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CLINICAL GUIDELINE

European Neuroendocrine Tumor Society (ENETS) 2024 guidance paper for the management of well-differentiated small intestine neuroendocrine tumours

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Abstract

Both the incidence and prevalence of well-differentiated neuroendocrine tumours from the small intestine (Si-NET) are gradually increasing. Most patients have non-functioning tumours with subtle GI symptoms and tumours are often discovered incidentally by endoscopy or at advanced disease stages by imaging depicting mesenteric lymph node and /or liver metastases while around 30% of the patients present with symptoms of the carcinoid syndrome. Adequate biochemical assessment and staging including functional imaging is crucial for treatment-related decision-making that should take place in an expert multidisciplinary team setting. Preferably, patients should be referred to specialised ENETS Centres of Excellence or centres of high expertise in the field. This guidance paper provides the current evidence and best knowledge for the management of Si-NET grade (G) 1–3 following 10 key questions of practical relevance for the diagnostic and therapeutic decision making.

KEYWORDS
guidance, neuroendocrine, small intestine, treatment

INTRODUCTION

Neuroendocrine neoplasms (NENs) arising from the small intestine (Si-NEN) are considered rare malignancies. Despite this, both the incidence and prevalence are gradually increasing.[1] NENs are divided into well-differentiated neuroendocrine tumours (NET) and poorly differentiated neuroendocrine carcinomas (NEC) according to the most recent World Health Organization (WHO) 2022 classification. NEC are very rare among Si-NEN and covered in a separate ENETS Guidance paper[2] Grading is an essential component of the WHO classification. Si-NETs are graded as follows: NET G1 (Ki-67 <3%; <2 mitotic count in 2 mm^2), NET G2 (Ki-67 3%–20%; mitotic count 2–20 in 2 mm^2), NET G3 (Ki-67 >20%; mitotic count >20 in 2 mm^2).[3,4]

According to the most updated data from the Surveillance, Epidemiology, and End Results (SEER) programme that analysed 64,971 cases of NEN, there was an age-adjusted annual incidence rate increase by 6.4-fold from 1973 (1.09 per 100,000) to 2012 (6.98 per 100,000).[1] This increase occurred across all NEN, for all sites, stages and grades. The commonest individual organ with the highest incidence is the lung (1.49 per 100,000 persons). Gastro-entero-pancreatic (GEP) NEN amount to 3.56 per 100,000 population and include a variety of primary tumours, the most common being Si-NEN (1.05 per 100,000 persons). Available data on incidences from national and regional cancer registries in North America, Western Europe and Japan, identified slight variations across countries with a trend toward slightly higher incidence rate for United States, Norway and Sweden compared to United Kingdom, Italy, Austria and France.[5] However, these variations may derive from heterogeneity of data sources and means of registration rather than a true variation.[5] In a more recent retrospective patient based study from the United Kingdom the incidence of SI NET was 1.46 per 100,000 in 2018 and equalled the incidence of lung NET.[6] Si-NET is also one of the sites with most pronounced increase of prevalence. This is most likely due to the indolent disease course of Si-NET with long overall survival (OS) reported in the SEER database (median OS of 14 years for Si-NET diagnosed at localised stages and median OS of 8.6 years for Si-NET with distant metastatic disease).

Most patients have non-functioning tumours with subtle or no symptoms while around 30% of the patients may present with symptoms of the carcinoid syndrome (CS), that may lead to specific symptoms including diarrhoea, flushing, and more rarely bronchial obstruction induced by hypersecretion of serotonin and other bioactive substances from the tumour. Some patients may develop carcinoid heart disease (CHD) as a long-term sequela of CS. Comprehensive information on diagnosis and treatment of CS and CHD are provided in a separate guidance paper.[7]

This guidance paper provides the current evidence and best knowledge for the management of Si-NET (predominantly jejunal and ileal primaries) G1-3 following 10 key questions (Table 1) of practical relevance for the diagnostic and therapeutic decision making. Grades of recommendations are provided based on criteria available in Appendix Figure A1.

1 | WHICH FEATURES NEED TO BE TAKEN INTO CONSIDERATION FOR THE MANAGEMENT OF SI-NET?

Overall, diagnosis and management of Si-NETs requires a specialised multidisciplinary team (MDT) approach (Figures 1 and 2). Si-NET are often diagnosed at an advanced stage of the disease either incidentally following abdominal imaging for another reason or due to unspecific symptoms associated with metastases, mesenteric fibrosis, or bowel complaints due to intestinal obstruction. Some patients present with specific symptoms of the carcinoid syndrome (CS) due to secretion of biologically active compounds such as serotonin and tachykinins or are discovered during surgery for intestinal obstruction or bleeding. Most Si-NET are indolent slow-growing, well -differentiated NET G1 or G2 and only rarely NET G3. Patients have an excellent 5- and 10-year survival, even in the metastasised setting.[8,9]

TABLE 1 Ten major questions on diagnostic and therapeutic management of NET.

Q. No.	Questions on diagnostic and therapeutic management of NET
Q1	Which features need to be taken into consideration for the management of Si-NET?
Q2	Is there any role of circulating biomarker measurement in Si-NET?
Q3	Which is the most suitable diagnostic and staging work-up for patients with small intestinal NET?
Q4	What is the role of surgery in localised SI-NET?
Q5	What is the recommended first-line systemic treatment for advanced disease?
Q6	What is the recommended treatment beyond first- line SSA therapy?
Q7	What is the role of locoregional and ablative therapies in advanced Si-NET?
Q8	Which is the best therapeutic strategy in patients with Carcinoid Syndrome and tumour growth control?
Q9	What are the most recent developments for Si-NET?
Q10	What is the recommended follow-up for Si-NET?

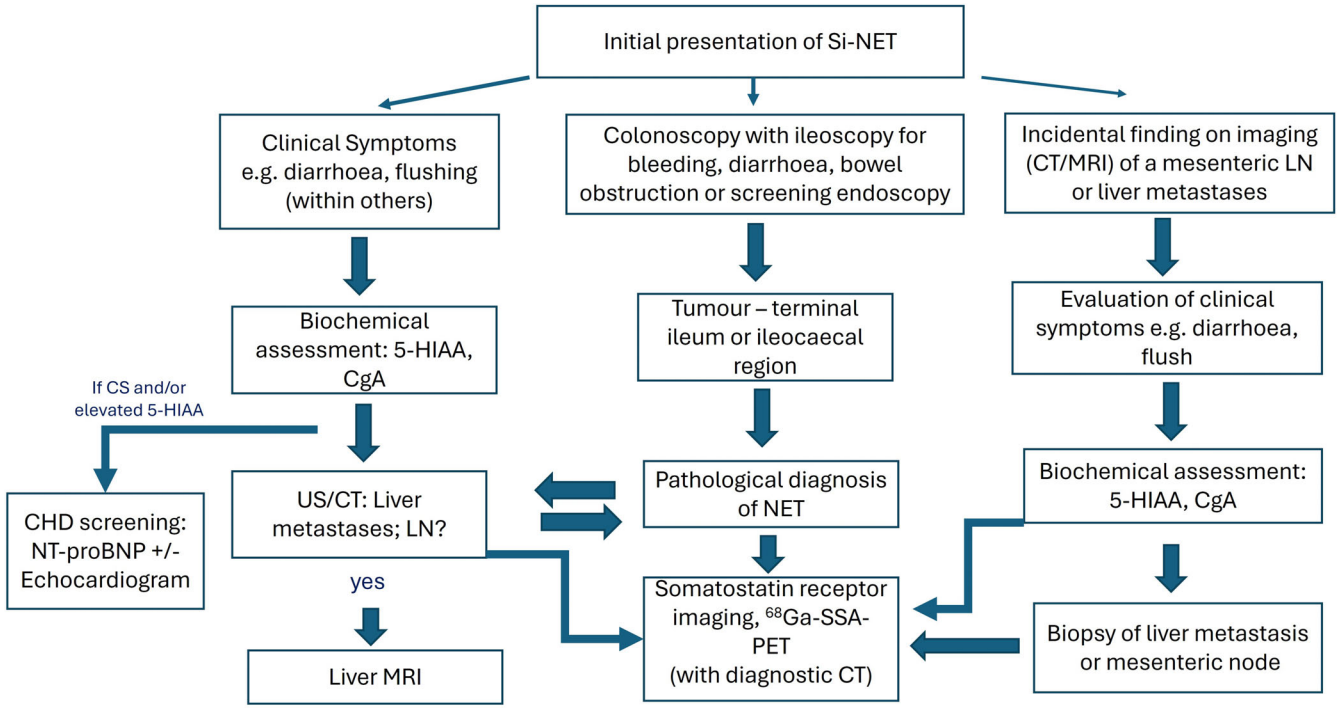
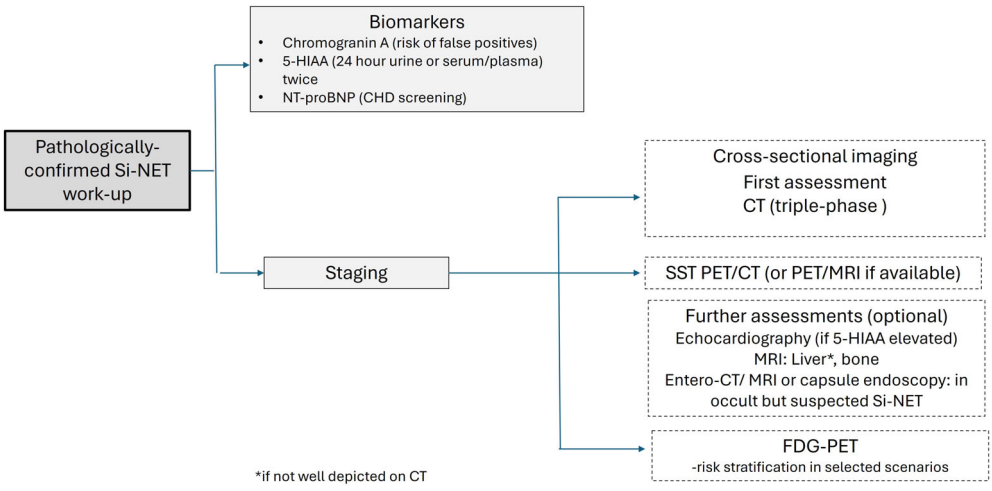


FIGURE 1 Diagnosis of Si-NET.

FIGURE 2 Staging and work-up of Si-NET.



Risk factors for developing Si-NET remain poorly understood. The relationship of their development with smoking and gallbladder diseases has been described.[10] There is emerging evidence of the presence of inherited variants of Si-NET, but the genetic background of this familial subgroup is still not identified.[11] It should also be noted that Si-NET may coexist with other neoplasms, such as gastrointestinal adenocarcinoma or breast cancer.[8,9]

From a molecular point of view, relatively few genetic alterations are found in Si-NET and the landscape is very different from that seen in Pan-NET.[10] 50%–78% of Si-NET show loss of chromosome 18, and about 10% of cases have mutations of the *CDKN1B* gene, however without any hotspot mutations in this gene.[12,13] Further research is needed to clarify whether genetic changes might give clues to new prognostic or predictive factors.

Assessment of symptoms with special focus on CS is crucial. CS can be the clinical sign leading to the diagnosis of Si-NET. Symptoms of CS occur when serotonin and other substances (tachykinins, prostaglandin and histamine) are secreted directly into the systemic circulation, therefore symptoms of the CS occur in general when NET are metastasised to the liver. CS not only significantly worsens the quality

of life of Si-NET patients, but it is also associated with CHD in up to 30% of the patients and adversely affects overall survival.[14,15]

It is important to note that patients suffering from CS are treated differently from patients with non-functioning Si-NET. Control of the CS has a priority before any other procedure to avoid carcinoid crisis[7]; the mainstay of treatment of CS is somatostatin analogues (SSA). The majority of patients however, have non-functioning NET although a transition into a functioning tumour in the course of the disease or with increasing tumour burden may occur. If the disease is not resectable, first-line treatment for most Si-NET patients is SSA. However, some patients with NET G1 and limited tumour burden may be appropriate for active surveillance.[7,16,17]

There are variable recommendations regarding the preparation of Si-NET patients for various medical procedures, including surgery, peptide receptor radionuclide therapy (PRRT) or locoregional therapies. It is recommended that in patients with CS, perioperative and periprocedural use of intravenous SSA is offered to patients regardless of the therapy with long-acting SSA.[7,16,18,19]

A pathognomonic feature on conventional imaging is the typical mesenteric metastasis, reported in a large series of Si-NET patients in 64% of cases[20] where radiating strands of soft tissue can be seen on CT-scan.[21] At pathology, a sclerosing fibrosis around the tumour mass is often found encompassing vessels and nerves leading to multiple clinical problems including small intestinal ischaemia, venous congestion, ascites and bowel obstruction.

Recommendations:
Management of Si-NET requires a specialised multidisciplinary team (MDT) for the complexity of the disease for appropriate diagnostic and treatment decisions. Specialised centres with high level of expertise should treat most of these patients, especially in the advanced setting (RECOMMENDATION A-5). Assessment of symptoms with special focus on CS is crucial (RECOMMENDATION A-2b).

2 | IS THERE ANY ROLE OF CIRCULATING BIOMARKER MEASUREMENT IN SI-NET?

Si-NET may produce and secrete polypeptides and amines, which play an important role for clinical symptoms related to the CS. These secretory compounds can also be used to guide diagnosis, follow-up after curative management and to monitor treatment response of Si-NET. Measuring such biomarkers at time of first diagnosis and as a baseline assessment at the time of starting a new treatment is recommended (Figure 2).

Chromogranin A (CgA) is a polypeptide secreted by neuroendocrine cells and not specific for Si-NET. The level of CgA in untreated Si-NET patients can be correlated to tumour burden. Changes during the initial phase of treatment have in some studies been correlated to treatment outcome even though this is less well documented.[22,23] Risk of false positives should always be considered, especially in the absence of visible malignancy on imaging. CgA should not be used for screening of Si-NET, since levels are increased in several non-malignant diseases such as impaired liver and kidney function, atrophic gastritis and inflammatory bowel disease among others. Another drawback of this biomarker is the existence of different assays with different cut-off levels. It is therefore important to use the same assay over time to be able to compare results.

Serotonin is the main amine produced by Si-NET. Measurement of serotonin in whole blood is not recommended since platelets contain high levels, which influences the results. Instead, the breakdown product 5-hydroxyindoleacetic acid (5-HIAA) is used and should be monitored in Si-NET patients.[24]

5-HIAA has traditionally been measured in acidified urine in two 24 h collections (due to large variations between days) and under diet restriction since serotonin-rich food may increase the levels significantly. Recently, testing of plasma and serum 5-HIAA has been assessed and compared to urine 5-HIAA,[7] and has become increasingly used in the clinic.[25] However, impaired kidney function may influence serum 5-HIAA levels and should be taken into consideration when interpreting the results.

Tachykinins are small peptides secreted from Si-NET. Circulating levels correlate to flushing and bronchospasms. However, since only few laboratories can provide the assay, general measurement is not recommended.[26]

In patients with CHD, measurement of N-terminal pro-brain natriuretic peptide (NT-ProBNP) is helpful to assess the degree of heart failure and should be monitored regularly.[7,27,28]

The NETest® (Wren Laboratories) is an mRNA-based test that analyses 51 gene transcriptome. It may be used to monitor treatment, but similarly to CgA it is not specific for Si-NET and the usefulness in clinical practice is still under evaluation.[29] This test is currently not widely available and its role in 'real-world' management as a biomarker remains to be determined.

In the few patients with Si-NET G3 it may be of interest to measure neuron specific enolase (NSE), lactate dehydrogenase (LDH) and aspartate aminotransferase (AST), since these biomarkers have shown to be of prognostic value in large cohort studies of G3 NEN patients.[30,31] However, there is very little specific data addressing their importance for Si-NET and more data is needed to determine their utility in this patient group.

Recommendations:
Circulating biomarkers can be used to guide diagnosis, follow-up after curative resection and to monitor treatment response of Si-NET (RECOMMENDATION A-2b).
CgA should not be used for screening of Si-NET (RECOMMENDATION B-2b), since levels are increased in several non-malignant diseases with significant number of false positive results.
5-HIAA, either measured in blood or 24 h urine, should be monitored in Si-NET patients with suspected CS and to assess treatment response in patients with CS (RECOMMENDATION A-2a).
In patients with CHD, measurement of NT-ProBNP is helpful to assess the degree of heart failure and should be monitored regularly (RECOMMENDATION A-2b).

3 | WHICH IS THE MOST SUITABLE DIAGNOSTIC AND STAGING WORK-UP FOR PATIENTS WITH SMALL INTESTINAL NET?

3.1 | Morphological imaging

Computed tomography (CT) with contrast enhancement is well established as the basic morphological imaging method for diagnosis and staging of patients with Si-NET and should be acquired as a triple-phase CT scan.[32] As an alternative or in combination with CT, contrast enhanced magnetic resonance imaging (MRI) may also be used; for accurate assessment of liver metastases, this is the preferred imaging method. MRI is also preferable in young patients with long-term need of follow-up to reduce irradiation dose. In general, MRI has a better soft-tissue contrast and is superior to CT in detection of liver lesions as well as bone and brain metastases.[32] Importantly, using conventional MRI small liver metastases are still missed,[33] the addition of diffusion-weighted MRI (DWI) raised sensitivity to 80% compared to all imaging. Furthermore, using hepatospecific contrast agent (Gd EOB-DTPA) raised the sensitivity to 100% (compared to other nuclear medicine images with positron emission tomography (PET) such as DOTA-TOC imaging).[34]

For detection of peritoneal metastases there is no accepted reference standard. One recent meta-analysis including 24 articles shows that DWI provided the highest sensitivity for the detection of peritoneal metastases of gastrointestinal cancer.[35] The most useful imaging tool to identify peritoneal carcinomatosis in NET is the combination of CT and somatostatin receptor (SST) imaging (SRI).[36] Many of the imaging recommendations rely on availability.

In scenarios where the primary tumour cannot be identified with regular imaging, CT or MRI enterography may be performed for identification of an occult bowel primary.[37] The use of capsule endoscopy is not generally recommended, but may be considered in very selected cases.

3.2 | Somatostatin receptor imaging

SST expression, in particular subtype 2, is present in most Si-NET and may be visualised using SRI. SRI is nowadays almost entirely based on positron-emitting radioligands that bind to SST and may be detected by PET. Currently used PET tracers include ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC (here named ^{68}Ga-SSA-PET) that at large perform similarly.[38] In addition, ^{64}Cu-DOTATATE has recently been approved and made available in the US and is used on a compassionate use basis in Europe. ^{64}Cu has a longer physical half-life (12.7 h vs. 1.1 h) and a shorter positron range compared with ^{68}Ga, making central labelling and distribution of ^{64}Cu-DOTATATE possible and the shorter position range leads to a better lesion detection rate.[39] ^{68}Ga-SSA-PET should be performed as PET/CT or PET/MRI with diagnostic quality CT or MRI. The use of ^{68}Ga-SSA-PET in Si-NET serves a dual purpose. Firstly, as the majority of the tumours express SST, ^{68}Ga-SSA-PET is valuable for diagnostic work-up and staging with a high sensitivity and lesion detection rate.[32] Secondly, non-invasive visualisation of SST expression may help determine whether patients are suitable candidates for SSA or SST-targeted PRRT with ^{177}Lu-DOTATATE or other SST targeting compounds. Finally, ^{68}Ga-SSA-PET may be used for therapy response monitoring.

3.3 | ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) PET

FDG is a glucose analogue that is widely used in cancer imaging outside NET. It is taken up by the same transporters as glucose but not further metabolised and thus accumulates in cancer cells. For NET it has been shown that more aggressive phenotypes (e.g., higher Ki-67 index) have higher ^{18}F-FDG uptake and that ^{18}F-FDG uptake is highly prognostic across all NEN grades.[40] In particular, ^{18}F-FDG PET is also highly prognostic for G1/G2 NET. A recent prospective study demonstrated that 39% (35 of 90) of Si-NET were ^{18}F-FDG positive.[40] The same study revealed that across tumour origins, 37% (21 of 57) of G1 NET and 58% (48 of 83) of G2 NET were ^{18}F-FDG positive.[40] Therefore, in addition to the use in high-grade tumours that are negative on ^{68}Ga-SSA-PET, there may be added value when using both ^{18}F-FDG and ^{68}Ga-SSA-PET more systematically in NET although prospective studies to document the value are warranted. In patients that are planned for PRRT, the additional use of ^{18}F-FDG PET to identify mismatched lesions, that is, lack of SST on lesions identified on ^{18}F-FDG PET may be used to identify patients that should be considered for other or additional treatment. Dual ^{18}F-FDG and SRI could be considered in G3 Si-NET and selected NET G2 patients (i.e., Ki-67 >10%).

3.4 | ^{18}F-DOPA PET – any role in Si-NET?

When comparing ^{18}F-DOPA with PET based SRI, studies have not been able to demonstrate any significant advantages. Accordingly, on a lesion basis several studies have shown better lesion detection performance of ^{68}Ga-SSA-PET when compared head-to-head with ^{18}F-DOPA.[41–43] Therefore, although it cannot be ruled out that ^{18}F-DOPA-may have value in single cases, especially in the rare events of SST negative Si-NET with low Ki-67, when also considering the availability of ^{18}F-FDG PET, we see no role for ^{18}F-DOPA in Si-NET in general.

A summary of the work up for Si-NETs is provided in Figure 2.

Recommendations:
The initial staging investigation should always be performed using CT or MRI with contrast enhancement and CT should be acquired as a triple-phase scan (RECOMMENDATION A-2a).
MRI using contrast (RECOMENDATION A-2a), is the best method for accurate assessment of liver metastases and in young patients to reduce radiation dose.
Use of SRI with PET/CT or PET/MRI is recommended in the diagnostic work-up and staging (RECOMMENDATION B-2a), selection of patients for PRRT (RECOMMENDATION A-1b) and therapy monitoring in selected scenarios (RECOMMENDATION B-2b). In addition, ^{18}F-FDG PET may be valuable for risk stratification and prior to PRRT in patients with NET G2/ G3 (RECOMMENDATION B-3a). The role of ^{18}F-DOPA, if any, is limited in Si-NET (RECOMMENDATION C-3b).

4 | WHAT IS THE ROLE OF SURGERY IN LOCALISED SI-NET?

All localised, resectable Si-NET should be operated, since this is the only chance for long-term cure given the high rate of lymph node metastases even in tumours <10 mm. A recent systematic review showed that the 90-day mortality after surgery for Si-NET is higher in low-volume centres compared to high-volume hospitals (4% vs. 1%).[44] Frequently, patients affected by Si-NET are operated in an emergency setting due to intestinal occlusion or bleeding in centres with different levels of expertise, and as consequence with risk for inappropriate surgical management with regard to lymphadenectomy and resection of all NET that are often multiple in the small bowel. Therefore, it is crucial to refer these patients to dedicated, high-volume centres, to properly evaluate Si-NET surgery and to plan for an adequate reoperation with vessel- and bowel sparing surgery. In those rare cases of asymptomatic localised Si-NET that are incidentally discovered, surgery is always the treatment of choice. The extent of nodal involvement and the degree of mesenteric fibrosis (MF) represent the main determinants of surgical resectability. In particular, the possibility to perform a successful radical resection with adequate lymphadenectomy is strictly related to the localisation of superior mesenteric vessel encasement. The definition of surgical resectability should take especially into account the degree of arterial involvement by lymph-node metastases according to the classification of Ohrvall and colleagues.[45] In particular, Si-NET with stage III nodal involvement might be difficult to resect, whereas Si-NET with stage 0, I, or II nodal involvement are generally considered resectable.[46]

An appropriate surgical resection of Si-NET has to meet specific criteria, including manual palpation of the entire small intestine and an adequate lymphadenectomy preserving as much small intestine as possible. An accurate manual palpation aims to detect multiple synchronous tumours. These tumours are found in 40%–60% of patients and are usually not detected by the preoperative imaging.[45,47] The aim of surgery is to perform a systematic lymphadenectomy avoiding a short bowel syndrome. For this reason, the surgical approach should not be a "pizza pie" approach (including a large intestinal resection), but a retrograde vessel-sparing lymphadenectomy.[45,47] It has been shown in a recent retrospective study that the resected bowel specimen is shortened by about half, when using this technique.[47]

Si-NET are frequently associated with MF that might cause bowel obstruction and bowel ischaemia. MF occurs more frequently in male patients than women and patients affected by MF have a significant poorer OS compared to those without MF.[20] Surgery remains the cornerstone of treatment in patients who report symptoms related to MF such as abdominal pain or present with bowel obstruction. Nevertheless, the oncological benefits of surgical resection in patients with MF remain controversial. A large retrospective series found that patients with MF and metastatic Si-NET showed no improvement of survival rates after palliative surgery.[20] There may however be a symptomatic benefit.

There are some conflicting results on the minimum number of lymph nodes to be retrieved during surgery but it seems that adequate lymphadenectomy should include at least 8 lymph nodes for examination.[48] A recent multi-institutional series on surgical treatment of Si-NET of the terminal ileum, found that patients who underwent formal right hemicolectomy had similar long-term outcomes compared to those who underwent ileocaecectomy.[49] Another single-centre study showed that right hemicolectomy is a positive prognostic factor regarding recurrence in localised Si-NET in the distal ileum.[50] Figure 3 summarises treatment planning for Si-NET.

The number of metastatic lymph nodes is the main prognostic factor and determinant of disease recurrence after radical surgery.[48] Patients with more than 4 metastatic nodes have a 3-year recurrence free survival of 80% compared to 90% and 93% in patients with 1–3 and 0 nodal metastases, respectively. 5-years recurrence rates of 30%–40% are reported in retrospective series (e.g., 48, 50). Since the role of adjuvant therapy, however, has yet not been explored, it is not indicated outside board approved studies.

A minimally-invasive approach for Si-NET resection has increasingly gained acceptance especially in high-volume centres.[51] Laparoscopic approach showed similar results in terms of number of resected lymph nodes and long-term outcomes compared to open approach.[51] Nevertheless, minimally-invasive surgery for Si-NET remains controversial, since an open approach has some proposed advantages such as manual palpation of the entire small intestine, a safer vascular control, especially when performing a vessel-sparing lymphadenectomy.[50] Even when sometimes small SI-NEN are diagnosed by colonoscopy, endoscopic removal should not be performed. Resection of the primary tumour might not be complete or complicated (e.g., risk of perforation) and potentially metastatic lymph nodes will not be targeted.

The role of prophylactic cholecystectomy during resection for Si-NET is another controversial issue. Recently, it has been demonstrated that on-demand surgery can be considered non-inferior to the prophylactic cholecystectomy in patients affected by Si-NET.[52]

Following curative resection, there is no evidence supporting the use of adjuvant strategies for NET[53] and current evidence supports follow-up only.

Recommendations:
All localised, resectable Si-NET should be operated on using organ-sparing techniques in high-volume centres (RECOMMENDATION-A-2b). The surgical gold standard includes an open approach with bimanual palpation of the entire small intestine and a vessel-sparing lymphadenectomy (at least >8 lymph nodes) aiming to limit the extent of small intestine resection (RECOMMENDATION A-2b). Adjuvant therapy following curative resection for Si-NET is not indicated. The oncological benefits of surgical resection in patients with MF remain controversial (RECOMMENDATION C-4).

5 | WHAT IS THE RECOMMENDED FIRST-LINE SYSTEMIC TREATMENT FOR ADVANCED DISEASE?

SSA are well established as first line treatment in patients with CS[7] and for antiproliferative effect (regardless of functionality) based on

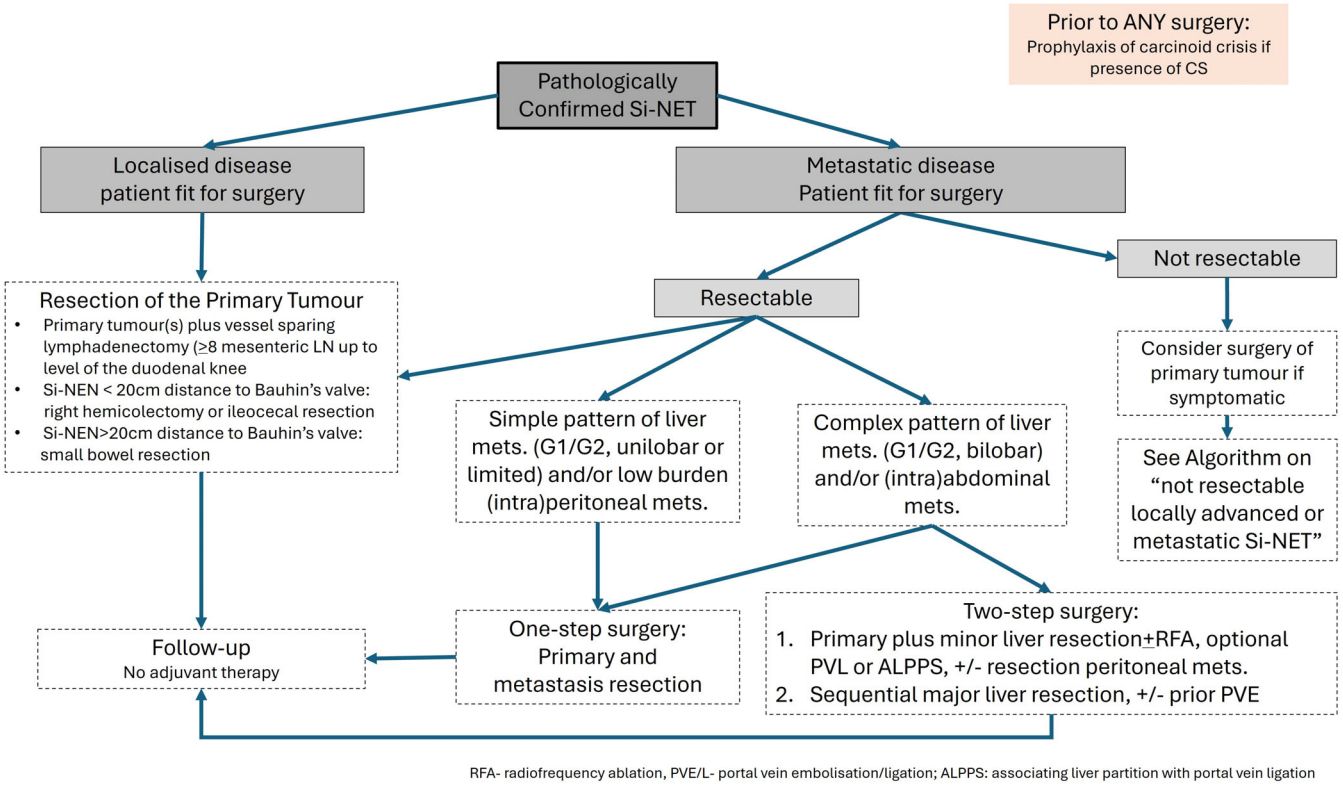


FIGURE 3 Treatment planning for Si-NET (part 1).

the results of two placebo-controlled phase 3 trials[54,55] (Figure 4). The PROMID trial included therapy-naïve midgut NET patients, the majority being NET G1 and SST positive although these were not inclusion criteria. The CLARINET trial included non-functioning SST positive advanced GEP-NET with a proliferation rate up to a Ki-67 of 10%.[56] Nearly all patients had a stable disease at the time of treatment start. These trials demonstrated significant prolongation of time to progression and progression free survival (PFS) compared to placebo, respectively, whereas a benefit on OS could not be proven, however the vast majority of patients crossed over to open label SSA upon progression on placebo.[57] Objective remissions with SSA are rare. No clear superiority of one SSA over another has been shown.[58] Quality of life is maintained or even improved during treatment.[59] It is therefore widely accepted that SSA (either lanreotide autogel [AG] or octreotide long acting release [LAR]) is the preferred first-line treatment in the presence of advanced G1 or G2 (especially if Ki-67 below 10%) Si-NET suitable for systemic therapy. SSA are generally a well-tolerated treatment except for mostly transient gastrointestinal (GI) side effects. Patients may develop pancreatic insufficiency with steatorrhoea, in which case pancreatic enzyme replacement therapy should be provided.

There are a few scenarios when SSA are not the preferred first-line treatment:

1. In grade 1, asymptomatic, low tumour burden and stable Si-NET a watch and wait strategy may be applied delaying start of treatment with SSA until progression occurs. The CLARINET study showed anti-proliferative activity of lanreotide AG in patients with progressive disease who crossed over from placebo.[60]
2. Around 10% of patients with well-differentiated Si-NET do not show expression of SST. In patients with tumour lesions less than 1 cm in size a SR-PET/CT should be performed (as generally recommended) to exclude false negative lesions. Although also receptor-independent mechanisms of SSA effects have been described, the antiproliferative effect is mediated via binding to SST.[61] Therefore, in patients with SST negative disease other treatment strategies are needed.
   - IFN-α has been used for three decades in Si-NET patients for antisecretory as well as antiproliferative purposes.[62] Prospective data are mainly available for combination treatment of IFN-α with octreotide in GEP-NET patients resulting in 6 months median time to progression in patients with progressive disease at baseline.[63] However, in a large phase 3 study in patients with "carcinoids" including a mixed patient population of NET G1 and G2 patients with either progressive disease or other poor prognostic factors including around 36% midgut NET, a median PFS of 15.4 months was achieved with octreotide LAR and IFN-α.[64] The objective response rate was lower with 4% as compared to older publications.[64] Side effects have to be taken into consideration. The use of IFN-α is limited due to lack of availability.
   - Everolimus is approved for progressive non-functioning Si-NET based on the results of the RADIANT-4 trial. The percentage of patients who were treatment naïve (first-line) in this study is

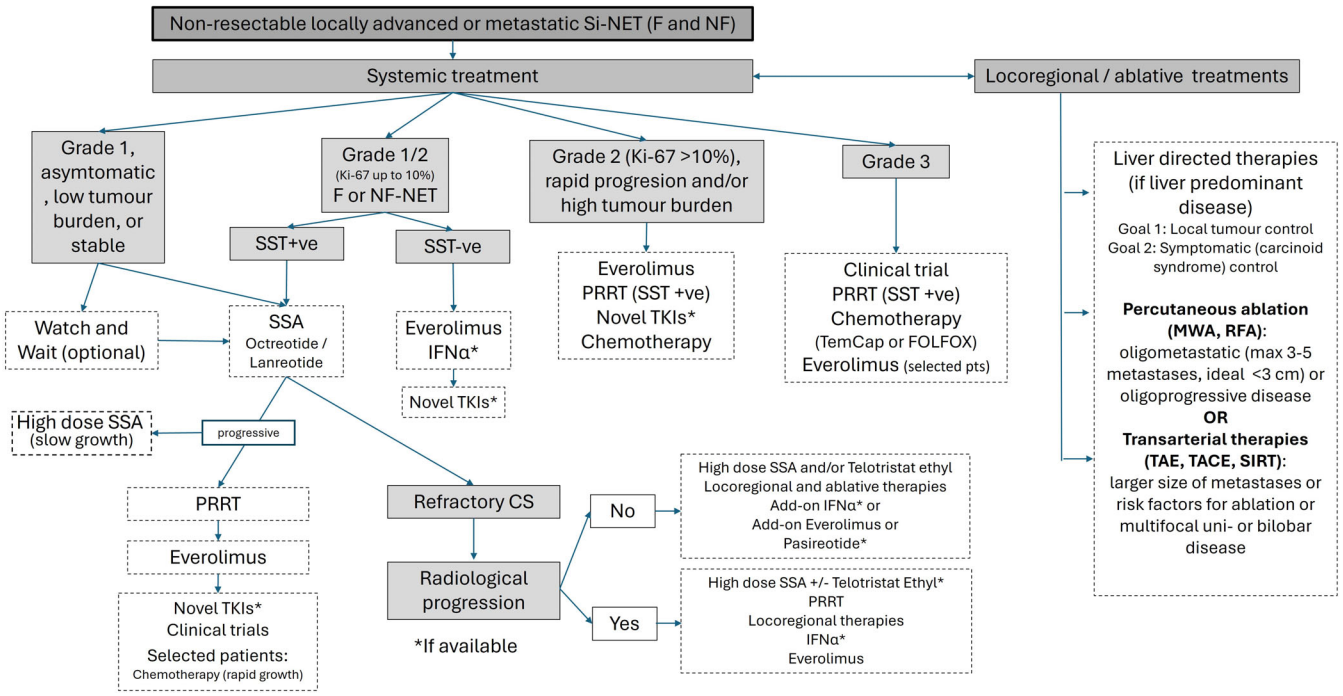


FIGURE 4 Treatment planning for Si-NET (part 2).

unclear. In patients with gastrointestinal primary the median PFS was 13.1 months in the everolimus arm compared to 5.4 months in the placebo-arm.[65,66] The response rate was 2% in patients treated with everolimus. Common toxicities include stomatitis, infections, diabetes, diarrhoea and pneumonitis, therefore careful follow up investigations and active side effect management is needed. Although everolimus is an approved therapy in progressive disease, locoregional therapies could be considered upfront.

3. The role of SSA in patients with NET G2 and proliferation rate above 10% is less clear, especially if a rapid progression is documented or if a high tumour burden is present.[56] In these scenarios, more intense treatments are probably needed. Options of first-line systemic treatment in this setting may include everolimus, PRRT or systemic chemotherapy.
   - Everolimus may be utilised in this patient group in the presence of moderate tumour burden and moderate progression (based on the RADIANT-4 trial).[65,66]
   - The use of upfront PRRT in selected SST positive NET patients with Ki-67 <10% is not an officially registered therapy but may be considered particularly in patients with high tumour burden if enrolment in a clinical trial is not feasible. It remains unclear which is the best treatment option in NET G2/ G3 patients with higher proliferation rate. The use of PRRT is supported by the NETTER-2 study results evaluating ^{177}Lu-DOTATATE versus high dose octreotide (double standard dose) in patients with higher proliferating tumours.[67] In this phase III study, patients with newly diagnosed somatostatin receptor-positive NET G2 or G3 (Ki-67 ≥10% and ≤55%) advanced GEP-NETs (29.2% of small intestine origin) who had been randomised to the ^{177}Lu-DOTATATE arm showed an improved median PFS (22.8 vs. 8.5 months); stratified HR 0.276 (95% CI 0.182, 0.418; $p < .0001$) and overall response rate (43.0% vs. 9.3%). It is expected that patients represented in the NETTER-2 study are highly selected (i.e., patients who could have been randomised to high-dose SSA and therefore not in need of urgent reduction of tumour burden or other more aggressive therapies). The issue of the appropriate therapy in NET with Ki-67 from 15% to 55% is currently further investigated in the COMPOSE trial (PRRT vs. physicians choice, either everolimus or systemic chemotherapy).
   - The best chemotherapy regimen is unclear[68] and could include temozolomide and capecitabine, 5-Fluorouracil-based schedules such as FOLFOX or combinations of capecitabine with SSA. A French phase II trial reported favourable results with capecitabine in combination with bevacizumab with a median PFS of 23.4 months.[69] Altogether, data for use of chemotherapy in Si-NET is very limited and patients with high Ki-67 should preferentially be considered for clinical trials. Chemotherapy should only be used in highly selected patients, especially when high Ki-67, high tumour burden and/ or rapid tumour progression within 6 months or less is present.
4. NET G3 of small intestinal origin are rare and the best strategy in patients with advanced disease is unknown. Despite having more evidence for pancreatic than for Si-NET, most centres use chemotherapy with temozolomide in combination with capecitabine or FOLFOX as a first-line therapy.[70,71] This is based on the fact that adenocarcinoma-like and alkylating-based chemotherapies may be the most effective treatments in this setting, especially in terms of response rate and PFS, with etoposide-platinum chemotherapy

showing poor efficacy.[71] In carefully selected patients everolimus could be utilised. In addition, in selected patients with homogeneous SST expression PRRT may also be an option.[72] The NETTER-2 study supports the use of PRRT in selected NET G3 (see section above).[67] The COMPOSE (NCT04919226) study will provide more insight into the management of NET G3 with PRRT as compared to other therapies, such as everolimus, and chemotherapy (Temozolomide + Capecitabine or FOLFOX). Patients with NET G3 should preferentially be included in clinical trials.

Recommendations:
In the presence of advanced unresectable Si-NET G1 or G2 long-acting SSA (either lanreotide or octreotide) is the preferred first-line treatment (RECOMMENDATION A-1b). Watch and wait may be an option in selected patients (G1, asymptomatic, low tumour burden and/ or stable Si-NET) (RECOMMENDATION B-2b). In patients with advanced disease and SST negative lesions IFNα (RECOMMENDATION A-2b) or everolimus (RECOMMENDATION A-1b) can be used as first-line treatment if locoregional therapy is not an appropriate option. In patients with advanced intestinal NET G2 with Ki-67 >10% everolimus (RECOMMENDATION A-1b) and PRRT (RECOMMENDATION A-1b) are treatment options for selected patients. Chemotherapy has a minor role in highly selected patients (especially NET G3, and/or rapid tumour progression) (RECOMMENDATION C-4). Patients with NET G3 should be enrolled in clinical trials.

6 | WHAT IS THE RECOMMENDED TREATMENT BEYOND FIRST-LINE SSA THERAPY?

When considering antiproliferative therapy in Si-NET pathological grade, SST expression, volume of disease, associated symptoms and comorbidities are key factors (Figure 4). However, clinical trial data and predictive biomarkers are currently lacking to guide the sequence of systemic therapy. Overall, following progression on SSA, treatment with PRRT for patients with SST positive tumour lesions and everolimus for patients with SST negative lesions are the most likely scenarios. Third-line therapy following these are more difficult to state and may rely on prior treatment and specific characteristics at the time of progression, making discussion in a multidisciplinary team of huge relevance.[73] The presence of CS may impact the choice of treatment for patients with Si-NET following SSA, this is further discussed in section 8.

6.1 | PRRT

In the NETTER-1 phase 3 study patients with advanced progressive Si-NET were randomised to four cycles of ^{177}Lutetium (^{177}Lu)-DOTATATE (every 8 weeks) combined with Octreotide LAR 30 mg every 28 days or high dose Octreotide LAR 60 mg every 4 weeks. This study showed a significant benefit in terms of PFS for ^{177}Lu-DOTATATE combined with SSA compared to high-dose SSA with a hazard ratio 0.21 ($p < .001$).[74] This was associated with a durable benefit (median PFS exceeding 28 months) and improved quality of life with the most significant benefit seen in global health but also overall physical and role function. Additionally there were symptomatic benefits for diarrhoea, pain and fatigue in terms of prolonged time to worsening of symptoms as compared to SSA.[75] The final analysis of NETTER-1 performed 5 years after the last patient was enrolled, reported no additional long-term safety signals with 2% of patients developing myelodysplastic syndrome.[76] Renal side effects may occur but are usually mild. PRRT is therefore considered the standard second-line treatment option in the presence of homogenous SST-positive disease. Major tumour shrinkage is, however, rarely achieved; the objective response rate in NETTER-1 was 18%. PRRT was followed by octreotide LAR at standard dose, however, it is not proven, that (in the absence of carcinoid syndrome) maintenance therapy with SSA is superior to just observation after application of PRRT, although some retrospective data suggest its additional value. Maintenance therapy with SSA should be given if patients have high tumour burden.

6.2 | Rechallenge on PRRT

In view of the significant beneficial outcome of treatment with ^{177}Lu-DOTATATE and with limited other treatment options, there is a strong rationale for rechallenge (retreatment) with PRRT in case of persistent homogenous SST expression. The current consensus is that rechallenge PRRT may have a role for selected patients and that it could be delivered outside clinical trials if available. This could be considered especially if the disease was controlled for at least 9–12 months following the last cycle of PRRT. If utilised, rechallenge with PRRT would be delivering two more cycles of PRRT, and this could be repeated again in the case of progression after another >12 months and if the treatment was well tolerated.[77] In a recent meta-analysis[78] the pooled median PFS in patients initially treated with either ^{90}Y- or ^{177}Lu-PRRT who were given rechallenge treatment with ^{177}Lu-DOTATATE (5 studies, 272 patients) was 12.26 months and the patients who received only ^{177}Lu-DOTATATE had PFS 13.4 months. The median OS in two studies included in the meta-analysis for rechallenge PRRT was 26.8 months from the start of retreatment. The safety profile after rechallenge was similar to initial therapy with grade 3 or 4 haematological toxicity reported in 9% of patients and no patients reported for grade 3 or 4 renal toxicity. Thus rechallenge PRRT appears to be safe and demonstrates encouraging efficacy for selected patients. Prospective studies are ongoing to assess its value as compared to alternative treatment options such as everolimus.

6.3 | High dose SSA

There are some retrospective and few prospective studies reporting data for tumour control with high dose SSA.[56,79,80] Although PRRT

with continuation of standard dose octreotide LAR was more effective as compared with double standard dose of octreotide LAR in midgut NET patients in the NETTER-1 trial, the median PFS was 8.4 months with octreotide 60 mg/month.[74] The CLARINET forte trial evaluating the efficacy of lanreotide AG 120 mg every 14 days in patients with progressive Si-NET or Pan-NET following first-line standard-dose lanreotide AG treatment (120 mg every 28 days) reported a very similar median PFS of 8.3 months in the midgut cohort.[81] In patients with Ki-67 ≤10% median PFS was 8.6 months. Median duration of response was 13.8 months. Based on these studies, above-label SSA is mainly an option in patients with slowly growing, low proliferative (Ki-67 ≤10%) and/or low tumour burden Si-NET where a meaningful delay to more toxic treatments can be reached. The control arm of the NETTER-2 study is challenging this assumption since a median PFS of 8.5 months was achieved with octreotide 60 mg/ month even in patients with Ki-67 above 10%. High dose SSA can also be used in patients with comorbidities such as severe renal insufficiency or impaired bone marrow function in whom PRRT is contraindicated or everolimus is not an option.

6.4 | Everolimus

Everolimus given orally at 10 mg/day is EMA approved for G1/G2 intestinal, pancreatic and lung NET. Across all NET the overall response rate (ORR) was <10% and this should be taken into consideration when selecting systemic therapy, as those patients with significant symptoms from large volume disease may not benefit symptomatically. The RADIANT-4 trial investigated everolimus in 302 GI and lung NET patients. The median PFS was 11 months with everolimus and 3.9 months with placebo [hazard ratio (HR) 0.48], with PFS prolongation seen in the GI subgroup [HR 0.56].[65] However, a heterogeneous response was identified on post hoc analysis with limited benefit identified in indolent Si-NET.[66] Everolimus is currently recommended following PRRT in patients with SST expressing NET given the good tolerability of PRRT, favourable impact on quality of life and durable benefit although data from a prospective randomised trial is still lacking. However, in patients with absent or insufficient SST expression without CS, everolimus is the treatment of choice in progressive G1/G2 Si-NET. The ongoing phase III COMPETE trial (NCT03049189) will compare everolimus to PRRT with ^{177}Lu-edotreotide and will provide further evidence regarding adequate sequencing of treatment.

6.5 | Tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKIs) are currently not approved in Si-NET in Europe but could be an option for patients with Si-NET with low or no SST expression or after failure to established standard therapies. Several phase II trials with TKIs including cabozantinib, lenvatinib, pazopanib and axitinib have demonstrated some efficacy in Si-NET.[82–88] Axitinib and octreotide LAR demonstrated a prolongation of median PFS compared to placebo and octreotide LAR in central review of a randomised phase III trial in patients with extra-pancreatic NET (however failed to reach significant results in local radiological analysis what was the primary endpoint of the trial). The activity of cabozantinib has been confirmed in a randomised placebo-controlled phase III study, that showed prolongation of PFS with decisions regarding approval for this indication still pending.[89] If accessible, a TKI may be considered (outside clinical trial setting) after failure of standard therapies (before chemotherapy) or in SST negative patients in case of intolerance to everolimus or IFN-α, or after failure of these therapies.

6.6 | Chemotherapy

Efficacy of systemic chemotherapy in G1/G2 Si-NET is poor with ORR of 11.5% (range 5.8%–17.2%).[68] However, in very selected cases of NET G2 with a higher Ki-67 (15%–20%) or in NET G3, in case of rapid clinical or radiological progression or where any aspects exclude other treatment options chemotherapy can be beneficial. When doing so, temozolomide and capecitabine or FOLFOX are the recommended schedules to use. Assessment of dihydropyrimidine dehydrogenase (DPD) testing to identify DPD deficiency (associated with poor metabolism of 5-FU or capecitabine) is recommended if these drugs are used; with dose adjustment if DPD deficiency is identified.

Recommendations:
The recommended second-line treatment in the presence of SST-positive Si-NET is PRRT (RECOMMENDATION A-1b), followed by everolimus (RECOMMENDATION A-1b). Rechallenge PPRT (RECOMMENDATION C-4) and high dose SSA (RECOMMENDATION B-2) may be considered in selected scenarios. TKI may be considered based on accessibility and reimbursement after failure to approved therapies or in SST negative NET (RECOMMENDATION C-2b). Chemotherapy is rarely recommended for Si-NET unless NET G2 with higher Ki-67 (15%–20%) or NET G3, with rapid tumour progression (RECOMMENDATION C-3).

7 | WHAT IS THE ROLE OF LOCOREGIONAL AND ABLATIVE THERAPIES IN ADVANCED SI-NET?

For Si-NET patients with resectable G1/G2 liver metastases without extrahepatic tumour spread identified after thorough work-up (including MRI as well as functional imaging) and with no significant comorbidities, a curative surgical approach is the treatment of choice. This is supported by large series reporting favourable 5-year OS rates of 71%–74%[90,91] and 85% for all resected and R0 resected patients,[92] respectively. For Si-NET, there is no established cut-off value for Ki-67 to exclude patients from surgery of resectable liver metastases. However, it has been shown in a retrospective study that the PFS is about half in patients with G3 liver metastases compared to G1/G2

metastases.[93] Therefore, surgery for Si-NET G3 patients with potentially resectable single or few liver metastases should be discussed critically in the MDT. Furthermore, the recurrence rate after R0 resection for G1/G2 tumours, is high (about 80% in 5 years) and therefore a follow-up strategy is needed.[90] The same is true for patients with resectable liver metastases of NET G1/G2 with unknown primary. In patients with not completely resectable liver metastases and/or unresectable extrahepatic metastatic disease debulking surgery might be considered after MDT discussion in case of functional NET (carcinoid syndrome) or local liver problems such as bile duct obstruction caused by the metastases.

For patients with G1/G2 Si-NET with predominant liver metastases who are not surgical candidates due to either performance status or extent of liver disease, liver-directed therapies such as radiofrequency ablation (RFA), microwave ablation (MWA), irreversible electroporation (IRE), transarterial embolization (TAE), or chemoembolization (TACE) and radioembolization (TARE), can be applied to provide local tumour control and improve symptoms of CS.[94–96] The details of advantages and disadvantages of the distinct techniques are beyond the scope of this guidance paper and high-quality evidence supporting one treatment approach over another as well as for the optimal treatment sequencing is still very limited. Centres are encouraged to take into account the treatment options in which they have most experience on at the time of decision making. From a clinical point of view, percutaneous ablation techniques (RFA, MWA, IRE) are the treatments of choice in patients with oligometastatic disease (preferably maximum of 3–5 metastases and <3 cm in size) or oligoprogressive disease (1 or 2 metastases not responding to systemic treatment). It has been reported that in patients who underwent locoregional treatment for focal liver progression, the median time to new systemic therapy was 32 months.[97] Larger size, hilar location, and the proximity to major bile ducts can increase the risk of complications, while proximity to large vessels can result in a cooling effect reducing its effectiveness. For patients with metastases >3 cm, aforementioned risk factors for ablation or with multifocal uni- or bilobular disease, transarterial therapies such as TAE, TACE or TARE are usually indicated. Few studies have compared different transarterial strategies. A recent retrospective study noted no difference between TACE and TARE regarding PFS and OS rates.[98] An ongoing randomised controlled trial comparing TAE, TACE and drug-eluting beads (DEB)-TACE had to close the DEB-TACE arm due to increased severe complications.[99] Based on the limited high-quality data, MDT decisions regarding liver-directed therapies are significantly influenced by institutional preferences and local experience of distinct techniques.[20,95]

Palliative resection of the primary Si-NET in patients with advanced disease is also a matter of debate. Surgical resection or intestinal bypass are mandatory in the presence of primary-related complications such as intestinal obstruction, ischaemia or haemorrhage. The advantage of prophylactic surgery in asymptomatic patients affected by Si-NET is more controversial. Several retrospective studies have been performed.[100] Most of these studies lack important information, such as the burden of metastatic disease, the cause of unresectable tumours, and the use and the type of associated systemic therapies. Moreover, palliative surgical resection has most probably been offered more frequently to patients with better performance status and less aggressive disease. Given this high-risk of bias, primary tumour resection is seemingly associated with a benefit in terms of survival compared to no resection.[101,102] However, there are at least three studies that have tried to remove selection bias by using propensity-score matching, and these studies show no benefit in terms of survival.[20,103,104] Regarding timing of prophylactic surgery, the need of an upfront surgical approach in patients with asymptomatic stage IV Si-NET, has been challenged by a large retrospective study.[103] In this study only 22% of patients in the surgery as needed group had to undergo surgery during follow-up. Delayed locoregional surgery (>6 months from diagnosis) in patients with advanced Si-NET is associated with similar overall and disease-specific survival compared to surgery performed within 6 months from initial diagnosis.[103] Two recent retrospective studies[105,106] have shown that the combination of Si-NET resection and PRRT provides the best disease-specific survival for patients with diffuse stage IV disease, especially if the metastatic liver burden is less than 50%.[106] At present the question is open and its firm answer requires a prospective controlled trial. Thus, benefit and risk of the primary tumour resection in asymptomatic patients with unresectable stage IV disease should be discussed with the patient and in the MDT. A rare consideration could be resection of the primary tumour to leave a patient with liver only disease and the consideration in selected individuals for orthotopic liver transplantation.

Cytoreduction for Si-NET with peritoneal carcinomatosis has been demonstrated to be effective with acceptable morbidity and mortality rates in selected patients.[107] In a recent retrospective analysis of 98 patients, Si-NET patients without liver metastases and only localised peritoneal carcinomatosis in one abdominal quadrant with lesions <5 mm benefit the most. Their OS was 76 months compared to 32 months in patients with diffuse peritoneal carcinomatosis and lesions >5 mm.[107] Thus, Si-NET patients with or without resectable liver metastases with limited peritoneal carcinomatosis are good candidates for cytoreductive surgery.[84] The role of hyperthermic intraperitoneal chemotherapy (HIPEC) in addition to cytoreduction in patients with peritoneal carcinomatosis has been retrospectively explored in Si-NET.[108] Based on these results it cannot be recommended for patients with Si-NET and peritoneal carcinomatosis at present.

Recommendations:
In patients with Si-NET G1/G2 stage IV disease and exclusive liver metastases a surgical approach is indicated, if R0 resection can be achieved (Recommendation B-4). In non-surgical candidates locoregional liver-directed therapies should be explored in predominant liver disease to control tumour growth, CS and oligometastatic progression (Recommendation B-3). Cytoreductive peritoneal surgery is recommended in patients with localised peritoneal carcinomatosis (Recommendation A-4). Benefit and risk of a primary tumour resection in asymptomatic patients with unresectable stage IV disease should be discussed critically with the patient and in the MDT.

8 | WHICH IS THE BEST THERAPEUTIC STRATEGY IN PATIENTS WITH CARCINOID SYNDROME FOR SYNDROME AND TUMOUR GROWTH CONTROL?

Refractory CS (especially with worsening bowel movements (BM) or flushing) may be a challenging scenario faced by clinicians treating NET. Refractory CS has recently been defined by ENETS as "recurring or persisting CS symptoms and increasing or persistently high u5-HIAA levels despite the use of standard doses of SSA". Refractory CS is classified as "non-aggressive or aggressive", based on symptom burden together with disease status (stable or progressive), hepatic tumour burden, and/or the presence of CHD.[7]

In the presence of CS, the recommendations for antiproliferative therapy as outlined above (see Q6) may not be applicable, and alternative approaches (i.e., early liver directed therapies) may be considered. The requirements for treatment may also be different since patients may suffer from increasing symptoms but may not necessarily display obvious tumour growth. It is of crucial importance to determine the treatment goals first, either improvement of CS symptoms, tumour growth control or both.

8.1 | Aiming for symptom control

In the scenario of refractory CS on SSA without evidence of disease progression, the aim of the treatment should focus on achieving an antisecretory effect.

High dose of SSA can be considered[7] and has often been applied in clinical routine. It is supported by retrospective analyses but there is a lack of high quality data or evidence based randomised controlled trials.[56] High dose SSA implies above labelled dose that can either be reached by shortening of the injection interval or by increasing the dose and maintaining the standard interval of 28 days. In retrospective trials symptomatic improvement for diarrhoea is reported in up to 79%[109] and for flushing in up to 91% of patients.[110] The only prospective randomised trial in patients with refractory CS compared an above label dose of octreotide LAR (40 mg) with pasireotide LAR 60 mg (a universal ligand to SST) every 28 days[111] and reported symptom control in 27% and 21% of patients, respectively. Based on these data high dose of SSA can be used for symptom control in refractory CS.

Addition of short acting octreotide s.c. to depot preparations of SSA as rescue therapy for breakthrough symptoms may also be an option.[112,113] Pasireotide may be considered off-label in patients suffering from CS when other options have been exploited.

Telotristat ethyl, an oral inhibitor of the serotonin synthesis, significantly reduced diarrhoea and 5-HIAA levels in patients with refractory CS in two randomised placebo-controlled trials.[107,108] Flushing was not significantly improved as expected since it is related to secretion of other bioactive compounds than serotonin. The drug was generally well-tolerated, treatment related adverse events included nausea, abdominal pain and elevation of gamma-glutamyl transferase.[114] Addition of telotristat ethyl to SSA is recommended in CS patients with refractory diarrhoea.

The use of liver directed therapies for poorly controlled CS should be considered upfront. In addition to debulking surgery, locoregional treatments can achieve symptomatic as well as tumour response. Evidence from prospective controlled trials is lacking. A recent review including more than 100 mainly retrospective studies and 5000 patients reported a symptomatic response in 55.2%.[95] Outcome did not significantly vary depending on the type of embolization performed with a tendency for better symptomatic and tumour size response after radioembolization. However, radioembolization should be used with caution in patients with Si-NET given the risk of long-term sequelae including liver fibrosis and cirrhosis, particularly in low grade Si-NET who may have a long life expectancy exceeding 8 years. In general, bland embolization is usually preferred. In patients with persisting symptoms of CS despite SSA treatment, locoregional treatment of liver metastases should be discussed early in the MDT.

IFN-α is an approved antisecretory treatment for patients with CS and may alleviate not only diarrhoea but also flushing. Due to more side effects compared to SSA, it is usually used as an add-on option in patients with refractory CS or upfront in SST negative NET patients. Symptomatic response was reported in 50%–70% of patients.[62,115] The recommended dose is 3–5 MU/week, an off-label pegylated formulation once weekly may be better tolerated,[116] but availability is limited due to discontinued production of some compounds.

PRRT is mainly used for its antiproliferative effects based on the results of the NETTER-1 trial and its labelled indication in progressive disease (see Q6).[74] The proportion of patients suffering from CS symptoms on PRRT plus standard dose of octreotide versus high dose octreotide was the same. However, in NETTER-1 the median time to deterioration (TTD) of diarrhoea in a subset of patients with CS was significantly longer with PRRT and standard dose of octreotide LAR as compared to high-dose octreotide ($p = .0107$), whereas TTD for flushing was not significantly different when comparing treatment arms.[75] A small retrospective monocentric study reported efficacy in refractory CS patients without documented disease progression; number of bowel movements as well as frequency of flushing episodes were reduced after PRRT with ^{177}Lu-DOTATATE.[117] In highly symptomatic patients, however, symptom control is crucial before PRRT, and withdrawal of long-acting SSA prior to PRRT may lead to worsening of diarrhoea (eventually associated with renal insufficiency). Therefore, other options should be considered upfront for improvement of symptoms. Caution is also required in patients with CHD, where compensation of heart insufficiency may be required first and an experienced cardiologist should be consulted, (see separate guidance paper on CHD).[7]

Everolimus plays a minor, if any role in patients where syndrome control is the goal. However, in the RADIANT-2 study, everolimus plus octreotide LAR resulted in greater reductions of urinary 5-HIAA compared with placebo plus octreotide LAR, but the efficacy on symptom control was not reported in this trial.[118] Reduction of 5-HIAA was sustainable and since reduction of 5-HIAA usually is associated with symptom improvement, an (off label) addition of everolimus may be considered in patients with CS, particularly if there is progressive disease and an antiproliferative therapy is warranted. A benefit on symptoms is also supported by a small retrospective study reporting symptom control in 7 of 10 patients with the addition of everolimus to SSA.[119] Patients should be controlled for development of hyperglycaemia or diabetes when everolimus is combined with SSA.

8.2 | Aiming for antiproliferative effect

In the presence of CS and evidence of disease progression, management may be complex since not all treatments with an antisecretory effect have proven anticancer effect (i.e., telotristat ethyl) and also because some treatments have not shown definitive activity in the presence of CS (i.e., everolimus).[118]

IFN-α, if available may be a preferred therapy in these patients because it also exerts antiproliferative effects. In addition to symptomatic response (see above) tumour control was reported with a median PFS of 15.4 months and a response rate of 4% when combined with SSA.[64]

The use of high-dose SSA is supported by the CLARINET forte study and the control arm of NETTER-1 study in patients with Ki-67 <10%. In patients with comorbidities, elderly patients or patients with indolent tumour growth, this may be an alternative approach when more aggressive therapies seem inappropriate or growth is slow over several years.

In the RADIANT-2 phase 3 trial, the primary endpoint PFS by central reading narrowly missed the prespecified threshold of significance ($p = .026$). Therefore, everolimus is not registered for patients with a history of CS. It may be considered in patients with significant growth when other options have been exploited (such as high dose SSA, locoregional therapies and PRRT).

PRRT is regarded as the standard antiproliferative second line treatment for metastatic and progressive SST positive Si-NET (see Q6). This treatment was more effective than high dose octreotide in patients regardless of the presence of carcinoid syndrome. PRRT is a good treatment option in patients with progressive disease especially if extrahepatic metastases are present. In liver predominant disease embolization treatment can induce fast symptomatic response and high radiological response rates (the objective response rate of pooled data in a recent review was 36.6%).[95] In the presence of CS even a higher symptomatic response rate was seen (70%).[7] PRRT can be recommended as preferred option although evidence from prospective controlled trials is not available.

Recommendations:
In patients with CS, a multidisciplinary approach is of crucial importance.
In patients with refractory CS and predominant diarrhoea, telotristat ethyl should be added to SSA (Recommendation A-1a). SSA dose escalation can be considered in patients with refractory CS (Recommendation A-3b) or alternatively addition of IFN-α (Recommendation B-2b). Locoregional and ablative treatments including debulking surgery, should be considered early for refractory CS (Recommendation B-3a). PRRT represents an option (Recommendation B-3b), especially if progressive metastatic disease is present. Everolimus may be considered in individual patients in combination with SSA if significant tumour growth is present after exploitation of other options (Recommendation C-4).

9 | WHAT ARE THE MOST RECENT DEVELOPMENTS FOR SI-NET?

9.1 | Molecular profiling and precision medicine

Despite molecular profiling being widely explored in Si-NET, precision medicine strategies in this patient population are scarce and remain investigational[120] due to lack of specific mutations and rather presence of epigenetic alterations. Routine genomic profiling of tumour tissue is not recommended, but might be considered in patients with Si-NET (if available and reimbursed) when all treatment options have been exploited, but it is important to manage patients' expectations regarding the very low likelihood of the results impacting their treatment options.[120]

9.2 | Latest developments on systemic treatments for Si-NET: targeting angiogenesis

Regarding new systemic therapy options for Si-NET, multiple clinical trials have been reported over the last few years related to antiangiogenic tyrosine-kinase inhibitors (TKIs) with promising results. However, only sunitinib is registered in Europe for Pan-NET so far.[121] Si-NET patients were not included in the pivotal phase 3 clinical trial with sunitinib, and thus the field was unexplored for some time, until the recent years when a variety of TKIs have been studied in phase II and III clinical trials including Si-NET.

Some of the TKIs that have been explored in this setting include lenvatinib,[84] surufatinib,[87,122] axitinib[88,123] and pazopanib.[124] However, these compounds are not yet registered for NET in Europe. Cabozantinib is an emerging drug in this field. A phase II study with cabozantinib included a cohort of 41 heavily pretreated Si-NET patients.[125] In this study the primary endpoint was ORR. Achieved ORR in the Si-NET cohort was 15%, with 26/41 patients having disease stabilisation. Median PFS was 31.4 months (95% CI 8.5-not reached). The CABINET phase III clinical trial data including 197 patients with extra-pancreatic NETs (129 randomised on cabozantinib and 68 on placebo) supports the activity of cabozantinib with

improvement of PFS (HR 0.41; *p*-value <.0001).[89] Data from the subgroup analysis in intestinal NET are still lacking.

Based on the study results, TKI preferably cabozantinib in view of the positive phase III trial but also lenvatinib (based on results from an uncontrolled phase 2 study with ORR 16.4% and mPFS 15.7 months in GI-NET patients) may be considered in patients in whom all treatment options have been exploited if available and reimbursed and no clinical trial available. TKI may also be a consideration in SST negative patients.

9.3 | Immunotherapy

Immunotherapy approaches in Si-NET have been disappointing. PD-L1 expression within tumour cells has been described to be present in 12.8% of Si-NET.[126] Monotherapy with checkpoint inhibitors (CPI) has not shown much activity, regardless of expression of PD-L1 or other potential biomarkers linked to immunotherapy activity.[127–129] Combination strategies of dual CPI such as durvalumab and tremelimumab (DUNE study) have been explored but no objective responses have been reported in the Si-NET group neither.[130] Despite this, the field is evolving and alternative combinations of immunotherapy and antiangiogenic compounds (i.e., atezolizumab and bevacizumab) look more promising (objective response rate of 15% in the extra-pancreatic NET cohort with durable benefit [median PFS 14.9 months]).[131] Novel approaches such as CAR-T cells are in pre-clinical stage[132]; combination of CPI with TKIs are under development.

Outside the setting of mismatch repair deficiency, microsatellite instability or high TMB, that is rather seen in poorly differentiated NEC than in well differentiated NET, immunotherapy for Si-NET cannot be recommended based on the current evidence. It remains investigational and patients should be included in clinical trials.

Recommendations:
After failure to standard therapies, novel TKIs (RECOMMENDATION B-2b) could be considered if available, while immunotherapy has currently no place in the management of Si-NET, and strategies in this setting remain investigational (RECOMMENDATION C-2b). Patients diagnosed with Si-NET who failed available treatment options should be considered for participation in clinical trials.

10 | WHAT IS THE RECOMMENDED FOLLOW-UP FOR SI-NET?

10.1 | Imaging follow-up after surgery: curative setting

No prospective studies are available regarding the timing of follow-up and the imaging modalities to be utilised in patients who have had potentially curative resection for Si-NET. Follow-up should last for a long time (it may be required to be life-long) after resection since disease relapse can occur also 15 years after surgery.[133,134] MRI of the liver can be offered as the preferred imaging modality of follow-up for its accuracy in detecting liver metastases as the most frequent site of distant metastasis and the advantage of not exposing patients to ionising radiation. Staging intervals range between 3 and 12 months depending on extent of disease, grade, and length of follow-up. We recommend imaging 3–6 months after surgery, followed by 6 months intervals in NET G1, and closer intervals in NET G2. Recurrence most frequently occurs within the first 5 years after curative surgery. After 5 years of being tumour-free, staging intervals may be prolonged to 1 year.[135] In patients with advanced disease (loco-regional LN involved, liver metastases), SRI is recommended after surgery within 3–6 months, and should be repeated in long-term follow up (after 3 years or if suspicious findings on conventional imaging or clinical examination).

10.2 | Imaging follow-up: palliative setting

Frequency of follow-up during palliative treatment depend on clinical factors (more frequent follow-up in rapidly progressing tumours or G2 Si-NET) as well as the treatment administered. Follow-up should be performed in the form of CT or MRI with higher sensitivity for visualisation of liver metastases with MRI. After a first assessment at 3 months from starting a new treatment, imaging every 6 months for G1 Si-NET, treated with SSA may be acceptable. In contrast, patients on everolimus, IFN-α, TKI and chemotherapy require imaging every 3 months as established in oncological practice. Follow-up on patients receiving PRRT should be performed first after 3–4 months from the first cycle of PRRT, since around 20% do not respond to PRRT. The rare event of pseudoprogression should be kept in mind and SRI with PET/CT should be interpreted in the context of clinical and biochemical findings. Further re-evaluation intervals may range between 3 and 6 months depending on grade (3 months in higher NET G2 and NET G3). SRI may be recommended if clinically indicated or every 1–3 years depending on disease spread/sites (lung, bone involvement, peritoneal carcinomatosis, diffuse LN metastases).

Staging intervals with conventional imaging should be every 3 months in NET G3 irrespective of type of treatment. An ^{18}F-FDG-PET may be required to visualise bone metastases or other distant metastases if there is no uptake on SRI or if PRRT is a treatment option.

Bone MRI may be required if symptoms occur indicating bone lesions.

10.3 | Biomarker follow-up

Assessment of circulating biomarkers such as CgA, and NSE (in NET G3) and 5-HIAA; see Question 2) at the time of first diagnosis and as a baseline assessment at the time of starting a new treatment is recommended. If elevated in these conditions, biomarker

reassessment (every 3–6 months depending on the characteristics of the NET and the treatment being monitored) along with imaging could be of use, particularly to inform about the need to expand imaging to other regions than the abdomen. In long-term follow-up circulating biomarkers, if informative in the individual patient (elevated in patients with measurable disease on imaging) may be used alternating with imaging and prompting to additional diagnostic work-up in case of significant increase.

Recommendations:
All patients should be followed-up long-term after curative surgery (RECOMMENDATION A-4) preferably using MRI of the liver/abdomen (RECOMMENDATION C-5). Assessment of circulating biomarkers at time of first diagnosis, and as a baseline assessment at the time of starting a new treatment is recommended (RECOMMENDATION B-4). Radiological and biomarker follow-up during palliative treatment depends on clinical factors, grading, and the type of treatment being administered. (RECOMMENDATION B-5).

11 | CONCLUSION

Management of Si-NET requires a multidisciplinary approach and referral to centres with adequate expertise. Accurate diagnosis and staging are crucial for proper treatment planning. Exploration of (epi)genetics, novel circulating biomarkers and improved radiology and nuclear medicine tools are ongoing areas of research in the field. Current management, especially in the setting of systemic therapies, relies on robust scientific evidence based on prospective clinical trials. Treatment options are still limited, but are expanding with novel TKIs and novel radiopeptides under development while immunotherapy has no role and novel approaches remain investigational. The most adequate sequence of therapies has still to be clarified. In the context of precision medicine the development of predictive biomarkers for tailored treatment planning is crucial.

AUTHOR CONTRIBUTIONS

Angela Lamarca: Conceptualisation; methodology; visualisation; project administration; supervision; writing – review and editing; writing – original draft; validation. **Detlef K. Bartsch:** Methodology; writing – original draft; writing – review and editing. **Martyn Caplin:** Methodology; writing – original draft; writing – review and editing. **Beata Kos-Kudla:** Methodology; writing – original draft; writing – review and editing. **Andreas Kjaer:** Methodology; writing – original draft; writing – review and editing. **Stefano Partelli:** Methodology; writing – original draft; writing – review and editing. **Anja Rinke:** Methodology; writing – original draft; writing – review and editing. **Eva Tiensuu Janson:** Methodology; writing – original draft; writing – review and editing; supervision. **Christina Thirlwell:** Methodology; writing – review and editing. **Marie-Louise F. van Velthuysen:** Methodology; writing – original draft; writing – review and editing. **Marie-Pierre Vullierme:** Methodology; writing – original draft; writing – review and editing. **Marianne Pavel:** Methodology; writing – original draft; writing – review and editing; supervision; visualisation; project administration; validation.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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APPENDIX A

1a	Systematic review (with homogeneity) of Randomised Controlled trials
1b	Individual RCT (with narrow confidence interval)
2a	Systematic review of cohort studies
2b	Individual cohort studies including low quality RCT (eg <80% follow-up)
3a	Systematic review (with homogeneity) of case-controlled studies
3b	Individual case-control study
4	Case series (and poor quality case-control studies)
5	Expert opinion with no explicit critical appraisal, based on physiology, bench research, or first principles.

FIGURE A1 Grade of recommendations. Grading according to published research. ("A" = Strong; "B" = Moderate; "C" = Low; "D" = Very low).