Current best practice in the management of neuroendocrine tumors

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Abstract: Neuroendocrine neoplasms are rare tumors that display marked heterogeneity with varying natural history, biological behavior, response to therapy and prognosis. Their management is complex, particularly as a number of them may be associated with a secretory syndrome and involve a variety of options. A number of factors such as proliferation rate, degree of differentiation, functionality and extent of the disease are mostly utilized to tailor treatment accordingly, ideally in the context of a multidisciplinary team. In addition, a number of relevant scientific societies have published therapeutic guidelines in an attempt to direct and promote evidence-based treatment. Surgery remains the treatment of choice with an intention to cure while it may also be recommended in some cases of metastatic disease and difficult to control secretory syndromes. Long-acting somatostatin analogs constitute the main treatment for the majority of functioning tumors, whereas specific evolving agents such as telotristat may be used for the control of carcinoid syndrome and related sequelae. In patients with advanced disease not amenable to surgical resection, treatment options include locoregional therapies, long-acting somatostatin analogs, molecular targeted agents, radionuclides, chemotherapy and recently immunotherapy, alone or in combination. However, the ideal time of treatment initiation, sequence of administration of different therapies and identification of robust prognostic markers to select the most appropriate treatment for each individual patient still need to be defined.

Keywords: neuroendocrine tumor, somatostatin analogs, radionuclides, everolimus, sunitinib

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Introduction

Neuroendocrine neoplasms (NENs) are rare tumors with an estimated annual incidence of 3–5 cases/100,000 inhabitants but due to increased sensitivity of currently used diagnostic tools their incidence has been rising over time.[1,2] NENs are located mainly in the gastrointestinal tract and bronchopulmonary system but they can also develop in the ovaries, the urinary bladder and other organs.[3] While NENs generally represent an indolent disease, a significant proportion develop metastases, and a subset display an aggressive behavior. Based on the proliferative index Ki-67, determined by immunohistochemical staining for nuclear Ki-67 protein expression, gastro-enteropancreatic NENs (GEP-NENs) are classified as NEN G1 (Ki-67 <3%), NEN G2 (Ki-67, 3–20%), NEN G3 (Ki-67 >20%) and mixed exocrine–endocrine carcinoma (miNEN).[4–6] Recently, the degree of tumor differentiation has been taken into consideration for pancreatic NENs, dividing G3 tumors into well-differentiated neuroendocrine tumors (G3 NETs) and G3 poorly differentiated carcinomas (G3 NEC) that show different molecular signatures and clinical behavior.[4] Lung NEN classification by the World Health Organization (WHO) on the contrary, is not based on Ki-67 but on mitotic counts and assessment of necrosis.[7]

NENs may be 'functioning' or 'nonfunctioning' depending on the presence or absence of a clinical syndrome related to hypersecretion of metabolically active substances.[8,9] General circulating

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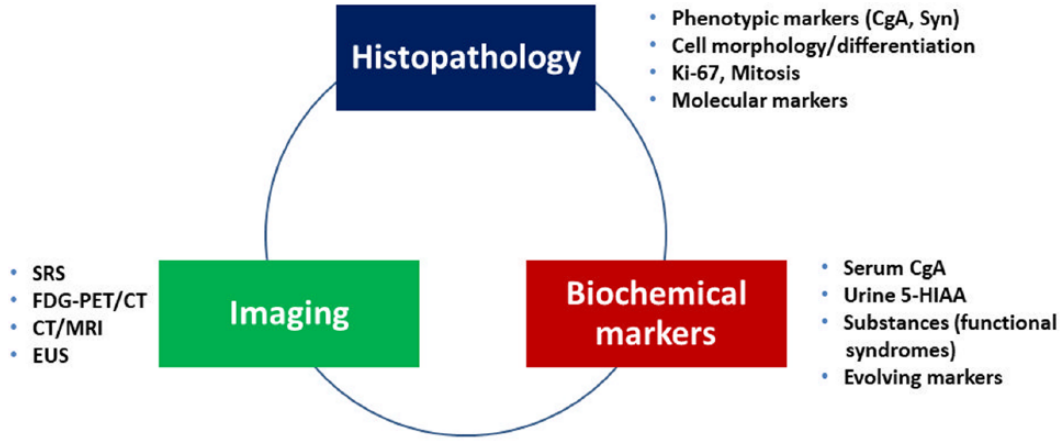

Figure 1. Diagnostic tools for NEN classification.
NEN, neuroendocrine neoplasm.

biomarkers associated to NENs are chromogranin A (CgA) and neuron-specific enolase, while specific markers related to clinical syndromes include gastrin, insulin, glucagon, vasoactive intestinal peptide, parathyroid hormone related peptide and adrenocorticotropic hormone.[10]

A full imaging work-up is necessary during the initial diagnosis in order to identify all sites of disease and optimize therapeutic management. Multiphasic contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), colonoscopy, gastroscopy and capsule endoscopy or CT/MRI enteroclysis can be used to identify the primary tumor or metastatic lesions.[11] Due to high levels of expression of somatostatin receptors (SSTRs) in the majority of NENs, these neoplasms can also be detected by somatostatin receptor scintigraphy (SRS; Octreoscan or Tektrotyd) or by positron emission tomography (PET; ^{68}Ga-DOTATOC PET/CT). These techniques allow whole body scanning while ^{68}Ga-DOTATOC PET/CT has been proved to be the most sensitive method for the diagnosis and staging of NENs.[11–13] Furthermore, fluorodeoxyglucose (FDG)-PET/CT is a whole imaging procedure that assesses glycolytic metabolism and has higher sensitivity than SRS in G3 tumors while high FDG uptake is associated with tumor aggressiveness.[14,15] However, recent studies have shown that FDG uptake can also be observed in low-grade NENs and represents an important tool for assessing tumor prognosis while observation of different uptake in somatostatin receptor imaging (SRI) and FDG-PET/CT reflects tumor heterogeneity and may result to different therapeutic management.[15–17] (Figure 1)

Treatment of NENs has traditionally been considered to be mainly surgical; however, in recent decades there has been a considerable evolution of a number of nonsurgical treatments that have expanded the therapeutic options of these neoplasms (Figure 2). In NENs G1 or G2, surgery with an intention to cure can be considered even in the presence of liver or lymph node metastases. In patients with advanced disease, tumor debulking techniques such as hepatic artery embolization (HAE), selective internal radiotherapy (SIRT), radiofrequency ablation (RFA) and palliative hepatic cytoreductive surgery may significantly decrease the tumor burden or lead to symptomatic improvement of hormone excess states.[8,18–20] As the majority of NENs express SSTRs, long-acting somatostatin analogs (SSAs) play an important role in the treatment of patients with NENs and may result in symptomatic, biochemical and objective responses.[8,18,21] Systemic treatment of patients with NENs involves also chemotherapy, interferon-α and targeted agents such as the mammalian target of rapamycin (mTOR) inhibitor, everolimus, or the tyrosine kinase inhibitor, sunitinib.[22,23] In addition, peptide receptor radionuclide therapy (PRRT) is a plausible therapeutic option in patients with tumors expressing SSTRs, as it has demonstrated antitumor efficacy and amelioration of refractory hormone secretion syndromes.[24] Treatment of G3 tumors is based on limited evidence and

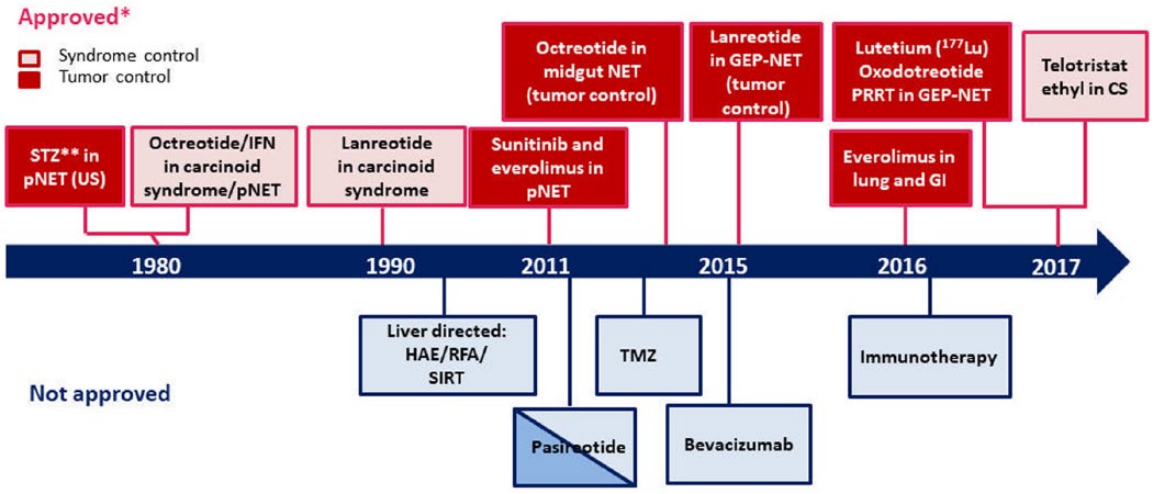

Figure 2. Evolution of therapeutic modalities of NENs.
*Depending on country.
CS, Carcinoid Syndrome; GEP, gastro-enteropancreatic; GI, gastrointestinal; HAE, hepatic artery embolization; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; RFA, radiofrequency ablation; SIRT, selective internal radiotherapy; STZ, streptozotocin; TMZ, temozolomide.

involves surgical resection and chemotherapy, or PRRTs in the case of well-differentiated tumors.[25] Furthermore, recently published case series report promising results of immunotherapy while multiple ongoing phase II trials study the activity of immune checkpoint inhibitors in NENs.[26,27]

A number of parameters need to be considered before deciding the most appropriate therapeutic approach in order to provide a patient tailored therapy. These need to adhere to the recently implemented guidelines from a number of international societies such as the European Neuroendocrine Tumor Society (ENETS) and ideally decisions should be taken in a multidisciplinary setting including all relevant specialties dealing with the totality of these tumors. Furthermore, there is evidence to suggest that patients managed by centers with extensive experience exhibit a better outcome and median overall survival (OS) compared with those managed elsewhere.[28] Central registration of these patients and response to treatments applied are required to optimize diagnosis and management of NETs.

Currently there is no established protocol regarding follow up of patients with NENs as evidence-based studies are missing. Recently published ENETS recommendations suggest that follow up should be performed in specialized centers with regular tumor boards with expert panels.[29] It is recommended to have life-long follow up that varies according to the tissue of origin, the grading and differentiation, the stage, the aggressiveness, the functionality, the surgical outcome and the presence of hereditary disease. Follow-up evaluation should include clinical examination, tumor marker measurement and imaging studies. Shorter intervals between follow ups are recommended in patients with high-grade tumors, a large tumor burden or aggressive disease, uncontrolled functional syndromes or extremely high CgA levels.[29]

As the tissue of origin is highly related to the metastatic potential and prognosis of NENs and affects their management, currently applied and evolving treatments will be presented according to tumor localization and origin.

Gastroduodenal NENs

Gastric NENs (g-NENs) originate from enterochromaffin-like (ECL) cells located in the gastric glands and are divided in three categories: type 1 that are associated with achlorhydria and chronic atrophic gastritis; type 2 that are related to Zollinger–Ellison syndrome; and type 3 gastric NENs that are rare and more aggressive tumors not related to any gastric mucosal abnormality.[30]

Type 1 tumors are the most common (70–80%) and are of low malignant potential, usually being

grade 1 neoplasms. They are typically found as polypoid lesions, usually multiple, in the gastric body and fundus during upper gastrointestinal endoscopy and are thought to derive from preceding ECL-hyperplastic lesions, that are usually discovered in the neighboring mucosa. Fasting gastrin serum levels should be determined and are always increased while CgA levels may also be elevated. Further evaluation should include screening for anti-parietal and anti-intrinsic factor autoantibodies as well as for autoimmune thyroiditis.[30]

G-NENs type 1 display a low metastatic risk directly associated with the tumor size.[30,31] EUS helps to determine the depth of tumor invasion in the gastric wall. ENETS guidelines recommend resection of lesions >10 mm or those affecting the muscularis propria. Surveillance or resection can be selected for tumors <10 mm as there are no randomized data comparing the two options and recent studies have observed no tumor-related deaths in patients who were submitted to endoscopic surveillance.[30,32,33] Biopsy forceps can be used for small lesions but endoscopic mucosal resection (EMR) is generally recommended for lesions >5 mm. Endoscopic submucosal dissection (ESD) is useful for the removal of submucosal lesions as it has the benefit of en-bloc resection allowing for complete histological examination.[34] Local excision or partial gastrectomy should be considered in the case of invasion beyond the submucosa or positive resection margins after EMR, or in those of higher grade. In addition, surgery should be performed in the case of lymph node or distant metastases, or in poorly differentiated tumors.[30,35] Surgical antrectomy could be an option to suppress hypergastrinemia, but the completeness of antrectomy is debated so this alternative is not widely recommended.[32,36]

SSAs are effective in reducing the size and number of g-NENs of type 1 but there are no randomized trials comparing their efficacy with endoscopic surveillance, so they are currently recommended only in patients with recurrent or multiple small lesions.[37] There are also no long-term studies addressing the duration of SSA administration, as in a proportion of patients lesions may recur with discontinuation of treatment and reemergence of hypergrastrinemia.[38] Furthermore, recent studies have shown that the gastrin receptor antagonist netazepide reduces gastric acid output and may also decrease the size and number of type 1 (and 2) g-NENs by inhibiting the mitogenic action of gastrin; however, further assessment with randomized controlled studies is needed in order to recommend its use in patients with such tumors.[32,39]

Overall, type 1 g-NENs are associated with an excellent prognosis with a survival rate of almost 100%. However, continuous endoscopic follow up is recommended as they are considered a recurrent disease and rarely (3–5%) metastatic spread can be observed.[30,31]

Type 2 g-NENs typically present as small polyps that are associated with hypergastrinemia, hyperchlorhydria and peptic ulcers (Zollinger–Ellison syndrome) while they are almost exclusively seen in patients with multiple endocrine neoplasia type 1 (MEN1) syndrome. In about 10–30% of cases they are metastatic at presentation and are associated with a mortality rate of <10%.[30,40] Local surgical resection is recommended for type 2 g-NENs but treatment should be individualized and addressed in a multidisciplinary team while resection of the co-existing duodenal or pancreatic gastrinoma should be considered.[30,41] In addition, a currently ongoing trial is testing the efficacy of netazepide in type 2 g-NENs.[32]

Type 3 g-NENs are typically large (>1 cm) sporadic tumors that are not related to hypergastrinemia and display significant infiltrative tendency with relatively high proliferative labeling index Ki-67.[42,43] They are usually metastatic at presentation and are related to nonspecific symptoms such as anemia, dyspepsia, weight loss or gastrointestinal bleeding. Rarely, an atypical carcinoid syndrome can be developed.[41] An extensive diagnostic work-up with multiple imaging studies such as MRI, SRS or FDG-PET/CT is required in order to determine the disease extension. Type 3 g-NENs should be treated as gastric adenocarcinomas with partial or total gastrectomy and lymph node dissection. Endoscopic resection has been proposed only for small lesions confined to the submucosa with no lymphovascular invasion.[30,32,44] Systemic therapies can be useful in the case of metastatic or inoperable tumors. Unfortunately, type 3 g-NENs are associated with a high mortality (25–30%) and metastatic rate (50–100%).[32]

Duodenal NENs (d-NENs) are rare tumors and comprise 1–3% of all duodenal neoplasms. Most

of these tumors are located in the first or second part of duodenum while 20% arise in the periampullary region.[45] D-NENs are generally small (<2 cm) and usually confined to mucosa or submucosa but in approximately 40–60% and 10% lymph node and liver metastases respectively have been reported. The majority (90%) of d-NENs are nonfunctional but can also be associated with Zollinger–Ellison (sporadic or related to MEN1) or rarely with carcinoid syndrome.[30,45]

Upper gastrointestinal endoscopy is the most sensitive method of detection and diagnosis of d-NENs while EUS can be helpful in determining the extension of the tumor invasion. CT, MRI and SRS can be used in order to determine the presence and the extent of metastatic disease.[30,35]

All d-NENs should be removed unless in the presence of metastatic spread. Endoscopic resection, either with EMR or ESD, is considered a well-tolerated option for tumors <10 mm confined to the submucosa with no lymph node or distant metastases. No recurrence was observed in a series of patients with d-NENs treated with endoscopic resection while ESD seems more efficacious than EMR in terms of radical excision rates.[46] However, for lesions located in the periampullary region surgical resection may be required as they are in general more advanced and no correlation has been reported between the size of these tumors and the risk of malignancy.[47,48] Large d-NENs or tumors of any size with lymph node involvement should be surgically removed. Surgical resection or ablative treatment may also be considered in patients with potentially resectable liver metastases and no contraindications to surgery.[30] Lesions of intermediate size (1–2 cm) can be treated either surgically or with endoscopic resection if no lymph node metastases have been detected.[30] In the case of advanced disease, SSAs are a useful antiproliferative option especially in patients with G1 tumors while chemotherapy is preferred in G3 neoplasms. Chemotherapy or treatment with PRRT should be considered in the case of metastatic advanced progressive disease based on specific tumoral characteristics.[49,50]

Endoscopic follow up is recommended at least every 2 years after resection of gastroduodenal NENs. Specifically for type 1 g-NENs, follow up can be performed in shorter intervals according to the recurrence rate.[32]

Small intestinal NENs

Small intestinal neuroendocrine neoplasms (siNENs), originally described as carcinoid tumors by Oberndorfer in 1907, derive from serotonin-producing enterochromaffin cells and present with an incidence of approximately 0.67–0.81/100,000/year.[3] Frequently they present with nonspecific symptoms (abdominal pain or weight loss) while 20–30% of patients with liver metastases develop carcinoid syndrome due to serotonin or tachykinin production. Occasionally, complications due to carcinoid fibrosis leading to mesenteric fibrosis and carcinoid heart disease (CHD), where right heart valve lesions may predominate the clinical presentation, while carcinoid crisis is a life-threatening condition characterized by excessive flushing, bronchospasm and hemodynamic instability that has to be urgently diagnosed and treated.[51] CT or MRI, CT/MRI water enteroclysis or endoscopic techniques and SRS or ^{68}Ga-DOTATOC PET can be helpful for the detection of the primary tumor and probable metastatic lesions while colonoscopy can detect tumors located in the terminal ileum. Serum CgA is a useful marker for the diagnosis and follow up of siNENs while urine 5-hydroxy indole acetic acid (5-HIAA), a product of the metabolism of serotonin, has 100% sensitivity and 85–90% specificity for detecting carcinoid syndrome.[52]

SiNENs are frequently multiple small lesions and have a great propensity to metastasize, as 80–90% of patients present with liver metastases at diagnosis. However, despite their malignant behavior most of them belong to the G1 histopathological group. All patients with siNENs should be considered candidates for curative resection.[52] Resection of the primary tumor and locoregional lymph node metastases along the superior mesenteric root and around the mesentery results in improved survival of patients with siNENs.[53] Owing to the frequent tumor multicentricity, complete preoperative imaging work-up and intraoperative palpation are required to achieve a curative resection. However, severe desmoplastic reaction around the artery may prevent complete resection. In patients with liver metastases surgery should still be attempted with a curative intent or as a palliative method to prevent complications attributed to tumor mass or reduce hormone related symptoms.[52] However, a recent retrospective study that included 363 asymptomatic patients with stage IV siNENs showed that

prophylactic locoregional surgery resulted to no significant survival advantage while delayed surgery was associated with fewer reoperations for intestinal obstruction.[54]

Locoregional or ablative therapies such as HAE, RFA or SIRT should be considered as an alternative option to control carcinoid syndrome or to treat nonfunctioning metastatic tumors in cases of disease limited to the liver.[50] Pre- and perioperative treatment with intravenous octreotide is required during surgery or other minor interventions to prevent a carcinoid crisis.[55]

SSAs, octreotide and lanreotide, are effective means for syndrome control in patients with functioning tumors but can also be used for antiproliferative purposes in the case of metastatic disease. Indeed, SSAs are recommended as first-line systemic therapy for the prevention or inhibition of tumor growth. Although there is no established Ki-67 cut-off value, SSAs are generally recommended for tumors with a Ki-67 of up to 10%, whereas patients with a less extensive tumor burden may have a better response. It remains however controversial whether SSAs should be started at diagnosis or after the observation of tumor growth and disease progression in the absence of a functioning syndrome.[56,57] Common adverse effects of SSAs include nausea, diarrhea, impairment of glucose tolerance and gallstone development. In the case of refractory carcinoid syndrome or uncontrolled syndrome, despite the proper use of all other treatment options, dose escalation of SSAs may be recommended.[58] In addition, a new synthetic analog, pasireotide, with high affinity for all SSTRs except $SSTR_4$, has been observed to be efficacious in cases of inadequate control with octreotide long-acting release (LAR).[59] Interferon-alpha (IFN-α) is a second-line option as add-on therapy to SSAs in cases of refractory carcinoid syndrome but may also be considered an option for tumor growth control. However, due to severe side effects, IFN-α is not well tolerated by all patients.[52,60] Telotristat etiprate is an oral inhibitor of the enzyme tryptophan hydroxylase, the rate-limiting step in the conversion of tryptophan to serotonin. According to recent studies, telotristat was associated with a significant decrease in bowel movement frequency and 5-HIAA levels and amelioration of flushing when prescribed in patients with inadequate symptom control despite treatment with SSAs. In addition, weight gain was observed in some patients.[61–63] Undesirable effects of telotristat include abdominal pain, nausea and a low rate of depression. Thus, telotristat can be recommended in cases of carcinoid syndrome refractory to SSAs while it can be assumed that the reduction of serotonin levels may limit the development of peritoneal and cardiac valvular fibrosis, but this needs to be further investigated.[61,62]

PRRT is a therapeutic option in progressive SSTR-positive small bowel NET as a second-line therapy after the failure of treatment with SSAs. The recently published NETTER-1 trial results showed significant prolongation of progression-free survival (PFS) and OS after treatment with ^{177}Lu-DOTATATE compared with treatment with increased dose of octreotide LAR.[50,64] Recent studies observed that patients with negative FDG-PET/CT showed a superior response to treatment with PRRT compared with patients with positive FDG-PET/CT.[65,66] Hence, a dual-tracer approach, assessing SSTR expression and glycolytic metabolism may lead to an individualized treatment of patients with progressive disease as patients with more aggressive FDG-positive tumors may benefit from combination of PRRT with radiosensitizing chemotherapeutic agents as capecitabine.[66–68]

The targeted drug, everolimus, is an mTOR inhibitor that is generally recommended as a second or third-line therapy for advanced siNENs after failure of SSAs or PRRT. However, everolimus is frequently associated with adverse events such as stomatitis, glucose intolerance or diabetes and pneumonitis that may limit its use.[50,69] The use of other targeted drugs such as sunitinib or bevacizumab is not recommended until the publication of the results of currently ongoing randomized clinical trials.

Systemic chemotherapy is not generally recommended for well-differentiated siNENs but in poorly differentiated tumors disease remission with variable duration has been observed after treatment with combination chemotherapy.[50,70] Recent data though have shown efficacy of temozolomide-based chemotherapy in carefully selected patients that have developed relatively early disease progression on first-line therapy, have extensive tumor burden, or relatively high Ki67 value, albeit being G2 tumors.[71–73]

Furthermore, liver transplantation may be an option in precisely selected patients with carcinoid syndrome and extended liver disease refractory to treatment with a combination of SSAs, IFN-α, PRRT or locoregional therapies.[74]

CHD develops in about 60% of patients with NENs and carcinoid syndrome and principally involves the right side of the heart.[75] The diagnosis and follow up of CHD is mainly based on two-dimensional echocardiography and Doppler examination while it is also recommended to measure N-terminal pro-brain natriuretic peptide (NT-proBNP), a neurohormone secreted by the atria and ventricles in response to increase in volume and pressure. NT-proBNP is considered to be a sensitive and specific marker for predicting CHD and is related to patient prognosis.[76] Treatment with SSAs and techniques that decrease the tumor load may limit the release of vasoactive agents and the development of heart failure but currently there is no evidence that progression of CHD can be prevented. However, telotristat etiprate could be a promising therapeutic or preventive measure for patients with CHD. Furthermore, general measures for heart failure such as loop diuretics, fluid and salt restriction and compression stockings may ameliorate the symptoms of right heart failure.[77] However, the definitive treatment is surgical valve replacement that if performed early is associated with low perioperative mortality. If cardiac valve surgery is not feasible, balloon valvuloplasty is an alternate option for tricuspid or pulmonary stenosis albeit with short term clinical benefit. In addition, the coexistence of a patent foramen ovale has to be ruled out and its closure performed prior to cardiac surgery.[77]

Patients with G1/G2 NENs that have been submitted to curative surgery should be followed up every 6–12 months with CgA and 5-HIAA measurement and conventional imaging studies. In patients with G3 tumors or metastatic disease shorter follow-up intervals are required. In the case of recurrence suspicion or after curative surgery of an unknown NEN prior to operation, SRI may be helpful.[52]

The prognosis of siNENs depends on histopathological grade and TNM staging and 5-year OS ranges between 50% and 60%. In siNENs with locally advanced disease 5-year survival reaches 80–100% while in the case of metastatic disease, survival ranges 35% and 80%.[50] Median OS after valve replacement varies between 6 and 11 years.[78]

Pancreatic NENs

Pancreatic NENs (pNENs) are neoplasms with an increasing incidence and represent less than 10% of all pancreatic tumors and around 10% of all NENs. A percentage of 60–90% are nonfunctioning while 10% occur as part of an inherited syndrome.[79–81] Functioning pNENs include mainly gastrinomas (Zollinger–Ellison syndrome), insulinomas, VIPomas, glucagonomas and somatostatinomas, while rarely pNENS that are associated with carcinoid or Cushing's syndrome have been reported.[82] MEN1 syndrome is the most important inherited condition related with pNENs while von Hippel Lindau, neurofibromatosis 1 and tuberous sclerosis have also been associated with p-NEN development.[83] Approximately 60–70% of patients present with liver metastases at diagnosis.[84]

The diagnosis of Zollinger–Ellison syndrome should be suspected in any patient presenting with peptic ulcers and diarrhea and is established by demonstration of hypergastrinemia in combination with increased basal gastric acid secretion (gastric pH$<$2).[82,85] Gastrinomas frequently develop as small multiple lesions in the duodenum and are rarely found in the pancreas. Patients suffering from insulinoma typically develop hypoglycemia while fasting or during exercise but sometimes symptoms may present postprandially. The diagnosis of endogenous hyperinsulinism requires a combination of hypoglycemia with increased insulin, c-peptide and pro-insulin levels.[82,85] Rare functioning tumors with characteristic clinical presentation include VIPomas and glucagonomas, whereas occasionally such tumors may also secrete serotonin.[86] Nonfunctioning pNENs are not related to specific symptoms and are usually discovered during imaging studies for other purposes and relatively late in the disease course.[84] Occasionally, paraneoplastic syndromes may develop from apparent nonfunctioning pNETs secondary to the ectopic secretion of bioactive compounds from such tumors.[87] In a recent study, it was observed that 16% of patients presenting with sporadic pNENs suffer from MEN1 while approximately 20% of patients with a gastrinoma will have MEN1.[88] Localization of tumors may be quite challenging especially in

cases of MEN1 since pNENs may be very small and multiple. A recent study showed that MRI and EUS play complementary roles in identifying pNENs in MEN1 patients since both miss a significant percentage of pancreatic lesions.[89] Imaging with ^{68}Ga-labeled SSAs with PET/CT is considered the most sensitive method for the localization and staging of pNENs.[90]

Patients with sporadic gastrinomas should have surgical exploration and removal of the tumor and regional lymph nodes with an intention to cure.[85] The role of surgery in treating patients with MEN1-related gastrinomas remains controversial since frequently, multiple tumors are developed and a complete tumor eradication is achieved in almost none of these cases.[82] Most centers indicate nonsurgical treatment for gastrinomas in MEN1 unless pancreatic lesions more than 2 cm are observed since the risk of metastases has been reported to increase and the prognosis to be deteriorated if lesions >2 cm are identified.[82,91] Proton-pump inhibitors are the drug of choice to control gastric acid hypersecretion in patients with gastrinoma. Monitoring for B12 deficiency and hypomagnesemia is recommended. Frequently, patients surgically cured may continue to suffer from gastrin hypersecretion and increased gastric output probably due to enterochromaffin-like cell (ECL) changes and it is also recommended to provide anti-secretory treatment although in lower doses.[82,85]

Surgical exploration with the intention to cure is recommended in all cases of insulinoma as these neoplasms are infrequently malignant (10%) and a high cure rate (98–100%) can be achieved. As insulinomas are usually small in size, preoperative localization with conventional imaging techniques (CT/MRI) may be challenging. EUS, PET/CT with ^{68}Ga-DOTATOC or with a radiolabeled GLP-1 agonist can be useful in this setting, while invasive modalities such as selective arterial catheterization and portal vein sampling after calcium stimulation can be utilized, especially in case of MEN1 and multiple pNENs. Surgery remains the treatment of choice in MEN1 patients with insulinoma and ranges from enucleation to distal or partial pancreatectomy or excision of the macroscopic tumors with enucleation of lesions in the remaining pancreas.[82,85] Prior to surgery, and in cases of tumor recurrence or malignant insulinomas, frequent small meals and treatment with diazoxide may be required to control hyperinsulinism. Approximately 30–50% of patients respond to SSAs but they should be used with caution because some patients may experience worsening of hypoglycemia due to the inhibition of counter-regulatory hormones.[92] In addition, recent studies have shown that everolimus can be an effective means for ameliorating hypoglycemia in cases of malignant insulinoma, while there is also a report of treatment of hypoglycemia with sunitinib.[93,94] Chemoembolization or antitumor treatment with PRRT (in SRS-positive cases) may also help control hypoglycemia.[85,95]

The management of small asymptomatic nonfunctioning pNENs (NF-pNENs) remains controversial. An increasing rate of metastases has been observed as the tumor size increases but there is no established consensus regarding the indications of surgery. Most centers recommend surgical excision of pNENs that are more than 2 cm in size. For tumors ⩽2 cm, either sporadic or in patients with MEN1, surgery is not generally recommended as the majority of these tumors do not change significantly during follow up.[85,96] However, further data are needed to confirm the safety of this approach. Enucleation or regional resection should be used when possible since pancreatoduodenal surgery is associated with significant complications that include diabetes mellitus, steatorrhea or other gastrointestinal symptoms.[97]

The management of sporadic pNENs generally is more straightforward as it is directed to the specific tumor and follows the same principles as the management of sporadic siNENs. In G1 or G2 pNENs surgery should always be considered with an intention to cure even in the presence of lymph node or liver metastases.[98–100] Debulking surgery is an option in patients with uncontrolled functional tumors or in case of NF-pNENS that remain stable during a 6-month period and cause symptoms attributed to tumor burden. However, it still remains unclear whether this approach is beneficial since there are no trials comparing the survival after surgical treatment and systemic therapy.[50]

Treatment with SSAs is recommended as first-line therapy for tumor growth control in cases of stable or progressive disease or in pNENs with unknown behavior and a Ki-67 preferably up to 10%. Although the antiproliferative effect of SSAs is considered a drug class effect, lanreotide Autogel is preferably recommended in pNENs,

based on the CLARINET study.[57] Although there is some controversy regarding the initiation of SSAs at diagnosis or if disease progression occurs most authorities initiate treatment with SSAs at diagnosis due to the relatively more aggressive behavior of these tumors compared with siNENs. A high tumor burden or extended disease are considered favorable factors for the early initiation of SSA treatment.[50]

The targeted agents, everolimus and sunitinib are recommended in progressive pNENs G1 or G2, generally after failure of SSAs or after chemotherapy. However, they may be used as first-line therapy if SSAs are not available and systemic chemotherapy is not required or tolerated. Careful follow up is required for potential toxicity.[50,70,101]

Systemic chemotherapy is recommended in G1 or G2 pNENs with a high tumor burden or significant tumor progression in <6–12 months and in G3 NENs.[48] STZ/5-FU and temozolomide as monotherapy or combined with capecitabine are the two regimens indicated for treatment of G1, G2 or G3 NETs.[72,102,103] In G3 NECs, cisplatin-based chemotherapy is indicated as a first-line treatment while FOLFOX or FOLFIRI are considered second-line options.[23,71,104]

There is no established indication for the use of PRRT in patients with pNENs. However, treatment with PRRT is generally recommended in the case of failure of targeted agents or chemotherapy. In addition, locoregional therapies such as HAE, RFA or SIRT should be considered as an alternative option in case of disease limited to the liver.[50]

Follow up of patients with G1/G2 tumors during treatment should be done every 3–9 months and involve measurement of biochemical markers and conventional imaging. SRI should be performed every 2 years or in case of suspicion of recurrence or progression.[83]

The median OS of patients with pNENs is approximately 38 months and the 5-year survival rate is 43%. The presence of distant metastases and the degree of differentiation are the most significant predictors of survival.[105,106]

Colorectal NENs

The incidence of colorectal NENs has been continuously increasing and has been documented to be approximately 0.2 and 0.86 per 100,000 for colonic and rectal NENs respectively.[3] Colonic NENs are often aggressive and metastatic at diagnosis while rectal NENs are frequently small of low to intermediate grade and are associated with a long-term survival.

NENs of the colon are treated in a similar way with adenocarcinomas and a localized colectomy with oncological resection of regional lymph nodes is often required. However, tumors of size <2 cm can be resected endoscopically or with EMR. In some cases, surgical removal of the primary lesion may be required even in metastatic disease to avoid intestinal obstruction.[107,108]

Rectal lesions <1 cm are associated with low risk for metastases and may be completely resected endoscopically. EUS should be used to determine the depth of invasion while pelvic MRI is considered to be most accurate in determining local lymph node status.[105] According to a recent meta-analysis, ESD results to higher rates of complete resection comparing to EMR.[109] Lesions between 1 and 2 cm display a risk of metastases of approximately 10–15%. However, despite the lack of strong evidence local resection is recommended if the mitotic index is low and no invasion of the muscularis propria is observed. Lesions >2 cm frequently invade the muscularis propria and are associated with a high metastatic rate. So, for these lesions, stage T3 or T4, with regional lymph node involvement or of G3 grade, treatment as adenocarcinoma is recommended.[108,110] However, a recent retrospective study indicated that resection of the primary tumor in high-grade colorectal NENs did not correlate with an improved prognosis.[111] Nevertheless, due to the retrospective nature of this study and the large clinicopathologic and treatment-related heterogeneity of patients included in the analysis, the role of primary tumor resection would be more precisely addressed in the context of prospective randomized studies but this would not be easily feasible. So, individual cases of G3 NEC have to be discussed in the context of multidisciplinary meetings for surgery in combination with neoadjuvant or adjuvant chemoradiotherapy as indicated.[25]

There is not enough evidence for the use of SSAs in metastatic colorectal NENs except for rare cases of carcinoid syndrome. As indicated by the RADIANT-2 trial the combination of SSA with

everolimus was associated with an increased PFS compared with SSAs with placebo in G1 or G2 tumors.[112] In metastatic G1 or G2 NEN chemotherapy or PRRT may be considered, while chemotherapy is the only recommended treatment for G3 NECs.[23,25,108]

A follow-up strategy after a curative endoscopic or surgical removal depends on tumor size and grade. Regular follow up is required in all tumors >2 cm and should involve one endoscopy, imaging scan and tumour marker evaluation within the first year. There are no data to recommend follow up for smaller lesions but in case of negative prognostic factors (G3 tumor, lymph node involvement, invasion of muscularis) an individualized schedule should be followed.[108]

Appendicial NENs

Appendicial NENs are often incidentally discovered during appendicectomy and represent the most common neoplasm of the appendix.[113,114] Despite the fact they are generally considered indolent, approximately 49% display lymph node metastases while 9% present with distant metastases. The risk of distant metastases is associated with tumor size and is considered significantly increased for tumors >2 cm.[3,115]

Tumors <1 cm and fully resected require no further follow up, while for tumors with maximal diameter between 1 and 2 cm abdominal imaging to rule out locoregional or metastatic disease may be considered. For tumors >2 cm or with angioinvasion and infiltration of the mesoappendix further imaging with abdominal CT/MRI and SRS or ^{68}Ga-DOTATOC PET is recommended.[114]

The mainstay of treatment of appendicial NENs is surgical and involves simple appendicectomy or right hemicolectomy. Well-differentiated tumors of maximal diameter 2 cm with clear resection margins and no vascular or mesoappendicial invasion can be cured by single appendicectomy. However, tumors with positive or unclear margins, deep mesoappendicial infiltration (>3 mm) or angioinvasion, G2 or G3 tumors and all tumors of maximal diameter >2 cm should be treated with right hemicolectomy.[114] However, a recent study showed that 1 cm is a more appropriate cut-off compared with 2 cm for predicting lymph node metastases, but the excellent prognosis of well-differentiated NENs with nodal involvement does not seem to be further improved by right hemicolectomy.[116]

For patients with totally resected well-differentiated NENs of maximal diameter <1 cm no regular follow up is suggested. In addition, no specific follow up is recommended after curative resection of well-differentiated tumors of 1–2 cm except for cases with risk factors. However, regular follow up is recommended for patients with tumors >2 cm, metastasis or R1 resection every 6 months for the first year and then annually. Unfortunately, there are no studies determining the sensitivity of tumor markers or imaging studies for detection of disease recurrence or metastases and no established protocol is recommended.[114]

The 5-year survival rate for appendicial NENs is approximately 100% for low tumor stages but falls to 12–28% in the case of distant metastases.[3,117,118]

Pulmonary NENs

Lung neuroendocrine tumors are rare neoplasms that display significant heterogeneity ranging from well-differentiated tumors to poorly differentiated small cell lung cancer. Their incidence has been calculated approximately to 1.57/100,000 inhabitants.[119] The WHO classification of bronchial NENs is based on a combination of mitotic index and the presence of necrosis. Thus, lung NENs are divided in five subtypes: typical carcinoid (TC; <2 mitoses per 2 mm^2 field without any necrosis), atypical carcinoid (AC; 2–10 mitoses per 2 mm^2 field and presence of focal necrosis), large cell neuroendocrine lung carcinoma (LCNEC), small cell lung carcinoma (SCLC) and miNEN.[7,120]

The most common clinical symptoms include cough, hemoptysis, recurrent respiratory infections and wheezing while rarely lung NENs can be associated with carcinoid or Cushing's syndrome.[118] More than 40% of these tumors are incidentally detected during chest X-ray but the gold standard imaging study is chest CT.[119–121] Bronchoscopy is indicated in lesions located centrally and enables histological diagnosis while SRS, ^{68}Ga-DOTATOC PET and FDG-PET/CT may be useful for staging the disease. A brain MRI should also be recommended especially in more aggressive tumors.[119–122]

The only curative treatment of bronchial NENs is surgical resection. Complete anatomic resection with systemic nodal dissection is considered the best choice in patients with peripheral tumors while in patients with centrally located tumors lung parenchymal sparing techniques should be preferred over pneumonectomy.[119] Currently, there is no recommendation for adjuvant treatment after complete resection. Locoregional recurrence can be observed even 10 years after initial resection and re-do surgery is a possible choice of treatment.[123,124] Surgery is not generally recommended in LCNEC and SCLC due to local or systemic spread but in some cases of early-stage localized LCNEC may improve survival.[125] In the presence of liver metastases, surgery should be considered with an intention to cure or to control symptoms in case of functioning tumors. This can be recommended in patients with TC or low-grade AC with no right heart insufficiency or unresectable extra-abdominal disease.[121]

There are not enough trials to guide medical treatment of advanced pulmonary NENs and any recommendations are extrapolated from studies of digestive NENs. SSAs may be used as antitumor treatment of patients with tumors of low proliferation index, low tumor burden and positive SRS according to recent prospective and retrospective trials that included lung NENs.[126,127] The RADIANT 2 trial showed a clear benefit of everolimus compared with placebo in the treatment of functioning NENs, including pulmonary, while RADIANT 4 observed a prolonged PFS after treatment with everolimus in a subgroup of patients with lung NENs.[128,129] Finally, the most recently presented LUNA study showed a significantly increased PFS after treatment with the combination of everolimus and pasireotide.[130] Overall, it seems reasonable to recommend treatment of advanced progressive and nonfunctioning tumors with everolimus.

Many cytotoxic drug combinations have been used in patients with lung NENs. Temozolomide alone or in combination with capecitabine has been proved effective while other options include streptozotocin/5-fluorouracil and cisplatin/etoposide for more aggressive tumors.[131]

The data regarding the use of PRRT in treating patients with pulmonary NENs are scarce. A retrospective trial showed a 28% response after treatment with PRRT in 84 patients with lung NENs. Based on these data PRRT may be considered a therapeutic option in selected patients with progressive TC or AC and strong expression of SSTRs.[121,131]

Patients with functional tumors need appropriate treatment to control symptoms. SSAs represent the gold standard of treatment of carcinoid syndrome while they can also be used in ectopic Cushing syndrome. Cushing syndrome may also be treated with specific agents involving ketoconazole, metyrapone, mifepristone or etomidate while bilateral adrenalectomy is an option in cases of refractory syndrome that is life-threatening. Locoregional therapies, PRRT or IFN-α are additional therapeutic options for functioning syndrome control.[121,132]

After curative resection of a TC, conventional imaging studies and CgA measurement are recommended at 3 and 6 months and then annually for the first 2 years. Closer monitoring may be required in case of R1 resection or lymph node infiltration as well as for AC. SRI is suggested at 12 months and then in case of suspicion of recurrence. In case of tumors with high proliferative index, FDG-PET/CT may be helpful.[122]

Prognosis differs widely between typical an atypical lung NENs. TCs are associated with 10-year survival of approximately 82–100% while ACs are 18–74%. For small cell, large cell and miNENs the prognosis of patients is very poor and combination therapeutic strategies including chemotherapy and radiotherapy may apply.[25]

Conclusion

NETs are rare neoplasms that represent a clinical challenge due to heterogeneity of their biological behavior, diagnosis and treatment options. The choice of therapy should be individualized according to symptoms, tumor type, disease burden and occasionally the presence of a familial syndrome while the patient's performance status is also a determining factor (Figure 3). Traditional therapeutic options include surgery, chemotherapy and SSAs. However, recent trials have changed the management of NENs towards more sophisticated options including targeted agents and PRRTs. A multidisciplinary approach is considered necessary for the optimal management of patients with NETs. Although several therapeutic algorithms have been developed, treatment is also

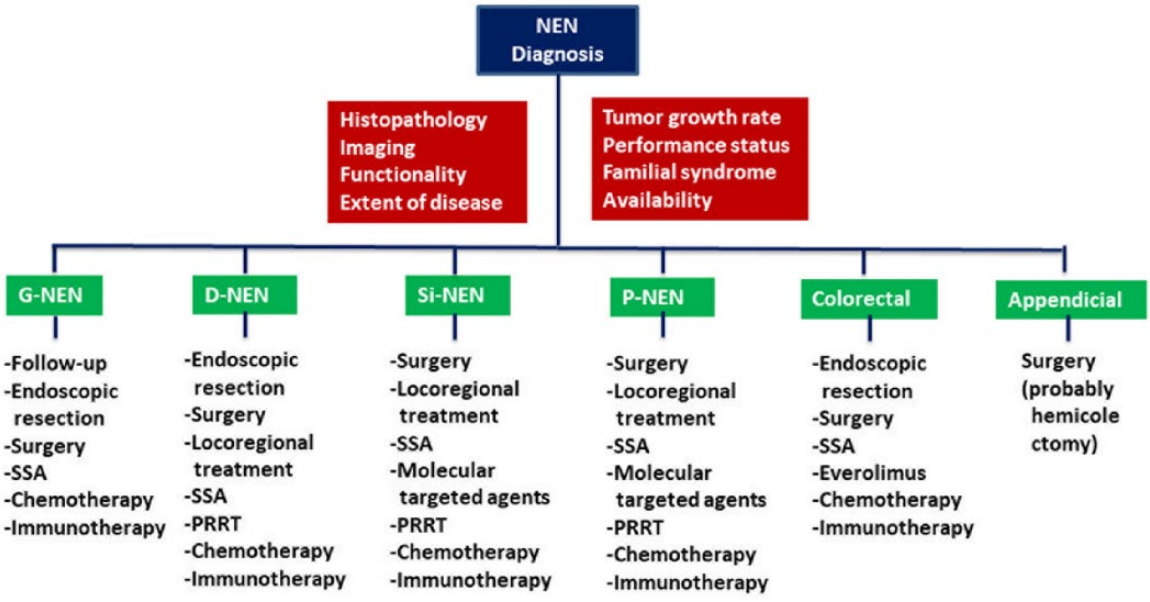

Figure 3. Possible therapeutic modalities in management of NENs.
NEN, neuroendocrine neoplasm.

determined by patient preference for specific treatments, the disease clinical course, and local availability of treatment modalities. Hopefully, advances in the pathogenesis of these tumors will lead to the application of tumor specific therapies in the form of personalized medicine to increase efficacy and ameliorate potential treatment-related side effects.

Author contributions

All authors contributed equally to the design of the study, data collection, analyses and drafting of the manuscript. All authors read and approved the final version of the manuscript.

Ethical Approval

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