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CLINICAL GUIDELINE

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European Neuroendocrine Tumour Society (ENETS) 2023 guidance paper for nonfunctioning pancreatic neuroendocrine tumours

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Abstract

This ENETS guidance paper for well-differentiated nonfunctioning pancreatic neuroendocrine tumours (NF-Pan-NET) has been developed by a multidisciplinary working group, and provides up-to-date and practical advice on the management of these tumours. Using the extensive experience of centres treating patients with NF-Pan-NEN, the authors of this guidance paper discuss 10 troublesome questions in everyday clinical practice. Our many years of experience in this field are still being verified in the light of the results of new clinical, which set new ways of proceeding in NEN. The treatment of NF-Pan-NEN still requires a decision of a multidisciplinary team of specialists in the field of neuroendocrine neoplasms.

KEYWORDS
diagnostics, guideline, neuroendocrine tumour, pancreatic nonfunctioning neuroendocrine tumour, treatment

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1 | INTRODUCTION

This ENETS guidance paper for the management of well-differentiated nonfunctioning pancreatic neuroendocrine tumours (NF-Pan-NET) aims to answer 10 major questions (Table 1) on the management of these neoplasms.

Data were identified by MEDLINE database searches and expert opinion. Recommendations are given according to the best available evidence and authors' experience and will have a level of evidence (1–5) and strength of recommendation (A–D) (Table 2) as per the GRADE system.[1]

The incidence of Pan-NET is rising, most recently reported as 0.48 per 100,000 new cases per year according to the Surveillance, Epidemiology, and End Results (SEER) Programme; although Pan-NET carry an unfavourable prognosis compared to NET from other primary sites, an improvement in overall survival (OS) has been observed over time (median OS of 3.6 years), particularly in patients with distant metastases.[2]

The majority (between 50% and 85%) of Pan-NET are nonfunctioning. Moreover, NF-Pan-NET tend to present with more advanced disease (more advanced tumour [T]-stage, lymph node involvement and liver metastases) and arise in the head of the pancreas. Consequently, patients with NF-Pan-NET have a significantly worse OS than their functioning counterparts ($p < .001$).[3,4]

In patients undergoing curative resection, a shorter survival was observed in patients with NF-Pan-NET, lymphatic invasion, and size >10 cm, while a shorter disease-free survival (DFS) was associated with advanced pT-stage (pT3–4), size >5 cm and histological grade (G) 2–3. Ki-67 > 10% predicted a poorer prognosis.[5]

TABLE 1 Ten major questions on management of nonfunctioning pancreatic neuroendocrine tumours.

Q1	How should we define and characterise a NF-Pan-NET patient at clinical presentation?
Q2	Which biochemical tests should be performed in a patient with NF-Pan-NET?
Q3	Which is the most suitable imaging work-up for NF-Pan-NET patients?
Q4	What is the appropriate surgical management of NF-Pan-NET?
Q5	What is the role of PRRT in patiente with NF-Pan-NET?
Q6	What is the role of biotherapy and molecular targeted therapies in patients with advanced NF-Pan-NET?
Q7	What is the role of chemotherapy in patients with advanced NF-Pan-NET?
Q8	In the setting of advanced disease, which is the most suitable first-line systemic therapy? Which sequence of treatments should be used?
Q9	Is there a specific work-up in MEN1-associated NF-Pan-NET patients?
Q10	What is the recommended follow-up in NF-Pan-NET patients?

2 | DIAGNOSIS

2.1 | Q1. How should we define and characterise a NF-Pan-NET at presentation?

While the diagnosis of functionality relies on the presence of a hormonal syndrome, the NET-diagnosis relies on histological or cytological analysis. Histopathological diagnosis is based on the neuroendocrine growth pattern, including nesting, trabecular, gyriform and solid architecture, as well as the expression of neuroendocrine markers including synaptophysin and chromogranin A (CgA).[6] It should be noted that in the pancreas, especially acinic cell carcinoma, solid pseudopapillary neoplasm and paraganglioma can be positive for these markers, and therefore they should be actively excluded.[7] More recently, the transcription factor INSM1 has emerged as a both sensitive and specific diagnostic marker of NET. Grading is assessed by

TABLE 2 Level of evidence and strength of recommendations.

Level of evidence	Therapy	Diagnosis
1a	Systematic review (with homogeneity) of RCT	Systematic review (with homogeneity) of level 1 diagnostic studies; clinical decision rules/validating cohort study with good reference standards
1b	RCT (with narrow confidence intervals)	
2a	Systematic review of cohort studies	Systematic review (with homogeneity) of level >2 diagnostic studies
2b	Individual cohort studies or low quality RCT	Exploratory cohort study with good reference standards; clinical decision rule after derivation.
3a	Systematic review (with homogeneity) of case-controlled studies	Systematic review (with homogeneity) of 3b and better studies
3b	Individual case-controlled studies	Nonconsecutive study; or without consistently applied reference standards
4	Case series (and poor-quality case-controlled studies)	Case–control study, poor or nonindependent reference standard
5	Expert opinion without explicit critical appraisal.	Expert opinion without explicit critical appraisal.
Grade of recommendation		
A	Strong	
B	Moderate	
C	Low	
D	Very low	

Abbreviation: RCT, randomised controlled trial.

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measuring proliferation using mitotic figures (expressed as mitoses/2 mm^2) and expression of the Ki-67 antigen (as percentage of all tumour cells), with cutoffs of 3% and 20% for NET G2 and G3, respectively.[8] DAXX and ATRX mutations that are accompanied by loss of nuclear expression of the respective proteins are indicative of chromosomal instability, epigenetic progression, and increased risk of recurrence after surgery with curative intent, and are therefore of additional prognostic value.[9] Specifically, analysis of a large international cohort of sporadic NET indicated that ATRX/DAXX and ALT were independent negative prognostic factors providing evidence suggesting their evaluation particularly in ≤2.0 cm tumours.[10] Somatostatin receptor-2 (SST2) expression can be assessed by immunohistochemistry, especially, if no preoperative somatostatin-receptor imaging (SRI) was performed.[11]

In the case of suspected pancreatic metastases from another primary cancer, transcription factors with some specificity for NET organs of origin (TTF-1 for lung and thyroid, CDX-2 for ileum and Islet-1 for pancreas) can be used.[12] Immunohistochemical expression of hormones is frequently observed in NF-Pan-NET, and their presence alone does not justify defining a Pan-NET as functioning unless a related clinical syndrome is present. Expression of cytokeratin excludes the rare occurrence of intrapancreatic paraganglioma.

Further molecular grouping using RNAseq and methylation arrays may provide additional diagnostic (cell and organ of origin) or prognostic value, but are as yet not routinely used. The clinical utility of these markers to predict benefit from specific therapies remains to be demonstrated in prospective studies.

In rare cases (<10%), NF-Pan-NET may become functioning and present hormonal symptoms during the clinical evolution of the disease. This underscores the importance of detailed assessment of symptoms at each follow-up visit, particularly in patients with familial NF-Pan-NET.

Histological confirmation of small (<1–2 cm) incidental NF-Pan-NET is recommended, if possible, to exclude the possibility of other somatostatin-avid lesions in the pancreas such as an ectopic spleen, PP-islets, or the rare occurrence of metastasis from other neoplasms. While small biopsy sample analysis carries a risk of under-grading due to sampling bias, it can allow the confirmation of NET diagnosis. If patients are to be followed-up only, exclusion of a higher grade or, as mentioned above, the presence of DAXX/ATRX loss, may be helpful.[6]

Genetic counselling is indicated in the setting of multiple Pan-NET, the combination with pancreatic nesidioblastosis, extra-pancreatic involvement suggestive of other polyendocrine tumours (type 1 or type 4 multiple endocrine neoplasia [MEN] or von Hippel–Lindau [VHL] disease), or if Pan-NET occur in young patients (30–50 years). The relevance of the reported observation of DNA damage repair gene mutations in up to 10% of apparently sporadic Pan-NET patients is not yet clear.[13]

2.1.1 | Recommendations

1. The histopathological work-up of a Pan-NET must include the demonstration of two endocrine markers and assessment of proliferation (Ki-67 index) (Level of evidence 1: Grade of recommendation A).
2. Suspected small (<2 cm) NF-Pan-NET with a positive somatostatin-receptor imaging should be histologically/cytologically confirmed if possible (Level of evidence 3: Grade of recommendation B).

2.2 | Q2. Which biochemical tests should be performed in a patient with NF-Pan-NET (current and novel biomarkers)?

2.2.1 | Nonspecific markers

The determination of CgA levels in serum is not a reliable marker for making a diagnosis of NF-Pan-NET; as this polypeptide is secreted by neuroendocrine cells, it is not specific for NF-Pan-NET and has many interferences causing false elevations.[14,15]

However, CgA may be reliable in the assessment of response to treatment, and for the detection of disease progression and recurrence. To monitor the course of the disease, it is advisable to determine CgA with the same assessment method, which should be standardised.[16]

A useful circulating marker for NF-Pan-NET might be the serum pancreatic polypeptide (PP), especially for NET included in the MEN-1 syndrome. Nevertheless, the percentage of patients with elevated PP concentration is much lower than that of patients with elevated CgA concentration.[16,17]

High hopes have been placed on new molecular markers. The NETest is a blood multianalyte biomarker test where the expression profile of selected gene transcripts characteristic for NEN is analysed. NETest has been reported superior to circulating CgA; it showed a significant advantage over other molecular biomarkers in the diagnosis and monitoring of NEN, may be used to monitor the effectiveness of treatment, and the assessment of disease progression.[18–21] It is not specific for NF-Pan-NET however, and its clinical-practical usefulness is therefore lessened.

Circulating microRNAs are potential biomarkers of NEN, not least due to their presence stability in body fluids and specificity for a given tumour,[22,23] but their clinical significance has to be further investigated.

2.2.2 | Specific markers

The assessment of the blood level of specific markers (gastrin, insulin, serotonin, vasoactive intestinal polypeptide [VIP], glucagon, somatostatin) can be determined at the first patient visit to identify patients with functioning syndromes. In the absence of hormonal symptoms, further monitoring of these tests is not recommended.

In patients with Pan-NET, tests for MEN-1 syndrome should be performed in the presence of clinical or pathological suspicion (cf Q1). Basic screening tests in patients with suspected or documented MEN-1 include the assessment of ionised or total calcium, parathyroid

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hormone (intact PTH), prolactin and insulin-like growth factor 1 (IGF-1). In patients with suspected MEN-1 based on these tests, genetic counselling and genetic testing should be performed to identify mutations in the menin-encoding MEN1 gene.[15–17,22,24]

2.2.3 | Recommendations

1. No routine circulating biomarkers are established for NF-Pan-NET diagnosis; CgA determination may be useful in monitoring the course of the disease. If the MEN-1 is suspected, it is advisable to determine the concentration of calcium, PTH, and pituitary hormones (mainly prolactin) (Level of evidence 3b: Grade of recommendation B).

2.3 | Q3. What is the most suitable imaging work-up for NF-Pan-NET patients

The imaging requirements will vary on the clinical scenario; these are set out below.

2.4 | Identification of NF-Pan-NET

The imaging modalities allowing identification and characterisation of NF-Pan-NET consist of multiphasic contrast-enhanced computed tomography (CECT), dynamic contrast-enhanced magnetic resonance imaging (MRI) including diffusion-weighted imaging (DWI) and magnetic resonance cholangio-pancreatography (MRCP), somatostatin receptor imaging (SRI) (preferably using positron emission tomography (PET)/CT) and endoscopic ultrasonography (EUS) (optionally with intravenous contrast material). Transabdominal ultrasound has limited sensitivity for Pan-NET even with the use of intravenous contrast material (contrast-enhanced ultrasound-CEUS).

The sequence of imaging modalities should be selected based on individual considerations. MRI is the least invasive modality (no endoscopy, no ionising radiation). Early arterial phases of contrast-enhanced CT and MRI should be performed to detect hyperarterialised NF-Pan-NET. Somatostatin receptor (SST) PET/CT is advantageous for definitive NET diagnosis (although it does not circumvent the need for pathological examination) and provides whole-body staging with high accuracy. EUS is highly sensitive for NF-Pan-NET, notably when their small size limits their detection with other imaging modalities.

Tumour sampling should be carried out on the most easily-accessible tumour site. Hence, it is recommended to perform EUS-guided fine-needle aspiration (EUS-FNA) or EUS-guided fine-needle biopsy sampling (EUS-FNB) of the primary Pan-NET (or percutaneous CT-guided biopsy in case of repeated failure) in the absence of metastases or in cases of inaccessible metastases. Otherwise, percutaneous ultrasound-, CT-, or MRI-guided biopsies of metastases are preferred, especially where there is liver involvement.

2.5 | Therapy planning

2.5.1 | Whole-body staging

Full staging of NF-Pan-NET should be performed using the best performing imaging techniques [CT, MRI, and SRI (preferably with PET/CT)] to obtain accurate information about the extension of the disease.

Transabdominal ultrasound is often an initial test, especially in the identification of liver metastases. Even though CEUS can improve the detection of liver lesions and may enable quick adjustment of the subsequent diagnostic pathway, its limited reproducibility and lack of comprehensive image material for later discussions in tumour boards support different imaging modalities to allow for therapy decisions.

Contrast-enhanced abdominopelvic CT is the basic imaging modality for initial work-up and follow-up as it has a significant yield for diagnosis, local and distant staging and restaging.[25] It must be performed with (at least) acquisitions at the arterial (25–30 s, bolus tracking recommended) and then the portal venous (70–90 s) phases, since some highly vascularised NF-Pan-NET are only visible at one phase or another.[26] Early hyperenhancement in multiphasic CT of NF-Pan-NET and related metastases may be associated with slower tumour progression.[27] Chest CT (optimally in full inspiration) must be performed for distant staging, at least for locally advanced (T4, N+) or metastatic NF-Pan-NET and in patients with MEN1.

The functional imaging modality of choice for initial staging is SST-PET/CT and should be considered for all patients with NF-Pan-NET. It has high diagnostic accuracy, superior to CT alone, and has demonstrated significant impact on clinical decisions.[28] SST-PET/CT has almost entirely replaced scintigraphy including SPECT. SST-PET is not a substitute for morphological imaging by contrast-enhanced CT or MRI because it lacks anatomic topography. SST-PET/CT may be performed using ^{68}Ga-DOTATATE, ^{68}Ga-DOTA-TOC or ^{68}Ga-DOTANOC, with no strong arguments for choosing one over another. In addition, SST-PET/CT may now be performed using ^{64}Cu-DOTATATE that has been approved in the USA, or under a compassionate use permission in Europe, and seems to have a better lesion detection ability.[29] Low uptake on SST-PET is correlated with poor prognosis[30] while high uptake predicts efficacy of peptide receptor radionuclide therapy (PRRT). Hence, it is recommended for the diagnostic, prognostic and theranostic evaluation of all patients with NF-Pan-NET associated with metastases or at metastatic risk.[25,28]

^{18}Fluorodeoxyglucose [FDG] PET/CT may be valuable for prognostication and therapy planning. SRI- and FDG-PET/CT provide complementary information. FDG-PET should be performed for staging of NF-Pan-NET if no uptake is shown on SST-PET/CT. In addition, high FDG uptake correlates with a higher grade and is a strong poor prognostic factor.[31] Hence, it can be performed in NF-Pan-NET of any grade and any uptake on SSTR-PET/CT, if a positive result is expected to change patient management.

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2.5.2 | Assessment of resectability

Resectability of NF-Pan-NET depends on the extent of the primary tumour and whether metastases are present and resectable with macroscopically negative margins. In this curative-intent setting, the highest accuracy for liver metastases detection and characterisation is needed. The optimal strategy consists of liver MRI including DWI, preferably using a hepatocyte-specific contrast agent (additionally to SST-PET/CT or as hybrid SST-PET/MR).[25,32]

With regard to the primary tumour, the morphological resectability criteria are similar to those of pancreatic ductal adenocarcinoma (PDAC), including degree of vessel involvement. This can be assessed by CE dynamic CT as the method of choice, or alternatively using MRI, which was comparable to CT in a recent meta-analysis on PDAC.[33]

EUS is also useful in patients with potentially resectable NF-Pan-NET to assess tumour size, vascular involvement, relationship to the main pancreatic duct, behaviour at dynamic contrast-enhanced EUS and for EUS-guided sampling.[34,35] However, EUS and EUS-guided sampling are not recommended in situations where they are not expected to change patient management.

2.5.3 | Recommendations

1. Dedicated pancreatic imaging to search for a NF-Pan-NET should employ multiphasic contrast-enhanced CT and/or dynamic contrast-enhanced MRI including MRCP and DWI, and SST-PET/CT, and/or EUS including intravenous contrast administration based on individual considerations (Level of evidence 2a: Grade of recommendation B).
2. SST-PET/CT should be considered as the first-line functional imaging method for the initial staging and characterisation of patients with NF-Pan-NET (Level of evidence 2a: Grade of recommendation B).
3. Whole-body staging relies on contrast-enhanced CT of Chest, abdomen (at least biphasic including an early arterial contrast phase) and pelvis, and SST-PET/CT (Level of evidence 3a: Grade of recommendation B).
4. Local resectability assessment of the primary requires contrast-enhanced CT and/or MRI (Level of evidence 2a: Grade of recommendation A).
5. Liver MRI including DWI and preferably using a hepatocyte-specific contrast agent should be performed to rule out liver metastases or to precisely assess their number, distribution, resectability and accessibility to non-surgical local therapy (Level of evidence 3a: Grade of recommendation B).
6. The use of FDG-PET/CT for prognostic evaluation can be of interest in patients with NF-Pan-NET of any grade and any uptake on SRI, if its result is expected to change patient management (Level of evidence 3b: Grade of recommendation C).

3 | TREATMENT

3.1 | Q4. What is the appropriate surgical management of NF-Pan- NET?

3.1.1 | Which are the principles/aims of treatment in a patient with localised stage NF-pancreatic NET?

Curative resection for NF-Pan-NET is associated with 5-year survival rates of 70%–80%.[36] Ensuring that surgery is indicated as an appropriate therapy still remains the most important factor in order to avoid unnecessary and possibly harmful surgical procedures. It is currently established that not all localised NF-Pan-NET have the same biology. On the one hand, small, low-grade and asymptomatic NET usually have a negligible risk of malignant progression. On the other hand, large and higher-grade lesions frequently exhibit an aggressive behaviour with a high propensity for extra-pancreatic spread. It is then of paramount importance to accurately select patients and to offer a personalised surgical approach, as indicated.

NF-Pan-NET ≤2 cm show a relatively indolent behaviour with a limited risk of progression. Therefore, a surveillance strategy has generally been advocated A multicentre prospective observational study from the Netherlands (PANDORA study) is currently ongoing with the aim to evaluate the feasibility of a follow-up protocol for NF-Pan-NET ≤2 cm.[37] After a median follow-up of 17 months, 89% of 76 patients had no signs of tumour progression, whereas 11% showed an increase in tumour size of more than 0.5 cm/year. Overall, 6% of patients underwent surgery during follow-up. Of those, one patient had an unexpected intraoperative detection of peritoneal lesion and had a recurrence diagnosed during the postoperative follow-up.

ENETS has promoted another larger prospective, observational study (ASPEN study) that involves more than 40 institutions worldwide, and is currently enrolling a total of 1000 patients affected by asymptomatic NF-Pan-NET ≤2 cm. The ASPEN study will describe the real-world clinical management of this disease, including an active surveillance strategy and surgical resection for these small lesions. An interim analysis of the study has observed that the vast majority (81%) of these patients underwent a 'watchful waiting' strategy.[38] Among patients underwent surgery, histological features of aggressiveness were associated with a dilation of the main pancreatic duct. Moreover, all the patients with histological features of aggressiveness and a nondilated main duct had a tumour diameter larger than 1 cm.

Alternative treatment surgical modalities for small NF-Pan-NET have been proposed. In particular, preliminary experience has shown that radiofrequency ablation (RFA) can be effective in the treatment of these tumours. Nevertheless, robust data on the routine use of RFA in NF-Pan-NET are still lacking. A prospective, single-arm, study on the safety and efficacy of EUS-guided RFA for Pan-NET is underway (ClinicalTrials.gov Identifier: NCT03834701). Despite some initial reports, there is no evidence supporting the use of somatostatin analogues in controlling disease progression of small NF-Pan-NET during surveillance.

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When indicated, surgical resection of NF-Pan-NET should be performed according to the site of the lesion. Parenchyma-sparing pancreatic resections have been proposed to reduce the risks of postoperative pancreatic function impairment. These procedures (i.e., enucleation and central pancreatectomy) are associated with a lower risk of severe complications and have similar long-term oncologic outcomes compared to standard resection.[39] The main drawback of atypical resections is the lack of an adequate lymphadenectomy, and, for this reason, they should be avoided in patients with Pan-NET at risk for nodal metastases. Unfortunately, there are no preoperative examinations able to accurately predict the presence of nodal involvement in NF-Pan-NET.[40] Consequently, lymphadenectomy should be routinely performed for NF-Pan-NET >3 cm. The opportunity to perform an enucleation or a central pancreatectomy for lesions between 2 and 3 cm, should be carefully considered in relation to patients' comorbidities and the risk associated with an anatomical pancreatic resection.

When surgery is indicated, a minimally invasive approach is associated with an improved postoperative outcome and it should be preferred to an open approach whenever feasible, especially for all resectable NF-Pan-NET located in the body-tail of the pancreas.[41] Robust data are still lacking regarding the safety and the efficacy of minimally invasive pancreaticoduodenectomy. Nevertheless, minimally invasive pancreaticoduodenectomy, when performed in experienced centres, can be offered in selected cases after a meticulous balance of risks and benefits for the patient.

3.1.2 | Recommendations

1. Patients with asymptomatic NF-Pan-NET ≤1 cm without dilation of the main pancreatic duct should undergo active surveillance. The management of patients with NF-Pan-NET >1 cm and ≤2 cm, without dilation of the main pancreatic duct, should be personalised according to the type of needed surgical resection as well as to patients' comorbidities (Level of evidence 3: Grade of recommendation B).
2. Surgery is strongly recommended for all NF-Pan-NET associated with main pancreatic duct dilation and/or larger >2 cm (Level of evidence 3: Grade of recommendation B). A minimally invasive approach for lesions of the body-tail, and for all those that can be enucleated, should be preferred whenever possible after a careful assessment of possible associated risks (Level of evidence 3: Grade of recommendation B).

3.1.3 | What are the principles/aims of treatment in a patient with advanced stage NF-pancreatic NET?

Pancreatic resections are complex procedures with perioperative morbidity rates up to 50% and a risk of death in up to 3% in high volume centres.[42] Hence, the indication for surgery in Pan-NET, in which the gland texture is softness, needs careful selection. In localised small tumours, avoidance of unnecessary operations in the light of surveillance seems a feasible option, whereas advanced tumours need a careful risk–benefit assessment.

To date, there is no validated consensus on the definition of resectability of NF-Pan-NET. In clinical practice, locally advanced or borderline resectable tumours are classified according to the National Comprehensive Cancer Network (NCCN) definition used for PDAC. This classification is based on the involvement of surrounding vessels, distant spread, or extra-regional lymph node disease. The ENETS as well as the American Joint Cancer Committee (AJCC) staging systems define T3 and T4 tumours as either a size of >4 cm or growth beyond the pancreas (T3) or invasion of adjacent structures or arterial vessels (T4), which fits quite well with the NCCN definition of borderline or locally advanced PDAC.

To evaluate the efficacy of any surgical procedure and outweigh the risk, prediction of tumour recurrence and estimation of the chance for cure is essential. The main risk factors for recurrence after surgical resection are based on pathological factors (grade, Ki-67 index, size, perineural invasion or lymph node or distant metastasis), clinical factors (symptomatic tumours, gender, CgA level, type of surgery or imaging) and molecular factors (e.g. DAXX/ATRX loss, high Vimentin expression and loss of E-cadherin).[43] In general, risk of recurrence is reported in the range 12%–18%, with the liver as the most common site, local relapse at the resection site is uncommon (2%).[42,44,45] Heidsma et al.[44] have recently reported a large validation cohort of 342 resected G1 and G2 NF-Pan-NET patients from seven centres in Europe, showing the high predictive value of a nomogram including lymph node metastasis, G2 tumours and perineural invasion. Patients with distant metastasis, G3 NET and hereditary syndromes were excluded. In the low-risk group without any of the 3 risk factors the 5-year recurrence rate was 8%, whereas in the high-risk group the recurrence rate was 65%. Another international study group developed a similar, validated recurrence risk score (RRS; 1–10 points) in 1006 resected NF-Pan-NET patients. Points were given for LN metastasis, symptoms (jaundice, pain, or bleeding), size >2 cm and Ki-67 index. Ki-67 index >20% had the highest impact for recurrence and was therefore given 6 points. After 2 years 33% developed recurrence in the high-risk group (6–10 points) whereas only 2% recurred in the low-risk group.[46] Hence, patients after resection could be stratified into a frequent or infrequent follow-up protocol. Furthermore high risk patients might be considered for adjuvant treatment, ideally within clinical trials.

Outcome data after resection of locally advanced NF-Pan-NET are scarce. A large international cohort compared 61 patients who underwent a pancreaticoduodenectomy (PD) with portal vein resection with 480 patients having a standard PD.[47] Perioperative mortality was 1% and the complication rate was 48% in the venous resection group versus 33% in the group without. After matched pair analysis, OS and recurrences rates were not different among the groups (71% vs. 69%). The conclusion was that even extended resection including vascular reconstruction is safe with good long-term outcomes. Advances in systemic therapies opened perspectives for neoadjuvant treatments. Better local control or tumour shrinkage

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might enhance resection rates of primarily unresectable patients and improve recurrence rates. PRRT seems a promising tool for SST-positive locally advanced NF-Pan-NET or even tumours with limited distant metastasis (oligometastatic disease). The first clinical study by Partelli et al. in 2018 retrospectively compared 23 patients operated after PRRT with patients who had undergone upfront resection.[48] In addition to a higher R0 resection rate and less positive lymph nodes in the PRRT group, the postoperative pancreatic fistula (POPF) rate decreased, which might be an important safety issue after this complicated type of surgery with POPF as its most dreadful complication. These data must be validated in a prospective study, one of such has recently completed the accrual (ClinicalTrial.gov Identifier: NCT04385992), and results will be expected in 2023. Another study from India[49] assessed 57 patients with unresectable primary tumours of pancreatic or duodenal origin and/or potentially resectable oligometastatic liver lesions. PRRT with ^{177}Lu-DOTATATE lead to a complete or partial response in 84% of patients, and one out of four patients became resectable. Although these data has to be viewed with caution due to its retrospective nature and high risk of bias, this treatment strategy seems at least safe and feasible.

In clinical practice, chemotherapy is another potentially effective treatment for neoadjuvant/preoperative purposes, given the potentially high response rate associated with this therapeutic option. However, there is a need for clinical trials to assess the role of chemotherapy in these specific settings.

3.1.4 | Recommendations

1. Patients with locally advanced NF-Pan-NET (stage T3 and T4) can be resected safely with low mortality and acceptable morbidity risk in expert centres (Level of evidence 3: Grade of recommendation A).
2. Radical local resection (R0) including portal-venous resection could be considered in selected cases (Level of evidence 3: Grade of recommendation A).
3. Nomograms after resection might help to estimate the risk of recurrence and guide clinical follow up schedules (Level of evidence 3: Grade of recommendation B).
4. Preoperative treatment with PRRT in locally advanced or oligometastatic SST-PET/CT positive grade 1 and 2 NF-Pan-NET may be considered in selected cases (Level of evidence 3: Grade of recommendation B).

3.2 | Q5. What is the role of PRRT in specific settings of NF-Pan- NET

PRRT is an effective and relatively safe therapeutic option for patients with NF-Pan-NET. The two-arm randomised phase II noncomparative OCLURANDOM trial of PRRT and sunitinib in SST-PET/CT-positive advanced Pan-NET patients met its primary endpoint by achieving a significant PFS with PRRT (177Lu-DOTATATE) (median 20.7 months of PRRT and 11.0 months of sunitinib, respectively).[50]

A recent retrospective study, NETTER-R, also suggested a potential benefit of 177Lu-DOTATATE as a treatment option in Pan-NET.[51]

Current clinical trials are focusing on the prospective evaluation of PRRT in Pan-NET (including G3) and in the first-line (NCT03972488, NCT04919226).

In 2020, a combined analysis of two prospective and six retrospective studies using PRRT in Pan-NET was published, showing a median PFS ranging from 20 to 39 months and median OS from 37 to 79 months (PFS and OS were comparable for gastroenteropancreatic (GEP)-NET from different locations).[52]

There are still limited data on the efficacy of PRRT for Pan-NET G3. In 2019, Zhang et al. reported the results of PRRT with ^{177}Lu/^{90}Y- (DOTATATE or DOTATOC) in 69 patients, including 46 patients with Pan-NET. Promising results have been obtained especially in patients with Ki-67 ≤ 55%.[53] Carlsen et al. published a study of NET G3 and NEC where 89 patients were G3 Pan-NET or Pan-NEC and they found promising response rates in these highly selected patient populations.[54] Similar results were obtained by Thang et al. in a group of 17 patients (17/28) with G3 Pan-NET with or without radiosensitising chemotherapy.[55] Nevertheless, it is necessary to perform prospective studies to fully define the role of PRRT in Pan-NET G3.

PRRT can be used in the treatment of NF-Pan-NET G3 with high SST expression only within clinical trials. Currently, the NETTER-2 trial (clinicaltrials.gov NCT03972488) comparing PRRT with high-dose octreotide LAR completed the accrual and its results are waiting. Furthermore the COMPOSE trial (NCT04919226) is ongoing, to compare PRRT with chemotherapy or everolimus in higher grade 2 and G3 GEP NET.[24,56–59]

Based on the studies published so far, it can be said that for SSTR-positive NF-Pan-NET there are several lines of treatment available, but the optimal sequences of treatment lines, including PRRT, have not been established to date.

3.2.1 | Retreatment with PRRT

In a meta-analysis of 13 studies by Strosberg et al. after re-PRRT, median PFS was 12.5 months, median OS 26.8 months. Based on data from 3 NET- referral centres (Erasmus, Rotterdam; Royal Free, London; and University of Bonn, with a total of 224 patients), the median PFS was 12.5 months and the safety profile of ^{177}Lu-PRRT retreatment was similar to the initial PRRT treatment.[60]

In the case of progression after effective radioisotope therapy lasting for a year or more, a repetition of PRRT may be considered. However, repeated PRRT is associated with a shorter PFS.[56–58] If a decision is made to repeat PRRT-due to the greater toxicity of ^{90}Y-the use of ^{177}Lu is recommended. Individual dosimetry measurements should also be considered.[56–58,60]

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3.2.2 | Recommendations

1. PRRT may be considered as a second-line treatment in patients with NF-Pan-NET G1-G2 with a positive SST-PET/CT (Level of evidence 2b: Grade of recommendation B).

3.3 | Q6. What is the role of biotherapy and molecular targeted therapies in specific settings of NF-Pan-NET?

Expression on the membrane of NET cells of the protein G-coupled receptors SST 1–5 has led to major advances in both diagnosis and treatment of GEP-NET. Lanreotide extended-release aqueous-gel formulation (lanreotide autogel) and octreotide long-acting repeatable (LAR), two somatostatin analogues (SSA) targeting SSTs, are normally used as first-line treatment of advanced NF-Pan-NET, particularly in patients with relatively slow-growing disease. CLARINET was the first clinical trial to prospectively demonstrate that lanreotide autogel prolonged PFS (hazard ratio [HR]:0.58; 95% confidence interval [CI]: 0.32–1.04) when compared to placebo in a cohort of NF-Pan-NET with a Ki-67 index <10%.[61] To our knowledge, there are no randomised data with octreotide LAR; however, both SSA were shown to exhibit similar efficacy and safety in a real-world practice report from the Spanish R-GETNE registry. This result was externally validated by an independent series of 535 patients with well-differentiated (Ki-67 ≤ 20%) metastatic GEP-NET treated with first line with SSA monotherapy; no clinically relevant differences in PFS where observed (HR 0.90: 95% CI: 0.71–1.12).[62] Conclusive data are lacking on the use of these agents at standard or high-dose in patients with NF-Pan-NET with G2 or Ki67 > 10% and more aggressive scenarios.[63,64]

Several preclinical studies supported the development of multikinase inhibitors (MKI) targeting the vascular endothelial growth factor-receptor (VEGFR) in Pan-NET. Sunitinib is the only tyrosine kinase inhibitor (TKI) approved until now by the major regulatory international agencies for the treatment of well-differentiated Pan-NET. This is based on an improvement in the PFS versus placebo found in a phase 3 trial conducted in 171 patients (HR 0.42: 95% CI: 0.26–0.66). In addition to the PFS prolongation, an objective response rate of 9.3% was achieved that compared favourably with no responses observed in the comparator arm.[65] Other MKI have shown promising data in this area like pazopanib, axitinib and lenvatinib, among others.

Genes related to PI3K-Akt–mTOR pathway such as *MEN1*, *TSC2*, or *NF-1*, are found to be altered in a significant proportion of Pan-NET.[66] Based on this strong biological rationale, mTOR inhibitors were developed such as everolimus, that in RADIANT-3, a prospective randomised phase 3 trial, demonstrated to significantly improved PFS compared to placebo (HR: 0.35; 95% CI: 0.27–0.45) in patients with progressive G1 and G2 Pan-NET.[67] As there are no comparative studies of targeted agents, the use of sunitinib or everolimus is mostly based on physicians' experience/preference or is driven by the safety profile that matches patient's clinical features, comorbidities and concomitant therapies.

Newer data suggest that sunitinib or everolimus could also be a potential useful tool for the management of patients with NET G3 with a Ki-67 < 55%.[68,69]

Patients with the VHL syndrome have a higher incidence of Pan-NET and other tumours owing to a rare autosomal dominant hereditary disorder associated with *VHL* gene inactivation and constitutive activation of the transcription factor hypoxia-inducible factor 2α (HIF-2α). Belzutifan is an approved agnostic oral inhibitor of HIF-2α in the USA, that at a dose of 120 mg once daily was associated with 90.9% objective response rates in patients with *VHL* germinal-mutated localised Pan-NET[70] Registration in the EU is pending, and a phase 2 trial with belzutifan is recruiting patients with advanced GEP NET and phaeochromocytoma/paraganglioma (unselected for VHL mjutation). Therefore, the value of Belzutifan in metastatic Pan-NET is still unclear.

As of today, no significant activity of promising new systemic therapies such as novel immune-checkpoint inhibitors (ICIs) or antibody drug conjugates (ADC) has been shown in patients with Pan-NET, probably based on the low tumour mutational burden (TMB), noninflamed microenvironment and lack of high proliferation rates.

3.3.1 | Recommendations

1. SSA is the recommended upfront treatment in slow-growing, SST-positive, advanced G1 and G2 NF-Pan-NET (Level of evidence 2b: Grade of recommendation A).
2. Everolimus and sunitinib are recommended in progressive G1 and G2 NF-Pan-NET (Level of evidence 1a: Grade of recommendation A).
3. Everolimus and sunitinib could be considered in progressive G3 NF-Pan-NET (Level of evidence 3b: Grade of recommendation B).

3.4 | Q7. What is the role of chemotherapy in NF-Pan-NET?

Chemotherapy has long been used for patients with Pan-NET. Early-generation alkylating agents (streptozotocin, chlorozotocin, doxorubicin) have been overtaken by temozolomide (an oral analogue of dacarbazine), either alone or in combination with capecitabine (an oral analogue of 5-fluorouracil [5-FU]). Encouraging data from retrospective studies provided the rationale for the randomised phase II ECOG-ACRIN E2211 trial in which 144 patients with advanced low- or intermediate-grade Pan-NET were allocated temozolomide ± capecitabine. The combination demonstrated a superior PFS, as primary endpoint (HR 0.58; $p = .022$).[71] In addition, the combination showed a trend to improved response rate (40% vs. 34%) and OS (58.7 vs. 53.8 months), although this was not statistically significant. Data by functional status are not yet available. Although O^6-methylguanine DNA methyltransferase (MGMT) deficiency was associated with greater likelihood of response, no significant correlation was seen with PFS or OS improvement. Therefore, evaluation of

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MGMT expression cannot be recommended so far for daily practice, although it might be of interest in situations where tumour debulking is the main therapeutic objective.

The ECOG-ACRIN E2211 study was limited to patients with Ki-67 of up to 20% (grades 1 and 2). A recent multicentre retrospective series[72] has demonstrated a response rate of 36% in patients with grade 3 GEP neoplasms (67% of patients had Pan-NEN, 49% were well-differentiated; and 92% received temozolomide with capecitabine – with 8% receiving temozolomide alone). Response rates (nonsignificantly) favoured well-differentiated NET (41% vs. 26% in NEC; $p = .63$) and NEN with Ki-67 < 55% (39% vs. 14% if Ki-67 > 55%; $p = .014$); responses were more commonly seen in patients with Pan-NEN and in the first-line setting.

Despite the robustness of the available data and wide use in daily practice, temozolomide has no official licensed indication for NET so far. Streptozotocin, either in combination with 5-fluorouracil or with doxorubicin are regimens which have been used since the 1970s with ORR of 38% and median PFS of around 12 months in modern trials.[72,73]

Patient selection favouring chemotherapy, in the setting of several other treatment options, relies on features of high mitotic activity (bulky disease, symptomatic disease due to high volume, or significant tumour growth) and aims of treatment (to reduce volume of disease versus stabilisation often seen with targeted therapies).

Limited data exist on the use of temozolomide combinations as neoadjuvant or conversion therapy approach with a view to curative surgery of locally advanced primary or relatively localised metastatic Pan-NET. In a retrospective study, 10 patients with locally advanced Pan-NET and 20 patients with potentially resectable liver metastasis from a Pan-NET were treated with temozolomide and capecitabine. The response rate was 43% and 26 patients (87%) underwent resection (primary and/or liver metastasectomy) with 63% of patients alive at 5 years.[74] It is always hard to extrapolate conclusions from retrospective data since selection bias could be behind these figures of activity; however, chemotherapy may facilitate surgical resection in selected patients.

The role of chemotherapy as adjuvant treatment in Pan-NEN is unknown and there is no robust study supporting the use of any chemotherapy regimen after complete resection of a G1 or G2 Pan-NET. The large number of patients required to conduct a phase 3 trial, along with the duration of follow-up needed make the feasibility of this kind of approach challenging and academic trials, are highly needed for this situation.

3.4.1 | Recommendations

1. Temozolomide in combination with capecitabine or streptozotocin + 5-FU may be considered systemic upfront treatments for patients with metastatic progressive and/or symptomatic NF-Pan-NET G1–G2 (Level of evidence 2b: Grade of recommendation B).
2. Temozolomide in combination with capecitabine can be also considered for the upfront treatment of patients with metastatic NF-Pan-NET G3 (Level of evidence 3b: Grade of recommendation B).

3.5 | Q8. In the setting of advanced disease, which is the most suitable first-line systemic therapy? Which sequence of treatments should be used?

Over the last decade, several systemic therapies have been approved by FDA and EMA as antitumour treatments for advanced NF-Pan-NET, including SSA,[61] everolimus,[67] sunitinib,[65] and PRRT with ^{177}Lutetium-DOTATATE.[75] All of them were approved for patients with progressive well differentiated Pan-NET with a Ki-67 up to 20% even though some studies included cases of NET G3 (Ki-67 > 20%). Chemotherapy with streptozotocin has been approved since the 1970s for Pan-NET, and more recently temozolomide + capecitabine has been proposed as an alternative regimen as first-line.[76,77]

So far neither predictive factors of efficacy nor specific sequencing of therapies have been validated, therefore no true gold standard exists as first-line therapy and therapy sequencing.

Factors influencing treatment choice can include[78,79]:

- Baseline tumour status (e.g., stable vs. progressive, slow- vs. fast-growing tumours, disease-free interval in case of metachronous metastases);
- Primary tumour site (head vs. body/tail);
- Extension of metastases (e.g., liver vs. liver + extrahepatic)
- Tumour load (especially in the liver and peritoneum)
- Ki-67 value;
- FDG-PET/CT uptake;
- Tumour-related mass-effect symptoms;
- SRI (^{68}Ga-PET/CT) (negative/positive, homogeneity, match/mismatch with morphological imaging and between 68GA and FDG)
- Potential resectability of the primary tumour and of metastatic disease;
- Patient characteristics (age, comorbidities, performance status);
- Inherited syndrome (mainly MEN1, VHL);
- Previous treatments and ongoing cumulative toxicity;
- Goals of treatment (e.g., tumour growth control, tumour shrinkage, debulking, QoL).

Patients with SRI-positive NF-Pan-NET with a very high liver tumour load,[80] or extensive peritoneal carcinomatosis[81] who are potentially candidates for PRRT, should be carefully evaluated within the NET-dedicated multidisciplinary team due to the risk of toxicity related to PRRT.

So far no published results of randomised prospective studies comparing different therapy sequences in the setting of advanced NF-Pan-NETs are available. The preliminary results of the randomised phase III SEQTOR study, which compared streptozotocin +5-FU followed by everolimus at tumour progression with the inverse sequence

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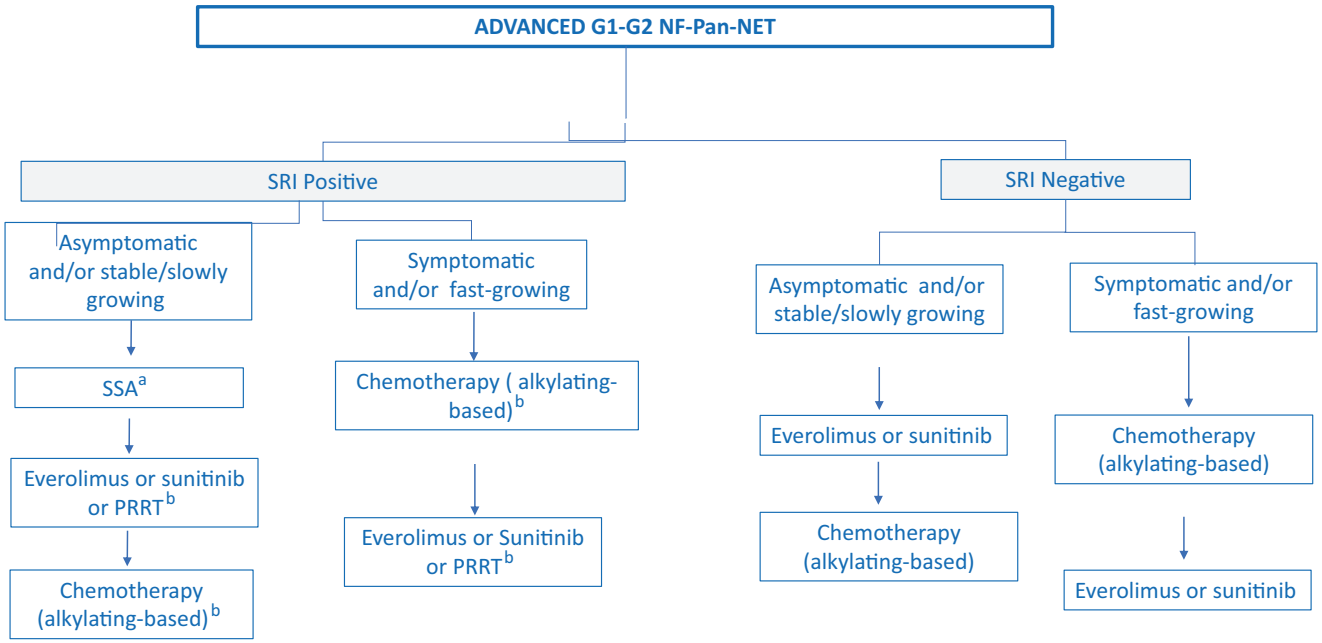

FIGURE 1 The proposed algorithm of G1-2 nonfunctioning pancreatic neuroendocrine tumours treatment. [a]Preferably for Ki 67 < 10%. [b]PRRT or chemotherapy or TAE/other liver directed therapy if cytoreductive intent.

in Pan-NET patients, showed no statistically significant difference in the primary endpoint, the one-year PFS rate.[82] On the other hand, the preliminary results of the randomised phase II noncomparative OCLURANDOM study with PRRT and sunitinib showed a longer PFS of PRRT (^{177}Lu-DOTATATE) in pretreated Pan-NET patients (median 20.7 months (90% CI: 17.2–23.7) and 11.0 months (90% CI: 8.8–12.4), respectively).[50] A large retrospective multicentre Italian nationwide study showed that second-line therapy with PRRT was more effective in terms of PFS than chemotherapy or everolimus or sunitinib in patients with GEP-NET (including NF-Pan-NET), which was confirmed in the Pan-NET and nonfunctioning subgroups.[10] Two ongoing international phase III studies are exploring the efficacy of PRRT in advanced GEP-NET with high Ki-67 index (10%–55%), in comparison with octreotide LAR 60 mg/q4w as first-line (NETTER-2 trial, NCT03972488) or in comparison with chemotherapy or everolimus as first- or second-line (COMPOSE trial, NCT04919226).[59]

The proposed algorithm of G1-2 NF-Pan-NETs treatment is presented in Figure 1.

3.6 | Q9. Is there a specific work-up in MEN1 patients?

The molecular bases of NF-Pan-NET tumorigenesis is not well understood and although 90% of cases are sporadic a minority may be included in the context of important genetic syndromes such as MEN1, VHL and tuberous sclerosis complex (TSC) syndrome.[83] A separate ENETS guidance paper on MEN1 syndrome is currently being worked on at the same time as this manuscript.

MEN1 is a rare autosomal dominantly inherited endocrine tumour predisposition syndrome, caused by germline heterozygous mutations in the MEN1 tumour suppressor gene, located on chromosome 11q13. The MEN1 gene encodes the menin protein involved in the regulation of gene transcription and mutation carriers will have clinical manifestations by the age of 50 years. The syndrome is associated with parathyroid adenomas, duodenopancreatic NET and anterior pituitary adenomas with a lifetime prevalence of 80% for NF-Pan-NET. MEN1 syndrome associates less frequently with thymic, lung and gastric NET and other tumours, and it is thus important to monitor patients for other neoplasms. Early recognition of relatives with MEN1 syndrome is of outmost importance due to 50% probability of first line family members being carriers and also in the light of possible genetic anticipation.[84]

Pan-NET arising in the context of MEN1 syndrome are usually multiple, nonfunctioning and may develop early in the second decade of life.[85] The current state of evidence suggests initial close follow up with MRI to assess growth rate alternating with EUS. SRI-PET may be carried out when it may change management such as in NF-Pan-NET >1 cm for detection of occult metastases or before interventions are considered.[86,87]

Several studies have indicated that MEN1-associated NF-Pan-NET usually exhibit a low propensity to grow and lesions <2 cm can be simply followed up by observation. If they are NET G2-G3, have lymph node metastases and are >3 cm in diameter, surgical excision is then considered as they may display metastatic potential.[88] For lesions between 2 and 3 cm there is uncertainty, and more studies are required prior to being able to make recommendations. ENETS recommends resecting MEN1-related NF-Pan-NET with a diameter of more than 2 cm, with a yearly size increment in diameter of more than

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0.5 cm or with a functioning syndrome such as insulinoma and VIPoma.[15,38]

There are still controversies related to issues of surgical treatment of Pan-NET, such as to what extent enucleation, lymph node sampling, and vascular reconstruction are beneficial for the oncologic outcome particularly in MEN1 patients and in tumours 1–2 cm in diameter. A comparison between sporadic and MEN1-related NF-Pan-NET has been previously presented showing several similarities such as prognostic factors (tumour size, grade, and cumulative methylation index) but also differences (younger age, multifocality and other concomitant tumours).[89]

3.6.1 | Recommendations

1. For MEN1 patients, NF-Pan-NET ≤2 cm may be observed, while surgical resection is advised for NF-Pan-NET >2 cm (Level of evidence 2: Grade of recommendation B).
2. Management decisions for selected NF-Pan-NET 2–3 cm and for grade 2 NF-Pan-NET should be made case-by-case within a NET-dedicated multidisciplinary team (Level of evidence 3: Grade of recommendation B).
3. Patients with MEN1 and their families should be treated and followed up by knowledgeable experts (Level of evidence 2: Grade of recommendation B).

4 | FOLLOW-UP

4.1 | Q10. What is the recommended follow-up in NF-Pan- NET?

The main objective of the follow-up is to propose an effective (ideally, curative) treatment in cases of recurrence.

As metachronous metastatic recurrence may occur very late, patients must be informed about the need for prolonged surveillance (at least 20 years, even lifelong), although intervals are progressively lengthened.[90]

1. In patients with NF-Pan-NET (initially metastatic or not) undergoing surgical resection with curative intent:
   - Morphological imaging and SST-PET/CT should be performed 3 to 6 months after surgery, then morphological imaging should be performed every 6 to 12 months for 5 years, then every 12–24 months for 10 years and then every 5 years. The intensity of follow-up can be modulated according to prognostic factors, notably tumour grade, stage, R0/R1 resection and life expectancy.[91]
   - Abdominal MRI including diffusion-weighted sequences are preferred. MRI is nonionising and more sensitive than CT-scan for the detection of small liver metastases.[32] Hence, abdominal MRI may be used in alternance with thoracoabdominal-pelvic CT-scan, which appropriately evaluates extra-hepatic lesions.
   - Assessment of local control after locoregional therapies for example, of liver metastases should be done every 3 months during the first 2 years with dedicated liver imaging (preferably MRI).
   - SRI (preferably using PET/CT instead of scintigraphy/SPECT) should be performed every 1 to 2 years if clinically indicated because of its superior sensitivity in regions like skeleton, heart and breast as compared to CT, although its role for surveillance has never been demonstrated. It is recommended if morphological imaging suspects recurrence.[28]
   - No biological marker is validated for follow-up. Nonetheless, the plasma level of CgA correlates with tumour burden and can be monitored, using the same assay kit throughout the follow-up.[92] NSE levels in patients with higher grade (NET G3) can be useful.
2. In patients with nonresected metastatic NF-Pan-NET
   - Imaging should be performed at 3 months and then every 3–6 months for 2 years, the interval can then be lengthened to 6 or even 12 months if the disease remains stable.
   - SST-PET/CT should be performed every 1–2 years, if clinically indicated.
   - The preferred imaging modality should be chosen on a case-by-case basis, depending on its ability to show target lesions and to cover the potential sites of new metastases; for example MRI, especially using hepatocyte-specific contrast material,[93,94] usually provides better reproducibility of measurements of liver metastases, and is more sensitive for detection of small liver lesions than CT.[32]
   - The evaluation of tumour evolution currently relies on RECIST 1.1 cutoffs for change in tumour size.[95] Throughout the treatment, the imaging modality should not be changed, neither the type of MR contrast material (extracellular versus hepatocyte specific), timing of contrast series, or SRI-tracer.[93,94] Tumour response to treatment is evaluated by comparing one scan with that performed at baseline (treatment initiation ± 1 month) or, in case of growth, with that performed at the best response (nadir), respectively.
   - Plasma CgA level can be monitored using the same assay kit throughout the follow-up. However, an isolated rise in CgA is not an indication to change the treatment if there is no evidence of progression but may suggest closer follow-up, including SRI.[92]
3. Late iatrogenic adverse events must be screened for, notably renal dysfunction (streptozotocin or PRRT), heart failure (sunitinib, doxorubicin) and bone marrow involvement (PRRT, alkylating agents).[96]

4.1.1 | Recommendations

1. Routine imaging follow-up consists of morphological imaging using contrast enhanced CT of the chest, abdomen and pelvis or, taking the cumulative radiation exposure of CT during the long follow-up period into account, Chest CT plus whole abdominal MRI every

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6 to 12 months after curative treatment for 5 years, then every 12–24 months for 10 years and then every 5 years (Level of evidence 5: Grade of recommendation B).
2. SST-PET/CT should be performed at 3–6 months (if no pretherapeutic scan had been performed) and every 1–2 years after curative treatment, if clinically indicated (Level of evidence 5: Grade of recommendation C). It is recommended if morphological imaging suspects recurrence (Level of evidence 2a: Grade of recommendation B).
3. Imaging follow-up of nonresected patients for RECIST-adapted evaluation of tumour growth should be performed every 3–6 months for 2 years and if stable every 6–12 months thereafter (Level of evidence 3a: Grade of recommendation B), combined with SST-PET/CT every 1–2 years if clinically indicated (Level of evidence 4: Grade of recommendation C).
4. Late iatrogenic adverse events must be screened for (Level of evidence 3b: Grade of recommendation A).

5 | SUMMARY

This ENETS guidance paper provides up-to-date practical advice on the NF-Pan-NET diagnosis and treatment.

Management of NF-Pan-NET patients requires a NET-dedicated MDT decision. ENETS Centres of Excellence should be strongly considered to be involved in the diagnostic-therapeutic strategy of these patients. Further studies are needed to fulfil the unmet needs in this field focusing on prognostic molecular markers, dilemmas concerning the selection of a therapeutic approach as well as the sequence of their use to achieve success in the management of NF-Pan-NET patients.

AUTHOR CONTRIBUTIONS

Beata Kos-Kudła: Conceptualization; data curation; formal analysis; project administration; resources; supervision; writing – original draft; writing – review and editing. **Justo Castaño:** Resources; supervision; validation; writing – review and editing. **Timm Denecke:** Data curation; funding acquisition; resources; validation; writing – original draft. **Enrique Grande:** Data curation; funding acquisition; resources; software; writing – original draft; writing – review and editing. **Andreas Kjaer:** Conceptualization; formal analysis; resources; supervision; writing – original draft. **Anna Koumarianou:** Data curation; formal analysis; funding acquisition; resources; writing – original draft; writing – review and editing. **Louis de Mestier:** Data curation; formal analysis; resources; validation; writing – original draft; writing – review and editing. **Stefano Partelli:** Data curation; funding acquisition; resources; validation; writing – original draft; writing – review and editing. **Aurel Perren:** Data curation; formal analysis; resources; software; writing – original draft; writing – review and editing. **Stefan Stättner:** Data curation; resources; validation; writing – original draft; writing – review and editing. **Juan Valle:** Conceptualization; data curation; resources; supervision; writing – original draft; writing – review and editing. **Nicola Fazio:** Conceptualization; data curation; methodology; resources; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Beata Kos-Kudła: consulting and honoraria – Merck, IPSA, Ipsen, Novartis, Pfizer. Justo P. Castaño: consulting and meeting attendance support: Ipsen, Novartis. Timm Denecke: consulting, meeting attendance support, and honoraria – Bayer, Siemens, Canon, Ipsen, MSD, Parexel, Calyx, Novartis, Roche, AstraZeneca, Takeda, bostonscientific; research funding: Guerbet. Enrique Grande: honoraria for speaker engagements, advisory roles or funding of continuous medical education from Adacap, AMGEN, Angelini, Astellas, Astra Zeneca, Bayer, Blueprint, Bristol Myers Squibb, Caris Life Sciences, Celgene, Clovis-Oncology, Eisai, Eusa Pharma, Genetracer, Guardant Health, HRA-Pharma, IPSEN, ITM-Radiopharma, Janssen, Lexicon, Lilly, Merck KGaA, MSD, Nanostring Technologies, Natera, Novartis, ONCODNA (Biosequence), Palex, Pharmamar, Pierre Fabre, Pfizer, Roche, Sanofi-Genzyme, Servier, Taiho, and Thermo Fisher Scientific. EG has received research grants from Pfizer, Astra Zeneca, Astellas, and Lexicon Pharmaceuticals. Andreas Kjaer: inventor/IPR on ^{64}Cu-DOTATATE for use in neuroendocrine tumour patients. Advisor/speaker: Novo Nordisk, IPSEN, Clarity Pharmaceuticals, Curium, Siemens. Anna Koumarianou: educational support from Faran SA, Ipsen and Novartis, speaker fees from Ipsen and Faran SA. Louis de Mestier: consulting and honoraria – AAA, Esteve, Ipsen, SIRTex; Research (Esteve). Stefano Partelli: no conflict of interest. Aurel Perren: no conflict of interest. Stefan Stättner: no conflict of interest. Juan W. Valle: personal fees from Agios, AstraZeneca, Baxter, Genoscience Pharma, Hutchison Medipharma, Imaging Equipment Ltd (AAA), Incyte, Ipsen, Mundipharma EDO, Mylan, QED, Servier, Sirtex, Zymeworks, grants, personal fees and nonfinancial support from NuCana. Nicola Fazio: AAA, Novartis, Ipsen, Hutchmed, MSD, Merck, Sanofi: Public speaking or Advisory board.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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APPENDIX A: PARTICIPANTS OF THE ENETS GUIDANCE PAPER CONSENSUS MEETING – OCTOBER 13, 2022

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