Evolution towards contemporary diagnostics and treatment of neuroendocrine tumors and current controversies

Based on
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) have 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 (PRRT) 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.

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 gastoenteropancreatic 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 were published in 2004, and in 2016 the third version of these guidelines have been published. In 2017, the second version of the ENETS *Standards of Care* were published, thereby pursuing one of the main goals of the society. In this review we will discuss the evolution of guidelines and standards over the recent years.

Radiological and nuclear imaging

If a neuroendocrine tumor 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 non-functional NET syndromes, somatostatin receptor-scintigraphy (SRS) was advised with a reported sensitivity and specificity at that time of respectively 90 and 80%. 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}FDG-PET/CT was considered not to be useful in the diagnostic work-up. 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 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 as first-line treatment. SRS detects tumors that express the somatostatin receptor subtypes 2 ,3 and 5. These are mainly NETs, including, pheochromocytoma and other paragangliomas but also meningiomas, 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-pentreotide (OctreoScan®) was the most widely used SRS until very recently.[8-11] Currently SRS with ^{111}In-pentereotide is rapidly losing ground to PET/CT with gallium-labeled somatostatin analogs (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 one hour in advance of the scanning procedure, whereas SRS can only be performed 24 hours after injection of ^{111}In-pentreotide. 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 ^{99m}Tc-biphosphonates 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 SSA's (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 on this change in diagnostic approach.[5]

Also, several studies have now shown the usefulness of ^{18}F-FDG-PET/CT in the diagnostic work-up 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 WHO2017 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 neuroendocrine carcinomas (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 and colleagues* in 2010 and the diagnostic sequences for the pathological diagnosis of NETs are now well defined.[25] 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 neuroendocrine tumor 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 have been changed in the new WHO2017 guideline: a very slight change in the grade 1-2 cut-off has been implemented (grade 1: Ki67 ≤ 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 WHO2017 guideline advises to classify neuroendocrine tumors with a Ki67 >20% as either grade 3 NET (well-differentiated) or as grade 3 neuroendocrine carcinoma (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 Peptide Receptor Radionuclide Therapy (PRRT) or targeted therapy. To aid in the grading of NETs immunohistochemical markers can be useful. Loss of Rb or abnormal p53 expression is often seen in grade 3 NEC while loss of ATRX and DAXX expression is associated with well-differentiated neuroendocrine tumors.[33]

After the correct diagnosis of neuroendocrine tumor, staging should always be performed. ENETS has been leading the effort for a standardized approach. On behalf of ENETS, *Rindi and colleagues* published a TNM classification for neuroendocrine tumors and this is also used in guidelines produced by ENETS and many other international studies and groups.[27,28] 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 trough 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 have screening for serotonin secretion by determining 5-hydroxy indole acetic acid (5-HIAA) levels in the urine or plasma. Patients with elevated levels of this serotonin breakdown product might require somatostatin analogue 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 2cm, 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 non-functioning 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 panceaticoduodenectomy).[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 the survival is 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 for 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, 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 NET >2 cm, but new and better evidence is urgently needed to select patients for this procedure.

For non-resectable, 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 50-88 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 to commence SSA's in patients with functioning (hormone or peptide secreting) NETs since clinical evidence for their growth-inhibiting potential is non-functioning 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 anti-proliferative effect of SSA's. In the pre-ENETS era, Scandinavia studies already showed growth inhibition in NETs with treatment of high doses of SSAs.[57,58] First published was the PROMID trial, demonstrating that 30mg of octreotide LAR every four 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 progression free survival increased from 18.0 months for placebo to median PFS not reached for lanreotide 120mg every four 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 for SSAs, new forms of SSAs (single- versus multiple SSA receptor), new formulations and whether to continue SSAs

during second-line therapy, like peptide receptor nuclide therapy (PRRT) using radiolabeled SSAs and targeted therapy.

PRRT

In the early ENETS guidelines, evidence for PRRT with radiolabeled SSAs was limited. The first large observational study on PRRT using ^{177}Lu-octreotate, including 310 patients with gastroentropancreatic NET was only published in 2008 by *Kwekkeboom and colleagues.* A median PFS of 40 months was reported, which at that time was far superior to any other available therapy (chemotherapy or interferon-α).[62] 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 60mg per four 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 to 0.33; P<0.001). Through this trial ^{177}Lu-DOTA-octreotate will 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 three 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 to 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 non-functional NETs.[67,68] Again everolimus was shown to increase PFS with a 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 NET. 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 has 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 SSA's.[4,55] Interferon is a cytokine that has anti-proliferative and anti-secretory effect in NETs.[70] Our knowledge on the response to interferon is largely based on the work of *Öberg* in the 1990's.[71-73] Partial response occurs in around 10-15% of NETs and this is comparable to treatment with SSA's . However, the burden of evidence for SSA's is higher and the unfavorable side-effects of interferon, make SSA's the first line treatment for metastatic NETs.[74] These side-effect comprise 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 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 patient with refractory carcinoid syndrome.

Chemotherapy

For the treatment of poorly differentiated grade 3 NEC chemotherapy is the first option. NEC's are treated similar to small cell lung carcinoma's, with platinum based chemotherapy and this not changed 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 to 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 NEC. New in current guidelines is the growing burden of evidence for second-line treatments with oxaliplatin- or irinotecan-based regimes.[76,77]

Since the first study of *Moertel* in 1980, the combination of streptozotocin and 5-flurouracil (STZ/5-FU) has been used for treatment for metastatic pancreatic NET.[79] 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 NET.[80,81] Chemotherapy with temozolomide and capecetabine 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. Radiofrequent ablation (RFA) is a commonly used technique for liver

metastases smaller than 5 centimeters.[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 ^{90}Ytrium show very promising response rate of up to 80% in selected studies, but on average around 50% (complete and partial response).[84-86] No Standard of Care by ENETS exists at this time for embolization, but it is included in the current guidelines for selected patients with high liver burden.

REFERENCES

1. (http://www.enets.org/what_is_enets.html) (http://www.enets.org/what_is_enets.html)
2. Ricke J, Klose KJ, Mignon M, Oberg K, Wiedenmann B. Standardisation of imaging in neuroendocrine tumours: results of a European delphi process. *Eur J Radiol* 2001; **37**(1): 8-17.
3. Vezzosi D, Bennet A, Courbon F, Caron P. Short- and long-term somatostatin analogue treatment in patients with hypoglycaemia related to endogenous hyperinsulinism. *Clin Endocrinol (Oxf)* 2008; **68**(6): 904-11.
4. Plockinger U, Rindi G, Arnold R, et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). *Neuroendocrinology* 2004; **80**(6): 394-424.
5. Sundin A, Arnold R, Baudin E, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Radiological, Nuclear Medicine and Hybrid Imaging. *Neuroendocrinology* 2017.
6. Elias D, Lefevre JH, Duvillard P, et al. Hepatic metastases from neuroendocrine tumors with a "thin slice" pathological examination: they are many more than you think. *Ann Surg* 2010; **251**(2): 307-10.
7. Krenning EP, Bakker WH, Breeman WA, et al. Localisation of endocrine-related tumours with radioiodinated analogue of somatostatin. *Lancet* 1989; **1**(8632): 242-4.
8. de Herder WW, Hofland LJ, van der Lely AJ, Lamberts SW. Somatostatin receptors in gastroenteropancreatic neuroendocrine tumours. *Endocr Relat Cancer* 2003; **10**(4): 451-8.
9. Lebtahi R, Cadiot G, Sarda L, et al. Clinical impact of somatostatin receptor scintigraphy in the management of patients with neuroendocrine gastroenteropancreatic tumors. *J Nucl Med* 1997; **38**(6): 853-8.
10. Balon HR, Brown TL, Goldsmith SJ, et al. The SNM practice guideline for somatostatin receptor scintigraphy 2.0. *J Nucl Med Technol* 2011; **39**(4): 317-24.
11. Balon HR, Goldsmith SJ, Siegel BA, et al. Procedure guideline for somatostatin receptor scintigraphy with (111)In-pentetreotide. *J Nucl Med* 2001; **42**(7): 1134-8.
12. Buchmann I, Henze M, Engelbrecht S, et al. Comparison of 68Ga-DOTATOC PET and 111In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. *Eur J Nucl Med Mol Imaging* 2007; **34**(10): 1617-26.
13. Gabriel M, Decristoforo C, Kendler D, et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. *J Nucl Med* 2007; **48**(4): 508-18.
14. Geijer H, Breimer LH. Somatostatin receptor PET/CT in neuroendocrine tumours: update on systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging* 2013; **40**(11): 1770-80.
15. Johnbeck CB, Knigge U, Kjaer A. PET tracers for somatostatin receptor imaging of neuroendocrine tumors: current status and review of the literature. *Future Oncol* 2014; **10**(14): 2259-77.
16. Yang J, Kan Y, Ge BH, Yuan L, Li C, Zhao W. Diagnostic role of Gallium-68 DOTATOC and Gallium-68 DOTATATE PET in patients with neuroendocrine tumors: a meta-analysis. *Acta Radiol* 2014; **55**(4): 389-98.
17. Ambrosini V, Nanni C, Zompatori M, et al. (68)Ga-DOTA-NOC PET/CT in comparison with CT for the detection of bone metastasis in patients with neuroendocrine tumours. *Eur J Nucl Med Mol Imaging* 2010; **37**(4): 722-7.
18. Putzer D, Gabriel M, Henninger B, et al. Bone metastases in patients with neuroendocrine tumor: 68Ga-DOTA-Tyr3-octreotide PET in comparison to CT and bone scintigraphy. *J Nucl Med* 2009; **50**(8): 1214-21.
19. Poeppel TD, Binse I, Petersenn S, et al. 68Ga-DOTATOC versus 68Ga-DOTATATE PET/CT in functional imaging of neuroendocrine tumors. *J Nucl Med* 2011; **52**(12): 1864-70.

20. Velikyan I, Sundin A, Sorensen J, et al. Quantitative and qualitative intrapatient comparison of 68Ga-DOTATOC and 68Ga-DOTATATE: net uptake rate for accurate quantification. *J Nucl Med* 2014; **55**(2): 204-10.
21. Binderup T, Knigge U, Loft A, et al. Functional imaging of neuroendocrine tumors: a head-to-head comparison of somatostatin receptor scintigraphy, 123I-MIBG scintigraphy, and 18F-FDG PET. *J Nucl Med* 2010; **51**(5): 704-12.
22. Binderup T, Knigge U, Loft A, Federspiel B, Kjaer A. 18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. *Clin Cancer Res* 2010; **16**(3): 978-85.
23. Kashyap R, Hofman MS, Michael M, et al. Favourable outcomes of (177)Lu-octreotate peptide receptor chemoradionuclide therapy in patients with FDG-avid neuroendocrine tumours. *Eur J Nucl Med Mol Imaging* 2015; **42**(2): 176-85.
24. Perren A, Couvelard A, Scoazec JY, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pathology: Diagnosis and Prognostic Stratification. *Neuroendocrinology* 2017.
25. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas* 2010; **39**(6): 707-12.
26. Pape UF, Niederle B, Costa F, et al. ENETS Consensus Guidelines for Neuroendocrine Neoplasms of the Appendix (Excluding Goblet Cell Carcinomas). *Neuroendocrinology* 2016; **103**(2): 144-52.
27. Rindi G, Kloppel G, Couvelard A, et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2007; **451**(4): 757-62.
28. Rindi G, Kloppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2006; **449**(4): 395-401.
29. Pape UF, Jann H, Muller-Nordhorn J, et al. Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors. *Cancer* 2008; **113**(2): 256-65.
30. Strosberg J, Nasir A, Coppola D, Wick M, Kvols L. Correlation between grade and prognosis in metastatic gastroenteropancreatic neuroendocrine tumors. *Hum Pathol* 2009; **40**(9): 1262-8.
31. Dhall D, Mertens R, Bresee C, et al. Ki-67 proliferative index predicts progression-free survival of patients with well-differentiated ileal neuroendocrine tumors. *Hum Pathol* 2012; **43**(4): 489-95.
32. Lloyd RV, Osamura RY, Klöppel G, et al. WHO classification of tumours of endocrine organs. 4th edition. ed.
33. Tang LH, Basturk O, Sue JJ, Klimstra DS. A Practical Approach to the Classification of WHO Grade 3 (G3) Well-differentiated Neuroendocrine Tumor (WD-NET) and Poorly Differentiated Neuroendocrine Carcinoma (PD-NEC) of the Pancreas. *Am J Surg Pathol* 2016; **40**(9): 1192-202.
34. Rindi G, Falconi M, Klersy C, et al. TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. *J Natl Cancer Inst* 2012; **104**(10): 764-77.
35. Oberg K. The genetics of neuroendocrine tumors. *Semin Oncol* 2013; **40**(1): 37-44.
36. Partelli S, Bartsch DK, Capdevila J, et al. ENETS Consensus Guidelines for Standard of Care in Neuroendocrine Tumours: Surgery for Small Intestinal and Pancreatic Neuroendocrine Tumours. *Neuroendocrinology* 2017.
37. Oberg K, Couvelard A, Delle Fave G, et al. ENETS Consensus Guidelines for Standard of Care in Neuroendocrine Tumours: Biochemical Markers. *Neuroendocrinology* 2017.
38. Kaltsas G, Caplin M, Davies P, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pre- and Perioperative Therapy in Patients with Neuroendocrine Tumors. *Neuroendocrinology* 2017.

39. Wiedenmann B, Jensen RT, Mignon M, et al. Preoperative diagnosis and surgical management of neuroendocrine gastroenteropancreatic tumors: general recommendations by a consensus workshop. *World J Surg* 1998; **22**(3): 309-18.
40. Sadot E, Reidy-Lagunes DL, Tang LH, et al. Observation versus Resection for Small Asymptomatic Pancreatic Neuroendocrine Tumors: A Matched Case-Control Study. *Ann Surg Oncol* 2016; **23**(4): 1361-70.
41. Gaujoux S, Partelli S, Maire F, et al. Observational study of natural history of small sporadic nonfunctioning pancreatic neuroendocrine tumors. *J Clin Endocrinol Metab* 2013; **98**(12): 4784-9.
42. Asymptomatic Small Pancreatic Endocrine Neoplasms. 2017. https://clinicaltrials.gov/ct2/show/NCT03084770.
43. Norton JA, Fraker DL, Alexander HR, Jensen RT. Value of surgery in patients with negative imaging and sporadic Zollinger-Ellison syndrome. *Ann Surg* 2012; **256**(3): 509-17.
44. Giovinazzo F, Butturini G, Monsellato D, Malleo G, Marchegiani G, Bassi C. Lymph nodes metastasis and recurrences justify an aggressive treatment of gastrinoma. *Updates Surg* 2013; **65**(1): 19-24.
45. Weber HC, Venzon DJ, Lin JT, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. *Gastroenterology* 1995; **108**(6): 1637-49.
46. Yu F, Venzon DJ, Serrano J, et al. Prospective study of the clinical course, prognostic factors, causes of death, and survival in patients with long-standing Zollinger-Ellison syndrome. *J Clin Oncol* 1999; **17**(2): 615-30.
47. Falconi M, Eriksson B, Kaltsas G, et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. *Neuroendocrinology* 2016; **103**(2): 153-71.
48. Ruszniewski P, Podevin P, Cadiot G, et al. Clinical, anatomical, and evolutive features of patients with the Zollinger-Ellison syndrome combined with type I multiple endocrine neoplasia. *Pancreas* 1993; **8**(3): 295-304.
49. Mullen JT, Savarese DM. Carcinoid tumors of the appendix: a population-based study. *J Surg Oncol* 2011; **104**(1): 41-4.
50. Moertel CG, Weiland LH, Nagorney DM, Dockerty MB. Carcinoid tumor of the appendix: treatment and prognosis. *N Engl J Med* 1987; **317**(27): 1699-701.
51. Fornaro R, Frascio M, Sticchi C, et al. Appendectomy or right hemicolectomy in the treatment of appendiceal carcinoid tumors? *Tumori* 2007; **93**(6): 587-90.
52. Bokey EL, Chapuis PH, Fung C, et al. Postoperative morbidity and mortality following resection of the colon and rectum for cancer. *Dis Colon Rectum* 1995; **38**(5): 480-6; discussion 6-7.
53. Niederle B, Pape UF, Costa F, et al. ENETS Consensus Guidelines Update for Neuroendocrine Neoplasms of the Jejunum and Ileum. *Neuroendocrinology* 2016; **103**(2): 125-38.
54. Capurso G, Rinzivillo M, Bettini R, Boninsegna L, Delle Fave G, Falconi M. Systematic review of resection of primary midgut carcinoid tumour in patients with unresectable liver metastases. *Br J Surg* 2012; **99**(11): 1480-6.
55. Pavel M, O'Toole D, Costa F, et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. *Neuroendocrinology* 2016; **103**(2): 172-85.
56. Imam H, Eriksson B, Lukinius A, et al. Induction of apoptosis in neuroendocrine tumors of the digestive system during treatment with somatostatin analogs. *Acta oncologica (Stockholm, Sweden)* 1997; **36**(6): 607-14.
57. Eriksson B, Janson ET, Bax ND, et al. The use of new somatostatin analogues, lanreotide and octastatin, in neuroendocrine gastro-intestinal tumours. *Digestion* 1996; **57 Suppl 1**: 77-80.

58. Eriksson B, Renstrup J, Imam H, Oberg K. High-dose treatment with lanreotide of patients with advanced neuroendocrine gastrointestinal tumors: clinical and biological effects. *Ann Oncol* 1997; **8**(10): 1041-4.
59. Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 2009; **27**(28): 4656-63.
60. Caplin ME, Pavel M, Ruszniewski P. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014; **371**(16): 1556-7.
61. Pavel M, Valle JW, Eriksson B, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms: Systemic Therapy - Biotherapy and Novel Targeted Agents. *Neuroendocrinology* 2017.
62. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol* 2008; **26**(13): 2124-30.
63. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med* 2017; **376**(2): 125-35.
64. Hicks RJ, Kwekkeboom DJ, Krenning E, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasia: Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogues. *Neuroendocrinology* 2017.
65. Pavel M, Baudin E, Couvelard A, et al. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* 2012; **95**(2): 157-76.
66. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364**(6): 514-23.
67. Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 2011; **378**(9808): 2005-12.
68. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 2016; **387**(10022): 968-77.
69. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364**(6): 501-13.
70. Platanias LC. Mechanisms of type-I- and type-II-interferon-mediated signalling. *Nat Rev Immunol* 2005; **5**(5): 375-86.
71. Oberg K, Funa K, Alm G. Effects of leukocyte interferon on clinical symptoms and hormone levels in patients with mid-gut carcinoid tumors and carcinoid syndrome. *N Engl J Med* 1983; **309**(3): 129-33.
72. Oberg K, Eriksson B. The role of interferons in the management of carcinoid tumours. *Br J Haematol* 1991; **79 Suppl 1**: 74-7.
73. Oberg K. Interferon-alpha versus somatostatin or the combination of both in gastro-enteropancreatic tumours. *Digestion* 1996; **57 Suppl 1**: 81-3.
74. Eriksson B, Kloppel G, Krenning E, et al. Consensus guidelines for the management of patients with digestive neuroendocrine tumors--well-differentiated jejunal-ileal tumor/carcinoma. *Neuroendocrinology* 2008; **87**(1): 8-19.
75. Pavel ME, Baum U, Hahn EG, Schuppan D, Lohmann T. Efficacy and tolerability of pegylated IFN-alpha in patients with neuroendocrine gastroenteropancreatic carcinomas. *Journal of interferon & cytokine*

research : the official journal of the International Society for Interferon and Cytokine Research 2006; **26**(1): 8-13.

76. Garcia-Carbonero R, Sorbye H, Baudin E, et al. ENETS Consensus Guidelines for High-Grade Gastroenteropancreatic Neuroendocrine Tumors and Neuroendocrine Carcinomas. *Neuroendocrinology* 2016; **103**(2): 186-94.
77. Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol* 2012; **24**(1): 152-60.
78. Moertel CG, Kvols LK, O'Connell MJ, Rubin J. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer* 1991; **68**(2): 227-32.
79. Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. *N Engl J Med* 1980; **303**(21): 1189-94.
80. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG, Eastern Cooperative Oncology G. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. *J Clin Oncol* 2005; **23**(22): 4897-904.
81. Dahan L, Bonnetain F, Rougier P, et al. Phase III trial of chemotherapy using 5-fluorouracil and streptozotocin compared with interferon alpha for advanced carcinoid tumors: FNCLCC-FFCD 9710. *Endocr Relat Cancer* 2009; **16**(4): 1351-61.
82. Ducreux M, Adenis A, Pignon JP, et al. Efficacy and safety of bevacizumab-based combination regimens in patients with previously untreated metastatic colorectal cancer: final results from a randomised phase II study of bevacizumab plus 5-fluorouracil, leucovorin plus irinotecan versus bevacizumab plus capecitabine plus irinotecan (FNCLCC ACCORD 13/0503 study). *Eur J Cancer* 2013; **49**(6): 1236-45.
83. de Baere T, Elias D, Dromain C, et al. Radiofrequency ablation of 100 hepatic metastases with a mean follow-up of more than 1 year. *AJR Am J Roentgenol* 2000; **175**(6): 1619-25.
84. de Baere T, Deschamps F, Tselikas L, et al. GEP-NETS update: Interventional radiology: role in the treatment of liver metastases from GEP-NETs. *Eur J Endocrinol* 2015; **172**(4): R151-66.
85. Devcic Z, Rosenberg J, Braat AJ, et al. The efficacy of hepatic 90Y resin radioembolization for metastatic neuroendocrine tumors: a meta-analysis. *J Nucl Med* 2014; **55**(9): 1404-10.
86. Maire F, Lombard-Bohas C, O'Toole D, et al. Hepatic arterial embolization versus chemoembolization in the treatment of liver metastases from well-differentiated midgut endocrine tumors: a prospective randomized study. *Neuroendocrinology* 2012; **96**(4): 294-300.