

# ENETS Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Neoplasms of the Digestive System: Well-Differentiated Pancreatic Non-Functioning Tumors

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## Introduction

### Definition

The term non-functioning (NF) neuroendocrine neoplasm (NF-NEN) of the pancreas refers exclusively to tumors without clinical symptoms of hormonal hypersecretion. However, NF tumors may well show immunohistochemical positivity for hormones (1) which may be produced, but not secreted, (2) which are clinically inert such as pancreatic polypeptide, and (3) whose serum concentrations are insufficient to induce symptoms.

### Classification and Epidemiology

The WHO 2010 classification [1] distinguishes between well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs) of small or large cell type. NETs are then divided according to a grading scheme based on mitotic count or Ki67 index in NETs-G1 (with a mitotic count <2 per 10 high-power fields (HPF) and/or ≤2% Ki67 index), and NETs-G2 (with a mitotic count 2–20 per 10 HPF and/or 3–20% Ki67 index). All NECs are graded G3 (with a mitotic count >20 per 10 HPF and/or >20% Ki67 index).

Most pancreatic NF-NENs are well differentiated (i.e. NETs); NF-NECs are uncommon. NF-NETs have a crude

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annual incidence of 1.8 in females and 2.6 in males, according to the Surveillance, Epidemiology, and End Results (SEER) [2, 3]. The incidence increases with age and peaks in the sixth and seventh decade of life. These data are in keeping with those reported in the European registries [4, 5], whereas a slightly higher incidence has been reported in a French study [6]. Data from Japan [7] indicate that the prevalence of pancreatic NET is 2.23/100,000 and NF pancreatic NET constituted 47% of all NET. These data are consistent with those from the SEER that indicate an incidence of 60–90% of NF forms. The advances in the accessibility of diagnostic imaging have led to an increase in the incidental detection of NF-NETs [8]. Autopsy studies searching for small (<1 cm) NETs reported frequencies ranging from 0.8 to 10% [9].

#### *Minimal Consensus Statements on Classification and Epidemiology*

Pancreatic NF-NENs are defined by the absence of a hormone hypersecretion syndrome. The majority of pancreatic NENs are NF. There appears to be a definite increase in pancreatic NETs (which includes NF forms). The classification of these neoplasms as of neuroendocrine origin refers to the immunohistochemical positivity of synaptophysin and chromogranin A (CgA). NF-NENs are separated and graded according to the 2010 WHO classification into NETs G1 or G2 and NECs G3.

#### *Clinical Presentation*

NF-NENs usually become clinically apparent when they reach a size that causes compression or invasion of adjacent organs, or when they metastasize. In this context, pancreatic NF-NETs are usually diagnosed late in the course of the disease. However, the mean tumor diameter decreased in the last decades and this is mainly due to the widespread use of cross-sectional imaging technique [8]. When symptomatic, the most common presenting symptoms are abdominal pain (35–78%), weight loss (20–35%), anorexia and nausea (45%). Less frequent signs are intra-abdominal hemorrhage (4–20%), jaundice (17–50%) or a palpable mass (7–40%) [10–14]. In rare cases, in both familiar and more rarely sporadic NF-NENs, the tumor may become functional during the clinical course and present hormonal symptoms. A recent Italian multicenter observational study [15] showed that 32% of NF pancreatic NETs present liver metastases at first diagnosis although this rate is slightly lower than those currently reported in the literature where rates ranging from 46 to 73% are described [3, 5, 16–23]. According to SEER data [3], localized, regional, and distant stages corresponded to 14, 23, and 54% of cases. Similar

rates for staging at diagnosis were 35, 32 and 44% for the Spanish registry [5]. A recent selective European series staged 131 pancreatic NETs as: stage I (5%), stage II (15%), stage III (22%) and stage IV (55%) [24].

#### *Prognosis*

In a population-based study the median overall survival for patients with NF pancreatic NET was found to be 38 months [3]. The survival is mostly affected by the presence of distant metastases [25–34]. Particularly, patients with distant metastases have a median survival of 23 months compared with 124 and 70 months of those with localized and regional disease, respectively [3]. Tumor grade has also been implicated as a significant predictor of survival [17, 31, 33–35]. Patients with G2 and G3 neoplasms showed significantly shorter 5- and 10-year survival and a respective 2- and 10-fold higher risk of death [36]. Others factors that negatively affect the survival are age >40 years [17, 34] and positive surgical margins [17, 22]. Rapid progression of liver metastases (more than 25% volume increase within 6–12 months) and the development of bone metastases also confer a poor prognosis [37]. Criteria for assessing the prognosis of endocrine pancreatic tumors are shown in table 1.

#### *Minimal Consensus Statements on Clinical Presentation and Prognosis*

NF pancreatic NETs were formerly thought to present as large tumors, with signs and symptoms related to the tumor burden; however, more recent data reveals that these tumors increased incidence appears related to smaller incidental tumors. At first diagnosis the incidence of liver metastases ranges from 32 to 73%. The median overall survival of NF pancreatic NETs is 38 months with a 5-year survival rate of 43%. The presence of distant metastases and the degree of differentiation are the most powerful predictor of poor survival.

#### *Hereditary Tumor Syndromes*

*Multiple Endocrine Neoplasia Type 1 (MEN-1).* MEN-1 is a rare autosomal dominant condition characterized by the development of well-differentiated tumors of the parathyroids, pancreas, duodenum and pituitary. MEN-1 patients are also prone to develop bronchial and thymic NETs, adrenal tumors, dermal lesions, thyroid disease, and meningeal tumors [38–42].

Although only a small number of patients with pancreatic NF-NETs have MEN-1 syndrome, these neoplasms occur in the 19% of patients diagnosed with MEN-1 with an incidence of 3, 34 and 53% of patients at age 20, 50, and 80 years. In the setting of MEN-1 syndrome, pa-

**Table 1.** Criteria for assessing the prognosis of endocrine pancreatic neoplasms

Biological behavior	WHO classification (2000)	WHO classification (2010)	Metastases	Invasion	Tumor size, cm	Angio-invasion	Ki67, %
Benign	Well-differentiated endocrine tumor	NET G1 or NET G2	-	-	≤2	-	usually around 2
Benign or low-grade malignant	Well-differentiated endocrine tumor	NET G1 or NET G2	-	-	>2	±	usually around 2
Low-grade malignant	Well-differentiated endocrine carcinoma	NET G1 or G2	+	+	any	+	usually >2
High-grade malignant	Poorly-differentiated endocrine carcinoma	NEC or G3	+	+	any	+	>20

NET = Neuroendocrine tumor; NEC = neuroendocrine carcinoma.

tients with NF tumors had a poorer survival than that of patients without pancreatic involvement. Moreover, the tumor size significantly correlates with the presence of metastasis and patients with smaller tumors had a significantly better prognosis [43].

*Von Hippel-Lindau Disease (VHL).* VHL is an autosomal dominant syndrome that predisposes individuals to a variety of neoplasms. VHL is associated with tumors in a variety of organs including kidney (renal cell carcinoma of clear cell type), the adrenal glands (pheochromocytoma), the central nervous system (hemangioblastoma), the eye (retinal angioma), the inner ear (endolymphatic sac neoplasm), the epididymis (epididymal cystadenoma), and the pancreas (serous cystic neoplasms and solid well-differentiated NETs). The frequency of pancreatic involvement in the largest series of VHL patients studied by imaging methods varied from 17 to 56% [44–46]. Specifically, the incidence of NF pancreatic NETs ranges from 11 to 17% [47, 48]. NETs in VHL have a good prognosis although a small fraction of patients have an aggressive disease.

*Tuberous Sclerosis.* Pancreatic NF-NETs may also be associated with tuberous sclerosis [49, 50].

#### *Minimal Consensus Statements on the Manifestation of Non-Functioning Pancreatic NETs in Hereditary Tumor Syndromes*

NF-NETs occur in association with the MEN-1 syndrome (up to 50% and greater some series). They usually appear at an earlier age than do sporadic pancreatic NETs, may precede other manifestations of the syndrome and determine the prognosis of the patients. Pancreatic NF-NETs occur in 13–17% of patients with VHL and may be seen in patients with tuberous sclerosis.

### **Diagnostic Procedures: Imaging, Nuclear Medicine and Laboratory Tests**

#### *Somatostatin-Receptor Scintigraphy (SRS)*

SRS has a sensitivity and specificity for pancreatic NETs of 90 and 80%, respectively [51, 52]. SRS is the central modality for localization of the primary and definition of the extent of the disease. Whole-body imaging allows for detection of distant metastases and thus influences therapeutic decisions [53]. SRS is indicated as the first staging procedure and whenever the demonstration of extrahepatic metastases is necessary for therapeutic decisions. The following details indicate the recommended standard procedure: a double- or triple-head gamma camera and a medium-energy, parallel-hole collimator, peaks at 172 and 245 keV with a window of 20%. <sup>111</sup>In-octreotide 200 MBq for planar, 200–220 MBq for SPECT images. At an acquisition time of 15 min and 4 h postinjection (p.i.) anterior and posterior abdominal views, at 24 h p.i. anterior and posterior views of the upper abdomen, head, chest and pelvis, as well as left and right lateral, anterior and posterior oblique views of the upper abdomen. Optional delayed images at 30–48 h p.i. are recommended. Whole-body imaging should be performed with a scanning speed of 3 cm/min. SPECT images should be acquired at 24 h p.i. with a 6° step rotation for 360°/40–60 s [54].

In comparison to scintigraphy, positron emission tomography (PET) has a 2- to 3-fold higher spatial resolution (3–6 vs. 10–15 mm) and facilitates quantification of tracer uptake. PET with the <sup>68</sup>Ga-labelled somatostatin analogue DOTA-D-Phe<sup>1</sup>-Tyr<sup>3</sup>-octreotide (DOTATOC) is superior to <sup>18</sup>F-fluorodeoxyglucose PET in the detection of NENs [55]. Moreover, <sup>68</sup>Ga-DOTATOC PET is better with respect to <sup>111</sup>In-DTPA-octreotide (<sup>111</sup>In-DTPAOC)

SPECT in imaging NEN manifestations, and  $^{68}\text{Ga}$ -DOT-ATOC PET findings are more clinically relevant. Nevertheless,  $^{68}\text{Ga}$ -DOTATOC PET and  $^{111}\text{In}$ -DTPAOC SPECT have similar accuracy regarding the imaging of pancreatic region although firm data are not available [56].

PET using the catecholamine precursor 6-[fluoride-18] fluoro-levodopa ( $^{18}\text{F}$ -DOPA) has emerged as a new imaging method for NENs [57]. The sensitivity of  $^{18}\text{F}$ -DOPA in staging and identification of carcinoid tumors, compared with SRS, is higher [58]. In comparison with another PET tracer for NENs, 11-carbon-5-hydroxytryptophan (5-HTP) [59], 5-HTP-PET was the optimal imaging modality for staging of pancreatic NENs, whereas F-DOPA PET showed a higher sensitivity in carcinoids [60]. Since F-DOPA PET is more available, it could add important information on tumor localizations and prognosis and be used to aid research in the response to new molecular-targeted drugs, possibly even replacing SRS. However, further studies are needed to confirm these preliminary results.

#### *Ultrasound and Contrast-Enhanced Ultrasonography*

Ultrasound (US) is an operator-sensitive modality leading to wide variation regarding sensitivity and specificity. For pancreatic NET diagnosis, a mean 39% detection rate was found [61]. The recent introduction of contrast-enhanced ultrasonography (CEUS) has led to improvement in the diagnostic capabilities of B-mode sonography, mainly of the liver [62] and the pancreas [63, 64]. The use of second-generation blood-poor contrast agents combined with low acoustic-pressure insonation technique has facilitated dynamic continuous evaluation of tumor enhancement patterns in the arterial, venous, and late phases, enabling depiction of the micro- and macrocirculation of pancreatic tumors. CEUS therefore allows continuous dynamic observation of contrast enhancement phases, enabling identification of hypervascular lesions, even in case of fast-flow tumoral circulation, as in NF pancreatic NETs. The CEUS is significantly superior to B-mode sonography in the diagnosis of NF pancreatic NETs with a correlation between CEUS enhancement pattern and the Ki67 index [65]. Moreover, CEUS is more sensitive than US in the detection of liver metastases that are visualized at CEUS as hyperenhancing inhomogeneous lesions [66]

#### *Endoscopic Ultrasound-Guided Fine-Needle Aspiration*

Endoscopic ultrasound (EUS) provides high-resolution images of structures within or just beyond the wall of the gastrointestinal tract [67, 68]. EUS is an effective tool and

a better modality with which to identify pancreatic NENs. The EUS-guided fine-needle aspiration (FNA) is a useful method for the diagnosis of pancreatic NENs [69–71]. The typical cytological findings, along with immunocytochemical stains, allow the accurate identification of NETs.

#### *CT Scan*

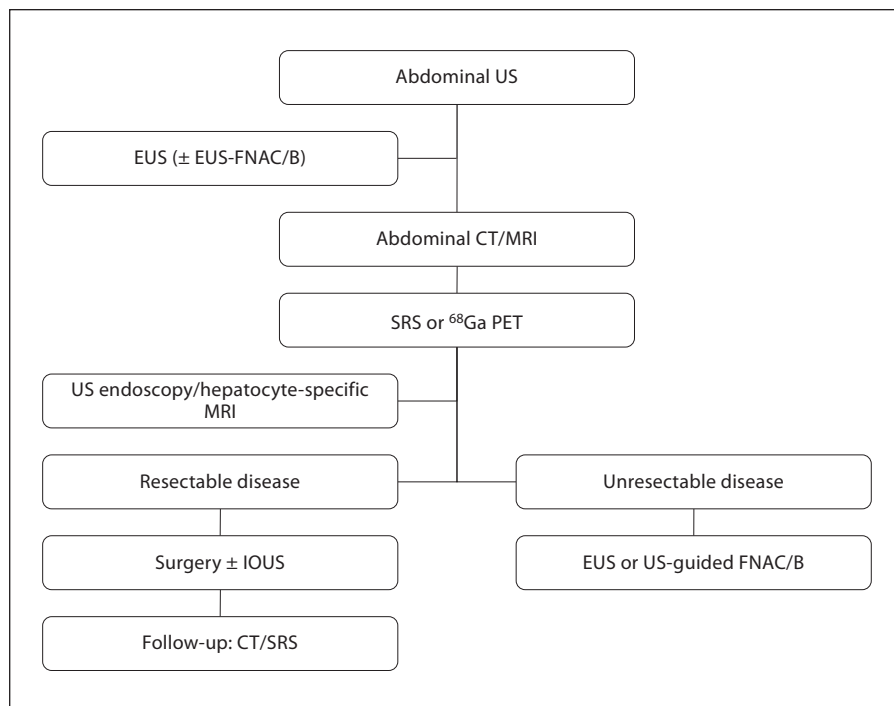
NF pancreatic NENs appear typically as hypervascular lesions at CT scan with enhancement, but are frequently moderately hypervascular particularly when the lesions are large in size [61]. They may have calcifications. In addition, areas of cystic degeneration are visualized as regions of reduced vascularity by contrast-enhanced computed tomography (CT). Images should be obtained with multidetector CT (1 mm or sub-millimeter section thickness) at the peak arterial phase of contrast enhancement and reconstructed at several thickness, allowing also reconstruction in three-dimensional volumes [54, 61, 72, 73]. In the evaluation of NF pancreatic NETs, the combination of arterial dominant-phase (AP) and portal venous-phase (PVP) CT improves the detection of hepatic metastases and primary tumors [74].

Particularly, multiphase (especially PVP) CT and magnetic resonance imaging (MRI) have similar effectiveness in the detection of islet cell tumors if fat-saturated  $T_1$ -weighted and delayed enhanced  $T_1$ -weighted MRI are included [75]. The sensitivity and specificity of CT scan in diagnosis pancreatic NET are 73 and 96%, respectively [61].

#### *Magnetic Resonance Imaging*

MRI plays an important role in the detection of pancreatic NETs, in particular with the use of fast spin echo and fat saturation techniques. MR with diffusion-weighted sequences are widely used, showing a high sensitivity for detecting all cellular lesion. Fat-suppressed  $T_1$ -weighted sequences are particularly useful in imaging pancreatic lesions. Pancreatic NENs are of lower signal intensity than normal pancreatic tissue and this explains the greater detection rate with fat-suppressed  $T_1$ -weighted images [76]. Additionally,  $T_2$ -weighted MR images differentiate the hyperintense neuroendocrine pancreatic tumor from the frequently scirrhous, and thus hypointense, adenocarcinoma. The sensitivity of CT and MRI is in the range of 75–79%, using comparable technical standards and equipment [75]. The technique which best visualizes the individual tumor should be used for follow-up. An algorithm of different diagnostic options for the identification, typing and staging of NF pancreatic NETs is given in figure 1.

**Fig. 1.** Suggested algorithm of different diagnostic options for the identification, typing and staging of non-functioning pancreatic NENs. US = Ultrasound; EUS = endoscopic ultrasound; FNAC/B = fine-needle aspiration cytology/biopsy; CT = computerized tomography; MRI = magnetic resonance imaging; SRS = somatostatin-receptor scintigraphy; PET = positron emission tomography; IOUS = intraoperative ultrasound.



### Minimal Consensus Statement on Imaging

US combined with state-of-the-art contrast-enhanced CT/MRI (including MRCP) is recommended. The decision whether to use CT or MRI depends on the preference, skill and expertise of the radiologist and the availability of the different techniques at each institution. Somatostatin receptor scintigraphy has been the mainstay single-screening method for extrahepatic disease manifestation although PET using  $^{68}\text{Ga}$  and  $^{18}\text{F}$ -DOPA appears to be challenging and may give better resolution and detect more lesions. Patients with small NF pancreatic NETs may be assessed using EUS, and EUS-FNAB has shown good results in confirming a diagnosis. Contrast-enhanced US appears to improve characterization of NET liver metastases and CE-EUS may prove effective in characterizing pancreatic NETs.

### Laboratory Tests

The diagnosis and staging of NETs are significantly improved by the introduction of the CgA assay in plasma or serum, as a tumor marker [77, 78]. Human CgA is a glycoprotein belonging to the family of the chromogranins, also known as secretogranins, which are present in the secretory granules storing peptide hormones and catecholamine throughout the neuroendocrine system. CgA is the best circulating neuroendocrine marker available for the management of differentiated NETs and its determination is useful to evaluate the response to therapy and to follow-up patients with liver metastases [79–82]. The

combined assessment of CgA and pancreatic polypeptide (PP) (quite often both the substances are immunohistochemically positive in the tumor; fig. 2a, b) leads to a significant increase in the diagnosis of pancreatic NETs with an increasing in sensitivity from 74 to 90% [83, 84]. Patients with pancreatic NETs as part of a MEN-1 syndrome have raised basal serum PP and gastrin levels [84]. On the contrary, the determination of serum PP and gastrin levels after a meal stimulation test in patients with MEN-1 adds no information about the presence of pancreatic endocrine tumors over that provided by basal values of the two peptides.

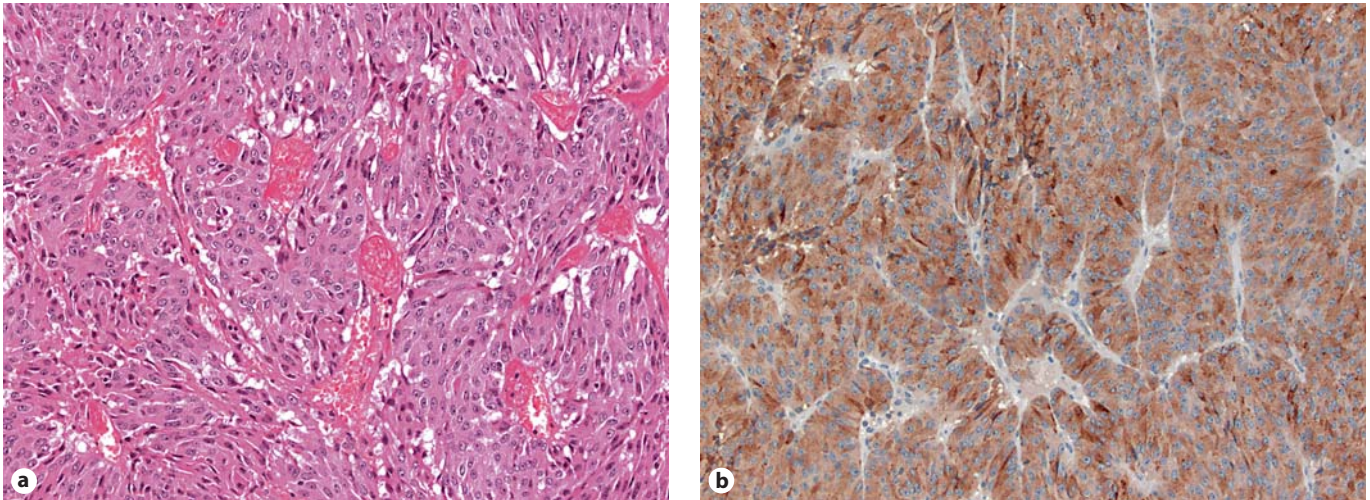
### Minimal Consensus Statement on Laboratory Tests

CgA is a recommended tumor marker, while the sensitivity and specificity of meal-stimulated PP are controversial. PP may be useful for early detection of pancreatic tumors in MEN-1. Extensive hormonal screening is not justified unless the patient during follow-up starts presenting hormonal symptoms.

## Pathology and Genetics

### Histopathology

Most NF-NENs are well-differentiated tumors showing various histological patterns (i.e. solid, trabecular,



**Fig. 2.** Non-functioning pancreatic NETs: (a) well-differentiated solid tumor cell nests (b) with immunostaining for PP.

glandular and others). While FNS cytology is not recommended as a standard diagnostic procedure, it may be helpful in establishing the correct pre- or intraoperative diagnosis. Immunostaining with general neuroendocrine markers (synaptophysin and CgA) establishes the neuroendocrine nature of the tumor [86, 87]. A variety of prognostic or treatment-related biomarkers (i.e. CK19) has been investigated, and some may have significant utility in the future, but currently, are not recommended to be routinely used outside of specific research settings [86]. According to the WHO classification the diagnostic report should include: (1) the histological classification of the lesion (as NET or NEC, small or large cell type), (2) the grade (G1, G2 or G3), (3) the relevant TNM stage (according to ENETS and UICC 2009), and (4) and expression of hormones, transcription factors or somatostatin receptors. The examination of the latter factors is optional and may be performed in order to establish functional activity, help to find the primary (in case of a CUP) and/or to identify somatostatin receptors for diagnosis and therapy of NETs [1].

#### Genetics

The genetic molecular diagnosis of MEN-1 syndrome should be considered only in selected cases [88]. When a VHL syndrome is suspected, all patients should be investigated for germline alterations in the VHL gene [89]. Mutational analysis should be performed to test for menin or VHL mutations.

#### Minimal Consensus Statement on Histopathology and Genetics

The pathological report should contain a detailed description of the macroscopic, microscopic and immunohistochemical findings, in order to support the diagnosis of a NET and to allow for its correct classification, according to the current WHO criteria. Germline DNA testing, e.g. mutational analysis, is only justified in clinical situations strongly suggesting MEN-1 or VHL.

#### Surgical Therapy

##### Curative Surgery

##### Indication

Surgery represents the treatment of choice for any localized pancreatic neoplasm since it is associated with significant benefits in terms of survival [90]. Nevertheless, the improvement of cross-sectional imaging techniques significantly increases the detection of small NF-NET and it is now debated if all the small and asymptomatic lesions should be routinely resected [91]. Most of neoplasms  $\leq 2$  cm are likely benign or intermediate-risk lesions and only 6% of NF pancreatic NETs  $\leq 2$  cm are malignant when incidentally discovered [92]. In this setting, a non-operative approach could be advocated in selected cases for tumors  $\leq 2$  cm that are discovered incidentally. An intensive 3-month follow-up for the first year and the 6 months up to 3 years could be recommended in these patients. Moreover, the choice of the appropriate management of these small tumors should be well balanced with the short- and long-term sequelae of pancreatic resection procedures.

An early diagnosis and surgical excision of MEN-1-related pancreatic NETs improve survival preventing or delaying the development of distant metastases [93]. It is mandatory to operate MEN-1-related NF pancreatic tumors with (1) metastases, (2) >2 cm, and (3) with a yearly increased size >0.5 cm [94]. On the contrary, pancreatic NETs ≤2 cm seem to have a more indolent behavior and their appropriate management is still debated.

#### Type of Surgery

The surgical treatment of localized endocrine pancreatic tumors includes typical and atypical resections. They differ according to the tumor site: lesions of the pancreatic head are treated with a pancreaticoduodenectomy (PD) while lesions of the body and tail with a left pancreatectomy (LP) with or without spleen preservation. Typical pancreatic resections are associated with a high incidence of perioperative complications [95] as well as exocrine and endocrine insufficiency. Atypical resections have been proposed in the management of NF pancreatic NETs, especially when well demarcated and small in size. Presently, no consensus exists on the diameter cutoff. Although the risk of malignancy cannot be completely excluded, a 2-cm cutoff should be sufficiently safe [96]. Middle pancreatectomy is performed only for small tumors of the pancreatic body, whereas an enucleation should be considered only if the main pancreatic duct can be safely preserved. The main advantage for atypical resections is that they are associated with a decreased long-term endocrine/exocrine impairment when compared to standard resections [97, 98]. On the other side, atypical resections are associated with a high rate of pancreatic fistulas although they are mostly transient and with a low clinical impact. Moreover, negative margins cannot be obtained after enucleation and in both enucleation and middle pancreatectomy a lymphadenectomy is not usually performed. As a consequence, a nodal sampling should be always performed and atypical resection considered only for small lesions with benign or uncertain behavior. Laparoscopic procedures play an important role in the treatment of pancreatic endocrine tumors. It has been demonstrated that laparoscopic distal pancreatectomy and enucleation are safe and feasible in patients with pancreatic endocrine tumors [99].

#### Surgical Strategies for Multiple Non-Functioning Pancreatic Neuroendocrine Tumors in MEN1

The surgical management of MEN-1-associated pancreatic NETs remains controversial for two main reasons. First, MEN-1-associated pancreatic NETs are almost al-

ways multifocal and, second, they are usually distributed throughout the pancreatic parenchyma [93, 100]. In this setting, careful microdissection of the pancreas demonstrates multiple, small microadenomas [100]. While only a minority of the microadenomas acquires the potential to grow unrestrictedly, larger lesions may be genetically unstable, develop secondary mutations and will grow into clinically relevant lesions. Prophylactic surgery could remove these lesions before malignancy develops. However, while recent data show that early diagnosis and surgery improve survival [93], others suggest a more conservative approach, as their data indicate that only tumors >2 cm are associated with an increased risk of malignancy [94]. When surgery is indicated, the potential operations range from enucleation to total pancreatectomy [101]. An intraoperative US is always mandatory due to the high rate of multicentric lesions. The potential high postoperative and long-term morbidity of this procedure is commonly compared to the increasing evidence of good long-term survival (100% at 15 years) of patients with gastrinomas <2 cm after conservative treatment [102].

#### Minimal Consensus Statement on Curative Surgery

Localized, small, malignant tumors should be operated on aggressively, while in small (<2 cm) possibly benign tumors the surgical risk-benefit ratio should be carefully weighted. In MEN-1 patients with multiple tumors, prophylactic surgery aims to remove the lesions before malignancy develops although this approach for small tumors is still controversial.

#### Palliative Surgery

##### Surgery of Locally Advanced Pancreatic NETs

An aggressive surgical approach is justified for pancreatic NECs in selected patients. In this setting, criteria for surgical resection include the presence of nearby organ invasion (stomach, spleen, colon, kidney, adrenal gland) or the invasion of vascular structures. Prior studies confirmed the survival advantages of an aggressive resection of pancreatic NETs when no residual macroscopic disease is left and no differences in terms of survival were observed in the comparison of R0 or R1 resection [103]. The resectability of NF pancreatic NETs should be assessed preoperatively excluding the surgical resection under the following conditions: (1) circumferential invasion of portal vein system with portal cavernoma (tumor thrombus excluded), and (2) circumferential invasion of superior mesenteric artery.

The presence of celiac trunk invasion is not an absolute limitation for distal pancreatectomy. The treatment

of choice is always a typical resection combined with lymphadenectomy and associated, if necessary, to nearby organs resection. Nevertheless, all available data are retrospective analyses from mixed series – functioning and non-functioning – and surgery is only part of a multimodal approach. No data support debulking surgery for unresectable, locally advanced NF pancreatic tumor although in selected cases surgery could alleviate mass-related symptoms by reducing tumor burden.

#### Surgery in Metastatic Non-Functioning Pancreatic NETs

*Surgery of the Primary.* In metastatic NF carcinomas, an advantage in terms of survival after primary tumor resection is not clearly demonstrated [104, 105]. Additionally, surgery of primary tumor is only recommended for G1 and G2 tumors. However, resection of the primary tumor allows focusing the treatment on liver metastases including liver transplantation. In those NF tumors, a pancreatic resection could be only justified to prevent life-threatening and obstructive complications, including bleeding or acute pancreatitis, jaundice or gastric obstruction. When the resection of primary pancreatic tumor is indicated, a standard resection eventually extended to nearby structures and regional lymphadenectomy should be provided. A two-step surgery for bilobar liver metastases has been proposed [106]. At first step, the primary tumor is resected along with part of liver metastases allowing liver hypertrophy for a second operation. This approach has an acceptable morbidity with no mortality.

#### Surgery for Liver Metastases

Whenever a resection leaves no residual disease, an aggressive approach, including liver resection, is recommended [107]. Nevertheless, there are some criteria that should be met before proposing any surgical resections. In particular, the conditions that have to be assessed preoperatively are (1) the absence of extra-abdominal disease, (2) the presence of low proliferative index (Ki67) by FNB (G1 or G2), and (3) the existence of somatostatin receptors in order to deliver radiolabelled therapies as they resulted effective after cytoreductive surgery [108]. Due to the high incidence of multifocal and bilateral metastases, a radical liver resection (90% of tumor removal) is possible only in 10% of the patients [109]. The 5-year survival of patients treated with hepatic resection ranges from 47 to 76% and this compares well with the 30–40% 5-year survival in untreated patients [110–112]. However, the rate of tumor recurrence is high, up to 76% [113, 114]. The type of hepatic resection depends on the number of

liver metastases, site and hepatic reserve itself. It can range from simple enucleation to segmental resection or to hepatectomy. An intraoperative US has to be routinely performed for detecting all the liver lesions.

In those patients with bilobar metastases or more than 75% of liver involvement, radical surgery can be rarely performed. In this light, medical, ablative and embolizing techniques can be provided in order to allow radical resection [114]. An algorithm of different treatment options for liver metastases in NF pancreatic NETs is given in figure 3.

#### *Minimal Consensus Statement on Palliative Surgery*

Debulking of an unresectable primary is advisable in selected patients to avoid tumor-related complications. Surgery of liver metastases may be justified if at least 90% of the tumor mass can be reduced. This may be the case in only 10% of the patients and the rate of tumor recurrence is high.

#### **Locoregional Ablative Therapy**

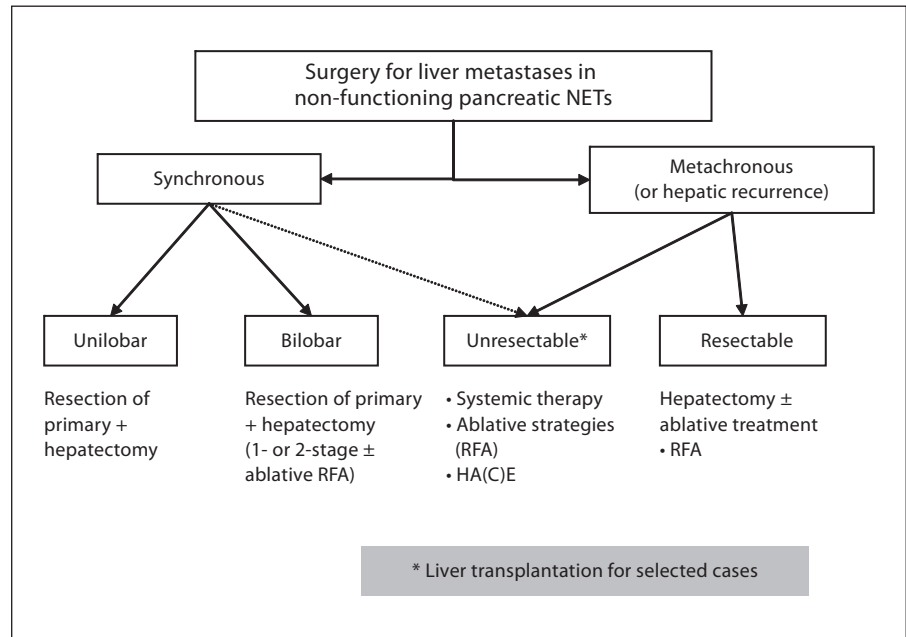
##### *Selective (Chemo)Embolization*

Hepatic arterial embolization (HAE) represents a valid palliative option in patients with pancreatic NETs with liver metastases who are not candidates for surgical resection [115]. Many authors have favored hepatic artery chemoembolization (HACE) over HAE for tumors although no studies have compared HAE with HACE in the treatment of metastatic NETs [116]. The improvement in techniques has reduced the incidence of complications related to embolization that is now a generally safe procedure [116]. HAE and HACE are effective in reducing tumor size, however, most of the studies have had relatively small populations [117–119]. Regarding HACE, the type of drug (5-FU, doxorubicin and mitomycin C), the appropriate dosage intervals and timing of the procedure are still controversial.

##### *Radiofrequency Ablation*

Various ablation techniques have been described, including cryoablation, alcohol ablation, and radiofrequency ablation (RFA) [120–122]. RFA involves conversion of radiofrequency waves to heat using a high alternating current that causes ionic vibration after the change in the current direction. RFA is an alternative treatment limited to patients with unresectable metastases >5–7 cm in diameter. Depending on the tumor location, RFA can be performed laparoscopically or percutaneously with a low





**Fig. 3.** Suggested algorithm of different treatment options for liver metastases in non-functioning pancreatic NETs. RFA = Radiofrequency ablation; HA(C)E = hepatic arterial (chemo)embolization.

morbidity and mortality [122–127]. In some patients, RFA may be used to convert an unresectable disease into a resectable one [128]. However, there are no data regarding a prolonged survival in patients who undergo ablative procedures.

#### Radioembolization

A novel approach to hepatic metastases involves arterial embolization of yttrium-90 microspheres, following intra-arterial hepatic injection. This technique enables direct delivery of radionuclide with a long-range tissue penetration of up to 11 mm to hepatic metastases. Early experiences with this technique seem to be encouraging, although certain data are lacking [129–131]. An algorithm for the treatment of liver metastases is given in figure 2.

#### Minimal Consensus Statement on Locoregional Ablative Therapy

(Chemo)embolization and RAF have been used as locoregional ablative therapy per se or as an adjunct to palliative surgery. Experience is limited, however, palliation seems possible in patients with a tumor burden of less than 75%, small metastases (<5 cm) and no extrahepatic metastases.

#### Liver Transplantation

In a few, highly selected cases, liver transplantation may be an option. However, experience with liver trans-

plantation is limited. Patients considered for transplantation have to be free of extrahepatic metastases, unresponsive to medical therapy, or not otherwise treatable. Patients with aggressive carcinomas should be excluded from liver transplantation. Most transplanted patients have recurrences within months to years, possibly due to postoperative immunosuppressive treatment and/or undiagnosed extrahepatic metastases prior to the procedure. Hence, improved methods for the detection of extrahepatic metastases are necessary before liver transplantation can be used or recommended [132–143].

#### Minimal Consensus Statement on Liver Transplantation

Liver transplantation may be an option in a patient without extrahepatic metastases, and low proliferation rate when all other therapeutic options have failed.

#### Medical Therapy in Advanced Disease

Treatment of advanced disease is updated in a separate and comprehensive chapter [144]. Here is a brief summary.

Somatostatin analogues may be of value also in subgroups of patients with slowly progressive low proliferative NET (G1) of pancreatic and gastroduodenal origin

and its use is supported by literature data on retrospective and non-randomized prospective trials in more than 500 patients [145–148]. In patients with gastric carcinoids, somatostatin analogues have been shown to exert antiproliferative effects in animals and in man, however, data is not available in cases of liver metastases [149].

Two prospective randomized trials in metastatic gastroenteropancreatic NET have shown that somatostatin analogues, IFN or the combination of both have comparable antiproliferative effects when used after prior disease progression [145, 146].

Chemotherapy is recommended in pancreatic NET, G2 foregut NET of the extrapancreatic site, and in NEC (G3) of any site.

Systemic cytotoxic drugs are indicated in patients with inoperable progressive liver metastases from well-differentiated NET of pancreatic tumor origin using combinations of streptozotocin and 5-FU and/or doxorubicin with objective response rates in the order of 35–40% [150–152]. These response rates are considerably lower than the 69% reported by Moertel et al. [153] in 1992. There is long-standing experience with streptozotocin-based chemotherapy since the 1980s.

PRRT is considered in both functioning and non-functioning NET and irrespective of the primary tumor site. Based upon small phase II trials and retrospective data, partial remission rates range between 0 and 33% [154].

Both everolimus and sunitinib are novel treatment options in advanced pancreatic NET. Everolimus is thus a treatment option after failure of chemotherapy in pancreatic NET, but can be considered as first-line therapy in selected cases as an alternative treatment to locoregional therapies or chemotherapy. The RADIANT-3 study included 40% therapy-naive patients, and efficacy was equally good in therapy-naive patients as in patients with previous therapies [155]. An early unselected use of the drug cannot be recommended, because long-term toxicity data are lacking.

Results from a phase III placebo-controlled trial support the efficacy of sunitinib [156], a multiple tyrosine kinase inhibitor that targets PDGF-R, VEGF-R, c-kit, RET and FLT-3, in progressive pancreatic NETs. The majority of the patients had undergone prior systemic therapy, especially systemic chemotherapy. The objective response rate was 9.3% in 8 patients who received sunitinib, 7 had NF tumors and in 1, tumor function was unknown. The main indication of sunitinib is its use as a second- or third-line therapy. Sunitinib should be considered as first-line therapy only in selected cases as an alternative

treatment option if somatostatin analogues, chemotherapy and/or locoregional therapies are not feasible or promising. The efficacy of sunitinib appears to be similar regardless of the number of previous treatments or previous exposure to somatostatin analogues.

#### *Minimal Consensus Statement on Medical Therapy in Advanced Disease*

The early combination use of SSA and IFN for antiproliferative purposes is not recommended.

The use of PRRT cannot be recommended as first-line therapy, but after failure of medical therapy. The presence of a strong expression of sstr2 as visualized by somatostatin receptor imaging is a prerequisite for the use of PRRT. The minimum requirements for PRRT are reported in a separate consensus guideline [142].

Everolimus and sunitinib represent novel therapeutic options in patients with surgically non-resectable progressive pancreatic NET as an alternative or after progression following streptozotocin-based chemotherapy.

#### **Follow-Up**

The aim of the surveillance after resection for pancreatic NETs is to evaluate the surgical results as well as other treatments. A follow-up program could be avoided in those patients with localized NET G1 (WHO 2010) who underwent radical pancreatic resection. Although no studies investigated the patterns of recurrence according to the latest WHO classification, disease recurrence in patients with NET G2 (WHO 2010) is likely. The follow-up program should include clinical, laboratory (CgA) and radiological examinations [157, 158]. Current imaging procedures encompass US with or without contrast medium, endoscopy, endoscopy US, CT, MRI, octreotide scintigraphy (Octreoscan®) and in some centers PET imaging with different tracers [159]. A possible scheme of surveillance could consist of a US or MRI/CT scans along with biochemical markers (CgA) on a yearly basis [157, 158]. Patients with pancreatic NEC should be strictly followed up since the high risk of early relapse even when the tumor is radically resected. These patients should be followed up every 6 months with biochemical markers (CgA) and CT/MRI scans.

The vast majority of patients with advanced pancreatic NETs undergo disease progression during follow-up after diagnosis. The proliferative index Ki67 is the major factor to predict tumor progression, with an increasing risk of progression of 2% for each increasing Ki67 unit [160]. The Ki67 index should be evaluated in order to plan

tailored follow-up programs in patients with advanced pancreatic NETs.

### Minimal Consensus Statements on Follow-Up

Follow-up investigations should be adjusted to the type of tumor (G1, G2 or G3) and the stage of the disease (radically resected or advanced disease). Clinical examination, CgA determination and radiological investigations (US, CT/MRI) are recommended with appropriate scheme according to the stage of disease.

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