

Well-Differentiated Pancreatic Nonfunctioning Tumors/Carcinoma

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Introduction

Nonfunctioning pancreatic neuroendocrine tumors (NET) are defined by their histopathological differentiation. Neuroendocrine cells are characterized by the expression of marker molecules like neuron-specific enolase (NSE), an unspecific cytosolic marker or vesicle proteins like chromogranin A or synaptophysin, indicating large and dense hormone-storing core vesicles and neuropeptides- or small neurotransmitter-storing synaptic vesicles, respectively [1–4]. These proteins define the neuroendocrine origin of the tumor cells. The term ‘nonfunctioning’ refers to the absence of clinical symptoms of hormonal hypersecretion. However, nonfunctioning tumors may well show immunohistochemical positivity for hormones, neuropeptides or neurotransmitters.

Massimo Falconi and Ursula Plöckinger both contributed equally to the paper. They and the following authors listed in alphabetical order equally contributed to the preparation of the Guidelines.

Classification and Epidemiology

The WHO classifies nonfunctioning pancreatic NETs according to the uniform classification scheme for endocrine tumors, independent of the site of the primary: (1) well-differentiated endocrine tumor, with benign or uncertain behavior at the time of diagnosis; (2) well-differentiated endocrine carcinoma, with low-grade malignant behavior, and (3) poorly differentiated endocrine carcinoma, with high-grade malignant behavior [5] (table 1). Most (60–100%, according to the series) are classified as well-differentiated endocrine carcinomas [6, 7].

Due to new and more sensitive imaging techniques, the number of neuroendocrine pancreatic incidentalomas has increased. The autopsic incidence is 1.6–10% per year [8], while the clinical incidence is 3.5–4/million/year [9]. Pancreatic endocrine tumors represent about 2–10% of all pancreatic tumors [9, 10]. In earlier series the percentage of nonfunctioning tumors out of all pancreatic endocrine tumors was estimated to be 18–66% [11–17]. In contrast, recent, large monocentric [7, 18, 19] or multicentric studies [20] classify 68–80% as nonfunc-

Table 1. Criteria for assessing the prognosis of endocrine pancreatic tumors

| Biological behavior | WHO classification | Metastases | Invasion | Histological differentiation | Tumor size, cm | Angio-invasion | Ki67, % |
|---|--------------------|------------|----------|------------------------------|----------------|----------------|------------------|
| Benign (low risk) | group 1 | – | – | well-differentiated | ≤2 | – | <2 |
| Benign or low-grade malignant (intermediate risk) | group 1 | – | – | well-differentiated | >2 | ± | usually around 2 |
| Low-grade malignant | group 2 | + | + | well-differentiated | usually >3 | + | usually >2 |
| High-grade malignant | group 3 | + | + | poorly differentiated | any | + | usually >20 |

tioning pancreatic neuroendocrine tumors. The peak incidence is during the fifth decade [6], with equal distribution among the sexes.

Minimal Consensus Statements on Classification and Epidemiology

Nonfunctioning pancreatic neuroendocrine tumors are defined by the absence of a hormone hypersecretion syndrome. The classification of the tumor as of neuroendocrine origin refers to the immunohistochemical positivity of chromogranin A and/or synaptophysin. Pathological grading is done according to the WHO classification of endocrine tumors; the majority are well-differentiated carcinomas. Pancreatic neuroendocrine tumors are rare.

Clinical Presentation

Due to the lack of symptoms related to hormonal hypersecretion, nonfunctioning pancreatic neuroendocrine tumors are diagnosed late in the course of the disease. The clinical signs and symptoms are due to the tumor mass, with local invasion and/or distant metastases. Abdominal pain is the major presenting symptom (35–78%), followed by weight loss (20–35%), anorexia and nausea (45%). The patient may present with intra-abdominal hemorrhage (4–20%), jaundice (17–50%) or a palpable mass (7–40%) [21–25]. Fifty-nine percent to 80% of the patients present with synchronous liver metastases at diagnosis [10, 25]. Given the mostly large primary (>5 cm), localizing the tumor at the head of the pancreas, followed by the body and tail, is straightforward [26].

Prognosis

Most neuroendocrine pancreatic tumors are well-differentiated (WHO group 2) endocrine carcinomas (table 1) [27]. Overall 5-year survival is 30–63%, with a median survival from diagnosis of 72 months [12, 25, 28, 29]. Actuarial 5- and 10-year survival rates after diagnosis of liver metastases were 46 and 38%, respectively. [10]. How-

ever, aggressive treatment may increase 5-year survival to 63 or 82% [25, 30]. Rapid progression of liver metastases (more than 25% volume increase within 6–12 months) and the development of bone metastases confer a poor prognosis [10]. Histopathological staging (table 1), including tumor differentiation, tumor size, proliferation marker and angioinvasion, correlates with survival. All patients with low-risk tumors were alive after 47 months, 10% of those with intermediate-risk tumors had died after 94 months, while 35% of patients with low-grade malignant tumors died after a period of 42 months. Few patients with a high-grade malignant tumor were alive after 4 months [27].

Minimal Consensus Statements on Clinical Presentation and Prognosis

Nonfunctioning pancreatic neuroendocrine tumors present as large tumors, with signs and symptoms related to the tumor burden. At diagnosis, the prevalence of synchronous metastases is 80%. Prognosis depends on the presence or absence of liver/bone metastases and histopathological classification. Overall 5-year survival is 60%.

Hereditary Tumor Syndromes

MEN-1. Multiple endocrine neoplasia type 1 (MEN-1) is a hereditary tumor syndrome with autosomal inheritance and high penetrance. The main manifestations of the disease are primary hyperparathyroidism, pituitary adenomas and pancreatic neuroendocrine tumors. Nonfunctioning pancreatic neuroendocrine tumors occur besides functional tumors. MEN-1-related tumors occur at an earlier age and demonstrate a more benign course than do sporadic tumors. They may be multiple and vary in size from small microadenomas to large tumors. The malignant potential is related to the size of the tumor [31]. Recent data indicate a prevalence of 55% for nonfunctioning pancreatic neuroendocrine tumors in MEN-1 patients [32]. However, only a small number of patients (8%)

with nonfunctioning pancreatic neuroendocrine tumors have MEN-1 syndrome [17].

Von Hippel-Lindau Disease (VHL). VHL is an autosomal-dominant disease with almost complete penetrance, characterized by the development of several types of neoplasia. Nonfunctioning pancreatic neuroendocrine tumors are part of the syndrome in up to 16% of the patients; frequently coexist with pheochromocytomas and may even precede the manifestation of other lesions [33–36].

Tuberous Sclerosis. An association of nonfunctioning pancreatic NETs with tuberous sclerosis has also been suggested [37, 38].

Minimal Consensus Statements on the Manifestation of Nonfunctioning Pancreatic NET in Hereditary Tumor Syndromes

Nonfunctioning pancreatic neuroendocrine tumors are part of the MEN-1 syndrome. They occur at an earlier age than do sporadic pancreatic NETs, may precede other manifestations of the syndrome and determine the prognosis of the patients. Nonfunctioning pancreatic NET are a rare, but recognized part of von Hippel-Lindau disease and may be seen in patients with tuberous sclerosis.

Diagnostic Procedures Imaging

Somatostatin-Receptor Scintigraphy (SRS)

SRS has a sensitivity and specificity for pancreatic neuroendocrine tumors of 90 and 80%, respectively [39, 40]. 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 [41]. 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%. ¹¹¹In-octreotide 200 MBq for planar, 200–220 MBq for SPECT images. At an acquisition time of 15 min and 4 h post injection (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 [42].

Positron emission tomography (PET) and/or PET CT, using Ga-DOTATOC to visualize somatostatin receptors is a promising new tool. However sufficient data are still lacking [43–45]. Additional tracers used so far (¹¹C-labelled L-Dopa, ¹⁸F-labelled L-Dopa and ¹¹C-5-hydroxytryptophan) are not useful in nonfunctioning pancreatic NET [46, 47].

Ultrasonography (US)

With US, most, especially small lesions, appear hypoechoic [48–50], while larger lesions are more heterogeneous, due to the different degree of hyalinized stroma, hemorrhage and cystic degeneration [48, 50]. Cystic areas are hypoechoic to anechoic.

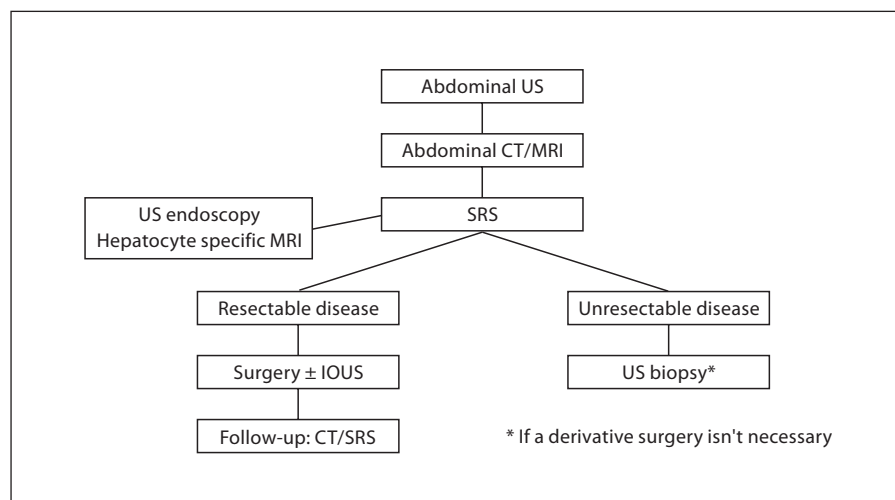
Computed Tomography (CT)

Non-contrast-enhanced computed tomographic images (NCE-CT) display iso- or hypodense lesions compared to the adjacent pancreatic parenchyma. In addition, calcification and hemorrhage are accurately depicted on NCE-CT. With contrast enhancement, the hypervascularity of endocrine tumors is apparent and characteristic [48, 51, 52]. In addition areas of cystic degeneration are visualized as regions of reduced vascularity by contrast-enhanced CT. Images should be obtained with multidetector CT (2.5 mm section thickness) at the peak arterial phase of contrast enhancement and reconstructed at 1.25 mm thickness [42, 53, 54].

Magnetic Resonance Tomography (MRT)

MRT displays hypointense or hyperintense lesions compared to the adjacent pancreatic parenchyma on T₁- or T₂-weighted MRT images, respectively. Fat-saturated T₁-weighted images during the injection of gadolinium chelates demonstrate the hypervascularity of endocrine tumors [48, 55, 56]. The hyperintensity is best depicted on fat-suppressed T₂-weighted images. High-resolution, fat-saturated T₂-weighted images, acquired during breath-hold acquisition, and volumetric T₁-weighted images (3 mm slice thickness) at the peak arterial phase of contrast enhancement, using a high-field (1.5 T) MRT, employing high-performing gradients and phased array surface coils, are recommended. Injection rates of contrast material for the evaluation of hypervascular lesions average 3–5 ml/s. MRT with a hepatocyte-specific contrast agent may depict small (<1 cm) liver metastases and thus influence decision-making with respect to surgical therapy.

Fig. 1. Suggested algorithm of different diagnostic options for the identification, typing and staging of non-functioning pancreatic NETs. US = Trans-abdominal ultrasound; CT = computed tomography; MRI = magnetic resonance; SRS = somatostatin receptor scintigraphy; IOUS = intraoperative ultrasound.



To differentiate the hypervascular pancreatic neuroendocrine tumor from hypovascular pancreatic adenocarcinoma, contrast-enhanced techniques (multidetector CT or MRT) [53, 54, 57, 58] are useful. In addition, T₂-weighted MR images differentiate the hyperintense neuroendocrine pancreatic tumor from the frequently scirrous, and thus hypointense, adenocarcinoma. Other helpful signs of differentiation are the mean larger volume, the occasionally cystic component and the lack of infiltration of peripancreatic fat and vessels of neuroendocrine tumors in comparison to the more aggressive growing adenocarcinoma [59, 60].

In patients with a high degree of clinical suspicion but negative non-invasive imaging studies (US, CT and/or MRT), further diagnostic investigations may include contrast-enhanced US (sensitivity and specificity 94 and 96%, respectively) [61] or endoscopic ultrasound (EUS) with biopsies (sensitivity 82–86%) [62–64]. The sensitivity of CT and MR imaging is in the range of 75–79%, using comparable technical standards and equipment [65]. For follow-up, the technique which best visualizes the individual tumor should be used. However, with progressive disease and before therapeutic decisions, a thorough staging (SRS, US and CT/MRT) is recommended.

Minimal Consensus Statement on Imaging

US combined with state of the art contrast-enhanced CT/ MR imaging (including MRCP) is recommended. The decision whether to use CT or MRT depends on the preference, skill and expertise of the radiologist and the availability of the different techniques at each institution. Somatostatin receptor scintigraphy

is the most sensitive, single screening method for extrahepatic disease manifestation. A possible algorithm is provided in figure 1.

Laboratory Tests

Chromogranin A (CgA) is a general tumor marker for neuroendocrine tumors [66]. Its concentration is supposed to correlate with the tumor mass. This correlation may be lost during SSA therapy [67]. In addition, basal and meal-stimulated pancreatic polypeptide (PP) may be useful for early detection of pancreatic involvement in MEN-1. The issue is controversial, as it has been demonstrated to substantiate the presence of a tumor in 75% of those tested [68], while others found no statistical difference between patients and controls for the meal-stimulated PP concentration [69].

Nonfunctioning pancreatic neuroendocrine tumors may secrete hormones and/or neurotransmitters, with plasma concentrations clearly above the normal range (e.g. so-called 'silent' tumors), but they are insufficient to induce a hypersecretion syndrome. However, the clinical impact of silent tumors compared to non-secreting, non-functioning tumors is as yet unknown. Thus, extensive screening for secreted hormones is not justified.

Minimal Consensus Statements on Laboratory Tests for Diagnosis and Follow-Up

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.

Table 2. Requirements for the histopathological diagnosis of a pancreatic endocrine tumor

| Macroscopic evaluation | Microscopic evaluation | Immunohistochemistry |
|---|--|---|
| Tumor size (largest diameter) | Mitotic index (expressed as the number of mitoses in 10 HPF) | Chromogranin A expression (yes/no; if yes, % of cells positive) |
| Lymph node metastases (yes/no; if yes, number and location of metastatic lymph nodes) | Angioinvasion (yes/no) | Synaptophysin expression (yes/no; if yes, % of cells positive) |
| Extrapancreatic invasion (yes/no) | Perineural invasion (yes/no) | Ki-67 index (expressed in % of cells positive) |
| Distant metastases (yes/no/unknown) | | |

HPF = High-power field.

Pathology and Genetics

Histopathology

Most nonfunctioning pancreatic neuroendocrine tumors present as well-differentiated tumors without distinctive histopathological features [5]. The growth pattern is usually of the nesting type. While fine needle aspiration cytology is not recommended as a standard diagnostic procedure, it may be useful in establishing the correct pre- or intraoperative diagnosis in the absence of a tissue specimen. New techniques, like monolayer cytology [70] or 'cellblock' sections, may improve the sensitivity of the procedure. Pre-operative histology is not required but is recommended. Histology is the gold standard in establishing a preoperative and definitive diagnosis. To demonstrate the endocrine nature of the neoplastic cells, immunohistochemical detection of CgA and synaptophysin are necessary and sufficient in most cases. To exclude tumors which may be confused with endocrine lesions, expression of vimentin, nuclear localization of beta-catenin for solid pseudopapillary tumors, and expression of trypsin for acinar cell carcinoma are useful [5]. While hormones/neurotransmitters like pancreatic polypeptide, glucagon, insulin, somatostatin, calcitonin and serotonin [5] may be expressed by silent neuroendocrine tumors, their immunohistochemical determination is not necessary for diagnosis and/or tumor subtyping. In contrast, the evaluation of the mitotic index is mandatory and that of the Ki67 index, at least in the primary tumor, is required.

Genetics

Germline DNA testing for hereditary tumor syndromes is only recommended in specific situations. These

include a family history or clinical findings suggesting MEN-1 or von Hippel-Lindau disease (VHL), the presence of multiple tumors or the demonstration of precursor lesions, such as nesidioblastosis-like features or microadenomas, in the peritumoral pancreatic tissue [71, 72]. 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 an endocrine tumor and to allow for its correct classification, according to the current WHO criteria (table 2). Germline DNA testing, e.g. mutational analysis, is only justified in clinical situations strongly suggesting MEN-1 or VHL disease.

Surgical Therapy

Indications

According to the WHO classification, the size of the endocrine tumor correlates with malignant growth. Therefore, in localized tumors larger than 2 cm, aggressive surgery and, if required, resection of nearby organs (stomach, colon, kidney, adrenal gland) and/or major vessel resection, is indicated [73, 74]. In contrast, no data exist with respect to a positive effect of surgery on overall survival in small (<2 cm), possibly benign or intermediate-risk pancreatic endocrine tumors. Thus, the possibility of surgical cure has to be weighed against the operative morbidity, mortality and long-term complications asso-

ciated with pancreatic surgery [75–77]. In patients with nonfunctioning pancreatic endocrine tumors as part of the MEN-1 syndrome, especially with small lesions, surgical intervention is still controversial [78–80].

Type of Surgery

The type of surgery depends on the localization, the size and suspected malignancy of the tumor. Small, non-malignant, easily accessible tumors can be treated by local atypical resection (enucleation or middle pancreatectomy). Middle pancreatectomy is advisable for lesions in the pancreatic body and close to the Wirsung duct. With atypical resection, pancreatic parenchyma can be preserved, avoiding exocrine and endocrine pancreatic insufficiency, while on the other hand the risk of a postoperative pancreatic fistula is high [81–83]. Localization of the tumor in the pancreatic head or suspected malignancy require larger, more typical resections, i.e. pancreatoduodenectomy or left pancreatectomy [84, 85].

Surgical Strategies for Multiple Nonfunctioning Pancreatic Neuroendocrine Tumors in MEN-1

Multiple nonfunctioning pancreatic NETs are part of MEN-1 and may cause up to 20% of MEN-1-related deaths [86–89]. Histopathological parameters cannot differentiate between benign and malignant disease in the absence of metastases or local invasion, and tumor size has no correlation to prognosis [31, 79, 90]. Careful microdissection of the pancreas demonstrates multiple, small (100 μ m to 5 mm) microadenomas [72, 91], indicating clinically unapparent, yet histologically visible disease in MEN-1. While only a minority of the microadenomas acquire the potential to grow unrestrictedly, larger lesions may be genetically unstable; develop secondary mutations and will grow into clinically relevant lesions. While surgical resection of the visible tumors fails to cure the patient, prophylactic surgery aims to remove these lesions before malignancy develops. However, while recent data show that early diagnosis and surgery improve survival [92], others suggest a more conservative approach, as their data indicate, that only tumors larger than 2 cm are associated with an increased risk of malignancy [79]. Therapeutic strategies thus range from follow-up, to enucleation of visible lesions [86] or aggressive interventions with enucleation of tumors in the head of the pancreas combined with distal, subtotal (80%) pancreatic resection as prophylaxis against tumor recurrence [78, 93, 94].

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.

Surgical Debulking of Locally Advanced Pancreatic NETs

Aggressive surgery, with curative intent for locally advanced nonfunctioning pancreatic NETs may prolong survival (5-year survival up to 80%, 72 and 77%, respectively) [75, 77, 85, 95]. However, all available data are retrospective analyses; most refer to a mixed – functioning and nonfunctioning – tumor cohort, and surgery is only part of a multimodal treatment approach. Thus, the effect of surgery alone is hard to estimate. In addition, surgery is mostly done in patients with less extensive disease and the prolonged survival of patients with debulking procedures may be primarily related to the stage of the tumor. Furthermore, most investigations give univariate survival analysis, which may be potentially misleading. Thus, the data are still inconclusive and only prospective randomized multicenter trials will provide an answer.

No data support debulking procedures in unresectable, locally advanced nonfunctioning pancreatic NETs. With partial resection of the primary, the risk of bleeding is high, tumors recur and survival advantage is not supported by the data [75, 77, 90, 95–97].

Surgery in Metastatic Nonfunctioning Pancreatic NETs

Surgery of the Primary. In metastatic disease, resection of the primary alone fails to improve survival. In selected, low-risk patients with a low volume of liver metastases, but life-threatening or unbearable symptoms, surgery of the primary may prevent tumor related complications (gastrointestinal hemorrhage or biliary/gastric outlet obstruction) and allow for a more effective treatment by limiting the disease to the liver [77].

Surgery for Liver Metastases. In the absence of extrahepatic disease, synchronous resection of the primary and liver metastases should be considered. The 5-year survival of patients treated with hepatic resection in recent series ranges from 47 to 76%, and this compares well with the 30–40% 5-year survival in untreated patients [98–101]. However, the rate of tumor recurrence is high, up to 76% [85, 98, 102–104], and half of these are seen within 2 years after resection [102]. Surgery should only

be undertaken if at least 90% of the tumor mass can be removed successfully. This may be possible in only up to 10% of the patients [98]. A prerequisite to hepatic surgery is sufficient hepatic reserve after resection. In addition, mortality and morbidity of palliative hepatic surgery should be less than 3–5% and 30%, respectively [103, 105, 106]. The type of surgery depends on the location of the metastases. The following procedures can be chosen: enucleation, one or more segmental resections, hemihepatectomy or extended hemihepatectomy. Intraoperative US must be performed for detection of all liver metastases. If feasible, the surgical procedure should include cholecystectomy to prevent possible side effects of somatostatin analogue or embolization therapy (gallstones or gallbladder necrosis, respectively).

If radical resection is not achievable, biliary and gastric outlet obstruction should be treated by surgical bypass rather than endoscopic or percutaneous procedures. Long-term survival, even in the presence of liver metastases, makes the surgical approach preferable since the short-term patency of endoscopic stents is poor [58, 107–109].

Minimal Consensus Statement on Palliative Surgery

Debulking of an unresectable primary is not recommended, with the exception of individual 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. Surgery should only be performed in experienced centers with mortality, and morbidity less than 5 and 30%, respectively.

Locoregional Ablative Therapy

Loco-regional ablative therapy is defined by a panel of mostly nonsurgical interventions, aiming at palliative reduction of hepatic lesions in patients without manifestation of extrahepatic disease. Locoregional ablative procedures have been used mainly in functioning metastatic NETs to reduce endocrine active tumor volume and thus improve symptoms of hypersecretion. There are insufficient data to define the role of loco-regional ablative strategies in nonfunctioning pancreatic NETs. Most investigations report on mixed tumor groups, the data are analyzed retrospectively and the procedure is part of a multimodal treatment. However, locoregional ablative therapies are widely used in clinical practice in patients who have failed systemic chemotherapy and/or are not

candidates for other procedures, due to the extent of liver involvement. The following options are available: selective (chemo-)embolization, radiofrequency ablation, and radio-embolization.

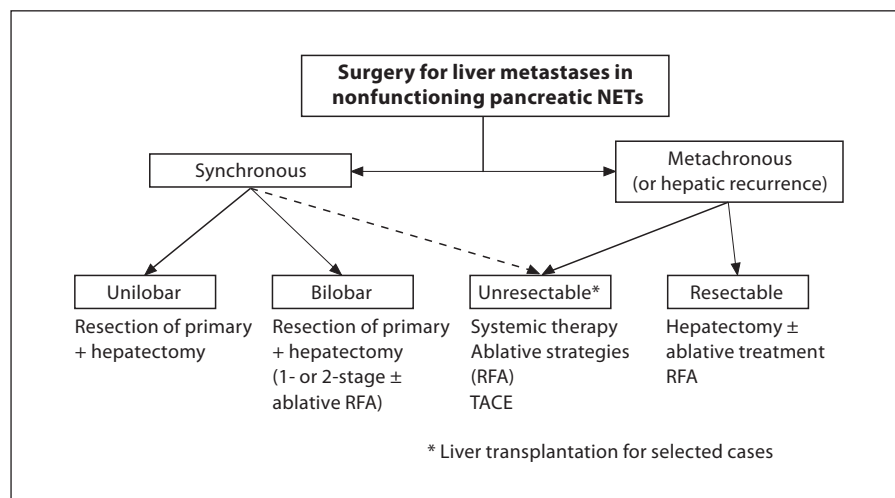
Selective (Chemo-)Embolization (TACE)

Selective embolization of peripheral arteries induces temporary, but complete ischemia. It has been suggested that embolization-induced ischemia sensitizes the tumor tissue to cytotoxic drugs, whose tumor concentration is increased by the slowing down of blood flow. The procedure can be performed repeatedly. Open questions are the type of drug (5-FU, doxorubicin and mitomycin C), dosage, intervals and timing of the procedure. Moreover, it has not been established whether chemo-embolization is more efficient than embolization alone. Results of (chemo-)embolization in 428 patients (14 trials, not all data are given in each trial) indicate a symptomatic response in 50–100%, biochemical response in 22–92%, and tumor volume response in 25–86% of the patients, overall median survival of 20–80 months and 5-year survival of 40–55% [110–123]. Positive prognostic factors are prior removal of the primary, metastatic liver involvement of less than 75%, diameter of the liver metastases < 5 cm and no extrahepatic metastasis [116, 123]. Mortality (0–3.3%) of the procedure is low; however, as morbidity may be significant, chemo-embolization should be performed in experienced centers. As it is not clear whether TACE prolongs survival, its main indication is the treatment of otherwise untreatable functionally active liver metastases [124].

Radiofrequency Ablation (RFA)

RFA is an alternative treatment limited to patients with no more than 8–10 lesions, and a diameter of the lesions below 4 cm. Depending on the tumor location, RFA can be performed laparoscopically or percutaneously [125–130]. Existing data report on all kinds of endocrine tumors. In the largest series so far (34 and 25 patients, 234 and 189 neuroendocrine metastases) symptomatic improvement occurred in 95 and 65%, partial or significant tumor volume reduction was observed in 65 and 68% of the patients, and median survival after RFA was 1.6 and 4.4 years, respectively. During the median follow-up of 1.6 years, 41% of the patients remained stable. Mortality was low and morbidity was 5–12% [131, 132]. In some patients, RFA may be used to convert an unresectable disease into a resectable one [105]. No data exist as to whether RFA has any effect on survival.

Fig. 2. Suggested algorithm of different treatment options for liver metastases in nonfunctioning pancreatic NETs. Hepatectomy = Oncological resection of the metastases; RFA = radiofrequency ablation; TACE = transarterial hemoembolization.



Radioembolization

Selective internal radiation therapy (SIRT) relies on the selective uptake by the tumor of yttrium-90 microspheres, following arterial hepatic injection. Due to the predominant arterial flow to liver tumors relative to normal liver tissue, the microspheres become trapped in capillary beds of tumorous lesions and deliver ionizing radiation to the tumor. Experience with this technique in NETs is lacking [133, 134]. An algorithm for the treatment of liver metastases is given in figure 2.

Minimal Consensus Statement on Locoregional Ablative Therapy

(Chemo-)embolization and radiofrequency ablation have been used as loco-regional 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 transplantation 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 un-

diagnosed 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 [135–146].

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

Biotherapy

Numerous studies have evaluated the effect of SSA or interferon on tumor proliferation. General conclusions should be interpreted with caution, as most studies report on a mixed tumor cohort. Demonstration of progressive disease before initializing somatostatin analogue/interferon therapy has been a prerequisite in only a small number of studies. No placebo group was included in any of the studies and most trials were performed in patients pre-treated with other therapeutic modalities. The duration of therapy was rather short in most trials, and standardized schemes for evaluating therapeutic efficacy had not been universally employed. There are only a small number of studies for SSA and none for interferon using a randomized, prospective, multicenter approach including only tumors with demonstrated progress. Most trials

Table 3. Somatostatin analogue therapy in patients with progressive tumor disease

| SSA | Dose | Patients* | Tm volume n eligible patients | CR | PR | SD | PD | Median survival (months) after | | Ref. |
|------------|--------------------|-----------|-------------------------------------|----------|--------|----------|-----------|-----------------------------------|-----------|------|
| | | | | | | | | therapy | diagnosis | |
| Lanreotide | 3,000 µg/day | 22 | 22 | 0 | 1 | 7 | 14 | 69 | 155 | |
| Lanreotide | 30 mg/2 weeks | 35 | 35 | 0 | 1 | 20 | 14 | 29 | 149 | |
| Octreotide | 600-1,500 µg/day | 52 | 52 | 0 | 0 | 19 | 33 | | 148 | |
| Octreotide | 1,500-3,000 µg/day | 58 | 58 | 0 | 2 | 27 | 29 | 22 | 169 | |
| Octreotide | 600 µg/day | 21 | 10 | 0 | 0 | 5 | 5 | | 170 | |
| Lanreotide | 15,000 µg/day | 30 | 24 | 1 | 1 | 11 | 11 | 69 | 171 | |
| | | 218 | 201 | 1 (0.5%) | 5 (3%) | 89 (44%) | 106 (53%) | | | |

SSA = Somatostatin analogs; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

* Patients are from mixed cohorts of neuroendocrine tumors.

used secondary endpoints, such as tumor shrinkage or a decrease of tumor markers for the evaluation of drug efficacy. Endpoint analysis, i.e. time to progression or overall survival, was reported only in a minority of trials.

Somatostatin Analogues (SSA)

In nonfunctioning pancreatic NETs somatostatin analogue (SSA) therapy aims at the stabilization of tumor growth. Partial and complete remission can be observed in fewer than 10% of the patients, while stabilization of tumor growth occurs in 24–57% of patients with documented tumor progress before somatostatin analogue therapy. Distant metastases and progressive disease during the first 6 months of therapy are negative predictors for a persistent stabilization of the disease [147]. SSA therapy should be initiated as first-line medical therapy, whenever tumor progress is documented and surgical or ablative treatment is no option (table 3). However, in low-differentiated tumors with a high Ki67 index (>15%) chemotherapy should be the first-line treatment strategy in patients without surgical or ablative therapeutic options.

The tolerability of somatostatin analogues (nausea, newly developed diarrhea, abdominal pain) should be tested by initiating therapy with a short-acting analogue (e.g. octreotide). Thereafter, depot formulations, usually lanreotide-SR i.e. (every 2 weeks), lanreotide autogel s.c. or octreotide-LAR i.m. (every 4 weeks), are effective. The efficacy of lanreotide and octreotide is comparable [148–150]. Minor, initial side effects, usually subsiding within a few weeks, are abdominal discomfort, bloating and sometimes steatorrhea [148, 149, 151, 152]. In patients

with steatorrhea, pancreatic enzyme supplementation may be of help. Major side effects are the development of gallstones (about 50%, rarely symptomatic). In a few cases, persistent steatorrhea resulting in malabsorption may occur [152, 153]. Follow-up of patients on SSA therapy should be performed in 6-month intervals. With documented, progressive disease during SSA therapy, SSA should be withdrawn.

Interferon

Interferon is given for the same indications as somatostatin analogues. However, data on interferon in nonfunctioning pancreatic NETs are rare. Results of 48 patients from 3 trials could be analyzed [28, 29, 154]. Progression has not usually been demonstrated before therapy and interferon was part of a multimodal therapeutic approach. Stabilization of the disease could be achieved in 23%, whereas partial remission of biochemical markers or tumor volume could be demonstrated in 48 and 23% of the patients, respectively. Progressive disease was observed in 23% (table 4). The usual dose is rIFN α 2b 3–5 million units 3–5 times per week subcutaneously. Due to a larger range of side-effects, interferon is generally used as a second-line therapy for symptomatic control in functioning carcinoid tumors and is only rarely indicated as an antiproliferative therapy in nonfunctioning pancreatic NETs. Interferon treatment may be particularly recommended for low-proliferating nonfunctioning tumors with a proliferation index less than 2–3%. However, this still must be confirmed in randomized clinical trials. Pegylated interferon, i.e. a long-acting formulation of interferon, is available but still not regis-

Table 4. Therapy with interferon-alpha in patients with nonfunctioning pancreatic neuroendocrine tumors

| Interferon | Dosage | Patients | CR | PR (biochem/radiol) | SD | PD | Year | Ref. |
|----------------------|--------------------------------------|----------|----|---------------------|---------|---------|------|------|
| hIFN/IFN α 2b | 3–6 million U/day | 9 | – | 6 (67%)/6 (67%) | ?? | ?? | 1986 | 154 |
| hIFN/IFN α 2b | 5 million U/3/week | 14 | – | 6 (43%)/3 (21%) | 3 (21%) | 4 (29%) | 1990 | 29 |
| hIFN/IFN α 2b | 6 million U/day or 5 million U3/week | 25 | | 10 (40%)/2 (8%) | 6 (24%) | 8 (32%) | 1993 | 28 |
| | | 48 | | 46 % /23 % | 23% | 31% | | |

NI = Not indicated; CR = complete response; PR (biochem/radiol) = partial response, reduction of tumor marker by more than 50%/reduction of tumor volume by more than 50%; SD = stable disease; PD = progressive disease.

tered for this indication. Studies comparing pegylated interferon with interferon s.c. are required.

Minor side effects are a flu-like syndrome, easily relieved by paracetamol, anorexia with weight loss and fatigue. Major side effects are hepatotoxicity, autoimmune reactions, depression and mental disturbances. Severe bone marrow depression is rare.

The combination of somatostatin analogues and interferon-alpha does not increase therapeutic efficacy as has been shown in a randomized prospective study by Faiss and co-workers [155, 156].

Minimal Consensus Statement on Biotherapy

Biotherapy, preferentially SSA therapy, can be used as first-line medical therapy in progressive tumors with a slow proliferation index. Stabilization of the disease may occur in about 50% of the patients. Side effects are less with SSA than with interferon. Combination therapy of SSA and interferon does not increase therapeutic efficacy.

Chemotherapy

For more than three decades, a combination of streptozotocin plus 5-FU or doxorubicin has been the gold standard for treatment of different types of endocrine pancreatic tumors. Early data indicated objective tumor responses in up to 60% of the patients [157]. More recent studies using MRI/CT evaluation have reduced the objective tumor responses down to 16–30% [158–161]. In a recent trial using 5-FU, doxorubicin and streptozotocin the response rate was 39%, 2-year progression-free survival 31% and 2-year overall survival was 74% [162]. Similar results were achieved in 50 patients with pancreatic NETs, half of them nonfunctioning, using dacarbazine (response rate 33%, median survival 39.2 months) [163]. Therefore, new randomized trials comparing cytotoxic treatment with new biological agents are necessary to

clearly delineate the role of cytotoxic treatment. Preliminary data indicate that temozolamide alone or in combination with octreotide may induce antitumor responses in a small number of patients [164]. In addition, tyrosine kinase inhibitors or anti-angiogenic treatment strategies may prove useful [165]. For the time being, streptozotocin plus 5-FU is indicated for metastatic nonfunctioning tumors, if locoregional approaches are not feasible or are in patients with localized progressive bulky tumors [158]. Patients with tumors presenting a higher proliferation index, i.e. above 20% Ki67-positive cells, usually receive a combination of cisplatin plus etoposide [159].

Adjuvant Chemotherapy

No studies have clearly indicated the value of cytotoxic treatment in an adjuvant setting. Yet, before prospective randomized trials for adjuvant chemotherapy can be suggested, the most effective cytotoxic therapy has to be delineated in malignant nonfunctioning pancreatic NETs. Thus, at present, adjuvant chemotherapy is not a therapeutic option in patients with pancreatic nonfunctioning NETs.

Minimal Consensus Statement on Chemotherapy

Chemotherapy is indicated as medical therapy in progressive tumors after biotherapy has failed. Streptozotocin and 5-FU or doxorubicin are used in tumors with a low proliferation index (Ki67 <20%), while cisplatin and etoposide are indicated in fast growing tumors. Stabilization of the disease may occur in about 30–50% of the patients. No data exist to support the use of adjuvant therapy in pancreatic nonfunctioning NETs.

Treatment Recommendations in Stable Disease

In patients with stable disease and low tumor burden after previous interventions, no medical therapy should

be initiated. Stable disease may prevail for some time. Unfortunately, there is no single predictive marker for tumor growth. Regular monitoring with CgA determinations and imaging methods will ultimately demonstrate the progression of the tumor disease.

Peptide Receptor Radionuclide Therapy

PRRT with somatostatin analogues coupled with beta-emitting radionuclides (e.g. ^{90}Y or ^{177}Lu) may be rewarding in patients with inoperable nonfunctioning pancreatic endocrine tumors which show sufficient uptake on the diagnostic SRS [166, 167]. After treatment with radiolabeled somatostatin analogues (^{90}Y -DOTA⁰, Tyr³] octreotide or [^{177}Lu -DOTA⁰, Tyr³] octreotate), tumor shrinkage, i.e. complete or partial remission, was observed in 3 or 17% and 1 or 29%, stable or progressive disease in 61 or 12% and 39 or 18% of the patients (n = 182 and n = 76), respectively. After therapy with [^{177}Lu -DOTA⁰, Tyr³], octreotate median time to progression was over 36 months, which compares favorably with other treatment modalities, especially chemotherapeutic regimens [166]. The results may be influenced by the type of tumor-treated; various administered doses and dosage schemes; the amount of SSA uptake due to different receptor density; the estimated tumor burden, and liver involvement [166]. Side effects are nausea and vomiting at administration of the drug. In addition, abdominal pain and mild reversible hair loss were observed, as were anemia, leukocytopenia and thrombocytopenia. In men, testosterone and inhibin-B decreased, with a reactive increase in LH and FSH. Damage to the kidneys can be prevented by co-administration of amino acids.

Minimal Consensus Statements on PRRT

PRRT is a new therapeutic option in tumors with high somatostatin receptor density. [^{90}Y -DOTA⁰, Tyr³] octreotide or [^{177}Lu -DOTA⁰, Tyr³] octreotate can be used. However, PRRT is still experimental, as randomized comparison to various treatments is lacking.

Follow-Up

Benign or Borderline Nonfunctioning Pancreatic NETs

Follow-up aims to evaluate the results of surgical therapy and/or the indications for additional treatment.

Follow-up includes clinical, laboratory (CgA) and radiological examinations [149, 168]. In general, the follow-up intervals should be close during the initial phase, following diagnosis, after therapeutic interventions or with progressive disease. No follow-up is probably necessary after complete resection of a benign nonfunctioning pancreatic NET (WHO 2000), as resection is curative. However, as long-time experience with the WHO classification is lacking follow-up every 12 months (CgA, US) is recommended even in patients with favorable prognostic factors. Patients with pancreatic lesions of uncertain behavior (WHO 2000), who have undergone radical surgery, cannot be considered cured. Therefore, long-term follow-up, every 12 months with US or MRI/CT scans and biochemical markers (CgA) is suggested [149, 168]. SRS should be done 6 months after surgery.

Malignant Nonfunctioning Pancreatic NET

Patients with radically resected malignant tumors should be followed up every 6 months with biochemical markers, US and/or MRI/CT scans to detect recurrences [149, 168]. A stricter follow-up can be advocated for poorly differentiated carcinomas in which radical resection was achieved. In this latter group, early relapse is quite often observed.

Advanced Malignant Nonfunctioning Pancreatic NET

In patients with rapid tumor growth, i.e. a proliferation index >30%, follow-up should be performed every 3 months. Initial follow-up investigations should include clinical, biochemical markers, ultrasound and/or MRT/CT.

All therapeutic schemes should be monitored closely and terminated as soon as there is further progression, indicating ineffective therapy. If no further therapeutic modalities are available, monitoring the disease should be kept at a minimum for the sake of the patient's convenience, as well as for the reduction of health costs.

Minimal Consensus Statements on Follow-Up

Follow-up investigations should be adjusted to the type of tumor (benign or malignant) and the stage of the disease (radically resected or progressive disease). The results of follow-up investigations clarify whether therapy is indicated or effective. Clinical examination, CgA determination and radiological investigations (US, CT/MRT) are recommended.

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