread.

Follow-Up

Follow-up investigations should include biochemical parameters and conventional imaging. In patients with R0/R1 resected NET G1/G2 it is recommended to perform imaging every 3–6 months, in NEC G3 every 2–3 months. The same schedule is recommended in patients with non-resectable liver disease with 3-month intervals at initial diagnosis and prolongation to 6–12 months if the disease is stable, especially in NET G1. SRI either as Octreoscan or PET/CT using a ^{68}Ga-SSA should be included in the follow-up and is recommended after 18–24 months if initially positive and reliable. SRI may be considered earlier to exclude extrahepatic disease if CgA or other biomarkers are increasing, especially if conventional imaging indicates stable disease in the liver. In the case of rapid tumor progression or if imaging information is lacking, it may be needed to biopsy liver metastases again to reassess the proliferative activity.

Minimal Consensus Statement on Follow-Up

Conventional imaging (CT and/or MRI) and assessment of circulating biomarkers (CgA and specific mediator) are recommended in NET G1/G2 every 3–6 months depending on length of disease duration and tumor growth. SRI should be performed after 18–24 months unless biomarkers or clinical condition are suspicious of tumor progression necessitating earlier whole-body imaging. In NEC G3, conventional imaging is recommended every 2–3 months. If CgA is not elevated, NSE represents an alternative biomarker.

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