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Consensus Guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site

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Introduction

The goal of this manuscript is updating a more extensive review and guidelines paper published in 2012 [1]. Generally, any pertinant update pertaining to the diagnosis and staging of individual primary tumours has been provided in the relevant sections elsewhere published in theses updated guidelines reviews. More specific issues with respect to therapy of stage IV NEN disease (focusing on G1/G2 tumors) is given below. A separate guideline is provided for poorly differentiated neoplasms (NEN G3). As some new large phase III trials have been published since the previous guidelines this has indeed led to specific modifications in our approach to therapy.

Metastatic disease from NEN is very prevalent in intestinal and pancreatic NEN [2-4]. At initial diagnosis 40-50% of patients with NEN present with distant metastases, with increasing prevalence over time depending on initial disease stage. Metastases are predominantly found in the liver and/or lymph nodes. In contrast, bone metastases are reported in less than 15% of cases [5,6], however the true prevalence of bony metastases is probably underestimated since reported figures are not based on most sensitive imaging methods such as bone MRI or ^{68}Ga-DOTATOC/NOC/TATE PET/CT. Other rare disease sites include lung, brain, and peritoneum and have also been covered in guidelines [6-9].

Treatment options in metastatic disease comprise liver surgery, and/or loco-regional and ablative therapies (see Figure 1). In general, these approaches are followed, if extrahepatic disease is excluded or in functioning tumors if the major tumor burden is located in the liver. Due to the rarity of the disease prospective randomized trials are limited, and most recommendations are based on uncontrolled studies, representing expert opinions. This is especially true for surgical treatment, different loco-regional or ablative therapies (embolisation, chemoembolisation, radiofrequency ablation (RFA), selective internal radiation therapy (SIRT)), and systemic chemotherapy. Somatostatin analogs (SSA) and novel targeted drugs, such as the multiple tyrosine kinase inhibitor sunitinib and the mTOR inhibitor everolimus, are the only drugs that have been evaluated in NEN within placebo controlled trials. Based on the results of these trials, SSA, sunitinib and everolimus have been approved and registered for antiproliferative therapy in different neuroendocrine tumor (NET) subtypes excluding neuroendocrine carcinoma (NEC). Recent data from a placebo controlled trial with lanreotide (CLARINET study) in enteropancreatic NET provide novel evidence for the antiproliferative activity of SSA. Furthermore, it has recently been reported that three large randomized controlled drug trials (e.g. Everolimus vs. placebo in lung and intestinal NET and NET of unknown primary tumor, RADIANT-4; ^{177}Lu-DOTATATE vs. high dose octreotide in midgut NET, NETTER-1; Telotristat etiprate vs placebo in refractory carcinoid syndrome, TELESTAR) reached their primary endpoint [10-12]. These well constructed phase III trials in NET have an impact on the current treatment recommendations and therapeutic algorithm. In addition, there is novel information available on the use of targeted drugs from application outside of randomized clinical trials.

Given the variety of treatment options,the heterogeneity of NEN and the indivual disease complexity it is strongly recommended if not mandatory to discuss NEN patients after accurate imaging and pathology review in a multidisciplinary tumor board for appropriate therapeutic decision making , especially to exploit surgical therapy in potentially resectable NEN patients and explore loco-regional therapies upfront. Choosing antiproliferative therapies is also challenging depending on the tumor primary, its functional status, its rate of growth, grade and overall burden and the goal of individual

therapies within the patients choice and status. Variation of treatment choices will also depend on physician expertise, the complexity of the treatment center and access to novel treatments. Recommendations for preferential use of targeted drugs or chemotherapy as first-line therapy are summarized in Table 1.

This review will focus on intestinal and pancreatic NEN and it will provide a therapeutic algorithm for both subtypes. The management of typical and atypical lung NET is similar to GEP NEN taking into consideration pathological features (mitotic count, Ki-67), somatostatin receptor expression, growth rate and disease extent. Best practice recommendations for the management of typical and atypical bronchial NET is reported in a separate recently published ENETS consensus paper [13].

Therapeutic options

In NET G1 and G2 surgery with curative intent has always to be considered even if liver and/ or lymph node metastases are present (Figure 1). In non-resectable disease the following treatment options should be considered to control symptoms secondary to hypersecretion of peptide hormones/amines leading to a functional syndrome (carcinoid syndrome, diarrhoea and other symptoms related to functionally active pancreatic NEN) and/or tumor growth control. In some patients it may be necessary to combine therapies for example to suppress symptoms using SSA in addition to loco-regional therapies or other antiproliferative agents.

Loco-regional therapies. In the absence of any large comparative trials of different loco-regional or ablative therapies (bland embolization, chemoembolisation, radioembolisation, radiofrequency ablation or microwave destruction) or systemic treatment , the choice of treatment is based on individual patient features (e.g. size, distribution, number of liver lesions, vascularization, proliferative index) and local physicians expertise [14]. Loco-regional therapies should be exploited early following SSA therapy to prevent carcinoid crisis in functionally active NET (especially midgut NET with classical carcinoid syndrome) and may be an alternative option to systemic therapies in patients with non-functioning tumors if the disease is limited to the liver. Loco-regional therapies may be considered repetitively in the disease course. There is consensus that selective internal radiation therapy (SIRT) is still investigational, and that a comparative trial of SIRT to bland embolization is required, as well as more safety data on long-term tolerability of SIRT to establish this procedure for the management of NEN [14-18].

Debulking surgery. This is an alternative option to loco-regional therapies, and could be considered in patients with uncontrolled functioning tumors, esp. in patients with carcinoid syndrome, refractory insulinoma, glucagonoma or vipoma or PTH-related peptide secreting tumors. Debulking surgery may be considered in patients with non-functional tumors if the disease is not progressive over a 6 months period and patients are suffering from symptoms related to tumor burden. Although some retrospective studies indicate that surgery for liver metastasis is associated with improved survival [19-22] it remains unclear if debulking surgery is of benefit in asymptomatic patients since comparative trials to systemic therapy are lacking. Even if surgery is performed with curative intent, there is a high rate of disease recurrence within 3-5 years [4,23]. In patients with carcinoid syndrome, it is important to control hypersecretion of serotonin with SSA prior to surgery, in order to prevent carcinoid crisis.

Liver transplantation. Transplantation is generally not recommended as a treatment option in advanced NEN; it may be an option in highly selected patients with carcinoid syndrome or other functional NET, and extended liver disease, early refractory to multiple systemic treatments including SSA, IFN-alpha, loco-regional therapies and PRRT [4]. Precise preselection of patients (e.g., well differentiated NET, exclusion of extrahepatic disease by optimized staging, low serum total bilirubin) for liver transplantation may increase 5-year survival rates in patients with NET undergoing liver transplantation [24-26].

Minimal consensus statement: *Surgery with curative intent and/or loco-regional or ablative therapies should be considered at initial diagnosis and in the course of the disease as an alternative approach to systemic therapies. In patients with functioning NET, all liver directed therapies require prior initiation of SSA therapy (or other specific symptom controlling measures). Debulking surgery is indicated in selected patients with functioning NET with predominant liver disease for improved syndrome control even if liver tumor burden can be reduced by less than 90%. Liver transplantation is an option in very highly selected patients, preferably in young patients with functional syndromes demonstrating early resistance to medical therapy.*

Systemic therapy

Somatostatin analogs (SSA) and novel compounds for syndrome control. SSA are first-line therapy in functionally active NEN including tumors associated with the *carcinoid syndrome* and in *functionally active endocrine pancreatic NET* (such as vipoma, and glucagonoma). The commercially available agents octreotide and lanreotide are considered equally effective for symptom control. In general, long-acting formulations (octreotide LAR 10-30 mg im per month; lanreotide Autogel 60-120 mg deeply sc per month) are used over a medium to long-term period. Initiation of therapy with a lower dose of the long acting formulation or with sc. octreotide 50-100 ug for 7-10 days twice to thrice per day is recommended [27-29], particularly in patients with severe symptoms.

In case of refractory syndrome dose escalation above upper labelled dosages is an option [30, 31]. In general dose escalation is performed by shortening of the injection interval from 4 to 3 weeks with long acting SSA. There is consensus that dose escalation can be recommended in refractory carcinoid syndrome for improvement of symptoms.

Pasireotide is a novel universal somatostatin ligand that binds to four of five sstr and that is not approved for treatment of carcinoid syndrome or other functional NEN, but for the treatment of pituitary tumors associated with Cushing's disease or acromegaly. In a phase II trial, in 27% of patients with carcinoid syndrome pasireotide demonstrated a benefit following failure with standard dose of octreotide LAR [32], however, in a comparative trial pasireotide 60 mg LAR was not superior to octreotide 40 mg LAR/ month [33]. Since there are limited treatment options available in refractory carcinoid syndrome pasireotide might be considered in individual highly selected patients when other treatments failed or are not feasible depending on accessibility, and this includes loco-regional therapies, debulking surgery, interferon-alpha, and novel drugs in clinical trials. Telotristat etiprate, an oral serotonin synthesis inhibitor is a potential novel option in refractory carcinoid syndrome [34,35]. In the phase III placebo controlled trial (TELESTAR) telotristat etiprate significantly reduced diarrhea in patients with refractory carcinoid syndrome while on SSA [12]. If approved, telotristat etiprate can be recommended in addition to SSA for refractory diarrhea in carcinoid syndrome patients.

Somatostatin analogs for tumor growth control. SSA are an established therapy for antiproliferative purposes in intestinal NET, based on 2 placebo controlled trials (PROMID and CLARINET studies). Both drugs, octreotide LAR and lanreotide Autogel are recommended as first-line systemic therapy in midgut NET, to control tumor growth [36,37]. There is consensus that SSA can be used as first-line systemic therapy in pancreatic NET (Ki67<10%) in view of lack of toxicity, and although the antiproliferative effects of SSA are considered a drug class effect, based on the CLARINET study lanreotide Autogel should preferably be used in pancreatic NET since prospective data on the use of octreotide LAR in pancreatic NET are lacking [37,38]. There are retrospective data supporting the use of octreotide LAR in low grade pancreatic NET [39]. SSA can be recommended for prevention or inhibition of tumor growth in both intestinal and pancreatic NET. Equally based on the CLARINET study design, the use of SSA in GEP-NET is recommended up to a Ki-67 of 10% [37]. However, for the overall group of NEN there was no consensus among experts on a clear cut-off value for the recommendation of SSA for antiproliferative purpose. When considering SSA as first-line therapy in intestinal or pancreatic NET some experts feel that 5% might be a more appropriate Ki-67 cut-off threshold. Prospective validation is required to determine the appropriate Ki-67 value for treatment

stratification to SSA or more aggressive therapies. Recommendation for the use of SSA expands to patients with higher hepatic tumor burden (>25% liver involvement) as supported by a subgroup analysis from the CLARINET study [37]. Although a benefit in overall survival could not be demonstrated by the placebo controlled trials with SSA that allowed cross-over from the placebo arm upon progression to open label SSA, it is expected that the use of SSA has an impact on the outcome of patients [40]. It remains however controversial if SSA should be started at initial diagnosis or after observation of the spontaneous tumor growth and initiated in case that disease progression occurs. There is consensus that SSA should be started at diagnosis in cases of high liver tumor burden and extended disease since these are worse prognostic factors. Another factor in favour of early SSA therapy is a pancreatic primary given the fact that the overall 5-year survival rate in stage IV disease does not exceed 40-60% [41, 42]. There is no data to support continued use of SSA when patients progress on SSA (they may be required however in continued suppression of functionally active tumours).

SSA may also be used in NET of other sites (e.g. rectal, bronchial NET) when SSTR receptor status is positive (on somatostatin imaging or histology) if slowly growing, G1 or G2, preferably with Ki-67 <10%. Prospective clinical trials will further evaluate the role of SSA (lanreotide AG and pasireotide, respectively) in typical and atypical lung NEN (www.clinicaltrials.gov).

SSA may be considered in somatostatin receptor (SSTR) negative NEN if small volume disease is present and it is expected that imaging may have provided falsely negative information on SSTR status. Immunostaining with SSTR2 antibodies may also be useful [43,44].

***Minimal consensus statement**: Somatostatin analogs, octreotide and lanreotide, are effective drugs for syndrome control in functionial NET. In refractory carcinoid syndrome or insufficient syndrome control in pancreatic NET, dose escalation of SSA may be recommended. The novel somatostatin analog, pasireotide might be considered in refractory carcinoid syndrome in case all other treatment options including ablative procedures, TAE and interferon alpha have failed, and there is no clinical trial available. If approved, the oral serotonin synthesis inhibitor telotristat etiprate will offer a novel treatment option in refractory carcinoid syndrome. For antiproliferative purpose, SSA may be used in stable or progressive disease or in patients with unknown tumor behaviour. SSA are recommended first-line therapy in midgut NET and can be considered in pancreatic NET as a first-line therapy (up to a Ki67 of 10%). While the antiproliferative efficacy of both available SSA is considered a class effect, there is a higher level of evidence for the use of lanreotide AG in pancreatic NET, and based on the respective study designs octreotide LAR is approved for tumor control in midgut NET whereas lanreotide AG is approved for enteropancreatic NET. SSA may be considered in low grade NET of other sites. There is no established Ki-67 threshold for the use of SSA, preferably SSA should be used if Ki-67 is ≤ 10%.*

Interferon-alpha is a second-line therapy in NEN that are functionally active. It is recommended to use IFN alpha as add-on therapy to SSA therapy in functioning tumors. The recommended dose of IFN-alpha 2b is 3x3 -3x 5 MU /week sc [28, 45]. In patients who do not tolerate the conventional regimen alternatively pegylated interferon alpha (50-180 ug/week sc) can also be used [46]. IFN alpha has antiproliferative activity and may be considered for antiproliferative purposes if other approved drugs are unavailable, esp. in midgut NEN. Interferon alpha has been explored in comparison to bevacizumab for antproliferative purpose in a large randomized trial in 400 patients with carcinoids (including different primary sites) who received octreotide LAR concomittantly (SWOG trial); the primary endpoint, median PFS, was not different between interferon-alpha and bevacizumab [47]. This study, however, confirms the antiproliferative activity of IFN-alpha 2b in advanced NET G1/2, NET with progressive disease or other poor prognostic features with a median PFS of 15.4 mo. reached in the IFN arm.

***Minimal consensus statement**: Interferon alpha is an established and approved therapy for syndrome control, and primarily used as second-line (add-on) therapy in refractory carcinoid syndrome or functioning pancreatic NET. Interferon is an option for inhibition of tumor growth, and due to limited therapy options in midgut NET may be considered an antiproliferative option (less so in pancreatic NET).*

Novel targeted drugs (everolimus and sunitinib) are approved for pancreatic NET based on the results of two placebo controlled trials in progressive pancreatic NET. Median progression free survival is around 11 months with either of the drugs, while tumor remission occurs in 5% and less than 10% of the patients with everolimus and sunitinib, respectively. Use of either everolimus or sunitinib is recommended in progressive G1/G2 pancreatic NET irrespective of Ki-67 and tumor burden. Standard dose is 10 mg everolimus /day, and sunitinib 37.5 mg/day as continous treatment. Side effects may require dose reduction to 5 mg everolimus /day or 25 mg sunitinib /day [48,49]. While comparative data of both drugs are lacking, selection of targeted drugs is based on the medical history of the patient, side effect profile of the drugs and accessibility to the treatment.
Targeted drugs, everolimus or sunitinib, are one of the different treatment options in pancreatic NET and may be used as 1st-line or 2nd line options with respect to chemotherapy or subsequent to SSA therapy (Table 1). Although targeted drugs may be the first therapy choice in pancreatic NET, there is consensus that targeted drugs *should not* be broadly used as first-line therapy for their potential toxicity. There is no evidence on the exact sequencing of different treatment options in pancreatic NET. Potential toxicity needs to be considered when sequencing therapies as indicated in a retrospective multicenter study in 169 patients from Italy where a markedly increased toxicity was reported with everolimus in patients previously treated either with PRRT and/or chemotherapy [50]. In contrast, a smaller retrospective study from the Netherlands in 24 patients indicated that the safety of everolimus is not influenced by previous PRRT [51]. An ongoing trial (SEQTOR) is currently investigating the antiproliferative efficacy of everolimus vs. STZ/5-FU in progressive pancreatic NET in a crossover design upon progression (www.clinicaltrials.gov).
Everolimus can be recommended in advanced NET of non-pancreatic origin in case of disease progression (e.g. NET of intestinal or lung origin). It can be used in midgut NET as second or third-line therapy after failure of SSA and/or IFN-alpha or PRRT. This recommendation is based on the results of the RADIANT-4 trial [10] that reached its primary endpoint, and demonstrates superior PFS with everolimus compared to placebo in non-functioning NET of intestinal or lung origin, and is supported by the RADIANT- 2 trial in advanced NEN associated with the carcinoid syndrome (that tended towards similar results) [52]. The sequencing of everolimus as second or third-line therapy for advanced intestinal NEN will also depend on other issues, including accessibility of PRRT. Individual patient selection is important. A strong somatostatin receptor expression on somatostatin receptor imaging is necessary to achieve better results with PRRT, while extensive hepatic and/ or bone disease as as well as decreased kidney function may limit its use. Otherwise, the use of everolimus may be limited by comorbidities such as uncontrolled diabetes or lung diseases. A comprehenisve review of the patients medical history, pathology and imaging will have an impact on the therapy allocation to either everolimus or PRRT after failure of SSA.
In the absence of approved drugs in metastatic lung NET, everolimus may be recommended as a first-line therapy in progressive disease. However, in patients with low proliferative activity (G1, typical carcinoid) with strong SSTR expression on imaging, SSA may be considered first-line therapy. Although comprehensive clinical data are lacking for the use of SSA in lung NET, it is expected that the clinical behaviour of typical carcinoids (mitotic count less than 2/10 HPF; NET G1) is similar to NET G1 of other sites. Ongoing and planned clinical trials (LUNA, Lanreotide vs. Placebo) will further elucidate the role of SSA in advanced lung NEN (www.clinicaltrials.gov).
There is not sufficient data to support the use of other targeted drugs including bevacizumab, sorafenib, pazopanib or axitinib in either pancreatic or non-pancreatic NEN. These drugs as well as

sunitinib in midgut NET (SUNLAND study), are currently explored in prospective randomized clinical trials but their results are not available yet and their use should be restricted to clinical trials.
It is standard practice to combine targeted drugs with SSA in functionally active NEN. The aim of a combination therapy of everolimus and SSA may not only be tumor growth inhibition, but also improved syndrome control, e.g. in patients with recurrent hypoglycemia related to metastatic insulinoma. Although prospective trials with everolimus are lacking to demonstrate an improvement of hormone related syndromes, the early use of everolimus may be justified to avoid hospitalization and sequelae related to hypoglycemia based on the experience in few patients (Fig. 3).
Although there might be a rational to combine targeted drugs with SSA also in non-functioning NEN given the expression of somatostatin receptors in the majority of NEN, there is no robust evidence yet that the combination therapy of targeted drugs with SSA is superior to monotherapy with either everolimus or sunitinib for antiproliferative purposes. A comparative trial in progressive pancreatic NET (COOPERATE-2) with everolimus vs. everolimus and pasireotide, a novel somatostatin analog with a broader binding affinity to SSTR compared to first generation SSA, failed to demonstrate superiority of the combination therapy with respect to PFS [53]. Although there might be a potential benefit of a combination therapy using other SSA, such as lanreotide or octreotide, and a recent open label phase II study indicates favourable response (disease control rate >90%) with everolimus in combination with octreotide in a first-line setting in GEP NET [54] in the absence of a comparative study of targeted drugs with either octreotide or lanreotide compared to the targeted drug alone, the upfront combination therapy of targeted drugs with SSA cannot be recommended. Furthermore, data are lacking to support the use of SSA beyond progression in combination with targeted drugs.
Minimal consensus statement: *Everolimus and sunitinib are approved antiproliferative therapies in progressive pancreatic NET, and represent one of the different treatment options next to SSA and systemic chemotherapy. They can be considered a first line therapy, especially if SSA is not an option, and if systemic chemotherapy is not clinically required, not feasible or not tolerated. Everolimus or sunitinib are generally recommended after failure of SSA or chemotherapy in pancreatic NET. In intestinal NET everolimus may be used as 2nd line after failure of SSA or as 3rd line after failure of PRRT while in progressive lung NET everolimus is recommended a first-line therapy unless SSA may be considered as first-line therapy (e.g. in typical carcinoid with slow growth expressing somatostatin receptors). The combined use of targeted drugs with SSA for antiproliferative purpose is not recommended in non-functional NET. Antiangiogenic drugs including sunitinib are not recommended in non-pancreatic NEN outside of clinical trials.*

Systemic chemotherapy is indicated in progressive or bulky pancreatic NET and in NEN G3. The term NEN G3 comprises well or moderately differentiated tumors with Ki67 >20% (NET G3) that are not termed in the WHO 2010 classification and large or small cell tumors with Ki67 >20% (NEC G3); presented in detail elsewhere). Chemotherapy may be considered in NET of other sites (lung, thymus, stomach, colon, rectum) under certain conditions (e.g., when Ki-67 is at a high level (upper G2 range), in rapidly progressive disease and/or after failure of other therapies, or if somatostatin receptor imaging is negative).
Chemotherapy is one of a different number of treatment options in pancreatic NET and can be used in G1 or G2 tumors. Cytotoxic therapy combinations include: streptozotocin with 5-fluorouracil (STZ/5FU) is established therapy; doxorubicin with streptozotocin is an alternative option, however, the use of doxorubicin is limited by a cummulative dose of 500 mg/m2 (as risk of cardiotoxicity). Therapeutic regimens according to Moertel et al (cycles every 6 weeks) or Eriksson et al (cycles every 3 weeks) can be recommended [55-57]. Data do not support three drug regimen associations including cisplatin, nor the replacement of 5-FU by capecitabine [58-60]. Systemic chemotherapy may be considered without prior progression in patients with high tumor burden. There is no established Ki-67 cut-off value for recommendation of chemotherapy. Patients with pancreatic NET with Ki-67 of 5-20% can be treated with chemotherapy. Other factors that favour chemotherapy compared to targeted drugs include:

- Bulky disease;
- Symptomatic patient;
- Rapid tumor progression in ≤ 6-12 months;
- Patients with a possible chance of achieving a response to allow for surgery (neoadjuvant option)

Although replacement of STZ/5-FU by temozolomide/capecitabine is gaining popularity, this approach cannot be categorically recommended since data for temozolomide are still limited. However, temozolomide +/- capecitabine may be considered as an alternative regimen depending on availability of STZ/5-FU. Reported objective response rates from small prospective and retrospective studies achieved with temozolomide either combined with antiangiogenic drugs or capecitabine range between 15 and 70% [61-63]. The value of temozolomide either as mono- or combination therapy with capecitabine or antiangiogenic drugs is further explored in prospective clinical trials (www.clinicaltrials.gov). Few studies indicate that MGMT status is correlated with tumor response to alkylating agents [64-66], however, determination of MGMT expression or methylation can currently not be recommended as selection criteria for the use of chemotherapy in NEN since studies are small, and prospective validation is lacking.
After failure of STZ-based chemotherapy alternative chemotherapeutic options are the following: temozolomide +/- capecitabine, oxaliplatin based chemotherapy + 5-FU or capecitabine. It remains unclear which treatment option is superior, however in pancreatic NET there is data supporting preferential use of temozolomide +/- capecitabine for promising response rates and low toxicity profile [62,67, 68].
Systemic chemotherapy is not recommended in non-pancreatic NET unless NET G2 (>15% Ki67) or displaying aggressive biological behaviour (RECIST progression in 3-6 months) or SSTR negative. Metronomic chemotherapy may be an option using temozolomide and/ or capecitabine +/ - SSA in NET G2 or in SSTR negative NET, or capecitabine + bevacizumab after failure of other treatments (such as loco-regional therapies, IFN-alpha or everolimus) [69-72]. Given the limited treatment options in bronchial carcinoids, temozolomide is a therapeutic option based on data from small studies [73,74]. Prospective validation is needed, as well as evaluation of the best sequencing of therapies in bronchial NET including SSA, everolimus and temozolomide.
In NEC G3 cisplatin based chemotherapy (e.g. cisplatin/ etoposide) is standard therapy and recommended as first-line therapy (see guideline on poorly differentiated tumors (NEN G3)). Cisplatin might be replaced by carboplatin based on the data from the Nordic NEC trial [75]. Although objective remission rates are high (40-67%), median PFS is limited with 4-6 months [76-78]. Second-line systemic therapy options include FOLFOX and FOLFIRI [79,80] while topotecan is not effective in NEC G3 [81]. Temozolomide based chemotherapy should be preferably used in pancreatic NET G3 or in GI NEC with Ki-67< 55% [67,78]; prospective studies are underway to assess the activity of temozolomide in this setting. Targeted drugs in combination with chemotherapy are under evaluation in clinical trials in NEN G3. Further details on the management of NEN G3 including recommendations for different primary tumor sites are summarized in a recently published comprehensive review on NEC G3 and are provided in a separate consensus paper [82, 83].
Minimal consensus statement: *Streptozotocin based chemotherapy is one of the treatment options in pancreatic NET G1/G2 next to SSA and novel targeted drugs, and is preferably recommended in patients with higher tumor burden with or without associated clinical symptoms, and/or in patients with significant tumor progression in ≤ 6-12 mo. time frame. Although data for temozolomide based chemotherapy are still limited, it may replace STZ/5FU regimen, if not available, in pancreatic NEN, and may be considered in NET G3 and in high risk NET of other primary site (e.g., pulmonary NET). In NEC G3 platinum-based chemotherapy is recommended as first-line therapy.*

Peptide receptor radionuclide therapy (PRRT) is a therapeutic option in progressive SSTR positive NET with homogenous SSTR expression (all lesions are positive). In general, use of PRRT follows failed first-line medical therapy. Radionuclide therapy with either ^{90}Y and/or ^{177}Lu-labeled SSA is most frequently used in NET, but ^{177}Lu-labelled SSA is increasingly used due to lower kidney toxicity. The minimum requirements for PRRT are reported in a separate consensus guideline [84]. Until recently, there were no results from prospective randomized trials available. The registrational trial of ^{177}Lu-DOTATATE in progressive midgut NET (NETTER-1), has reached its primary endpoint, with significant prolongation of PFS compared to high dose octreotide (60 mg/month). Based on this trial, and cummulative data from prospective and retrospective trials over the last 15 years, PRRT may be recommended in midgut NET as second-line therapy after failure of SSA if the general requirements to apply PRRT are fulfilled [84, 85-87] or as third line therapy after failure of everolimus. Given the different established and approved therapeutic options in pancreatic NET and the lack of a prospective trial with PRRT in pancreatic NET, PRRT (if available) is in general recommended in NET G1/G2 after failure of medical therapy including SSA, chemotherapy or novel targeted drugs. However potential increasing toxictiy, e.g., after prior chemotherapy or targeted therapy needs to be considered and requires close surveillance and might justify earlier use of PRRT in selected patients (Table 1).

Minimal consensus statement: *PRRT is recommended after failure of medical therapy. Data from the prospective trial in midgut NET support its role as a second-line therapy option in intestinal NET if the general requirements for PRRT are fulfilled and as an alternative option to everolimus. The optimal sequencing with targeted drugs and/or chemotherapy needs to be defined in pancreatic NET when data from prospective randomized trials in pancreatic NET become available.*

Management of neuroendocrine tumors with unknown primary tumor

In approximately 13% of patients who are diagnosed as having NEN, the primary site is not known. In patients with unknown primary tumor the primary tumor site is most frequently localized in the intestine, or the lung. Additional tools should be exploited to identify the primary tumor. This includes immunohistochemistry of transcription factors (CDX-2, Islet-1, TTF-1) [88], SR- PET/CT (eg., ^{Ga}68-SR, ^{11}C-5-hydroxytryptophan or ^{18}F-DOPA) [89, 90] and upper and lower GI endoscopy and optionally capsule endoscopy [91,91]. If the primary tumor remains unknown therapeutic decision making is essentially based on grading, functionality, somatostatin receptor status, tumor extent and hepatic tumor burden.

Please also refer to consensus guideline updates for other gastro-entero-pancreatic (GEP) neuroendocrine tumours [93-98, this issue].

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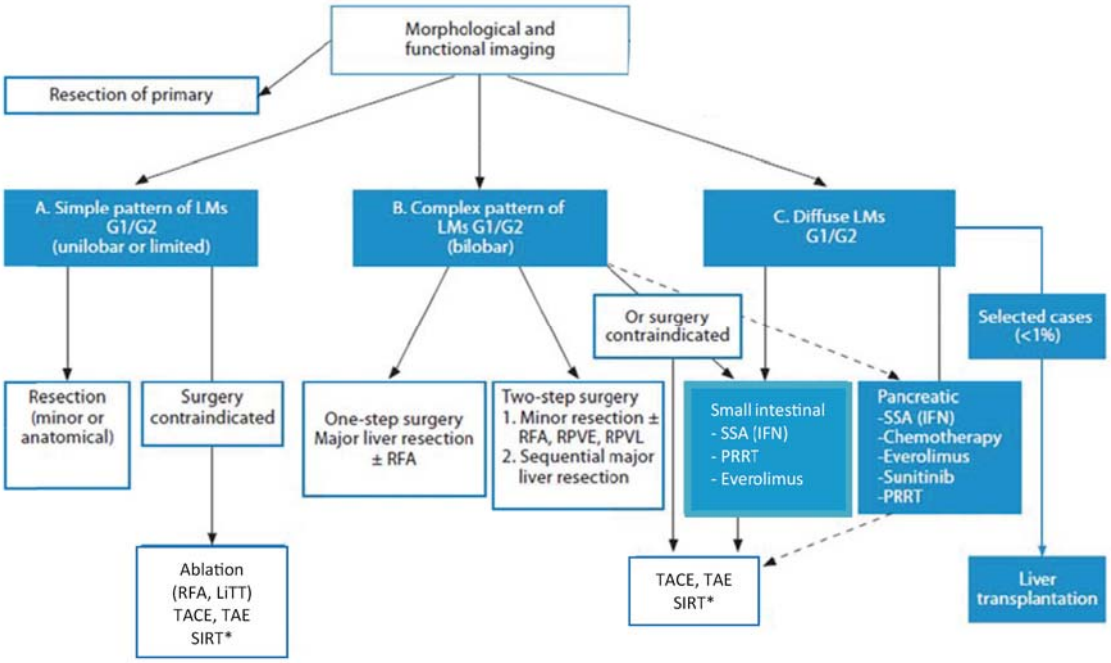

Figure 1: Management of liver metastases without extrahepatic disease in NEN G1/G2

* SIRT, selective internal radiotherapy is still an investigational method

LM liver metastases, TAE transarterial embolisation, TACE transarterial chemoembolisation, RFA Radiofrquency ablation, RPVE right portal vein embolisation, RPVL right portal vein ligation, LiTT laser induced thermotherapy

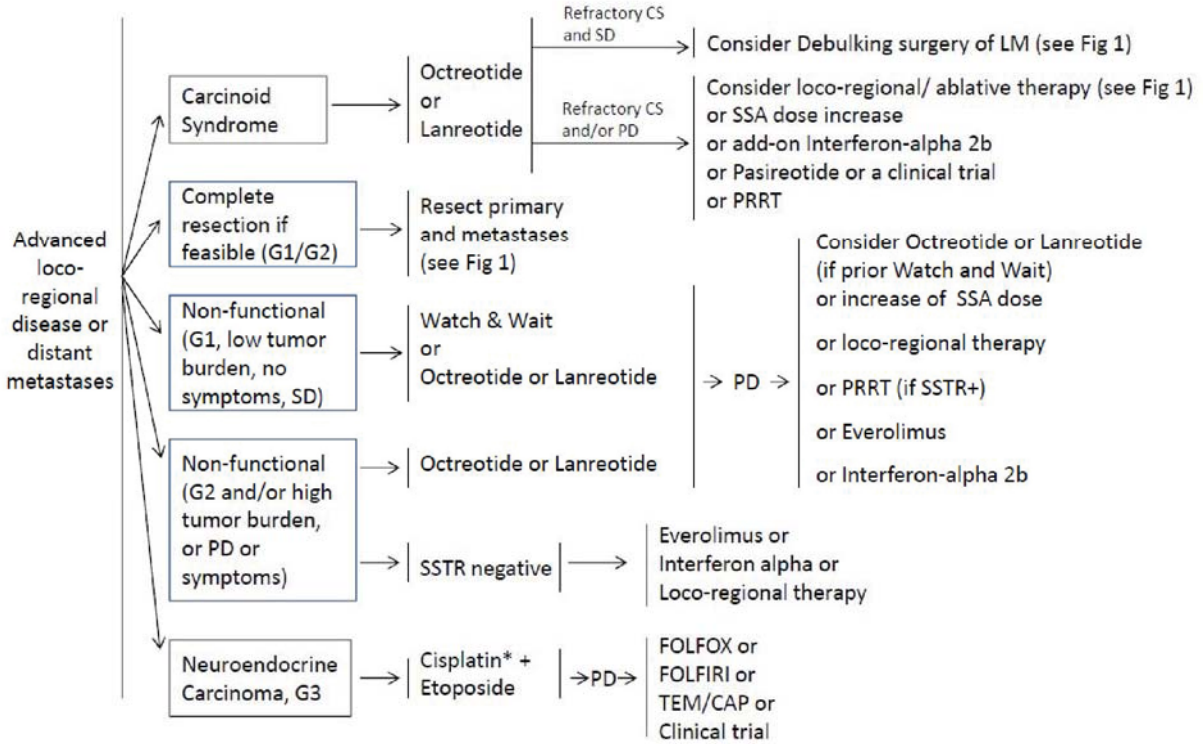

Figure 2: Therapeutic algorithm for the management of intestinal (midgut) NEN with advanced loco-regional disease and/ or distant metastases

Legend : PD progressive disease, SD stable disease, SSTR somatostatin receptor, SSA somatostatin analogs, CS carcinoid syndrome, PRRT peptide receptor radionuclide therapy, LM liver metastases, TEM/CAP temozolomide/capecitabine

*cisplatin may be replaced by carboplatin

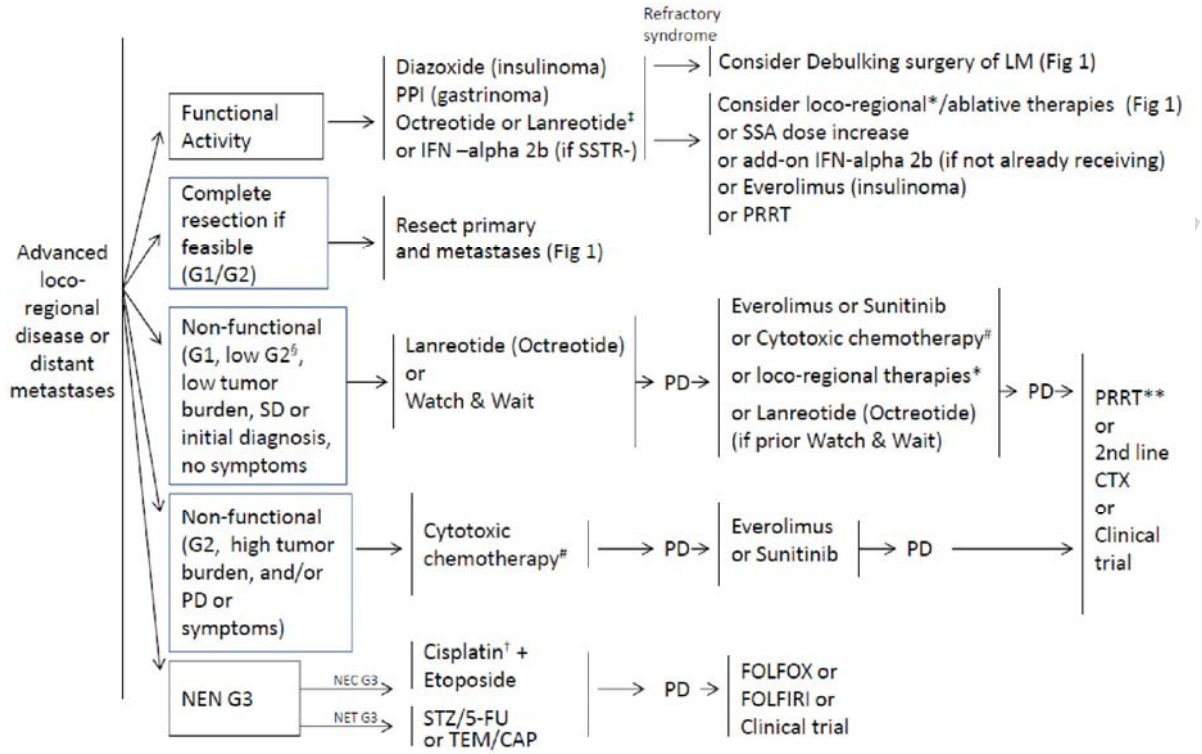

Figure 3: Therapeutic algorithm for the management of pancreatic NEN with advanced loco-regional disease and/ or distant metastases

Legend : PD progressive disease, SD stable disease, SSTR somatostatin receptor, SSA somatostatin analogs, CS carcinoid syndrome, PRRT peptide receptor radionuclide therapy, LM liver metastases, TEM/CAP temozolomide/capecitabine, STZ streptozotocin, 5-FU 5-fluorouracil

§ Ki-67 <5-10%; *loco-regional therapies are contraindicated after Whipple procedure; # recommended chemotherapy includes STZ/5-FU or STZ/ doxorubicin; TEM/CAP is an alternative chemotherapy regimen if STZ- based chemotherapy is not available; ** if somatostatin receptor imaging is positive; ‡patients should be closely monitored for paradoxical reaction (increasing hypoglycemia);†cisplatin may be replaced by carboplatin; NET G3 is coined for tumors with Ki67 >20% but well or moderately differentiated morphology

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

Drug	Functionality	Grading	Primary site	SSTR status	Special considerations
Octreotide	+/–	G1	midgut	+	low tumor burden
Lanreotide	+/–	G1/G2 (–10%)	midgut, pancreas	+	low and high (>25%) liver tumor burden
Interferon-alpha 2b	+/–	G1/G2	midgut		if SSTR negative
STZ/5-FU	+/–	G1/G2	pancreas		progressive in short-term* or high tumor burden or symptomatic
TEM/CAP	+/–	G2	pancreas		progressive in short-term* or high tumor burden or symptomatic; if STZ is contraindicated or not available
Everolimus	+/–	G1/G2	lung		atypical carcinoid and/or SSTR negative;
			pancreas		insulinoma or contraindication for CTX
			midgut		if SSTR negative
Sunitinib	+/–	G1/G2	pancreas		contraindication for CTX
PRRT	+/–	G1/G2	midgut	+ (required)	extended disease; extrahepatic disease, e.g. bone metastases
Cisplatin§/ etoposide	+/–	G3	any		all poorly differentiated NEC

CTX = Chemotherapy; STZ = streptozotocin; 5-FU = 5 fluorouracil; TEM = temozolomide; CAP = capecitabine; SSTR = somatostatin receptor; * 6 months; § cisplatin can be replaced by carboplatin.

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