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Guidelines

Digestive Neuroendocrine Neoplasms (NEN): French Intergroup clinical practice guidelines for diagnosis, treatment and follow-up (SNFGE, GTE, RENATEN, TENPATH, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR)

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ABSTRACT

Introduction: This document is a summary of the French Intergroup guidelines regarding the management of digestive neuroendocrine neoplasms (NEN) published in February 2020 (www.tncd.org).
Methods: All French medical societies involved in the management of NEN took part in this work. Recommendations were graded into four categories (A, B, C or D), according to the level of evidence found in the literature until May 2019.
Results: The management of NEN is challenging because of their heterogeneity and the increasing complexity of diagnostic and therapeutic procedures. Pathological analysis is required for their diagnostic and prognostic characterization, which mainly relies on differentiation, grade and stage. The two main emergency situations are functioning syndromes and poorly-differentiated carcinoma. Chromogranin A is the main biochemical marker of NET, although of limited clinical interest. Initial characterization relies on morphological and isotopic imaging. The treatment of localized NET relies on watchful follow-up and local or surgical resection depending on its supposed aggressiveness. Treatment options for metastatic disease include surgery, somatostatin analogues, chemotherapy, targeted therapies, organ-driven locoregional therapies and peptide-receptor radionuclide therapy. As specific predictive factors of treatment efficacy are yet to be identified and head-to-head comparisons have not or only rarely been performed, the therapeutic strategy currently depends on prognostic factors. Cumulative toxicity and the impact of treatment on quality of life must be considered since survival is relatively long in most patients with NET.

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Conclusion: These guidelines are proposed to achieve the most beneficial therapeutic strategy in clinical practice as the therapeutic landscape of NEN is becoming ever more complex. These recommendations are permanently being reviewed.

1. Introduction

The present article is a summary of the French intergroup guidelines published in March 2020 on the website of the SNFGE society www.tncd.org. These guidelines were written by a multidisciplinary committee originating from the main medical societies (SNFGE, GTE, RENATEN, TENPATH, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR) and including several experts from different specialties involved in the management of patients with neuroendocrine neoplasms [NEN] (gastroenterologists, surgeons, pathologists, radiation oncologists, medical oncologists, endocrinologists, nuclear physicians and radiologists). The initial document was reviewed and modified after further evaluation by a review committee and the last version was finally validated by the steering committee made up of members from the participating National Societies. These guidelines are an up-to-date comprehensive overview of the characterization, pretherapeutic examinations and management of patients with NEN. Recommendations were graded in 3 categories (grades A–C) according to the level of evidence. Expert opinion (agreement or not, grade D) was noted when no scientific evidence was validated (Table 1). Importantly, because most NET-related recommendations (especially, non-therapeutic) have not been demonstrated by studies reaching a significant level of evidence, many of them correspond to expert opinion. Unless stated otherwise, the recommendations proposed herein correspond to expert agreement (grade D).

2. General considerations and epidemiology

- Primary NEN can occur anywhere within the digestive system. According to the last US epidemiological data (SEER), the most frequent digestive NEN arise from the small intestine or the rectum (age standardized incidence rate of (approximately 1.2/100,000/year each), the pancreas (approximately 0.8/100,000/year), the stomach or the appendix (approximately 0.4/100,000/year each) [1]. Other primary locations, such as the esophagus, the liver or the biliary tract, are exceptional. The incidence of NEN has been increasing steadily in recent decades, although this may essentially be a consequence of improved diagnostic methods, new World Health Organization [WHO] classifications, the diversity of primaries and better knowledge [2].
- Digestive NEN are characterized by remarkable heterogeneity with regard to stage, inheritance, functioning status and somatostatin receptor expression. Their prognosis is highly variable, notably depending on their histological differentiation (by definition, neuroendocrine tumors [NET] are well differentiated, and neuroendocrine carcinomas [NEC] are poorly differentiated), Ki67 proliferation index and stage [1]. However, no validated prognostic classification exists for metastatic NEN, except for the distribution of the metastases [3].
- Most patients with NET have prolonged survival. This must be taken into account in their management. While imaging remains the keystone of follow-up, repeated computed tomography [CT]-induced irradiation should be avoided, especially for patients with slowly- or non-progressive NET and/or with hereditary predisposition syndromes. Imaging techniques without ionizing exposure (notably magnetic resonance imaging [MRI]) should be considered for surveillance, as an alternative to CT.
- The main therapeutic objectives must be established on a case-by-case basis and discussed with each patient, at each phase of the disease: cure, increased survival, local control, symptom control, improved quality of life, etc.
- The rarity and the heterogeneity of NEN make their management challenging and explain the small number of randomized studies and the overall low level of evidence. All cases of patients with NEN should be discussed in expert multidisciplinary meetings. In France, expert multidisciplinary meetings are organized within the RENATEN network (https://www.reseau-gte.org/renaten/). Promoting inclusion in therapeutic trials is a priority, even in situations where recommendations exist. A list of ongoing studies is available online and is regularly updated (https://www.reseau-gte.org/protocoles-du-gte/).

3. Pre-therapeutic explorations of digestive NEN

3.1. Initial work-up: morphological examinations

Unless stated otherwise, the following recommendations correspond to grade D.

3.1.1. Conventional cross-sectional imaging

- ***Contrast-enhanced abdominopelvic CT-scan*** with acquisitions at the delayed arterial (30 s) and then the portal venous (70–90 s) phases, since some highly-vascularized NET are only visible at one phase or the other (level of recommendation: grade C) [4,5].
- ***Thoracic CT-scan*** if the tumor is metastatic or locally advanced (T4, N1), if the primary site is unknown, in cases of type 1 multiple endocrine neoplasia [MEN1] or if pulmonary adverse events of treatments may be expected.

Table 1
Grades of recommendations.

Grade	Quality of evidence	Definition
A	High	Strongly recommended based on highly robust scientific evidence (e.g. several randomized controlled trials/meta-analysis) Further research is very unlikely to change our confidence in the estimate of effect
B	Moderate	Usually recommended based on scientific presumption (e.g. one randomized controlled trial) Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
C	Low	Option based on weak scientific evidence (e.g. one or several non-randomized trials) Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
D	Very low	Expert opinion (agreement or not) Any estimate of effect is very uncertain

- ***MRI with gadolinium-enhanced and diffusion-weighted sequences*** is more sensitive than CT-scan for the detection of liver and bone metastases (level of recommendation: grade C) [6,7]. An abdominopelvic MRI is recommended together with a thoraco-abdominopelvic CT-scan to obtain a comprehensive assessment of possible distant metastases, notably small liver lesions. If liver metastases can only be detected by MRI, it should then be used as the main examination procedure for the follow-up [5].
- ***MRI of the spine or whole-body MRI*** can be performed in patients with liver metastases, in order to identify other metastatic sites (especially, bone or peritoneal) [8]. However, this procedure is restricted by its limited availability. The sensitivity of MRI seems to be similar to that of Ga-DOTA positron-emitting tomography [PET] (91% vs. 92%, respectively), except for liver (99% vs. 92%, respectively) and bone (96% vs. 82%, respectively) metastases for which MRI was superior [9].
- ***Brain MRI (or CT-scan)*** is recommended in patients with symptoms suggestive of brain metastases, which are however rare even in digestive NEC (4% of patients [10]). Although recommended in the ENETS guidelines, there is no consensus regarding a systematic brain MRI at initial diagnosis in patients with metastatic NEC [11].

3.1.2. Endoscopy

- ***Upper gastrointestinal endoscopy*** is recommended:
  - o In patients with gastric NET, to perform multiple antrum/fundus biopsies and search for etiologic orientation (aspect of fundic atrophic with neuroendocrine cell hyperplasia in cases of pernicious anemia, arguments for Zollinger-Ellison Syndrome [ZES], presence of *Helicobacter pylori*) [12];
  - o In patients with ZES, to search for duodenal gastrinomas and type 2 fundic NET, and verify adequate control of gastric hypersecretion (healing of erosions and ulcers);
  - o In patients with MEN1, to search for arguments for ZES and gastric and/or duodenal NET.
- ***Ileo-colonoscopy*** is recommended in all patients with ileal, colonic or rectal NET, because of the risk of concurrent digestive NET and colorectal adenoma/adenocarcinoma (level of recommendation: grade C) [13].
- ***Endoscopic ultrasonography***(EUS) is recommended in the following situations, in the absence of metastatic disease:
  - o Gastric NET that appear resectable, except for multiple small fundic NET < 10 mm developed on fundic atrophic gastritis (type 1), to assess tumor size, parietal invasion and regional lymph nodes (level of recommendation: grade C) [12,14,15];
  - o Duodenal or peri-ampullary NET of any size that appear resectable, to assess tumor size, parietal invasion and regional lymph nodes [14,16];
  - o Rectal NET that appear resectable, to assess tumor size, parietal invasion and perirectal lymph nodes; or following upfront endoscopic resection to assess perirectal lymph-nodes and look for residual tumor, except for those measuring ≤10 mm that were completely resected and showed no factors predictive of metastases (T1, G1, no lymphovascular invasion) (level of recommendation: grade C) [17,18];
  - o Pancreatic tumors that appear to be resectable, to assess tumor size, vascular involvement, relationship to the main pancreatic duct, behavior at dynamic contrast-enhanced EUS and to perform EUS-guided sampling (level of recommendation: grade C) [12,19]. However, EUS and EUS-guided sampling cannot be systematically recommended in situations where they are not expected to change patient management;
  - o Secretory syndrome (evidenced by clinical and biological examinations) evocative of a functioning duodeno-pancreatic NET with normal conventional imaging [12];
  - o In patients with proven or suspected MEN1, to search for pancreatic and/or duodenal NET, which are frequently multiple, and gastrinoma in cases of ZES.
- ***Capsule enteroscopy*** has no indication, especially if a small-intestine primary NET is known and/or if small-intestine surgery is already indicated, because its diagnostic yield is low and there is a significant risk of obstruction.

3.1.3. Nuclear medicine imaging

- ***Somatostatin-receptor imaging***:
  - o Somatostatin-receptor scintigraphy [SRS] (Octreoscan®) and preferentially, if available, Ga-DOTA-PET should be performed in all patients with NET associated with metastases or with a risk of regional/distant spreading (level of recommendation: grade C);
  - o Ga-DOTA-PET has higher sensitivity (97%) than SRS (52%) and should thus be preferred, especially in situations where a precise distant evaluation is necessary (e.g., before major surgery); however, there is no strong argument to recommend one Ga-DOTA-PET modality over the others (DOTATOC, DOTANOC or DOTATATE) [5,20];
  - o It is performed to search for distant metastases and to evaluate the expression of somatostatin receptors for theranostic purposes (possible indication of peptide-radionuclide receptor therapy [PRRT]) [5];
  - o Somatostatin-receptor imaging is not routinely indicated for NEC.
- ***18Fluorodeoxyglucose [FDG]-PET:***
  - o High FDG uptake is considered a hallmark of malignancies with high metabolism and proliferation, although not specific to NEN. It correlates with a higher grade and is an independent poor prognostic factor (level of recommendation: grade C) [21];
  - o FDG-PET is recommended for the evaluation of NEC, especially before curative surgery, but should not delay treatment initiation (level of recommendation: grade C) [11];
  - o It should be performed in NET with negative somatostatin-receptor imaging (exception: negativity of SRS for lesions <10−15 mm may be due to its low resolution rather than true negativity);
  - o It can be performed in somatostatin-receptor positive NET of any grade, if high FDG uptake is expected to change patient management.
- ***18Fluorodihydroxyphenylalanine [FDOPA]-PET:***
  - o High FDOPA uptake is specific to NEN with high amino-acid metabolism, especially in small-intestine NET. It is more sensitive than cross-sectional morphological imaging and SRS [22] although it has been poorly compared to Ga-DOTA-PET (level of recommendation: grade C).
  - o It can be useful as part of the initial and postoperative evaluation of small-intestine NET, or when a precise evaluation is necessary (e.g., before major surgery) [23,24];

3.2. Pathological analysis

Unless stated otherwise, the following recommendations correspond to grade D.

- NEN samples must always be obtained (biopsy, surgery) before any medical antitumor treatment, although it should not delay the initiation of symptomatic treatment. If there is not enough tumor tissue for appropriate pathological analysis, it may be necessary to take another sample. Besides, taking a new sample is

Table 2
2019 WHO histo-prognostic classification of digestive neuroendocrine neoplasms (modified according to Ref. [25]).

	Ki67 index[a]	Mitotic count[b]
Grade 1 (G1)	<3%	<2
Grade 2 (G2)	3%–20%	2–20
Grade 3 (G3)	>20%	>20
	Grade	Differentiation
G1 NET	G1	Well differentiated
G2 NET	G2	Well differentiated
G3 NET	G3	Well differentiated
NEC[c]	G3	Poorly differentiated, of small cell or large cell types
MiNEN		Mixed neuroendocrine–non-neuroendocrine neoplasm

NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.
[a] The Ki-67 proliferation index value is determined by counting at least 500 cells in the regions of highest labelling (hot spots).
[b] Mitotic rate is to be expressed as the number of mitoses per 2 mm^2 (equaling 10 high-power fields at ×40 magnification) as determined by counting in 50 fields of 0.2 mm^2 (i.e. a total area of 10 mm^2). The final grade is based on whichever of the two proliferation index/rate places the neoplasm in the higher grade category.
[c] NEC are considered high grade (G3) by definition.

advised when the evolution is unusual (unexpected recurrence, dissociated evolution, unusually quick progression), although it may be questioned in the absence of any expectable therapeutic impact.

- The pathological diagnosis and precise characterization of NEN can be challenging. Hence, any case with a difficult diagnosis should be referred to an expert pathologist, especially for NEN with an incomplete immunostaining profile, G3 NEN, mixed neoplasms (MiNEN) or NEN from an unusual primary location. In France, this should be done within the dedicated TENPATH network (http://www.reseau-gte.org/index.php?section=article&id_article=264).
- All NEN should be classified according to the WHO classification, based on histological differentiation (NET vs. NEC) and grade, which relies on the proliferation index assessed by the Ki67 and mitotic index (level of recommendation: grade B). The last version, published in 2019 (Table 2), recognized the G3 NET category in all digestive locations [25].
- It may be difficult to distinguish between G3 NET and G3 NEC according to histological differentiation only. This can be facilitated by the use of additional markers, especially in pancreatic G3 NEN (p53, Rb, DAXX, ATRX, menin, TTF1), although these techniques require further validation [25–27].
- All NEN should also be classified according to the TNM classification (Table 3) (level of recommendation: grade C). The last version (8th edition) was published in 2017 and was close to those proposed by ENETS in 2006 and 2007 [3], except for appendix NET (see Section 4.2.6). Importantly, in this classification, TNM staging of NEC follows that for exocrine neoplasms of the same primary site.
- In patients with revealing metastases from NET of an unknown primary, the following markers could help identify the origin of the primary tumor, although their sensitivity and specificity are rather unsatisfactory [27]:
  - o TTF1 for lung NET;
  - o CDX2 and serotonin for intestinal NET;
  - o PDX1, ISL1, DAXX/ATRX for pancreatic NET (menin is not specific);
  - o Calcitonin, TTF1 and CEA for medullary thyroid carcinoma;
  - o Pan-cytokeratins (not limited to CK7 and CK20) to exclude paraganglioma and pheochromocytoma (usually negative).

3.3. Biological examinations

Unless stated otherwise, the following recommendations correspond to grade D.

- ***Plasma chromogranin A***
  - o It is the general biochemical marker with the highest performance in NET, although its sensitivity for NET diagnosis is only satisfactory for metastatic NET (70–100%) in comparison with localized NET (10–50%) (level of recommendation: grade C) [28–30].
  - o There are numerous causes of false positives, including any situation with hypergastrinemia (treatment with proton pump inhibitors [PPI], fundic atrophic gastritis, infection with *H. pylori*) and severe kidney failure [31]. It is advised to consider high chromogranin A levels only if the serum gastrin level is normal.
  - o PPI should be interrupted at least 7 days (preferentially 14 days) before measuring chromogranin A (except in patients with ZES, in whom PPI must not be stopped) [30,32].
- ***Hormones related to functioning duodeno-pancreatic NET (gastrin, insulin, VIP, glucagon,* . . .*)*** (level of recommendation: grade C)
  - o These assays should not be performed systematically but depending on the clinical suspicion of a functioning syndrome. Dynamic tests have been validated in some functioning syndromes [30];
  - o Suspicion of ZES: secretin test, to be performed in a specialized center because even slight modifications of PPI doses may expose patients to a risk of hemorrhage and perforation;
  - o Suspicion of insulinoma: hypoglycemia and inappropriate hyperinsulinism (in the absence of hypoglycemic treatment) and/or fasting test in a specialized center;
  - o Suspicion of Cushing syndrome: 24-h free urinary cortisol, low-dose dexamethasone suppression test.
- ***Urinary 5-Hydroxy-indolacetic acid [5HIAA]*** (level of recommendation: grade C)
  - o Its sensitivity (50–70%) and specificity (90–100%) are relatively good for the diagnosis of small-intestine (and right colon) NET and are increased in metastatic and/or functioning settings. It should only be measured in patients with small-intestine NET (or bronchial NET, which can secrete serotonin), as part of the search for a primary NET in cases of isolated metastases, to document a carcinoid syndrome, or as part of the follow-up of patients with initially increased levels [33].
  - o It should be measured in urine collected for 1–2 days, after an appropriate diet excluding both tryptophan-containing foods and nutritional supplements [30].
  - o ***Serotonin*** levels must no longer be measured because of countless false positives.
- ***Neuron-specific enolase*** has an acceptable diagnostic performance for NEC (but is a matter of debate in NET) and correlates with tumor differentiation and volume.
- ***NT-pro-BNP*** can be used for the screening and clinical evaluation of carcinoid heart disease (level of recommendation: grade C) [34,35].
- ***DPD phenotyping*** should be assessed whenever fluoropyrimidine-based chemotherapy is envisaged (5-fluorouracile [5FU] or capecitabine), by measuring plasma uracil concentrations.
- ***As part of the etiological evaluation of gastric NET***, type 1 gastric NET (conversely to type 3) are associated with hypergastrinemia (also type 2 gastric NET), frequently positive anti-intrinsic factor and anti-parietal cell antibodies (pernicious anemia), vitamin B12 deficiency (not always found), and frequent iron deficiency.

Table 3
UICC Tumor-Node-Metastases classification of neuroendocrine tumors, 8th edition (2017). Of note, neuroendocrine carcinomas should be classified as for exocrine carcinomas of the same location.

	Stomach	Duodenum, ampulla	Pancreas	Small intestine	Appendix[a]	Colon, rectum
TX	Primary tumor cannot be assessed					
T0	No evidence of primary tumor					
T1	Invades the lamina propria or submucosa and ≤1 cm	Duodenum: invades the mucosa or submucosa and ≤1 cm Ampulla: confined to the sphincter of Oddi and ≤1 cm	Limited to the pancreas and <2 cm	Invades the lamina propria or submucosa and ≤1 cm	Tumor size <2 cm	Invades the lamina propria or submucosa T1a: size <1 cm T1b: size 1–2 cm
T2	Invades the muscularis propria or >1 cm	Duodenum: invades the muscularis propria or >1 cm Ampulla: invades duodenal submucosa or muscularis propria, or >1 cm	Limited to the pancreas and 2–4 cm	Invades the muscularis propria or >1 cm	Tumor size 2–4 cm	Tumor invades muscularis propria or >2 cm
T3	Invades the subserosa without invading the serosa	Invades the pancreas or peripancreatic adipose tissue	Limited to the pancreas and >4 cm, or invading the duodenum or common bile duct	Invades the subserosa without invading the serosa	Tumor size >4 cm or with subserosal invasion or mesoappendix involvement	Invades the subserosa without invading the serosa
T4	Invades the serosa or other organs	Invades the serosa or other organs	Invades adjacent organs or the wall of large vessels (celiac axis or superior mesenteric artery)	Invades the serosa or other organs	Invades the serosa or other organs (excluding direct mural extension to adjacent subserosa or bowel)	Invades the serosa or other organs
NX	Regional lymph nodes cannot be assessed					
N0	No regional lymph-node metastasis					
N1	Regional lymph-node metastases			<12 regional lymph-node metastases	Regional lymph-node metastases	
N2	–	–	–	>12 regional lymph-node metastases Or large mesenteric mass (>2 cm)	–	–
Mx	Metastatic status not evaluable					
M0	No distant metastasis					
M1	Distant metastases M1a, Metastases confined to liver M1b, Metastases in at least one extra-hepatic site M1c, Both hepatic and extrahepatic metastases					

[a] Please refer to Section 4.2.6 regarding the TNM classification of the appendix NET.

The same assay method for peptides, hormones and chromogranin A should be used throughout the follow-up. Of note, a secondary secretory syndrome or a change in secretion is rare but may occur during the follow-up, mainly for pancreatic NET [36].

3.4. Echocardiography

- It should be performed to search for carcinoid heart disease in patients with carcinoid syndrome or high urinary 5HIAA levels and/or high NT-pro-BNP levels (level of recommendation: grade C) (cf. Section 6.2.2).
- Echocardiography should be performed by a cardiologist experienced in carcinoid heart disease screening and management [35].

3.5. Screening for a genetic predisposition

Unless stated otherwise, the following recommendations correspond to grade D.

- Screening for a predisposition syndrome (MEN1, VHL) should always be considered in cases of duodeno-pancreatic NET:
  - o ***In a syndromic setting evocative of MEN1***, characterized by a personal (or family) history of parathyroid adenoma/hyperplasia, pituitary adenoma, thymus/bronchial NET, and/or adrenocortical adenoma [37];
  - o ***In a syndromic setting evocative of von Hippel-Lindau disease [VHL]***, characterized by a personal (or family) history of central nervous system and/or retina hemangioblastoma, clear cell carcinoma, renal and/or kidney multiple cysts, pheochromocytoma or paraganglioma and/or endolymphatic sac tumor [38];
  - o Isolated (no other condition evocative of syndromic setting) but with a family history of duodenopancreatic NET;
  - o Isolated and sporadic (no family history) but multiple primary pancreatic NET, or < 50 years old, or associated with ZES;
  - o Other predisposition syndromes (type 1 neurofibromatosis, von Recklinghausen disease, *BRCA1/2* mutations) may predispose to duodeno-pancreatic NET; however, these situations are exceptional.
- As MEN1 is the most frequent oncogenetic syndrome involving duodenopancreatic NET, it should be suspected systematically. Especially, MEN1-related hyperparathyroidism has a penetrance of nearly 100% at the age of 60, and should always be searched for by measuring blood calcium (corrected for albumin) or blood ionized calcium, 24-h urinary calcium, phosphorus, parathyroid hormone and vitamin D [37].
- If a predisposition mutation is found, relatives should be screened, and other syndromic-related conditions should be searched for.
- Multiple ileal tumors (30–50% of patients with small-intestine NET): ask patients about possible family history of small-intestine NET. Rare family cases have been described, although no predisposing molecular alteration has been confirmed to date [39,40].
- It is unnecessary to screen for a genetic predisposition for the following NET locations: esophagus, appendix, jejunum, rectum, colon or stomach (unless if associated with ZES) and NEC whatever the site.

3.6. Examinations recommended in patients with metastases from NET of unknown primary

Unless stated otherwise, the following recommendations correspond to grade D.

- Clinical/biological: signs of hormone secretion can suggest a duodenopancreatic NET (gastrin, insulin, VIP, glucagon, ...) or an intestinal/bronchial NET (carcinoid syndrome, 5HIAA).
- Pathological: immunohistochemical profile (see Section 3.2).
- Ga-DOTA-PET and/or FDOPA-PET, which have the highest sensitivity for the detection of somatostatin-receptor-expressing NET, and NET with high amino-acid metabolism (essentially small-intestine NET), respectively.
- In patients with a history of appendectomy, check for the absence of appendiceal NET on the pathology report.
- Endoscopy and EUS of the stomach, duodenum, papilla and pancreas, if it could change management.
- In the presence of enlarged mesenteric lymph nodes, the presence of a small-intestine primary NET is highly suspected and should be explored by FDOPA-PET, CT enterography, ileo-colonoscopy, and/or upfront surgical resection with intra-operative exploration of the small intestine [24].
- Explore the possibility of a non-digestive primary NET:
  - o Medullary thyroid carcinoma (calcitonin, which is very sensitive: diagnosis excluded if it is negative; and carcinoembryonic antigen);
  - o Paraganglioma, pheochromocytoma (urinary or plasma metanephrines).

4. Treatment of digestive (well-differentiated) NET

4.1. Treatment of symptoms related to tumor secretions

Unless stated otherwise, the following recommendations correspond to grade D.

- The treatment of symptoms related to tumor secretions is a priority; it must be started as soon as a blood sample has been taken for biological markers (except for ZES: introduce PPI immediately) (level of recommendation: grade A).
- ***Carcinoid syndrome***:
  - o The treatment relies on long-acting somatostatin analogues [SSTA]. The dose is generally that prescribed with antitumor intent (octreotide LAR 30 mg/28d or lanreotide Autogel 120 mg/28d (level of recommendation: grade A)) [41]; <3 bowel movements and flushes per day may constitute a reasonable objective since these thresholds are associated with decreased quality of life;
  - o Patients without carcinoid syndrome but elevated 5HIAA could be treated with antisecretory-intent SSTA;
  - o Diarrhea related to carcinoid syndrome is almost always associated with a marked increase in urinary 5HIAA levels. If this is not the case, other causes of diarrhea should be explored (especially in patients with previous surgery), such as malabsorption of biliary salts, bacterial overgrowth, chronic mesenteric ischemia or steatorrhea due to SSTA;
  - o As an option, interferon α (pegylated forms are better tolerated) can be used in patients with uncontrolled symptoms (level of recommendation: grade C) [42];
  - o Telotristat, an oral inhibitor of tryptophan hydroxylase and serotonin synthesis, significantly reduced diarrhea in patients with refractory carcinoid syndrome in a phase III study [43], and may be thus used in association with SSTA in this setting, if available (level of recommendation: grade B).
- ***ZES***: the treatment relies on PPI at doses adapted to the clinical and endoscopic response (level of recommendation: grade A). The recommended starting dose is equivalent to omeprazole 40–60 mg twice daily [44]. Patients should be aware of the lifelong treatment and the absolute necessity to never stop PPI under any circumstances.

- ***Insulinoma***:
  - o Explain to the patient and his/her entourage the risks of hypoglycemia, dietary recommendations and the need for sufficient sugar intake in cases of confusion;
  - o Surgical resection of the pancreatic NET responsible for the insulinoma syndrome;
  - o Diazoxide 5–10 mg/kg/d, with progressive dose increases (level of recommendation: grade C) [45];
  - o SSTA in refractory forms, using short-acting formulations and initial surveillance in hospital (risk of paradoxical hypoglycemia);
  - o Everolimus in patients with metastatic insulinoma and persistent hypoglycemia despite other treatments (level of recommendation: grade C) [46];
  - o Other treatments, such as pasireotide or sunitinib, might be discussed on a case-by-case basis, in expert centers, with initial surveillance in hospital [47].
- ***VIPoma, glucagonoma***:
  - o SSTA at doses adapted to symptoms (level of recommendation: grade C);
  - o In refractory VIPoma, sunitinib may enable symptom control [48].
- SSTA are generally well tolerated, but they can cause or foster (level of recommendation: grade C):
  - o Diarrhea/steatorrhea related to exocrine pancreatic insufficiency, for which pancreatic enzymes are an effective treatment [49];
  - o Impaired glycemic control in patients with preexisting diabetes mellitus or not;
  - o Gallbladder or biliary complications in patients without prior cholecystectomy [50]; hence it is recommended to discuss systematic cholecystectomy during abdominal surgery in patients likely to receive SSTA during their subsequent management (level of recommendation: grade C).
- In cases of uncontrolled functioning syndrome of any type, consider supposedly effective antitumor treatments to reduce tumor volume, notably chemotherapy, PRRT, liver transarterial embolization or debulking surgery.

4.2. Treatment of non-metastatic digestive NET

4.2.1. Precautions regarding surgery for digestive NET

- Prior to any surgical procedure, all surgical indications and procedures must be discussed by a multidisciplinary team.
- If there is the least doubt about the possible existence of a paraganglioma, measure plasma or urinary metanephrine and normetanephrine before any biopsy or surgery.
- Any hormone hypersecretion and its biological and clinical consequences must be controlled before surgery [51].
- The anesthesiologist (ideally experienced in NET surgery) must include antisecretory therapy within the perioperative management, such as high-dose PPI for ZES, SSTA for carcinoid syndrome (especially for the prevention of carcinoid crises), VIPoma or glucagonoma, and control of glycemia for insulinoma.

4.2.2. Treatment of non-metastatic gastric NET

Unless stated otherwise, the following recommendations correspond to grade D.

- There are 3 types of well-differentiated gastric NET [14,15]:
  - o Type 1 NET (70%–80%) consist of multiple, small (<1 cm in 80% of cases) fundus NET arising in a context of hypergastrinemia, mainly related to pernicious anemia (in this case there is fundic atrophic gastritis) or rarely to *H. pylori* infection; they are generally G1 but can be G2 and have very low metastatic potential.
  - o Type 2 NET (<5%) are multiple fundic NET associated with ZES-related hypergastrinemia occurring in MEN 1 patients.
  - o Type 3 NET (15–25%) are solitary sporadic NET, sometimes ulcerated, often large (> 1 cm in 70% of cases) not associated with hypergastrinemia; they can arise in the fundus or antrum. They are generally G2 or G3 and have a high risk of metastasis (≥50%).
- In practice, it is important to distinguish between type 1 and type 3 gastric NET, using endoscopic (cf. Section 3.1.2), pathologic and biological (cf. Section 3.3) arguments [52].
- ***Treatment of type 1 gastric NET:***
  - o Lesions ≤1 cm and G1: the risk of metastasis is very low (≤1%). No additional evaluation or specific follow-up (other than that of chronic gastritis to monitor the risk of development of intestinal metaplasia, dysplasia and adenocarcinoma) is recommended (level of recommendation: grade C). Endoscopic or surgical resection of the largest NET can be performed alternatively to simple follow-up [14,15].
  - o Lesions between 1 and 2 cm, G1 (or low G2), without muscularis invasion, or suspicious perigastric lymph nodes at EUS: endoscopic mucosal resection (EMR) with cap aspiration or ligation-assisted or endoscopic submucosal dissection (ESD) [14,15].
  - o Lesions ≥ 2 cm, or in cases of G2, muscularis invasion (8–12% of cases), or suspicious perigastric lymph nodes (8–20% of cases) at EUS: discuss surgical resection (partial gastrectomy with lymph-node picking or resection) (level of recommendation: grade C). No adjuvant therapy is recommended [14].
  - o No benefit was demonstrated with SSTA in this setting.
- ***Treatment of type 2 gastric NET:*** similar to type 1 gastric NET.
- ***Treatment of type 3 gastric NET:***
  - o Carcinologic surgery with lymphadenectomy is the treatment of reference, as in gastric adenocarcinoma (level of recommendation: grade C) [14]. No adjuvant therapy is recommended.
  - o The management of type 3 gastric NET < 2 cm is not defined. The risk of metastasis is relatively high (25%) thus advocating the use of radical surgery, although endoscopic resection might be considered for G1 lesions <1 cm if an appropriate evaluation is unremarkable.

4.2.3. Treatment of non-metastatic duodenal or ampullary NET (Fig. 1)

Unless stated otherwise, the following recommendations correspond to grade D.

- The factors associated with an increased risk of lymph-node metastasis and shorter survival are: the periampullar location, tumor size, G2, lymphovascular invasion, the invasion of the muscularis layer, and gastrinomas [16].
- Radical surgery is recommended for any periampullar tumor, in case of tumor size ≥20 mm or in the presence of pejorative factor(s) (level of recommendation: grade C).
- Although the role of parenchyma-sparing surgery in duodenal or periampullary NET is not clearly defined, ampulla resection might be sufficient for small (<10–15 mm) periampullary NET without lymph-node metastases (negative preoperative evaluation, negative frozen section assessment of intraoperative lymph-node picking), especially in patients with comorbidities who may be unfit for pancreaticoduodenectomy. Such surgery should be performed in expert centers.
- Endoscopic resection is recommended for duodenal NET ≤ 10 mm with no pejorative factors and without suspicious lymph nodes at EUS (level of recommendation: grade C) [53].
- Endoscopic resection is possible for duodenal NET measuring 10–20 mm with no other pejorative factors [54].

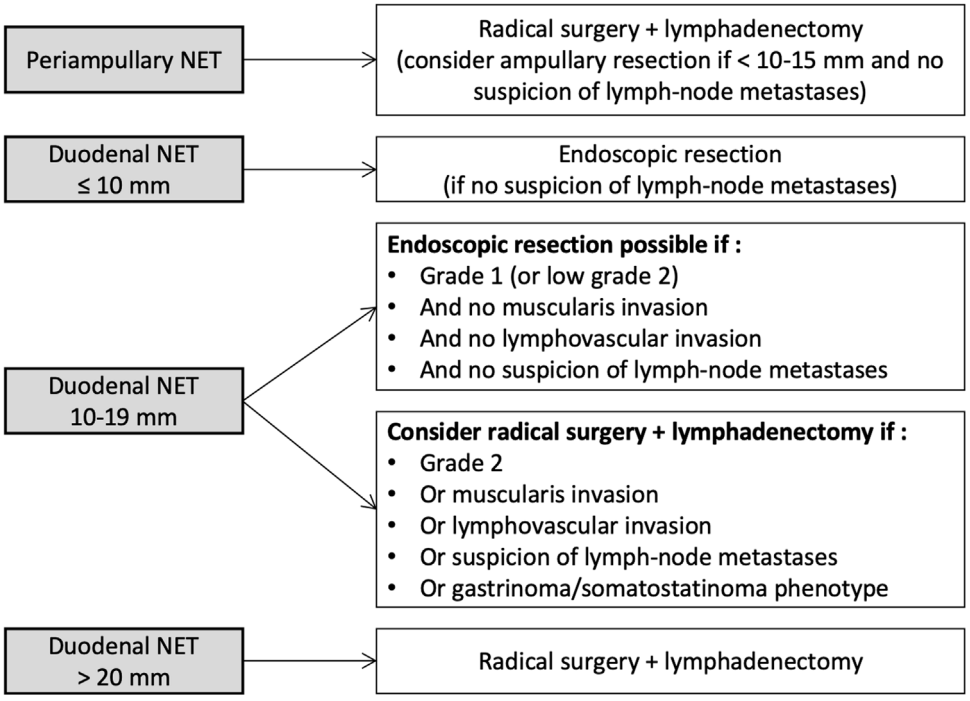


Fig. 1. Algorithm for the local management of non-metastatic duodenal/ampullary NET.

- Endoscopic resection of duodenal NET is associated with significant morbidity and difficulty to achieve R0 resection; hence, it should be restricted to expert centers. Standard polypectomy/EMR should be avoided (50% of R1 rate) and cap aspiration or ligation-assisted EMR should be preferred. ESD may be superior to EMR to improve the R0 resection rate, while its morbidity rate is high because of the risk of duodenal perforation (level of recommendation: grade C) [54].

4.2.4. Treatment of non-metastatic pancreatic NET

Unless stated otherwise, the following recommendations correspond to grade D.

- The surgical indications depend on prognostic factors and the existence or not of MEN1, which must be searched for in conditions as described above (cf Section 3.5.) before considering surgery.
- Surgery in patients with pancreatic NET must be performed in expert centers, notably in cases of oncogenetic syndrome (MEN1, VHL), to propose parenchyma-sparing surgery in selected patients, appropriate lymphadenectomy and to limit the perioperative risk.

4.2.4.1. Sporadic pancreatic NET.

- ***Surgical resection*** should always be considered, even in patients with loco-regional extension, unless the operative risk is too high, or the predictable postoperative functional consequences are too severe (level of recommendation: grade C).
- There is no indication for adjuvant treatment.
- Any pancreatic resection must be associated with standardized ***lymphadenectomy*** as best defined for patients with pancreatic adenocarcinoma [55], with a minimal number of 13 lymph-nodes to be resected (level of recommendation: grade C) [56]. This does not apply to small insulinomas, which are eligible for enucleation.
- If enucleation is considered for pancreatic NET with good prognostic features (size ≤2 cm, G1, asymptomatic), it should be associated with lymph-node picking [57,58].
- ***Cholecystectomy*** should be systematically discussed in patients with pancreatic NET with a high risk of recurrence, because of the ulterior risks of cholelithiasis associated with SSTA, and cholecystitis with liver transarterial embolization (level of recommendation: grade C) [50].
- Small (≤2 cm) pancreatic incidentalomas can be followed without surgical resection, provided that (level of recommendation: grade C) [59–61]:
  - o They are discovered incidentally and are thus asymptomatic and non-functioning;
  - o They are histologically-proven well-differentiated G1 NET (or eventually low G2 with Ki67 < 5%: threshold not precisely defined);
  - o Size <2 cm (T1 stage);
  - o They have features of typical low-grade NET: marked arterial-phase contrast enhancement on CT or MRI, positive somatostatin-receptor imaging (SRS can be negative in small lesions), and probably negative FDG-PET if performed;
  - o There is no suspicion of lymph-node involvement or distant extension;
  - o There is no pancreatic or biliary ductal dilation on imaging;
  - o There is no progression at follow-up imaging.
- Surveillance of non-resected small pancreatic incidentalomas can be performed by MRI if it enables the perfect visualization of the NET, or CT-scan as a second choice (taking into account the long-term risk of repeated radiation). Although not yet defined precisely, follow-up can be proposed at 6 months and then yearly. Surgery must be considered if the size increases (threshold not defined).
- Although EUS-guided radiofrequency ablation of small pancreatic tumors seems feasible [62], it is still under evaluation and is not recommended in routine practice.

4.2.4.2. In patients with MEN 1.

- The surgical indications are identical to those for sporadic pancreatic NET, with the exception of gastrinomas, for which the role of surgery remains a matter of debate [60,63].

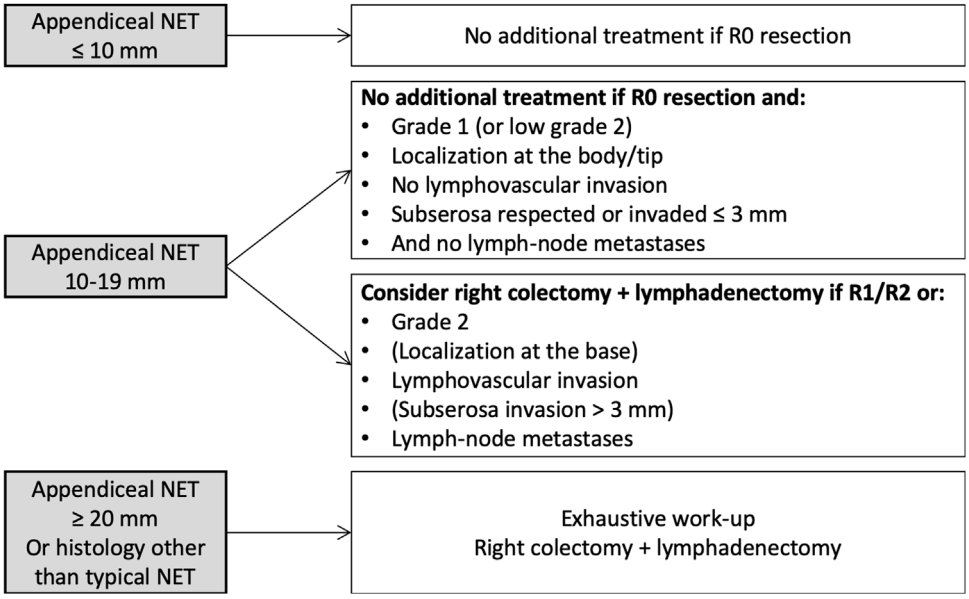


Fig. 2. Algorithm for the local management of non-metastatic appendiceal NET.

- The procedure must be defined in a multidisciplinary meeting with a surgeon experienced in MEN1.
- The whole abdominal cavity must be systematically explored intraoperatively, and in cases of ZES, duodenum endoscopic transillumination with duodenotomy must be used to search for gastrinomas (which are often < 1 cm in diameter).
- Hyperparathyroidism must be operated on before or during surgery for ZES-related gastrinomas.
- Otherwise, conservative management for patients with MEN1-related non-functioning pancreatic NET ≤ 2 cm is associated with a low risk of disease-specific mortality and should thus be considered in this setting [60,63].

4.2.5. Treatment of non-metastatic small-intestine NET

Unless stated otherwise, the following recommendations correspond to grade D.

- The treatment of reference is ***surgical resection of the primary tumor*** and associated mesenteric lymph-nodes, with the aim to preserve as much as possible small bowel length (level of recommendation: grade C) [24,64,65]. This surgery decreases the risk of subsequent local complications (mainly occlusion, which may occur in 20–30% of cases).
- Comprehensive lymph-node dissection and avoiding subsequent short-bowel syndrome must remain the two main objectives of small-intestine NET surgery.
- Surgery should be performed by laparotomy, eventually laparoscopically-assisted with exteriorization of the small bowel for entire digital palpation [24,64,65], since small-intestine NET are multiple in 30–50% of cases [40,66].
- If there is an indication for emergency surgery, the procedure should focus on the life-threatening condition (e.g., intestinal occlusion) [67]. If optimal oncologic surgery cannot be achieved, to avoid subsequent difficult reoperation, consider limited resection of the diseased intestine zone, with or without restoring continuity and with no extensive intraperitoneal dissection. A reoperation should be planned after the usual explorations with the aim to focus on the oncological resection [68].
- ***Mesenteric lymphadenectomy*** should be performed routinely, regardless of the size of the primary small-intestine NET (even if < 1 cm) (level of recommendation: grade C) [24,65,69]. Lymph-node and vascular involvement should be assessed on preoperative imaging (CT angiography and/or MRI frontal sections) in order to anticipate the difficulty and the extension of the lymphadenectomy, and avoid unnecessary laparotomy for unresectable metastatic lymph nodes (involvement of the trunk of the mesenteric superior artery and the first jejunal arteries) [64].
- Lymphadenectomy is associated with a better prognosis [68], although its optimal extent is not clearly defined in patients with non-metastatic small-intestine NET (level of recommendation: grade C). Lymphadenectomy along the trunk of the superior mesenteric artery up to the retropancreatic area has been suggested but its usefulness requires confirmation and the benefit/risk ratio should be demonstrated [70].
- Lymphadenectomy must harvest at least 8 (and possibly 12) lymph nodes to adequately identify N+ tumors (level of recommendation: grade C) [71,72]. When < 8 lymph nodes have been harvested, especially in cases of emergency surgery, repeat surgery to obtain adequate lymphadenectomy should be routinely discussed in multidisciplinary meeting in the light of the results of a complete investigation including FDOPA-PET or Ga-DOTA-PET.
- Conversely, extensive lymphadenectomy is associated with a significant risk of post-operative short-bowel syndrome, which should be avoided at all cost. Hence, it is recommended that such surgery should be performed in expert centers, in which specific morbidity is controlled [64,65]. Retractile mesenteritis, large mesenteric lymph nodes and/or resectable peritoneal carcinomatosis should not contraindicate surgery.
- Routine ***cholecystectomy*** should always be discussed in patients with small-intestine NET with a high risk of recurrence, because of the risk of cholelithiasis associated with SSTA, and the risk of cholecystitis with liver transarterial embolization (level of recommendation: grade C) [24,50].
- There is no indication for adjuvant treatment.

4.2.6. Treatment of non-metastatic appendiceal NET (Fig. 2)

Unless stated otherwise, the following recommendations correspond to grade D.

- Appendiceal NET are generally discovered fortuitously on the resected specimen of an appendectomy, generally performed

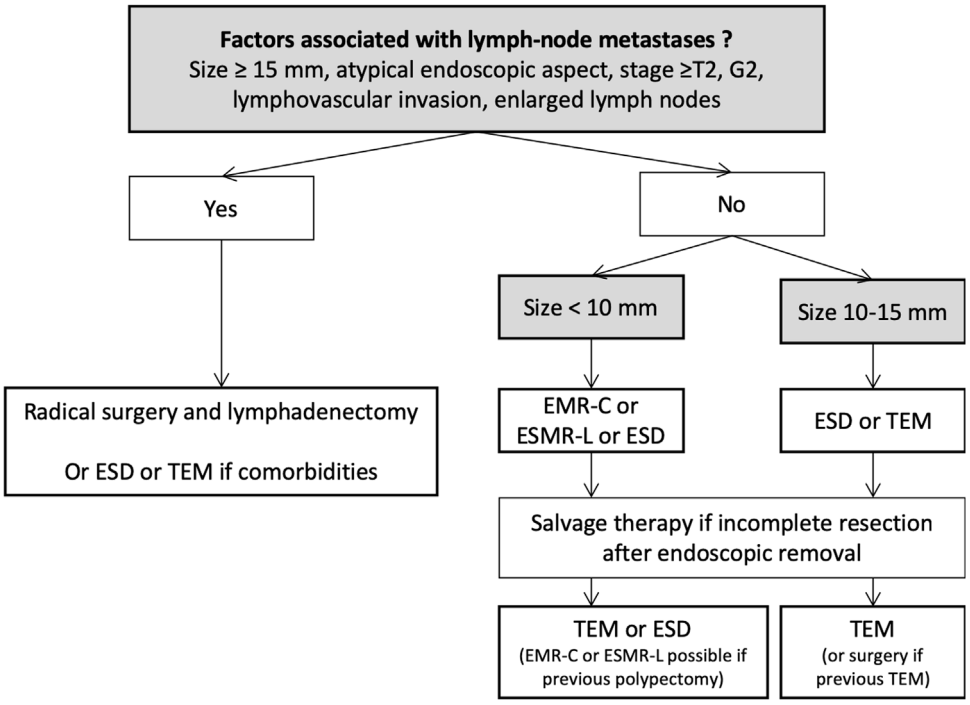


Fig. 3. Algorithm for the local management of non-metastatic rectal NET.
EMR-C, endoscopic mucosal resection with cap aspiration; ESD, endoscopic submucosal dissection; ESMR-L, ligation-assisted endoscopic submucosal resection; TEM, transanal endoscopic microsurgery.

without examinable lymph nodes. Distant metastases are exceptional. No benefit of colectomy over simple appendectomy has been demonstrated whatever the presentation.

- The 8th edition of the UICC TNM (Table 3) appears questionable for appendiceal NET since the invasion of the subserosa/mesoappendix and the size cut-off of 4 cm have not been validated. In supplement to this classification, we propose to add the ENETS 2007 TNM classification [73], which is based on clinically relevant size thresholds:
  - o T1, tumor ≤1 cm invading the submucosa and muscularis propria,
  - o T2, tumor ≤2 cm invading the submucosa, muscularis propria and/or minimally (up to 3 mm) invading the subserosa/mesoappendix,
  - o T3, tumor >2 cm and/or extensive (more than 3 mm) invasion of subserosa/mesoappendix,
  - o T4, tumor invading the peritoneum/other organs.
- Appendiceal NET ≤ 1 cm [74–76] (level of recommendation: grade C):
  - o No additional exploration or treatment is recommended if G1 and R0 resection;
  - o There is no recommendation on whether simple appendectomy or additional colectomy is most appropriate for G2 appendiceal NET ≤ 1 cm.
- Appendiceal NET > 2 cm or atypical histology (MiNEN, goblet-cell adenocarcinoma) right colectomy with lymphadenectomy after a complete evaluation (level of recommendation: grade C).
- Between 1 and 2 cm: consider additional surgery (right colectomy with lymphadenectomy) in cases of suspected lymph-node metastases, extension to the meso-appendix > 3 mm (pT3) (although not confirmed in recent series), venous or lymphatic emboli, G2 or R1 resection (which is frequent when the tumor is located in the appendix base) (level of recommendation: grade C) [74–76].
- There is no indication for adjuvant treatment.

4.2.7. Treatment of non-metastatic colonic NET

Unless stated otherwise, the following recommendations correspond to grade D.

- Colonic NET are rare and specific data are very limited.
- The treatment recommended is carcinologic surgery with lymphadenectomy as for adenocarcinoma.
- No adjuvant therapy is recommended.

4.2.8. Treatment of non-metastatic rectal NET (Fig. 3)

Unless stated otherwise, the following recommendations correspond to grade D.

- It is of paramount importance to recognize rectal NET during the initial endoscopy for appropriate management decision-making. If a rectal NET is suspected, advanced resection techniques (see below) must be preferred to standard polypectomy or endoscopic mucosal resection (EMR), which should be avoided because of the high rate of positive margins. If advanced resection techniques are not available on site, it is preferable to perform a superficial biopsy (except in very small lesions ≤5 mm because of the risk of inappropriate resection using the biopsy forceps and the difficulty to identify the lesion afterwards) and an appropriate evaluation, and then refer the patient to an expert endoscopic center rather than attempt standard polypectomy/EMR.
- The main factors associated with the risk of lymph-node metastases are tumor size ≥15 mm, atypical endoscopic aspect (depression, ulceration), suspicious lymph node at EUS and/or pelvic MRI, invasion of the muscularis propria (T2), G2, and lymphovascular invasion (level of recommendation: grade C) [17,18].
- Total colonoscopy is mandatory for all patients with rectal NET to exclude concomitant colon cancer and other colorectal NEN, which can occur in up to 8% of cases (cf. Section 3.1.2).
- No additional explorations are required for rectal NET that are G1, <10 mm, T1 and R0 after the initial resection [17,18].

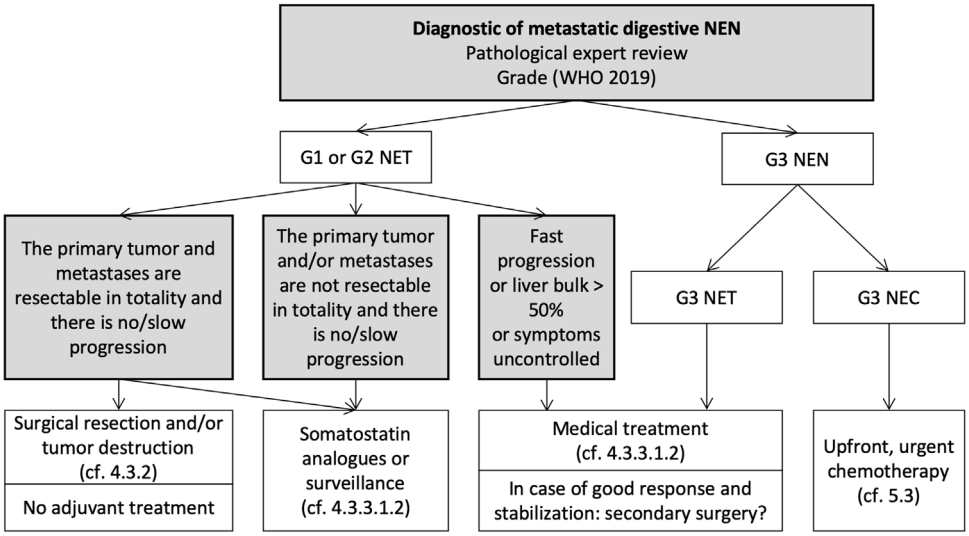


Fig. 4. Algorithm for the management of metastatic digestive neuroendocrine neoplasms.

- Rectal NET without factors associated with metastatic risk (and no suspicious lymph-node metastases at EUS and pelvic MRI) are good candidates for local resection (level of recommendation: grade C). The most appropriate resection techniques may be:
  - o For lesions <10 mm: cap aspiration or ligation-assisted EMR, or ESD [17,77];
  - o For lesions measuring 10–15 mm, ESD or transanal endoscopic microsurgery, depending on local expertise. These techniques should be restricted to expert centers [17,78,79].
- Salvage resection by ESD or transanal endoscopic microsurgery can be proposed for rectal NET at low risk of metastases with an initial R1 endoscopic resection and should be restricted to expert centers (level of recommendation: grade C) [17,18].
- Rectal NET with any risk factor for metastasis should be considered for surgical resection with lymphadenectomy.
- Completely resected rectal NET < 10 mm with no pejorative factors may not require follow-up. Otherwise, follow-up relies on regular endoscopic examination and abdominal/pelvic MRI.

4.3. Treatment of metastatic digestive NET

4.3.1. General considerations regarding the treatment of patients with metastatic NET

Unless stated otherwise, the following recommendations correspond to grade D.

- All cases must be discussed in a NET-dedicated multidisciplinary meeting (RENATEN network in France).
- Oncological treatment of metastatic NET is indicated in cases of (Fig. 4) [80]:
  - o Metastases with morphological progression on consecutive (3–12 months) imaging examinations, especially in cases of extra-hepatic metastases;
  - o Uncontrolled hormone hypersecretion despite symptomatic treatment;
  - o High tumor burden as defined by metastatic involvement of the liver >50% or symptoms related to tumor bulk.
- Additional elements to take into account for case-by-case therapeutic decision-making include:
  - o Location of the primary tumor (duodeno-pancreatic vs other);
  - o Tumor grade and differentiation (especially regarding G3 NEN);
  - o Disease-free interval or tumor growth rate;
  - o SST receptor expression at nuclear imaging;
  - o FDG-PET uptake;
  - o Tumor volume, notably the degree of liver metastatic involvement, which can be classified semi-quantitatively in four classes (0–10, 11–25, 26–50 and ≥50%) [81];
  - o Extra-hepatic metastases (bone, peritoneum);
  - o Resectability of the primary tumor and metastatic disease;
  - o Patient characteristics (age, comorbidities, performance status);
  - o Previous treatments and cumulative toxicity;
  - o The therapeutic objective in a given patient including quality of life. This is particularly important as patients with NET may survive for more than 5–10 years, even those with metastases.
- Any therapeutic decision should always be discussed with the patient after appropriate information has been provided.
- In the absence of evidence supporting any survival benefit for some treatments (e.g., chemotherapy), clinical judgement and an individualized approach to care are important and must take into account the patient's preferences.

4.3.2. Macroscopically nonresectable, stable or slowly progressive liver metastases

Unless stated otherwise, the following recommendations correspond to grade D.

- Although there is no validated definition, slow progression might be arbitrarily defined by an increase in tumor size ≤ 20% (RECIST criteria) in 12 months.
- The resection and/or destruction (percutaneous or intraoperative) of all visible metastases should always be discussed, whenever feasible (eventually combining different procedures) (level of recommendation: grade C) [80,82]. Indeed, this strategy seems to achieve the longest survival, although it was never compared properly with other treatments [80,82]. Nevertheless, recurrence is usually observed due to persistent microscopic tumors in all patients [83].
- In patients with initially non-resectable metastases that show an objective response to antitumor treatment, the possibility of surgical resection must be reconsidered.
- In selected patients, a two-step surgery approach can enable complete resection with acceptable morbidity (level of recommendation: grade C) [84]. The morbidity and mortality of extensive procedures and the predicted remaining liver volume

must be balanced with the almost unavoidable risk of long-term metastatic recurrence.
- Consider cholecystectomy during the same procedure.
- No adjuvant antitumor treatment is recommended.

4.3.3. Non-resectable metastases

4.3.3.1. Duodenopancreatic NET with non-resectable metastases.

4.3.3.1.1. Primary tumor resection in cases of metastases. Unless stated otherwise, the following recommendations correspond to grade D.

- Surgical resection of the primary pancreatic tumor in patients with unresectable metastatic disease might be associated with a survival benefit, but this has not yet been confirmed prospectively [85]; hence it cannot be routinely recommended, especially when pancreaticoduodenectomy is necessary. The indication for surgery, although rare, can be discussed on a case-by-case basis, in order to prevent eventual local complications (portal hypertension) or to anticipate liver transplantation.
- The most appropriate candidates might be those with a G1 or low G2 NET located mainly on the body/tail of the pancreas (less invasive surgery, with no subsequent contra-indication for liver locoregional treatments), with no/low disease progression after several months of surveillance or systemic treatment (level of recommendation: grade C).
- In this context, indications for pancreaticoduodenectomy are exceptional. The existence of a bilio-digestive anastomosis is a strong limitation to future locoregional treatments (liver transarterial embolization, percutaneous destruction) [86].
- Routine cholecystectomy must always be considered in this setting, because of the risk of cholelithiasis associated with SSTA, and the risk of cholecystitis with liver transarterial embolization (level of recommendation: grade C) [24,50].

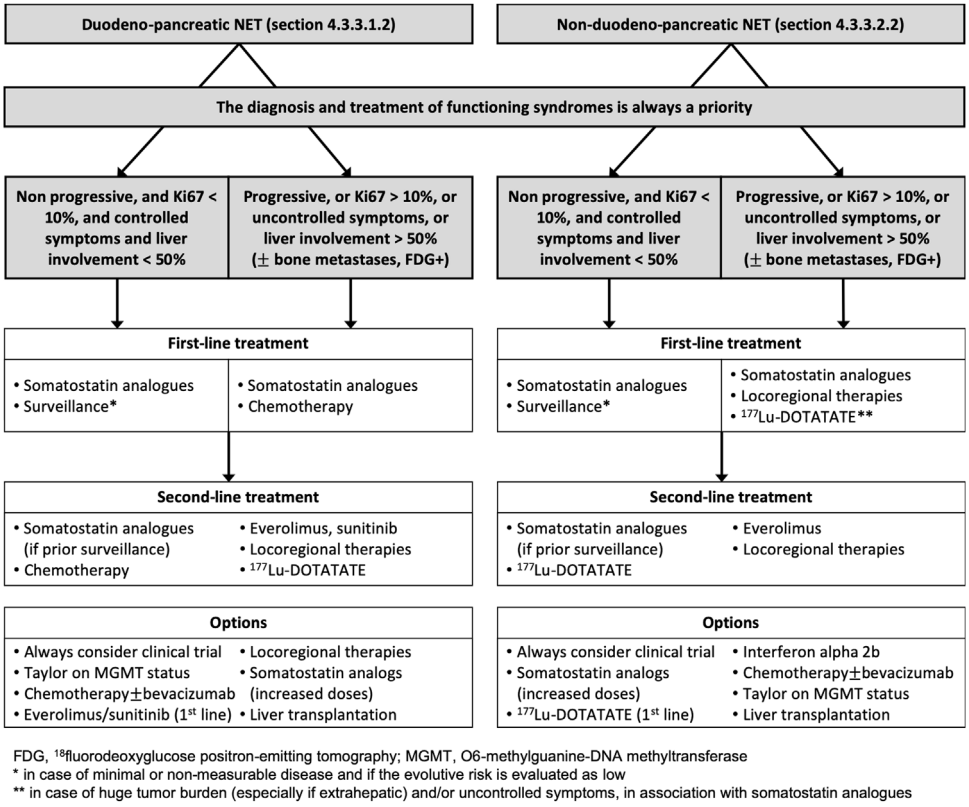
4.3.3.1.2. Treatment of non-resectable metastases (Fig. 5). Unless stated otherwise, the following recommendations correspond to grade D.

RECOMMENDATIONS

- First-line treatment:
  - ***In patients with no symptoms, liver involvement*** **<**50%**, *Ki67* <** 10%***and no morphological progression:***
    - ***SSTA***: lanreotide Autogel 120 mg/28d (level of recommendation: grade A) or octreotide LP 30 mg/28d (level of recommendation: grade C) [41,87];
    - or ***surveillance*** in cases of minimal or non-measurable disease and if the evolutive risk is evaluated as low.
  - ***In cases of progressive and/or symptomatic metastases (despite symptomatic treatment) and/or liver invasion*** **>**50%***and/or Ki67 >*** 10%***(especially in cases of bone metastases and/or positive FDG-PET):***
    - ***Chemotherapy*** notably in cases of rapid progression (progression following RECIST criteria <1 year), in G3 NET, and/or if the main therapeutic objective is reducing tumor bulk (especially if surgery of metastases could be possible in cases of a good response).
      - ***Streptozotocin + 5FU*** (level of recommendation: grade B) [88,89]. Nephrotoxicity can be avoided by strict management and surveillance [90]. Doxorubicin-based associations carry high toxicity and have been supplanted by alternative chemotherapy regimens.
      - ***Dacarbazine + LV5FU2*** (level of recommendation: grade C) [91].
      - ***Temozolomide + capecitabine*** (level of recommendation: grade C) [91,92].
    - ***SSTA*** in cases of slow progression (level of recommendation: grade B) [41,87].
- Second-line treatment (and beyond):
  - ***Chemotherapy*** (cf. first line).
  - ***Sunitinib*** (37.5 mg/d) (level of recommendation: grade A) [93,94].
  - ***Everolimus*** (10 mg/d) (level of recommendation: grade A) [95,96].
  - ***Liver transarterial (chemo)-embolization*** if the disease is predominantly located in the liver (level of recommendation: grade C) [86]. Because of the high morbidity risk with this technique, the indication must be validated in a NET-dedicated meeting attended by an interventional radiologist. In cases of extra-hepatic metastases (notably bone metastases), liver transarterial embolization is not strictly contra-indicated. To reduce morbidity, the liver volume can be segmented in 2–3 parts to be treated successively with a delay of 4–8 weeks between them [86]. Chemoembolization may be more effective than bland embolization in metastatic duodenopancreatic NET [86,97]. Chemoembolization is generally performed using streptozotocin (under general anesthesia) or adriamycin. Absolute contraindications for (chemo)-embolization are biliary anastomosis or stent or dilatation and complete portal thrombosis.
  - ***PRRT using 177Lu-DOTATATE*** yielded a 55% objective response rate and 30% stability rate as best response and a median PFS of 30 months in patients with metastatic pancreatic NET in a large retrospective study (level of recommendation: grade C) [98]. It may thus be used in patients with a strong homogeneous expression of somatostatin receptors at Octreoscan® (Krenning grade ≥ 2) or Ga-DOTA-PET (uptake ≥ that of the liver) [80,99].

OPTIONS:

- Inclusion in clinical trials should be considered whenever possible, otherwise prospective registration should be encouraged.
- Following disease control with one treatment modality, watchful follow-up can be considered (therapeutic pause).
- ***SSTA at increased doses or at reduced intervals*** may be used in patients progressing after prolonged stabilization under first-line SSTA [100,101].
- ***The MGMT status*** (O6-methylguanine-DNA methyltransferase expression or promoter methylation) may be determined before selecting a chemotherapy regimen, because high MGMT activity seems to be associated with decreased efficacy of alkylating agents (streptozotocin, dacarbazine, temozolomide) [102,103]. Nevertheless, techniques (immuno-histochemistry or methylation-specific PCR) and thresholds remain undefined, and reproducibility must be better evaluated [104].
- ***Oxaliplatin + LV5FU2 (FOLFOX),*** or + ***capecitabine (XELOX),*** or + ***gemcitabine (GEMOX)***, which yielded a 30–38% response rate, a 43–48% stabilization rate and a median PFS of 7.3 months [105,106]. These regimens can be used as alternative chemotherapy, notably in cases of high MGMT tumors.
- ***Bevacizumab*** has shown promising results (median PFS 24 months, 56% partial response) in combination with 5FU and streptozotocin (level of recommendation: grade C) [107].
- ***Irinotecan + LV5FU2 (FOLFIRI)*** yielded few objective responses as the best response (5%), but a high stabilization rate (75%) (level of recommendation: grade C) [108].
- ***Temozolomide alone***: although the TEM-CAP combination may yield a higher response rate than temozolomide alone, the latter may be used in more fragile patients in whom an objective response is not the main therapeutic goal [109].



FDG, ^{18}fluorodeoxyglucose positron-emitting tomography; MGMT, O6-methylguanine-DNA methyltransferase
* in case of minimal or non-measurable disease and if the evolutive risk is evaluated as low
** in case of huge tumor burden (especially if extrahepatic) and/or uncontrolled symptoms, in association with somatostatin analogues

Fig. 5. Algorithm for the management of patients with progressive non-resectable metastatic digestive neuroendocrine tumors.

- o ***Everolimus*** and ***sunitinib*** can be used as the first-line (as described above), particularly when somatostatin receptor imaging is negative or chemotherapy is contra-indicated and/or when an objective response is not the main therapeutic goal [93,95]. Everolimus frequently allows the control of hypoglycemia due to malignant insulinoma [46].
- o ***Liver selective internal radiation therapy (SIRT) using 90Yttrium microspheres*** has shown an average 50% objective response rate in the literature but long-term tolerance is questioned [86,110]. Although it compared poorly with (chemo)-embolization, SIRT could have similar efficacy and better short-term tolerance but is more expensive (level of recommendation: grade C) [111]. It could be considered in very selected patients, notably in those with miliary hepatic metastases, impaired liver function and/or a contra-indication to embolization.
- o ***Debulking surgery*** can be considered in very selected situations, notably in patients with uncontrolled functioning syndrome despite optimal antisecretory therapy.
- o ***Liver transplantation*** can be considered in cases of diffuse non-resectable liver metastases, stable or very slowly progressive metastases, with a low Ki67 (<5–10%, not precisely determined), in the absence of extra-hepatic metastases, if the patient is young (<55–60 years old) without hepatomegaly, in whom the primary tumor has been resected and after a sufficient time from the diagnosis of the metastatic disease (level of recommendation: grade C) [112].

4.3.3.2. Small-intestine NET (and other non-duodenopancreatic NET) with non-resectable metastases.

4.3.3.2.1. Primary tumor resection in cases of metastasis. Unless stated otherwise, the following recommendations correspond to grade D.

- Resection of mesenteric lymph-node metastases (and associated primary small-intestine NET) may be considered routinely because it may avert subsequent local complications, except in patients in poor general health and/or those with an expectable high risk of short-bowel syndrome (level of recommendation: grade C) [64,70]. It has been suggested that primary small-intestine NET resection affects positively the prognosis in patients without related symptoms, but this hypothesis is controversial [113].
- Routine cholecystectomy must always be proposed in this setting, because of the risk of cholelithiasis associated with SSTA, and the risk of cholecystitis with liver transarterial embolotherapy (level of recommendation: grade C) [24,50].
- In cases of diffuse peritoneal carcinomatosis, surgical resection must be discussed in expert centers (except in an emergency setting).

4.3.3.2.2. Treatment of non-resectable metastases (Fig. 5). Unless stated otherwise, the following recommendations correspond to grade D.

RECOMMENDATIONS

- First-line treatment:
  - o ***In patients with no symptoms, liver involvement*** <50%, ***Ki67*** <10%***and no morphological progression:***
    - ■ ***SSTA***: lanreotide Autogel 120 mg/28d or octreotide LP 30 mg/28d (level of recommendation: grade A) [41,87,114];
    - ■ or ***surveillance*** in cases of minimal or non-measurable disease and if the evolutive risk is evaluated as low.
  - o ***In cases of progressive and/or symptomatic metastases (despite symptomatic treatment), and/or liver invasion*** >50%, ***and/or Ki67*** >10%***(especially in cases of bone metastases and/or positive FDG-PET):***

- ***SSTA*** in cases of liver involvement < 50%, Ki67 < 10% and slow progression (level of recommendation: grade B) [41,87,114].
- ***Liver transarterial (chemo)-embolization or ablation*** if the disease is predominantly located in the liver (level of recommendation: grade C) [86]. Due to the high risk of morbidity with this procedure, the indication must be validated in a NET-dedicated meeting attended by an interventional radiologist. In cases of predominant extra-hepatic metastases (notably bone metastases), liver transarterial embolization is not strictly contra-indicated. To reduce embolization-related morbidity, the liver volume can be segmented in 2–3 parts to be treated successively with a delay of 4–8 weeks between them [86]. Chemoembolization does not seem more effective than bland embolization in patients with metastatic small-intestine NET, hence the latter may be preferred in this setting [86,97].
- ***PRRT using 177Lu-DOTATATE*** in patients with strong expression of somatostatin receptors at Octreoscan® (Krenning grade ≥ 2) or Ga-DOTA-PET PET (uptake ≥ that of the liver), in those with a huge tumor burden (especially if extra-hepatic) and/or uncontrolled symptoms, in association with SSTA.

- Second-line treatment (and beyond):
  - ***PRRT using 177Lu-DOTATATE*** in patients with strong expression of somatostatin receptors at Octreoscan® (Krenning grade ≥ 2) or Ga-DOTA-PET PET (uptake ≥ that of the liver) (level of recommendation: grade A) [100,115].
  - ***Everolimus*** (10 mg/d), especially in non-functioning intestinal NET, if there is no uptake at somatostatin-receptor imaging and significant extra-hepatic disease (level of recommendation: grade A) [116]. Several studies also suggested that everolimus had antitumor activity in functioning intestinal NET [117].
  - ***Liver transarterial (chemo)-embolization*** as described above.

OPTIONS:

- Inclusion in clinical trials should be considered whenever possible, otherwise prospective registration should be encouraged.
- Following disease control with one treatment modality, watchful follow-up can be considered (therapeutic pause).
- ***SSTA at increased doses or at reduced intervals*** may be used in patients with slow progression under first-line SSTA [101].
- ***Chemotherapy*** can be used notably in cases of a contra-indication or failure of other treatment modalities, notably in cases of quick progression and high Ki67 index, since small-intestine NET (and other non-duodenopancreatic NET) have very low chemo-sensitivity (level of recommendation: grade C) [118]. In one randomized study, 5FU-streptozotocin procured no survival benefit compared with interferon [119]. Dacarbazine + LV5FU2 (median PFS 9 months, 14% partial response and 64% stability as best response) and temozolomide + capecitabine (median PFS 7 months, no partial response and 87% stability as best response) can be used (level of recommendation: grade C) [91]. Low responses to alkylating agents may be related to high MGMT expression, which can be assessed before deciding on the chemotherapy. Alternatively, an oxaliplatin-based regimen can be used.
- ***Bevacizumab*** has shown promising results (median PFS 23.4 months, 18% partial response and 70% stability as best response) in combination with capecitabine (level of recommendation: grade C) [120]. However, no benefit was shown in other studies (including a phase III in association with SSTA [121]) and its efficacy should be further confirmed.
- ***Interferon alfa*** (3 MUI/ 3 times a week) can be used in cases of a contra-indication or failure of other treatment modalities, notably in patients with persistent secretory syndrome despite SSTA. In a phase III study, the interferon-octreotide combinations yielded a median PFS of 15.4 months [121] (level of recommendation: grade C). In another phase III study, interferon achieved a non-significant PFS benefit over 5FU-streptozotocin (14.1 months vs 5.5 months) [119]. The pegylated forms do not have marketing approval but are better tolerated and possibly more effective than standard forms [42].
- ***SIRT using 90Yttrium microspheres*** has shown an average 50% response rate in the literature but long-term tolerance is questioned [86,110]. Although it was poorly compared with (chemo)-embolization, SIRT could have similar efficacy and better short-term tolerance but is more expensive (level of recommendation: grade C) [111]. It could be considered in very selected patients, notably in cases of miliary liver metastases, impaired liver function and/or a contra-indication to embolization.
- ***Debulking surgery*** can be considered in stringently selected situations, notably in patients with uncontrolled functioning syndrome despite optimal antisecretory therapy.
- ***Liver transplantation*** can be considered in cases of diffuse non-resectable liver metastases, stable or very slowly progressive metastases, with a low Ki67 (<5–10%, not precisely determined), in the absence of extra-hepatic metastases, if the patient is young (<55-60 years old) without hepatomegaly, in whom the primary tumor has been previously resected and after a sufficient time from the diagnosis of the metastatic disease (level of recommendation: grade C) [112].

4.3.3.3. Treatment of particular metastatic locations. Unless stated otherwise, the following recommendations correspond to grade D.

4.3.3.3.1. Bone metastases.

- Bone metastases may affect 10–20% of patients with metastatic digestive NET. They can be symptomatic and could be associated with an impaired prognosis [122]. Their presence may indicate that the disease is more aggressive.
- The incidence of bone metastases may rise with the increasing use of highly sensitive imaging modalities, such as Ga-DOTA-PET and FDOPA-PET, and may be due to the increasing number of patients with prolonged survival. However, it is unknown whether the presence of bone micro-metastases (ill-defined, <5 non-symptomatic micro-metastases with low uptake) should lead to changes in patient management.
- In cases of symptoms (pain, compression), the following treatments can be considered: radiotherapy, surgery, radiofrequency ablation, cryotherapy. Bisphosphonates or denosumab can also be considered.

4.3.3.3.2. Peritoneal carcinomatosis.

- Consider, whenever possible, complete resection of the associated peritoneal carcinomatosis (level of recommendation: grade C) [123–125]. Complete resection of the peritoneal carcinomatosis seems to be beneficial if it is minimal to moderate as proposed by ENETS [123].
- The addition of hyperthermic intraperitoneal chemotherapy to macroscopically complete surgical cytoreduction does not seem to be associated with a survival benefit but carries high morbidity; hence it cannot be recommended (level of recommendation: grade C) [123–125].

5. Treatment of digestive (poorly-differentiated) NEC

5.1. General considerations regarding digestive NEC

- NEC account for less than 5% of digestive NEN. They are characterized by poorly-differentiated cell morphology, Ki67 > 20% (generally > 50%) and high biological aggressiveness; they are mostly diagnosed at a metastatic stage, with frequent tumor-related symptoms [11].
- Once the diagnosis of NEC is made, specific antitumor treatment must be initiated as an emergency.

5.2. Treatment of non-metastatic digestive NEC

Unless stated otherwise, the following recommendations correspond to grade D.

- ***Curative-intent surgical resection*** should always be considered, if surgery is feasible within 4 weeks, if there are no distant metastases after an extensive morphological assessment including liver MRI and FDG-PET, and if the risks of morbidity and mortality are acceptable given the expected high risk of recurrence (level of recommendation: grade C).
- ***Neoadjuvant chemotherapy*** can be considered before surgery of resectable non-metastatic NEC, using etoposide + cisplatin (or carboplatin) (3–4 cycles) especially when timely surgery cannot be organized [11].
- ***Adjuvant chemotherapy*** using etoposide + cisplatin (or carboplatin) (3–4 cycles) should be considered if surgical resection was performed with curative-intent (level of recommendation: grade C) [11,126].
- If surgery is not expected to achieve complete resection, is contraindicated or considered high risk, chemotherapy is recommended using etoposide + cisplatin (or carboplatin), eventually associated with radiotherapy (notably for locations such as the esophagus, duodenum, ampulla, head of the pancreas, rectum, and anal canal).
- Secondary surgical resection can exceptionally be possible, although its benefit has not been demonstrated.

5.3. Treatment of metastatic digestive NEC

Unless stated otherwise, the following recommendations correspond to grade D.

- First-line treatment
  - The treatment of reference is ***chemotherapy*** using etoposide + cisplatin (or carboplatin), which may achieve response rates of around 40%–50%, a PFS of approximately 6–9 months and a median overall survival of approximately one year (level of recommendation: grade B) [10,127,128].
  - The efficacy of chemotherapy should be evaluated every 2–3 cycles.
  - First-line therapy should be administered up to a total of 6 cycles, then patients who have not progressed can be given a therapeutic pause. No maintenance therapy is recommended.
  - If tumor progression occurs after 4–6 months of pause, the same chemotherapy can be used again. If tumor progression occurs within the first 4–6 months, second-line chemotherapy should be considered.
- Second-line treatment (and beyond):
  - There is no therapeutic standard.
  - Inclusion in clinical trials should be considered whenever possible, otherwise prospective registration should be encouraged.
  - ***FOLFIRI*** achieved an objective response rate of 24% and a median PFS of approximately 3 months [129,130].
  - ***FOLFOX*** achieved an objective response rate of 21–29% and a median PFS between 2.5 and 4.5 months [130,131].
  - Combinations containing ***alkylating agents*** (temozolomide or dacarbazine) might be considered although their efficacy has been insufficiently studied [132].
  - It is possible that ***bevacizumab*** may have antitumor activity in combination with chemotherapy such as FOLFOX or FOLFIRI [133]. However, this requires further confirmation; hence bevacizumab should be restricted to research settings [134].

6. Post-therapeutic follow-up

Unless stated otherwise, the following recommendations correspond to grade D.

6.1. Situations not requiring follow-up

- Follow-up is unnecessary when the risk of local or distant recurrence is negligible:
  - Well-differentiated rectal G1 NET < 10 mm, without muscularis invasion (T1a), without lymphovascular invasion, without suspicious lymph nodes and fully resected (R0);
  - Appendiceal NET for which there is no indication for additional colectomy and lymphadenectomy (Section 4.2.6);
  - Appendiceal NET < 2 cm with low Ki67 (threshold undefined) in patients who underwent additional colectomy and lymphadenectomy without lymph-node invasion.

6.2. Follow-up of digestive NET

6.2.1. Follow-up of non-metastatic digestive NET

- One essential 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 being lengthened.
- For NET that were surgically resected with curative intent: morphological imaging and the initially positive nuclear imaging technique should be performed after 3–6 months, then morphological imaging should be performed every 6–12 months for 5 years, then every 12–24 months for 10 years and then every 5 years.
- CT-scan and MRI with diffusion-weighted sequences must be preferred. MRI is a non-ionizing technique and is more sensitive than CT-scan for the detection of small liver metastases. Hence, abdominal MRI may be used in alternance with thoraco-abdominal-pelvic CT-scan, which appropriately evaluates extra-hepatic lesions.
- In situations with a very low risk of recurrence, ultrasonography can stand as an economical alternative.
- The value of performing periodical nuclear imaging, if it was initially positive, has not been demonstrated, but ENETS recommends such examination every 1–2 years for NET [135]. We recommend nuclear imaging (Ga-DOTA-PET, or FDOPA-PET for small-intestine NET) if there are doubts regarding possible recurrence.
- No biological marker has been validated for follow-up. It is nonetheless recommended to measure the plasma level of chromogranin A and of other initially abnormal biomarkers. The same assay kit must be used throughout the follow-up.

- This proposition of follow-up, notably the surveillance interval, must be modulated according to prognostic factors, notably tumor grade, stage, R0/R1 resection, predictable life expectancy, etc.
- In cases of a hereditary syndrome, appropriate specific surveillance is required.

6.2.2. Follow-up of metastatic digestive NET

- In patients who underwent surgery for liver metastases, MRI with diffusion-weighted sequences or CT-scan should be performed at 3 months then every 3–6 months or at shorter intervals if there is a clinical/biological suspicion of tumor recurrence. The initially positive nuclear imaging technique should be performed within the first 6–12 months, and thereafter if there is a suspicion of tumor recurrence.
- In patients with non-resected liver metastases, imaging should be performed at 3 months and then every 3–6 months for 2 years, the interval can then be lengthened to 6–24 months if the disease is stable.
- The evaluation of tumor evolution relies on RECIST 1.1 criteria [136]. It must be assessed by comparing imaging examinations using the same technique (e.g., CT-scan or MRI). Tumor response to treatment is evaluated by comparing one imaging examination with that performed at baseline (treatment initiation +/- 1 month). Tumor progression is evaluated by comparing one imaging examination with that corresponding to the best response (nadir). Because NET often grow slowly, tumor progression must sometimes be assessed over long periods of time. A mesenteric mass associated with small-intestine NET is mostly fibrous and should not be considered a target lesion.
- The preferred imaging modality should be chosen on a case-by-case basis, depending on its ability to show target lesions [137]. MRI generally provides better reproducibility of measurements of liver metastases than do CT-scans.
- The level of plasma chromogranin A and of other initially abnormal biomarkers should be measured at the same rhythm as the clinical/imaging follow-up. The same assay kit must be used throughout the follow-up. However, an isolated rise in biological markers is not an indication to change the treatment if there is no evidence of progression, but may suggest closer follow-up.
- The value of a periodical nuclear imaging (SRS, or better Ga-DOTA-PET, or FDOPA-PET for small-intestine NET), if it was initially positive, has not been demonstrated. Although ENETS recommend such imaging examinations every 1–2 years, it did not reach a consensus for systematic screening [135,137].
- Patients with carcinoid syndrome and/or an increase in urine 5HIAA should undergo a periodical (6–12 months) echocardiography in order to look for signs of carcinoid heart disease [138]. Although its usefulness has not been demonstrated, patients with non-functioning small-intestine NET may also undergo periodical (every 1–2 years) echocardiography.
- Late iatrogenic adverse events must be screened for, notably renal failure (streptozotocin or PRRT), heart failure after certain treatments (sunitinib, doxorubicin) and bone marrow involvement (PRRT, alkylating agents).

6.3. Follow-up of digestive NEC

6.3.1. Follow-up of non-metastatic digestive NEC

- In patients operated on with curative intent, imaging (MRI or CT-scan) should be performed every 2 months for 6 months and then every 3 months for 1 year and then every 6 months for 5 years.
- The value of FDG-PET for the follow-up has not been demonstrated; its indication must be decided on a case-by-case basis.

6.3.2. Follow-up of metastatic digestive NEC

- In patients under treatment for metastatic disease, follow-up should be performed at short intervals (2 months).
- The reference imaging modality is thoracic-abdominal-pelvic CT-scan. The interest of follow-up with FDG-PET has not been demonstrated.

Conflict of interest

Louis de Mestier: Boards: Ipsen, Novartis, Pfizer.

Come Lepage: Boards: Novartis, AAA.

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Romain Coriat: Boards: Ipsen, Novartis, AAA, Pfizer; Speaker: AAA, Ipsen, Novartis.

Frédéric Courbon: Boards: AAA, Covidien/Mallinckrodt, Ipsen, Novartis, Norgine, Bayer, GEHC, Cyclopharma; Research: Covidien/Mallinckrodt, IBA, Roche, GEHC.

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Pierre Goudet: Ipsen, Novartis.

Catherine Lombard-Bohas: AAA, Ipsen, Novartis, Pfizer.

Gilles Poncet: Speaker: Ipsen, Novartis.

Denis Smith: Boards: Ipsen, Novartis, Pfizer.

Philippe Ruszniewski: Boards and scientific advisor: Ipsen, Novartis, AAA, ITM, Keocyt.

Thierry Lecomte: Board: Novartis, Speaker : Novartis, Ipsen.

Olivier Bouché: Boards: Roche, Amgen, Merck.

Thomas Walter: Boards : AAA, Keocyt, Ipsen, Novartis.

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