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Pancreatic Neuroendocrine Tumors: from diagnosis to therapeutics

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Resumo

Introdução

Os tumores neuroendócrinos do pâncreas são um grupo heterogéneo de neoplasias, cuja incidência tem vindo a aumentar nas últimas décadas. Surgem habitualmente na sexta ou sétima décadas de vida e afetam ambos os géneros igualmente.

São classificados como funcionais, quando as hormonas excretadas produzem sinais e sintomas ou como não-funcionantes, descobertos incidentalmente.

O estudo diagnóstico incorpora a apresentação clínica, analítica e imagiológica dos tumores neuroendócrinos do pâncreas, sendo que este varia consoante o tipo de tumor. Apesar disto, o diagnóstico definitivo só é possível após a análise imunohistoquímica do tumor.

Objetivos

Salientar a importância do diagnóstico precoce destes tumores, assim como apresentar a evidência mais recente no que diz respeito ao diagnóstico e tratamento.

Metodologia

A pesquisa foi realizada através da base de dados do PubMed, utilizando as palavras chave "pancreatic neoplasms" e "neuroendocrine tumors". Artigos de investigação dos últimos 10 anos e escritos em inglês foram incluídos. Foram excluídos todos os que não se relacionavam com os propósitos desta revisão. Sempre que pertinente e excecionalmente, artigos de revisão e guidelines foram incluídos.

Resultados

A abordagem cirúrgica deve ser considerada como tratamento de primeira linha. Somente nos tumores assintomáticos e inferiores a 2 cm, a abordagem conservadora deve ser ponderada.

Os tratamentos médicos são úteis para controlo sintomático, assim como para evitar a progressão tumoral, principalmente em tumores irressecáveis ou metastizados.

Conclusão

Uma abordagem multidisciplinar é essencial para acompanhar corretamente estes doentes, visto que várias áreas da medicina estão envolvidas desde o diagnóstico à terapêutica.

Palavras-chave: "pancreatic neoplasms", "neuroendocrine tumors".

Abstract

Introduction

Pancreatic Neuroendocrine Tumors are an heterogenous group of neoplasms, which incidence has been increasing in the last decades. They usually appear in the sixth and seventh decades of live and affect both genders equally.

They are classified as functional when the hormones secreted produce typical signs and symptoms or as nonfunctional, incidentally found.

The diagnostic workup includes the clinical, analytical and imaging presentation of pancreatic neuroendocrine tumors, which varies according to the type of tumor. Besides that, the definite diagnosis is only possible after immunohistochemical analyses of the tumor.

Goal

The aim of this literature review is to highlight the importance of recognizing these tumors, as well as presenting the most recent evidence in terms of diagnostic and management.

Methods

The PubMed database was searched using the following medical subjects heading (MeSH) terms: “pancreatic neoplasms” and “neuroendocrine tumors”. Clinical trials and studies of the last 10 years and written in English were included. Articles whom were not related to this review were excluded. Review articles and guidelines were included exceptionally, whenever pertinent.

Results

Surgical approach must be considered as first-line treatment. Only in asymptomatic and smaller than 2 cm tumors, conservative management can be weighted.

Medical therapies are useful to symptomatic control, as well as antitumor purposes, mainly in advanced tumors with unresectable primary and metastatic disease.

Conclusion

A multidisciplinary approach is essential to correctly manage these patients, since many fields of medicine are included from diagnoses to treatment.

Keywords: “pancreatic neoplasms”, “neuroendocrine tumors”.

List of Abbreviations

5-FU – 5-fluorouracil

CAP – Capecitabine

CgA – Chromogranin A

CT – Computed Tomography

ENETS - European Neuroendocrine Tumor Society

EUS – Endoscopic Ultrasound

FDG – ^{18}F-fluorodeoxyglucose

F-pNETs – Functioning Pancreatic Neuroendocrine Tumors

FSG – fasting serum gastrin

HPF – High power fields

MEN1 - Multiple Endocrine Neoplasia type 1

MiNEN – Pancreatic Mixed Neuroendocrine-non-neuroendocrine Neoplasms

MRI – Magnetic Resonance Imaging

mTOR – Mammalian target of rapamycin

NF-pNETs – Nonfunctioning Pancreatic Neuroendocrine Tumors

OS – overall survival

PET – Positron Emission Tomography

PFS – Progression-free Survival

pNEC – Pancreatic Neuroendocrine Carcinoma

pNET – Pancreatic Neuroendocrine Tumor

PPIs – Proton Pump Inhibitors

PRRT – Peptide Receptor Radionuclide Therapy

SPECT – Single-photon Emission Computerized Tomography

SRS – Somatostatin Receptor Scintigraphy

SSA – Somatostatin Analogue

SSTR – Somatostatin Receptor

STZ – Streptozotocin

TEM – Temozolomide

TKI – Tyrosine Kinase Inhibitor

VIP – Vasoactive Intestinal Polypeptide

ZES – Zollinger-Ellison Syndrome

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Introduction

Pancreatic Neuroendocrine Tumors (pNETs) are a group of rare, heterogenous[1] and indolent growing neoplasms[2]. Due to this indolent growth, they are detected in advanced stages, resulting in high rates of mortality and morbidity[3]. Their heterogeneity is related to clinical, functional and pathologic characteristics[4].

According to the Surveillance, Epidemiology and End Results program of the National Cancer Institute, the incidence has been increasing in the last decades from 1,09 to 5,25 per 100,000 people from 1973 to 2004[5]. Primarily because of the high-quality imaging performed, detecting incidental asymptomatic small lesions, as well as earlier therapeutic interventions and improvement of treatment techniques. However, pNETs represent only 12,1% of all neuroendocrine tumors in the digestive system[6] and 1 to 2% of all pancreatic malignancies[1].

The islets of Langerhans[3] appear to be where such neoplasms emerge, while some authors defend they arise from the pancreatic duct epithelial cells[1].

Older patients, mainly between 60 to 70 years[7], regardless of gender[1], are the most affected by these tumors. Apart from family history in first-degree relatives, no definitive risk factors have been postulated for neuroendocrine tumors of the pancreas[6].

Usually, pNETs occur as sporadic tumors and a minority is related to inherited syndromes, as Multiple Endocrine Neoplasia type 1 (MEN1), Zollinger-Ellison syndrome (ZES), Von Hippel Lindau disease[2], tuberous sclerosis and neurofibromatosis. Whenever inherited, they are multifocal and appear 10 to 20 years earlier than sporadic ones[8].

Pancreatic neuroendocrine tumors can be classified in either functioning (F-pNETs) or nonfunctioning tumors (NF-pNETs), much more prevalent (60 to 90%). Both tumors can secrete diverse biogenic amines and peptide hormones[6], for example, pancreatic polypeptide, chromogranin A, insulin or gastrin. When those hormones cause signs and symptoms resulting in known clinical syndromes, they are classified as functioning tumors. The main examples and more prevalent functioning pNETs are insulinomas and gastrinomas, secreting insulin and gastrin, respectively. Nonfunctioning tumors can also cause symptoms, usually due to the mass effect of the tumor, invasion of proximal structures or metastatic disease[7].

Not only diagnosis but also treatment of pNETs have recently changed, making the management of these patients challenging[4].

Objectives

Despite the rarity of these pancreatic neuroendocrine tumors, their increased incidence and the continuum of changes in diagnosis and management of patients, requires constant physicians' update.

Thus, this bibliographic review aims to reunite current information about managing pNETs, including epidemiology, pathophysiology, diagnosis and treatment.

Methodology

A comprehensive review of the literature was undertaken for the purposes of this bibliographic review. The PubMed database was searched using the Mesh words "pancreatic neoplasms" combined with "neuroendocrine tumors", published in the last 10 years (from April 2010 until April 2020). Only clinical studies and clinical trials in humans were selected, written in English. Articles whom were not related to the purpose of this review, were excluded.

Studies about gastroenteropancreatic neuroendocrine tumors were included, since they included pNET patients. Review articles were utilized exceptionally, to describe the epidemiology, physiopathology mechanisms and clinical presentation of pNETs, such as European treatment guidelines by European Neuroendocrine Tumor Society (ENETS) and European Society for Medical Oncology (ESMO).

Clinical Presentation

Clinically, pNETs are divided into functional or non-functional, according to their capacity of producing signs and symptoms related to an excessive hormonal secretion[9].

Starting by the most common, NF-pNETs are mainly diagnosed incidentally when patients are submitted to imaging techniques because they grow slowly and only manifest symptoms later on the course of the disease[2]. These symptoms, when present, are related to mass effect and usually are nonspecific, as abdominal pain, weight loss, anorexia or nausea[10].

There are many types of F-pNETs, all described in table I, being insulinomas and gastrinomas the most frequent.

The pancreas is the almost exclusive site of origin of insulinomas, which are benign in 90% of the cases. These tumors produce insulin, resulting in the Whipple's triad. This triad is confirmed when there is a documentation of low plasma glucose levels, the presence of hypoglycemic symptoms or signs and the relief of symptoms with increased plasma glucose[2]. Mainly when fasting or exercising, hypoglycemia in central nervous system manifests as visual disturbances, confusion or headaches; or by catecholaminergic response with tremor, palpitations or sweating associated.

Gastrinomas secrete gastrin and produce the Zollinger-Ellison syndrome, which, due to the gastric acid excess, causes peptic diseases as gastroesophageal reflux and peptic ulcer disease[9], leading to abdominal pain and diarrhea. Gastrinomas should be suspected, mainly in patients with multiple or complicated ulcers, with uncommon locations[1]. Their incidence is 0,5 – 21, 5/ million population/ year and most of them are malignant (60 to 90%), although only 25% of gastrinomas arise from the pancreas[2].

Vasoactive intestinal polypeptide (VIP) inhibits electrolyte and water absorption and stimulates intestinal secretion, therefore, VIPomas cause the Verner-Morrison syndrome or the WDHA syndrome, characterized by profuse watery diarrhea as well as hydroelectric imbalance, including hypokalemia and achlorhydria.

Glucagonomas secrete glucagon, inducing hyperglycemia, weight loss, venous thromboses, glossitis and necrolytic migratory erythema, which is a specific dermatitis characterized by erythematous macules, papules or plaques, that progressively enlarge and necrose[6].

Somatostatinomas are rare F-pNETs that produce somatostatin, leading to the development of Diabetes Mellitus, cholelithiasis and diarrhea, and almost half of them are associated with MEN1 syndrome[2]. Even though they are classified as functional and associated with a known clinical

syndrome, there is one study where none of the 821 participants with duodenal or pancreatic NETs had all the signs and symptoms described as the somatostatinoma syndrome, suggesting there might be a different clinical syndrome[11].

Diagnosis

Definitive diagnosis is only achieved after immunohistochemical examination of the tumor, however, blood testing and imaging methods play an important role in the diagnostic workup. The order in which these tests are performed varies according to clinical presentation.

Biochemical investigation

Biochemical testing includes pNET biomarkers, as well as the specific hormone produced by the suspected F-pNET[10], which, if elevated, should be monitored over time since it correlates with progression and response to treatment[6].

Chromogranin A (CgA) is a commonly used biomarker, since it is present in the secretory granules of neuroendocrine cells and associated with survival and tumor burden[10]. However, in insulinomas, it is not a useful serum marker, since it´s specificity decreases from 92% in non-insulinoma pNETs to 73% in insulinomas[12]. In contrast, when it comes to NF-pNETs, CgA is important, not only evaluating disease progression, but also treatment response and recurrence[13].

Despite being less sensitive, pancreastatin, which derives from CgA, is another useful biomarker. Neuron-specific enolase, chromogranin B and pancreatic polypeptide are other potential biomarkers, although they are less validated than CgA[10].

A novel polymerase chain reaction-based test, the NETest, is a blood-based multianalyte NET gene transcript measurement created for diagnostic and surveillance purposes for neuroendocrine neoplasms. Although this assay is more sensitive (94%) and specific (96%) than CgA, the associated costs decrease its use in clinical practice[14].

Concerning insulinomas, after the confirmation of the Whipple's triad, a 72-hour fasting plasma glucose test should be performed[2]. The test is considered positive when in presence of symptoms and/or signs of hypoglycemia plus plasma glucose concentration less than 55 mg/dl (3,0 mmol/l), insulin equal or higher than 3,0 μU/ml (18 pmol/l), C-peptide equal or higher than 0,6 ng/ml (0,2 nmol/l), proinsulin equal or higher than 5,0 pmol/l, β-hydroxybutyrate equal or less than 2,7 mmol/l and an increase in plasma glucose of at least 25 mg/dl (1,4 mmol/l) after intravenous glucagon[15].

When suspecting a gastrinoma, the fasting serum gastrin (FSG) levels should be measured first. If they are not elevated, gastrinoma is unlikely. Only in high suspicion cases, gastrinoma resection should be performed and FSG repeated. If it is still not elevated, but the suspicion is maintained, a secretin test is recommended.

On the other hand, if the FSG levels are elevated, we should measure gastric pH next. If pH is higher than 2, without acid-suppressive drug, gastrinoma is not present; if the patient takes these drugs, he should repeat the gastric pH measurement with lesser dosages per day or less quantity per dose. If not successful, the patient must be referred to a specialty center or initiate an H2 receptor antagonist, stop the acid-suppressive drug and repeat both measures.

If pH is less than 2, we can diagnose gastrinoma either when the FSG is ten-fold increased and a retained antrum is excluded or when the FSG is less than ten-fold increased, which occurs in 60% of patients, but the provocative test is positive[2]. In addition, a basal acid output test should be performed, confirming the diagnosis of gastrinoma, when the result is greater than 15 mEq/h[1].

In fact, the widespread use of acid-suppressive drugs, such as proton pump inhibitors (PPIs), has difficulted the correct diagnose of gastrinoma, due to their long duration of action and the fact that they lead to hypergastrinemia, resulting in false positives[2]. Nevertheless, their withdrawal is contraindicated because it can cause peptic complications in gastrinoma patients[16]. After diagnosing a gastrinoma, we should evaluate the presence of MEN1, by measuring plasma PTH, ionized Ca^{2+} and prolactin levels, since 20 to 25% are associated with that syndrome[2].

Patients presenting with unexplained secretory diarrhea and VIP levels higher than 75 pg/dL enable VIPoma diagnosis, however significant elevations, for example, VIP levels higher than 200 pg/dL, may be enough[17].

If serum glucagon levels are higher than 500/1000 pg/mL, a glucagonoma can be diagnosed, nevertheless, a single measure may not be enough, since glucagon secretion may be episodic[18].

For somatostatinomas, the diagnosis is made when somatostatin levels are more than three times higher than normal. Whenever the results are indeterminate, meaning, greater than normal but less than three times higher than normal, provocative tests, such as secretin or calcium stimulations tests are useful[19].

Localization/ Imaging studies

The first imaging exam to be performed must be the Computed Tomography (CT), since it is widely available and has high reproducibility rates. However, Magnetic Resonance Imaging (MRI) has

approximately 79% sensitivity to diagnose pNETs and it is currently used as part of the preoperative studies[8], due to its superiority when it comes to detect liver metastases[10].

On MRI, pNETs appear as hypointense on fat-suppressed T1-weighted sequences, in contrast, they are hyperintense on fat-suppressed T2 and diffusion images. After gadolinium, the lesion enhances, becoming isointense[20]. A retrospective observational study postulated certain morphologic characteristics in the MRI as the "duct-road sign" that may indicate the presence of a pNET. Those characteristics were "a straight road", when the main pancreatic duct wasn´t dislocated; "a typical curved road", when the displaced main duct passed around the pancreatic body or neck; and finally, the "atypical curved road", when distal or proximal main pancreatic duct displacement was observed in head or tail located pNETs[21].

Functional imaging using Positron Emission Tomography/Computed Tomography (PET/CT) with ^{68}Ga-labeled somatostatin analogues are the method of choice to localize non-insulinoma pNETs, due to high sensitivity (93%) and specificity (91%)[2], since only 50 to 70% of insulinomas express somatostatin receptors[22].

Somatostatin Receptor Scintigraphy (SRS) with Single-photon Emission Computerized Tomography (SPECT) and endoscopic ultrasound (EUS) should be considered as second-line diagnostic imaging methods[2]. EUS is useful when in presence of smaller pNETs, enabling biopsies for histopathologic exam[8], moreover, when combined with CT, they may reach 100% sensitivity for the localization of insulinomas[23].

According to recent guidelines, after diagnosing an insulinoma, an MRI or a CT scan must be performed first, in order to localize the tumor. If there are no visible lesions, an EUS should be ordered and finally, a Glucagon-like Peptide 1 scan or an Arterial Stimulation Venous Sampling should be considered last[2].

Metastatic disease is present in 21 to 80% of patients at the time of diagnosis and the most affected organs are the liver (40 to 93%), bones (12 to 20%) and lungs (8 to 10%)[24]. Concerning liver metastases, they are hypervascular as the primary lesion, appearing as hypodense on CT, enhancing during arterial and portal phases[25]. On MRI, they also present similarly as the primary lesion, hypointense on T1, hyperintense on T2 and show restricted diffusion on diffusion-weighted images. After gadolinium, they demonstrate arterial enhancement and washout[26]. Fast spin-echo T2-weighted and hepatic arterial phase are the most sensitive sequences[27], comparing imaging techniques, MRI has higher sensitivity than CT[28].

Pathology

In order to confirm the presence of a pNET, an immunohistochemistry and histologic examination of the tumor is essential. Whenever possible, preoperative analyses should be performed, either by fine needle aspiration and EUS examination or percutaneous core needle biopsy of potential liver metastases, and then confirmed by the examination of the surgical resection piece[10].

Therefore, once a neuroendocrine tumor is suspected, an immunohistochemical analysis is made for detection of neuroendocrine biomarkers as synaptophysin or CgA[8], as well as markers indicative of pancreatic primary tumor in liver tissue as PAX6 (paired box 6), PAX8 (paired box 8) and ISL1 (insulin gene enhancer protein 1)[10].

Molecular genetics

A study found four dysregulated signaling pathways typical from pNETs, which include mammalian target of rapamycin (mTOR) activation, telomere maintenance, chromatin remodeling and DNA damage repair[29]. Despite that, there is still unknown the exact sequence of gene mutations that lead to a neuroendocrine tumor[6].

Genetic studies targeting death domain-associated syndrome/α-thalassemia mental retardation syndrome (DAXX/ATRX) or p53/RB mutations can help discriminating pNETs from neuroendocrine carcinomas, respectively[8]. Chromosome instability due to loss of genes DAXX or ATRX is associated with poorer survival[30], however these studies should only be performed when a genetic syndrome is suspected[2].

Classification, grading and staging systems

The two most important independent prognostic factors are tumor grading and staging, therefore their assessment is mandatory and of paramount relevance[8].

Classification

According to the 2017 WHO classification (Table II), pancreatic neuroendocrine neoplasms can be classified in well-differentiated pancreatic neuroendocrine tumors (pNETs), poorly differentiated pancreatic neuroendocrine carcinomas (pNECs) and pancreatic mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs), depending on cell morphology. When the cells produce hormones, have negligible atypia, no necrotic evidence and express neuroendocrine differentiation markers such as intense synaptophysin or CgA staining, we classify the tumor as well-differentiated. On the other hand, when there is a clear presence of atypia with slight staining of the

neuroendocrine differentiation markers, the tumor is classified as poorly differentiated. Pancreatic MiNENs represent mixed acinar or ductal cell carcinoma with pNETs or pNECs.

Grading system

In well-differentiated tumors, they will be graded based on their Ki-67 index, which correlates with cell proliferation and disease prognosis, and number of mitoses per 10 high power fields (HPF). Whenever discordant, the higher grade must be attributed. Thus, well-differentiated neoplasms are divided into 3 grades, defined numerically, in which low-grade (grade 1/G1) tumors have a mitotic rate from 0 to 2 per 10 HPF or a Ki-67 index less than 3%; intermediate-grade (grade 2/G2) tumors have a mitotic rate from 2 to 20 per 10 HPF or a Ki-67 index between 3% and 20% and high-grade (grade 3 /G3) tumors have a mitotic rate greater than 20 per 10 HPF and a Ki-67 index greater than 20%.

In contrast, poorly differentiated neoplasms all belong to grade 3, having more than 20 mitoses per 10 HPF and a ki-67 index higher than 20%, and are divided based on the size of tumor cells, small-cell type and large-cell type[4].

Concerning 5-year survival, G1, G2 and G3 pNETs have respectively, rates of 75%, 62% and 7%[6], revealing worse prognosis for higher grading.

Staging system

Then, well-differentiated pNETs must be staged using the ENETS tumor, node and metastasis (TNM) staging system (Table III). There are 4 T (primary tumor) stages: T1 stage when the tumor is smaller than 2 cm and confined to pancreas; T2 stage when the tumor is also confined to the pancreas but between 2 to 4 cm in size; T3 stage when the tumor is larger than 4 cm or invades duodenum or bile duct; finally T4 stage when it invades contiguous organs or main vessels. Concerning the N (regional lymph nodes), N0 when there are no regional lymph node metastases and N1 when there are. Finally, related to M (distant metastases), the M0 when there are no distant metastases and M1 when there are[4].

The median overall survival (OS) for pancreatic neoplasms is approximately 3,6 years, more specifically, up to 20 years in localized disease and up to 12 years in grade 1 tumors, in contrast only 21 months in advanced disease and 15 months in grade 3 tumors. However, the metastatic pNETs have demonstrated the higher increase in OS from 2004 to 2012[31].

Even though definitive classification is obtained by resection specimens or core biopsies, several imaging features can help predict histologic grading. In CT, neuroendocrine carcinomas are typically larger than pNETs, present with bile duct dilatation and vascular invasion, appearing as

hypoenhanced when compared to contiguous pancreatic parenchyma, especially on portal venous phase imaging, whereas pNETs appear as well-enhanced in both arterial or portal venous phase imaging, since they are highly vascularized lesions[32]. Additionally, "progressive enhancement" or "early enhancement and plateau" patterns in tumors are associated with more fibrosis and worse prognosis compared with those with the "early rapid enhancement with washout" pattern[33]. Functional imaging studies as SRS and ^{18}F-fluorodeoxyglucose Positron Emission Tomography (FDG-PET) can also help to distinguish tumors. As SRS evaluates the quantity of somatostatin receptor expressed on the surface of the tumor, well-differentiated tumors will appear as strongly positive , whilst in FDG-PET, since it indicates glucose metabolism, poorly differentiated carcinomas will demonstrate high FDG uptake[34]. In conclusion, a well-differentiated pNET will present as well-enhanced in CT, strongly positive in SRS and with little or no FDG uptake, whereas a poorly differentiated carcinoma will appear as an hypoenhanced in CT, low uptake on SRS and high FDG uptake[35].

Moreover, in well-differentiated pNETs, preoperative calcifications on CT scans are associated with lymph node metastases and intermediate grade[36].

Management

In well-differentiated pNETs, surgical approach should be the first line treatment in patients with locoregional tumors or in those with metastasis when complete resection is feasible, and the tumor is symptomatic[37].

For the rest of patients with unresectable metastatic tumors, there are two options: if asymptomatic, with low tumor volume and stable disease, the patient can be managed conservatively or with octreotide; when the patient is symptomatic, with high tumor volume or has progressive disease he can be managed by medical therapies as octreotide, everolimus or sunitinib, cytotoxic chemotherapy, transarterial embolization, ablative therapy, cytoreductive surgery or Peptide Receptor Radionuclide Therapy (PRRT)[4]. Plus, a palliative resection of the pancreatic body or tail may be discussed in low surgical risk pNETs with Ki-67 index less than 10%[8], since the 5-year survival rates reaches up to 90% compared to non-surgical treatments[38].

Since there are no large comparative trials, the treatment's choice should take into consideration several features, as tumor characteristics and physicians' experience[39].

Concerning neuroendocrine carcinomas, since they have similar characteristics as those in small-cell lung cancer[40], the management is alike, using a combination of platinum and etoposide[41]. When

they are resectable, either the patient is submitted to resection and then adjuvant chemotherapy with or without radiation therapy, or definitive chemoradiation can be considered. In case of unresectable or locoregional tumors, the patient should have the tumor resected followed by chemotherapy, considering octreotide if functioning tumor. Finally, in the presence of metastatic disease the patient should receive chemotherapy, adding octreotide whenever functioning tumor[4].

Since there are no comparative randomized trials concerning therapy in advanced non-resectable disease, the decision must be based in patients' characteristics and SRS positivity[8].

Surgical Treatment

A curative resection (R0: more than 1 mm margin or R1: less or 1 mm margin) in gastroenteropancreatic NETs with liver metastases correlates with a 5-year OS rate of approximately 85%[42].

One study recommends the surgical removal of pNETs despite vascular invasion or involvement, since they're safely removed and associated with long-term survival in 30% of patients[43], although bearing in mind risk factors[8].

Histopathology, size and location of the tumor, plus the predictable resting pancreatic function post-surgery, enable the choice of the adequate surgical procedure[24]. Enucleation is a suitable surgical technique for smaller than 2cm peripheral (distant from pancreatic duct) non-insulinoma pNETs[4], moreover, these parenchyma sparing resections must be preferred in younger patients[8]. In non-insulinoma pNETs, all possibly affected lymph nodes must be routinely removed due to their prognostic value[2]. Larger than 2 cm or profound tumors should be resected using a standard pancreatectomy (pancreaticoduodenectomy for head-located tumors or distal pancreatectomy for body or tail tumors) with peripancreatic lymphadenectomy[4], since the presence of local metastases is expected[8], resulting in longer survival rates[44].

A systematic review compared open surgery with laparoscopic approach in Insulinomas and concluded that the laparoscopic option was safe and associated with lesser hospitalization stay[45], therefore, this approach should be preferred in sporadic imaged tumors[46]. Other techniques described successful are radiologically guided percutaneous or endoscopic ablative therapy, for localized tumors, not suitable for surgery[2].

One study demonstrated that patients with sporadic gastrinoma patients benefit from surgical exploration by a trained surgeon after negative imaging studies, since 98% of tumors where found and half were cured, as it happens in patients with positive imaging studies[47]. Moreover, the usage

of intraoperative ultrasound and pancreatic palpation is recommended for precise tumor localization[24]. If the tumor smaller than 2 cm, it can be managed by frequent follow up[2].

A conservative approach can be considered in selected asymptomatic patients with sporadic NF-pNETs smaller than 2 cm, since it is safe[48]. Therefore, a yearly high-quality imaging is required for appropriate surveillance. Enucleation is a surgical option for patients in which a wait-and-see management is contraindicated.

Patients with high tumor burden F-pNETs, particularly with Ki-67 index higher than 10%, may benefit from debulking surgery, a technique without curative purposes which a partial removal of tumor facilitates subsequent therapies and alleviates symptoms[8], improving the patients' prognosis[24].

Medical Therapy

The purpose of medical therapy is to diminish hormonal symptoms and tumor progression.

The first-line option in F-pNETs are SSAs, namely octreotide or lanreotide, which are well-tolerated excluding brief digestive side effects[8]. A placebo-controlled, phase III study, the CLARINET study together with the open-label extension study, demonstrated that lanreotide 120 mg significantly extended progression-free survival (PFS) in patients with metastatic grade 1 or 2 pNETs, regardless of hepatic metastases, confirmed anti-tumor effects, and presented long-term tolerability and safety profiles[49].

The RADIANT-3 study demonstrated that the mammalian target of rapamycin (mTOR) inhibitor everolimus 10 mg/day, prolonged median OS in 6 months in patients with advanced, progressive pNETs[50] and significantly prolonged median PFS irrespective of preceding chemotherapy use[51]. Therefore, everolimus is approved by the European Medicines Agency (EMA) and it is indicated in progressive grade 1 or 2 pNETs regardless of previous chemotherapy[8].

The COOPERATE-2 study revealed that the addition of SSA pasireotide to everolimus did not improved PFS or OS[52], therefore, the association of everolimus with SSAs is not recommended[8]. Moreover, a single-arm phase II study showed that, despite antiproliferative activity in advanced NETs, pasireotide caused hyperglycemia in 79% of patients, raising concerns about its utility[53].

The multiple tyrosine kinase inhibitor (TKI) sunitinib is approved by the EMA and suitable for advanced progressive pNETs[8]. A phase IV trial confirmed safety and efficacy of sunitinib in patients with advanced, well-differentiated pNETs irrespectively of previous treatments[54]. A phase IV clinical trial using sunitinib in patients with advanced well-differentiated pNETs, demonstrated that single

nucleotide polymorphism in IL1B is associated with pNET etiology and development, since a higher objective response rate was observed[55].

Comorbidities and side effects of targeted drugs must guide their usage, since there are no clear order in which they should be administered[8].

Gastric acid hypersecretion in gastrinoma patients is preferably controlled by oral PPIs[2], and long-term users should access magnesium and vitamin B_{12} levels regularly mainly in the elderly[56]. A study showed that even after curative resection, 62% of patients continued to suffer from acid hypersecretion, therefore, the PPIs should not be immediately discontinued postoperatively and the patient should be closely monitored[57].

Patients with malignant insulinomas need medication to control hypoglycemia prior to surgery, including SSAs, TKI sunitinib or mTOR inhibitor everolimus[2], although, due to their low expression of SSTR, the response to SSA is usually non satisfactory[6]. These drugs may worsen hypoglycemia, since they inhibit glucagon secretion as well, so close monitoring is required.

Systemic Chemotherapy

Chemotherapy is recommended in advanced well-differentiated pNET and in poorly differentiated neuroendocrine pancreatic carcinomas, particularly when the Ki-67 index is between 15 and 20% and the disease is progressing. The association of 5-FU and STZ is recommended in G1 or G2 pNETs with non-resectable metastases. TEM-based chemotherapy or associated with CAP is another option considered in pNETs[8], moreover, a prospective randomized study reveals a superiority in the associated therapy CAPTEM in progressive pNETs, since it extends PFS from 14,4 to 22,7 months[58]. Systemic chemotherapy with CAPTEM or STZ/5-FU is the first option for G3 pNETs with Ki-67 index inferior than 50%[8].

One observational retrospective multicenter study revealed the predictive value of the MGMT promoter methylation concerning TEM-based chemotherapy, in term of PFS, OS and objective response to treatment, however, it is not widely used[59].

Regarding metastatic poorly differentiated neuroendocrine pancreatic carcinomas, the combinations etoposide plus cisplatin or carboplatin are indicated[8].

Peptide Receptor Radionuclide Therapy (PRRT)

Peptide Receptor Radionuclide Therapy (PRRT) is a nuclear medicine technique which comprises the administration of a radiolabeled peptide that targets receptors in tumors. The main side effects are haematotoxicity and nephrotoxicity. ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE have promising results

in inoperable or metastatic G1 or G2 pNETs, expressing numerous somatostatin receptor subtype 2 (SSTR2)[60], however ^{177}Lu is associated with less kidney impairment. ^{177}Lu-DOTATATE is approved by the EMA for pNETs[8] and this therapy should be considered whenever symptoms are refractory to SSAs[61].

The multicenter prospective phase III NETTER-1 trial, which compared octreotide LAR alone or combined with ^{177}Lu-DOTATATE, concluded that the association of ^{177}Lu-DOTATATE with octreotide lead to longer PFS of 28,4 months, while the high-dose octreotide alone only reached 8,5 months and a presumable advantage in terms of OS[62]. Moreover, the therapy was responsible for better control of the symptoms and quality of life (QoL)[63].

Whether during or after PRRT, hormonal symptoms may exacerbate, so close management is required[8].

Patients' response to ^{90}Y-DOTATOC correlates with longer survival and SRS positivity is predictive for survival after treatment and nephrotoxicity[64].

Surgery/ Locoregional or Ablative therapies for metastatic disease

Regardless of Ki-67 index, the extent of liver or extra-abdominal metastases are good survival predictors[65], so liver metastases resection is recommended in G1 or G2 pNETs whenever feasible and no other distant metastases are present[24].

Despite that and even though curative surgery is only achievable in 10 to 25% of patients with liver metastases and up to 80% of them recurs in 5 years[66], after complete resection of liver metastases, the 5-year survival rates reaches up to 85% and 10-year survival rates reach up to 90,4%. Therefore, the aggressive resection of liver metastases is recommended[67].

A partial or systematic segmentectomy is recommended when there is only one simple hepatic lesion, although when the patient has contraindications for surgical procedures, the treatment options are radiofrequency ablation, laser-induced thermotherapy, trans-catheter arterial chemoembolization or embolization.

If resectable metastases are bilobular, the procedure of choice is major and or minor hepatectomy. When multiple or unresectable metastatic liver disease is present, the treatment options are systemic therapies, such as cytotoxic agents or molecular targeted drugs, trans-catheter arterial chemoembolization or embolization[24].

Liver transplantation is only considered in selected cases, namely patients younger than 60 years, with G1 or G2 pNETs with Ki-67 index lesser than 10%, after primary removal, with more than half liver volume preserved, without extrahepatic metastases, with at least 6 months of stable disease[8].

One small study suggests a synchronous removal of both primary tumor and liver metastasis with low mortality rates, excluding major hepatectomy and pancreaticoduodenectomy simultaneously[68], although bearing in mind the possibility of complications[24].

A debulking surgery of more than 70% of hepatic metastases can be considered, since it showed no differences when compared to 90 or 100% debulking surgeries[69].

Multiple Endocrine Neoplasia type 1 (MEN1)

The Multiple Endocrine Neoplasia type 1 (MEN1) is an autosomal-dominant syndrome, occurring when the tumor-suppressor MEN1 gene located on the chromosome 11q13.3 suffers inactivating mutations and results in neuroendocrine tumor of the anterior pituitary, parathyroid glands and pancreas[70].

Approximately 5 to 10% of patients with MEN1 phenotype don't have mutations in the MEN1 gene, in those cases, deepen genetic studies can be weighted as mutations in cyclic-dependent kinase inhibitor genes (p21, p18, p15, CDK1B)[2].

MEN1 patients have a 30 to 80% probability of developing pNETs[71], plus, a large prospective study revealed that up to 30% of MEN1 patients die from a pNET related cause[72], enhancing the importance of screening pNETs in these patients. According to a comparative study, EUS has higher sensitivity (80%) in detecting pancreatic lesions than MRI (66%)[73].

Whenever pancreatic resection is an option, an intraoperative ultrasound is required[8].

MEN1 patients with rapid growing, larger than 2 cm, F-pNET or symptomatic NF-pNETs with resectable lymph node metastases must be surgically approached[24].

In MEN1 insulinomas larger than 2 cm, the enucleation and limited pancreatic resection should be the procedures of choice[74] given the higher cure rates[75], whereas pancreaticoduodenectomy or laparoscopic approach must be reserved for selected cases[76]. In gastrinoma MEN1 patients, aggressive surgery and lymphadenectomy is recommended since metastases occur in 70% of patients[24].

Follow-up

During follow-up, physicians should monitor patients' symptoms, order biochemical exams and conventional and SSTR imaging. Specific biomarkers for F-pNETs and CgA must be included in biochemical exams, neuron-specific enolase can be useful in grade 2 and 3 tumors and lactate dehydrogenase in neuroendocrine carcinomas.

Patients with grade 1 or 2, with Ki-67 index below 5%, resected pNETs, must perform an imaging study such as a CT or an MRI every 6 months. Whenever the Ki-67 index is higher than 5% in grade 2 pNETs, the scans must be performed every 3 months, and finally, neuroendocrine carcinomas must repeat imaging studies every 2 to 3 months[8]. Extended intervals should be considered in stable disease. Whenever positive or in suspected progression, a functional imaging study as a SRS must be performed within 2 years[2]. SSTR imaging should be performed 12 to 36 months after the SSTR2 expression has been demonstrated, either in previous SSTR imaging or immunohistochemical studies. FDG-PET may be considered in suspected recurrence and in locally advanced grade 3 neoplasms to rule out the possible distant metastases.

These follow-up investigations should be lifelong. Grade 3 tumors must maintain the monitoring intervals, while others may extend staging intervals in 1 to 2 years, mainly after 5 years of close monitoring[8].

Conclusion

A multidisciplinary approach to pancreatic neuroendocrine tumors is necessary, since surgical, medical, interventional radiological and radiotherapeutic modalities are implemented.

There are still many challenges concerning the management of pancreatic neuroendocrine tumors, as the right approach to grade 3 pancreatic neuroendocrine tumors, since they only appeared in the WHO 2017 classification, lacking proper studies focusing on this type of tumors.

Moreover, there are no comparative or randomized studies to enable the best treatment choice in unresectable disease, neither in pancreatic neuroendocrine carcinomas, nor the order in which targeted drugs should be administered.

To conclude, research in this topic is essential to discover the most adequate treatments to employ in each patient in order to improve not only survival but also quality of life outcomes.

Tables

Table I – Functional Pancreatic Neuroendocrine Tumor Syndromes[2]

Name	Biologically active peptide(s) secreted	Incidence (new cases/10^6 population/ year)	Tumor location	Malignant, %	Associated with MEN1, %	Main symptoms/signs
The most common F-pNET syndromes						
Insulinoma	Insulin	1 - 32	Pancreas (> 99%)	<10	4 - 5	Hypoglycemic symptoms (100%)
ZES	Gastrin	0,5 - 21,5	Duodenum (70%) Pancreas (25%) Other sites (5%)	60 - 90	20 - 25	Pain (79 - 100%) Diarrhea (30 - 75%) Esophageal symptoms (31 - 56%)
Established rare F-pNET syndromes (>100 cases)						
VIPoma (Verner-Morrison syndrome, pancreatic cholera, WDHA)	Vasoactive intestinal peptide	0,05 - 0,2	Pancreas (90%, adult) Other (10%, neural, adrenal, periganglionic)	40 - 70	6	Diarrhea (90 - 100%) Hypokalemic (80 - 100%) Dehydration (83%)
Glucagonoma	Glucagon	0,01 - 0,1	Pancreas (100%)	50 - 80	1 - 20	Rash (67 - 90%) Glucose intolerance (38 - 87%) Weigth loss (66 - 96%)
Somatostatinoma	Somatostatin	Rare	Pancreas (55%) Duodenum/Jejunum (44%)	>70	45	Diabetes mellitus (63 - 90%) Cholelithiasis (65 - 90%) Diarrhea (35 - 90%)
GRHoma	Growth hormone-realeasing hormone	Unknown	Pancreas (30%) Lung (54%) Jejunum (7%) Other (13%)	>60	16	Acromegaly (100%)
ACTHoma	ACTH	Rare	Pancreas (4 - 16% all ectopic Cushing's syndrome)	>95	Rare	Cushing's syndrome (100%)
pNET causing carcinoid syndrome	Serotonin	Rare (43 cases)	Pancreas (<1% all carcinoids)	60 - 88	Rare	Same as carcinoid syndrome above
pNET causing hypercalcemia (PTHrPoma)	PTHrP	Rare	Pancreas (rare cause of hypercalcemia)	84	Rare	Abdominal pain due to hepatic metatases
Very rare F-pNET Syndromes (1 - 5 cases)						
pNET secreting renin	Renin	Rare	Pancreas	Unknown	No	Hypertension
pNET secreting luteinizing hormone	Luteinizing hormone	Rare	Pancreas	Unknown	No	Anovulation Virilization (female) / reduced libido (male)
pNET secreting erythropoietin	Erythropoietin	Rare	Pancreas	100	No	Polycythemia
pNET secreting insulin-like growth factor 2	Insulin-like growth factor 2	Rare	Pancreas	Unknown	No	Hypoglycemia
pNET secreting CCK (CCKoma)	CCK	Rare	Pancreas	Unknown	No	Diarrhea Ulcer disease Weigth loss Cholelithiasis
pNET secreting GLP-1	GLP-1	Rare	Pancreas	Unknown	No	Hypoglycemia

WDHA = watery diarrhea, hypokalemia, achlorhydria; ACTH = Adrenocorticotropic hormone;

PTHrP = Parathyroid hormone-related peptide; CCK = Cholecystokinin; GLP-1 = Glucagon-like peptide-1

Table II – WHO 2017 classification[4]

	Mitoses/10 HPF	Ki-67 Index (%)
Well-differentiated NENs		
NET grade 1	<2	<3
NET grade 2	2-20	3-20
NET grade 3	>20	>20
Poorly differentiated NENs		
NEC grade 3 **Small-cell type** **Large-cell type**	>20	>20
MiNEN		

Table III – ENETS TNM staging system[4]

T – primary tumor	
T1	Limited to pancreas, <2 cm
T2	Limited to pancreas, 2-4 cm
T3	Limited to pancreas, >4 cm, or invading duodenum or common bile duct
T4	Invades local structures
N – regional lymph nodes	
N0	No regional lymph nodes metastasis
N1	Regional lymph node metastases
M – distant metastases	
M0	No distant metastasis
M1	Distant metastases

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