

The Evolution of Neuroendocrine Tumor Treatment Reflected by ENETS Guidelines

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Abstract

In 2016, the third version of guidelines for the diagnosis and treatment of neuroendocrine tumors (NETs) has been published by the European Neuroendocrine Tumor Society (ENETS). These guidelines reflect the progress in treatment of NETs, and by comparing the newest guidelines with the first guidelines of 2001, this progress can be clearly recognized. Diagnostic accuracy has been increased by the introduction of PET-CT with Ga-labelled somatostatin analogs, and multiple new treatments and treatment schedules have been developed, like peptide receptor radiotherapy with radiolabeled somatostatin analogs, or targeted therapies. Evidence and indications for these therapies are discussed in the ENETS guidelines. In this review, we aim to show the progress in NET diagnosis and treatment on the basis of the advances in the guidelines, but also to discuss the unsolved questions and unmet needs which still remain.

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Introduction

In 2004, the European Neuroendocrine Tumor Society (ENETS) was founded by a group of European medical specialists in the field of neuroendocrine tumors (NETs). The main goal of the society since then has been “to integrate basic and clinical research with teaching and to establish guidelines for the diagnosis and therapy for gastroenteropancreatic neuroendocrine tumors” [1]. The first guideline of this European consortium was a consensus paper in 2001 on the imaging of NETs associated with the Multiple Endocrine Neoplasia type 1 (MEN-1) syndrome [2]. This paper was the result of a Delphi process initiated in 1998 by the European Network for Neuroendocrine Tumors, ENET. ENET was the basis on which ENETS was founded. The first set of guidelines by ENETS was published in 2004, and in 2016 the third version of these guidelines was published. In 2017, the second version of the ENETS *Standards of Care* was published, thereby pursuing one of the main goals of the society. In this review, we will discuss the impact of these guidelines and standards on the clinical practice for patients with a NET over the recent years.

Radiological and Nuclear Imaging

If a NET is suspected, the first guidelines of 2001 by ENET advocated a chest X-ray and abdominal ultrasonography as the imaging procedures of first choice [2]. In both functional and nonfunctional NET syndromes, somatostatin receptor-scintigraphy (SRS) was advised with a reported sensitivity and specificity at that time of 90 and 80%, respectively. At this stage, only ^{111}In -pentetreotide planar and SPECT images were available. Thereafter, CT and MRI were additionally performed for staging and for follow-up to document progression. SRS was already discussed to have limited use in localized insulinomas. If this was due to the small size of insulinomas or the expression profile of the somatostatin receptor subtypes was still unclear [3]. In case of a negative SRS, an enteroclysis was advised in patients with metastatic NETs from an unknown primary source. At that time, ^{18}F FDG-PET/CT was considered not to be useful in the diagnostic workup. The guidelines written by ENET(S) in 2001 and 2004 advised to perform CT, or MRI in combination with SRS, without reporting on the limitations and evidence for these strategies [2, 4]. For conventional imaging, the biggest improvement of the guidelines is that we can now substantiate the diagnostic strategies based on evidence and that this has helped us also to identify the limitations and pitfalls of the radiological and nuclear medicine modalities [5]. The sensitivity of CT is limited to 61–93% for detection of NETs, but its specificity is fairly high: reported to be between 71 and 100%. However, it seems that many small lesions can still be missed with the use of 3-phase CT. Compared to thin slice histopathology, CT only detects 37.6% of liver metastases in patients undergoing a hemihepatectomy [6]. In these cases, superior imaging techniques could be used to exclude or identify patients for potential curative surgery. With the use of MRI, the detection rate of liver metastases already increased to 48.8% in the same study.

SRS was already fully incorporated in the first ENET(S) Standards and Guidelines. SRS has two specific advantages: it often detects more metastases – at more sites – than conventional imaging, and it assesses the expression of somatostatin receptor subtypes on the tumor. The latter is required for peptide receptor radionuclide therapy (PRRT) using beta emitting somatostatin receptor radioligands and for the selection of somatostatin analogs (SSAs) as first-line treatment. SRS detects tumors that express the somatostatin receptor subtypes 2, 3, and 5. These are mainly NETs, including pheochromocytomas and other paragangliomas, but also menin-

giomas, medulloblastomas, and granulomatous diseases can display high expression of these somatostatin receptor subtypes. The first SRS used [^{123}I -Tyr 3]octreotide, but a large number of drawbacks (short half-life, hepatic clearance resulting in high liver uptake and costs) made the development of alternative radiolabeled analogs necessary [7]. SRS using ^{111}In -pentetreotide (OctreoScan[®]) was the most widely used SRS until very recently [8–11]. Currently, SRS with ^{111}In -pentetreotide is rapidly losing ground to PET/CT with gallium-labeled SSAs, because there are distinct advantages to this technique. Patients can be injected with the gallium-labeled SSA (^{68}Ga -DOTA-TOC/TATE/NOC) only 1 h in advance of the scanning procedure, whereas SRS can only be performed 24 h after injection of ^{111}In -pentetreotide. But the main advantage of ^{68}Ga -SSA PET/CT is its higher detection rate as compared to SRS. Sensitivity and specificity of ^{68}Ga -SSA PET/CT for NET detection varies between 88 and 95% in several studies and outperforms SRS in head-to-head comparisons [12–16]. For detection of bone metastases, ^{68}Ga -SSA PET/CT even outperforms the current gold standard: the $^{99\text{m}}\text{Tc}$ -bisphosphonates scintigraphy [17, 18]. This makes ^{68}Ga -SSA PET/CT the modality of choice for nuclear imaging in the current standards of care. The performance of the different gallium-labeled SSAs (either DOTA-TOC, DOTA-TATE or DOTA-NOC) shows only small variations thus no specific preference exists [19, 20]. The most recent ENETS guidelines already anticipate this change in diagnostic approach [5].

Also, several studies have now shown the usefulness of ^{18}F -FDG-PET/CT in the diagnostic workup of NETs. The sensitivity for detecting NETs is generally relatively low, ranging from 37–72%. Its usefulness, however, seems to be the better detection and prognostic stratification of higher grade NETs and neuroendocrine carcinomas (NECs). In tumors with high proliferation rates and subsequent dedifferentiation, there can be loss of somatostatin receptor expression with concomitant increase in glucose metabolism and thus FDG avidity [21]. Furthermore, FDG avidity is a negative prognostic sign and might even be superior to the MIB-staining of the Ki67 protein for predicting prognosis [22]. With the upcoming WHO 2017 guidelines for diagnosis and grading of NETs, the role of FDG-PET will be of most relevance for the diagnosis and therapeutic approach of patients with grade 3 NETs and NECs. Also, the combination of ^{18}F -FDG-PET/CT and SRS imaging can be used to select patients for PRRT. Mainly high grade NETs, positive for FDG and SRS imaging, could benefit from PRRT [23].

Thus, combining FDG and ^{68}Ga -SSA PET/CT will give the most complete picture of NETs. It is superior in detecting NETs, but the combination also gives a more complete picture of the biological behavior of the NET by knowing the SRS and FDG avidity.

Pathology Diagnosis

Selecting the optimal treatments and diagnostics for NET patients starts with making a correct diagnosis. This makes the Standards of Care on pathology reports of great value [24]. Uniform diagnosis is also required to be able to interpret results of trials and cohort studies. The groundwork for the standard for pathology reporting was finally published after a Delphi Consensus process by Klimstra et al. [25] in 2010, and the diagnostic sequences for the pathological diagnosis of NETs are now well defined. It requires more than 50% of cells to stain positive for one of the neuroendocrine markers, synaptophysin or chromogranin. Tumors demonstrating lower percentages of cells with positive staining can be either designated as mixed adenoneuroendocrine carcinoma (MANEC) or a carcinoma with neuroendocrine differentiation. These should not be considered as, nor treated as a NET, and ENETS emphasized this fact by finally completely removing the goblet cell carcinoid (a misnomer) from the appendix NET guidelines [26]. ENETS produced its pathology grading system for foregut and midgut NETs in 2007 [27, 28]. Two landmark papers were published explaining how this grading system should work. Since then, several groups have published on the clinical usefulness of such a system, and until now the cut-off criteria for the different tumor grades did not need to be changed [29–31]. Recently the cut-off for grading has been changed in the new WHO 2017 guideline: a very slight change in the grade 1–2 cut-off has been implemented (grade 1: Ki67 $\leq 3\%$) [32]. This small change will probably not influence clinical practice, but the newly advised classifying of grade 3 tumors can possibly change future guidelines. The WHO 2017 guideline advises to classify NETs with a Ki67 $>20\%$ as either grade 3 NET (well-differentiated) or as grade 3 NEC (poorly differentiated) on the basis of morphological characteristics as necrosis and differentiation. Grade 3 NEC should hardly always be treated with systemic chemotherapy, whilst in well-differentiated grade 3 NET, there might still be room for PRRT or targeted therapy. To aid in the grading of NETs immunohistochemical markers can be useful. Loss of Rb or ab-

normal p53 expression is often seen in grade 3 NEC, while loss of ATRX and DAXX expression is associated with well-differentiated NETs [33].

After the correct diagnosis of NET, staging should always be performed. ENETS has been leading the effort for a standardized approach. On behalf of ENETS, Rindi et al. [27, 28] published a TNM classification for NETs and this is also used in guidelines produced by ENETS and many other international studies and groups. A similar staging system was developed by the International Union for Cancer Control/American Joint Cancer Committee/World Health Organization (UICC/AJCC/WHO), although there are several differences identified between these two major systems. In a head to head comparison in a large cohort of pancreatic NETs, the ENETS system performed generally better [34]. In future guidelines, prognostic stratification through molecular markers may take a more prominent role [35].

Surgery

Early ENETS guidelines already defined preoperative standards and recognized the importance of a correct preoperative biochemical analysis. Especially patients with a small intestinal NET should be screened for serotonin secretion by determining 5-hydroxyindoleacetic acid levels in the urine or plasma. Patients with elevated levels of this serotonin breakdown product might require SSA therapy to prevent carcinoid crises during surgery or other invasive procedures [36, 37]. ENETS recently updated its recommendations in this field [38]. The only curative option for NETs has always been a surgical resection, and this has not changed until now and probably will remain for a long period of time [4, 39]. But while surgery can always be considered, current guidelines also define selected patients who might not need immediate treatment and just have to be observed according to a well-defined watchful waiting protocol. Observation seems reasonable in pancreatic NETs smaller than 2 cm; however, follow-up was only limited to 3 or 4 years in these studies [40, 41]. Importantly, these recommendations are based on studies in patients with inherited tumor syndromes, like von Hippel Lindau disease, or MEN-1. As always, larger cohorts and preferably studies randomizing between observation or intervention would shed further light on this issue. The generally slow growth rate of small pancreatic NETs will, however, require such a long follow-up and a large study cohort rendering further studies almost infeasible. Shared decision-making will

probably remain the standard for small nonfunctioning pancreatic NET in the coming years. However, ENETS has developed a plan to further study these issues in its ASPEN trial [42]. The second pancreatic or duodenal NET type that should not be primarily resected is the gastrinoma in MEN-1 patients. At presentation, these are often metastasized to lymph nodes requiring extensive resections (like pancreaticoduodenectomy) [43, 44]. Curation rates are lower in MEN-1 patients, but prognosis is still better than in patients with sporadic gastrinomas [45]. Only in MEN-1 patients with multiple liver metastases of gastrinomas is the survival significantly reduced [45, 46]. Therefore, in most MEN-1 patients with a gastrinoma smaller than 2 cm, only medical therapy with proton pump inhibitors (PPIs) is recommended and SSAs in patients with symptoms refractory to PPIs [47, 48].

The extent of resection for appendiceal NETs also remains a matter of debate. A large majority of appendiceal NETs are diagnosed incidentally during appendectomy, and most are often smaller than 1 cm. Appendectomy alone suffices for these patients as long-term survival is near 100% [26]. For appendiceal NETs larger than 2 cm, the risk of (lymph node) metastasis has been reported to be close to 25% with one study even finding lymph node metastases in 86% of these NET patients [49–51]. A right hemicolectomy is still recommended for these NETs, but in high-risk patients this procedure can result in morbidity in up to 30% of patients [26, 52]. The survival benefit of this procedure has never been demonstrated. Hemicolectomy is still advised for appendiceal NETs >2 cm, but new and better evidence is urgently needed to select patients for this procedure.

For nonresectable or metastatic NETs, there has been a large increase in different therapeutic options. On the surgical side, there is further debate on whether resection of the primary tumor is indicated. Resection is currently recommended if curation can still be reached by resecting the primary including all metastases or in symptomatic patients (e.g., with abdominal pain or diarrhea) [53]. Some studies also suggest a benefit for resection of the primary in asymptomatic, incurable patients increasing overall survival from 50 to 88 months in small bowel NET patients not undergoing resection to over 100 months in patients undergoing resection [54]. These studies, however, are retrospective, and a large bias is very likely due to the selection of patients for surgery based on performance status and extent of mesenteric fibrosis.

Systemic Therapy

Multiple medical therapies have become available for the treatment of metastatic NETs. All have shown their effect in randomized controlled trials, but head-to-head comparisons are not available. It is, therefore, difficult to select which drug is the most suitable for a selected patient. ENETS has developed an algorithm for treatment of metastatic NET aiding in the selection of the most suitable treatment for individual patients [55].

Somatostatin Analogs

The earliest ENETS guidelines could only recommend commencing SSAs in patients with functioning (hormone or peptide secreting) NETs since clinical evidence for their growth-inhibiting potential in nonfunctioning NETs was not available at that time. However, experimental studies as well as clinical experience in individual cases had already hinted at these effects [4, 56]. The recommendations were based on reduction of biomarkers and symptoms in patients with carcinoid syndrome, and only data on the initial responses were available (stable disease in 24–57% of patients). Nowadays, there is substantial clinical evidence for the antiproliferative effect of SSAs. In the pre-ENETS era, Scandinavian studies already showed growth inhibition in NETs with treatment of high doses of SSAs [57, 58]. First published was the PROMID trial, demonstrating that 30 mg of octreotide LAR every 4 weeks increased median progression-free survival (PFS) from 6.0 months (placebo) to 14.3 months in patients with a metastatic small intestinal NET [59]. This trial included also patients with not so severe carcinoid syndrome (36% of patients). The CLARINET trial followed several years later: including pancreatic and small intestinal NETs, median PFS increased from 18.0 months for placebo to median PFS not reached for lanreotide 120 mg every 4 weeks [60]. These results combined with the high tolerability finally led to ENETS advising first-line SSA treatment for patients with a pancreatic or small intestinal NET with a Ki67 tumor index of 10% or less [55]. Besides SSAs, ENETS separately published instructions for safe use of systemic therapy. [61]. Future interests lie in optimal dosing of SSAs, new forms of SSAs (single versus multiple SSA receptor), new formulations and whether to continue SSAs during second-line therapy, like PRRT using radiolabeled SSAs and targeted therapy.

Peptide Receptor Radionuclide Therapy

In the early ENETS guidelines, evidence for PRRT with radiolabeled SSAs was limited. The first large obser-

ational study on PRRT using ^{177}Lu -octreotate, including 310 patients with gastroenteropancreatic NET was only published in 2008 by Kwekkeboom et al. [62]. A median PFS of 40 months was reported, which at that time was far superior to any other available therapy (chemotherapy or interferon- α). This was the basis for the recently published NETTER-1 trial: patients with metastasized small intestinal NET were randomized to ^{177}Lu -DOTA-octreotate or octreotide LAR 60 mg per 4 weeks [63]. Median PFS was not reached in the PRRT arm at publication of the trial in 2017 after more than 2.5 years of follow-up, while median PFS in the octreotide LAR arm was 8.4 months (hazard ratio: 0.21; 95% CI: 0.13–0.33; $p < 0.001$). Through this trial, ^{177}Lu -DOTA-octreotate will probably be the first widely approved agent for PRRT. The ENETS Standard of Care for PRRT clearly describes evidence, treatment protocols, and patient selection for treatment with PRRT [64].

Targeted Therapy

The major advances in the field of targeted therapy for NETs can hardly be left unnoticed. Targeted therapy was first included in the ENETS guidelines of 2012 [65]. Currently, both sunitinib and everolimus are registered for the treatment of progressive metastatic pancreatic NET, and everolimus is also registered for progressive metastatic small intestinal NET [55].

Everolimus was studied in at least 3 large randomized controlled trials. First published in 2011, the RADIANT-3 trial studied patients with a progressive pancreatic NET, and in this trial everolimus increased PFS to 11.0 months compared to 4.6 months when treated with placebo (HR 0.35, 95% CI: 0.27–0.45; $p < 0.001$) [66]. Shortly thereafter, the RADIANT-2 and RADIANT-4 trials were also published, studying PFS respectively in patients with carcinoid syndrome and nonfunctional NETs [67, 68]. Again, everolimus was shown to increase PFS with an HR for progression of, respectively, 0.77 (95% CI: 0.59–1.00, $p = 0.026$ one-sided) and 0.48 (95% CI: 0.35–0.67, $p < 0.001$ one-sided), but toxicity is higher than treatment with SSAs [66–68].

Sunitinib has been studied in pancreatic NETs. In the SUNNET trial with 171 patients with a pancreatic NET, sunitinib increased PFS from 5.5 (placebo) to 11.4 months, resulting in a hazard ratio of 0.42 for progression (95% CI: 0.26–0.66, <0.001 two-sided) [69].

There is no specific preference for sunitinib or everolimus in progressive pancreatic NET as head-to-head comparisons are not available and, therefore, selection of therapy still is depending on the physician's preferences

and/or multidisciplinary team's opinions [55]. For example, for the patient with hypertension everolimus could be more suitable and vice versa for the patient with diabetes. The characteristics and treatment of side effects have been described in the standard of care for systemic therapy [61]. An important role for ENETS will continue to be the judging of the available evidence for drugs to advise the clinician through its guidelines on selecting the most appropriate drug for the patient.

Interferon-Alpha

From the first guideline onwards, interferon-alpha has been recommended as second-line treatment after progression during treatment on SSAs [4, 55]. Interferon is a cytokine that has antiproliferative and antisecretory effect in NETs [70]. Our knowledge on the response to interferon is largely based on the work of Öberg et al. [71–73] in the 1990s. Partial response occurs in around 10–15% of NETs, and this is comparable to treatment with SSAs. However, the burden of evidence for SSAs is higher, and the unfavorable side effects of interferon make SSAs the first-line treatment for metastatic NETs [74]. These side effects consist of flu-like symptoms and fatigue. While interferon is still recommended as second-line drug, newer therapies as PRRT and immunotherapy have less side effects, higher efficacy, and are supported by more evidence. A pegylated formulation, administered weekly, can decrease side effects [75]. The role of interferon in future guidelines will probably be reduced to selected patients with refractory carcinoid syndrome.

Chemotherapy

For the treatment of poorly differentiated grade 3 NECs, chemotherapy is the first option. NECs are treated similar to small cell lung carcinomas, with platinum-based chemotherapy, and this is stated in all ENETS guidelines [4, 76]. The combination of cisplatin with etoposide results in relatively high response rates of 17–67%, but median survival is still only 7–19 months [76–78]. Platinum-based chemotherapy has only little effect in NETs with Ki67 of 20–55%, and the use should be limited to poorly differentiated grade 3 NECs. New in current guidelines is the growing burden of evidence for second-line treatments with oxaliplatin- or irinotecan-based regimens [76, 77].

Since the first study of Moertel et al. [79] in 1980, the combination of streptozotocin and 5-fluorouracil (STZ/5-FU) has been used for treatment of metastatic pancreatic NET. At that time, grading was not performed, and therefore STZ/5-FU could potentially be used in all metastatic

pancreatic NET. The 2016 ENETS guidelines limit the use of STZ/5-FU to NETs with a Ki67 of 5–20%, with bulky disease or rapid progression [55]. There is no evidence for chemotherapy in small intestinal NETs [80, 81]. Chemotherapy with temozolomide and capecitabine is currently not recommended by ENETS due to lack of evidence, but it shows promising results in phase II trials [55]. Combining chemotherapy with targeted inhibitors of angiogenesis (bevacizumab) looks promising, but has not proven superior to current regimes [82].

Interventional Radiology

Lastly, there have been major developments in the fields of interventional radiology for the treatment of NETs. Radiofrequency ablation is a commonly used technique for liver metastases smaller than 5 cm [83]. Larger tumors, especially in patients with liver-only disease, can be treated with embolization. Multiple options for embolization exist, namely bland embolization, chemoembolization, or radioembolization. At this time, no preference can be made for a certain treatment due to lack of comparative trials, but especially bland embolization and radioembolization with ⁹⁰Yttrium show a very promising response rate of up to 80% in selected studies, but on average around 50% (complete and partial response) [84–86]. Currently, no standard of care by ENETS exists for embolization, but it is included in the current guidelines for selected patients with high liver burden.

Future Perspectives

When we compare the current with the past guidelines, it is clear that the field of NET research has come a long way in the past decades. It is impossible to measure the exact impact of these guidelines on patient care, but they do reflect the vast developments in the field. The first guidelines by ENET could only recommend a few diagnostic and treatment options with limited evidence to support the guidelines [2]. There has been a large increase in diagnostic accuracy with the development of the ⁶⁸Ga-SSA PET/CT, and the pathology reporting has been standardized to correctly diagnose patients and to select correct treatment. Multiple randomized controlled trials have been published demonstrating the antiproliferative effect of SSAs, targeted therapy and PRRT with radiolabeled SSAs. But the burden of evidence has also significantly increased: the first guideline was based on limited data and expert opinion mainly, but the most

recent guidelines are based on prospective trials and are much more capable of quantifying benefits of diagnostics and treatments. The most robust association, proving the effects of the guidelines is that with increasing treatment options in the guidelines, an increasing survival for NET patients has been recorded. ENETS of course does not develop new treatments, but the main role of ENETS should be to critically appraise the available evidence and therewith facilitate the transfer of knowledge to the clinicians and advise these clinicians on the correct treatment for their patients with the expertise of specialists behind the guidelines. With increasing burden of evidence, an important next step for ENETS is to develop the next guidelines with levels of evidence and strength of recommendations [87]. Also, ENETS should highlight important clinical questions which are currently unanswered, resulting in unclear or unsupported recommendations. They are already doing so, and this has resulted in promising future research and trials. One of the main clinical enigmas remains the choice of second-line therapy when patients are progressive while using SSA. PRRT with radiolabeled SSAs, targeted therapy and several chemotherapy regimens have been proven effective in progressive patients. The results of the NETTER-1 trial are superior to any therapy presently available and will most probably become the second-line therapy of choice. However, the sequence of therapy is arbitrary and based on the inclusion criteria for trials. The first true trial on sequencing therapy has recently been initiated in collaboration with ENETS: the SEQTOR trial compares the sequence of consecutively STZ/5-FU and everolimus [88].

But also in the surgical field, many questions remain. For which appendiceal NET is hemicolectomy indicated, and should we resect the primary tumor in metastatic small intestinal NET? But also, can surveillance be justified in small pancreatic NETs? ENETS have initiated prospective trials studying resection of the primary and surveillance of small pancreatic NET.

Outside the guidelines, ENETS have developed their Centers of Excellence programs. The greatest benefit for patients is that expert centers are clearly identifiable, but also that patient care is monitored by the yearly submission of treatment data for quality control.

In conclusion, the guideline is only a small part in patient care. Reaching a high standard of patient care starts with organizing scientific meetings to exchange basic science on which the eventual treatments of the future are based and ends with monitoring the quality of care at the bedside through the ENETS Centers of Excellence pro-

gram. In between lie the guidelines which advise the clinician on the treatment of choice. The effect of the ENETS guidelines on patient care cannot simply be quantified, as end points would be biased and flawed, but sometimes evidence is not necessary to notice the benefit.

For the ENETS guidelines, this benefit lies in its advice to the unexperienced clinician, the critical appraisal of the literature, and the identification of gaps in current evidence.

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