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PANCREATIC NEUROENDOCRINE NEOPLASMS (pNENs)

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Abstract

Pancreatic neuroendocrine neoplasms (pNENs) are relatively rare lesions that have been increasing in incidence over the past few decades largely because of the diagnosis of pancreatic incidentalomas on cross-sectional imaging. Most of these tumors are nonfunctioning presenting with symptoms secondary to mass effect, metastatic disease or as incidental findings. Diagnostic work-up aims to assess the stage and the grade of the disease as these parameters represent the main driver for treatment choice. The treatment of pNENs varies from conservative management to extensive surgical resection. Different medical treatments have been recently validated in large randomized clinical trials.

1. Introduction

According to a population–based study, malignant pancreatic neuroendocrine neoplasms (pNENs) account for approximately 1% of pancreatic cancers by prevalence (55). An estimated 40% to 91% of pNENs are non-functioning. The remainder exhibit clinically evident hormonal symptoms (32). In the last decade, three different classifications have been proposed by the World Health Organization (WHO) (45). In the last classification, pNENs are divided according to tumor grading that is still the most powerful predictor of survival in these tumors. Recent years have seen a dramatic increase in interest and effort in conducting large randomized trials in order to explore different treatments. In this chapter, we focus on the current status of clinical and pathological aspects of pNENs.

2. Epidemiology

pNENs are relatively rare as their incidence is below 1 case per 100,000 inhabitants representing approximately 8-10% of all pancreatic neoplasms (19). The reported incidence of pNENs is about 0.32 per 100,000 inhabitants per year, which is lower than the incidence of lung, ileal and rectal NET (i.e. 1.35, 0.67, 0.86 per 100,000 respectively) (55). In the largest and most recent series of pNENs, including gastroenteropancreatic, thoracic and unknown primary NEN, the age adjusted incidence has risen from 1.1 to 5.2 per 100,000 inhabitants per year over the years 1973-2004 (20). Several factors may have contributed to this rise, including the improvement in classification of NENs, the widespread use of endoscopy for cancer screening and of other sensitive imaging procedures such as endoscopy ultrasound (EUS) and computed tomography CT (50). As a direct consequence, the incidence of pNETs <2 cm in the United States has increased by 710% over the last 22 years (20).

Table 1. 2010 WHO classification of neuroendocrine tumors (7)

Diagnosis	Grade	Mitosis	Ki67	Differentiation
Neuroendocrine tumour (NET)	1	< 2/10HPF	≤ 2%	Well differentiated
Neuroendocrine tumour (NET)	2	2-20/10HPF	3-20%	Rather differentiated
Neuroendocrine carcinoma (NEC)	3	> 20/10HPF	> 20%	Poorly differentiated
Mixed neuroendocrine - adenocarcinoma (MANEC)	-	-	-	Poorly differentiated
Hyperplastic and pre-neoplastic lesions	-	-	-	Histological Abnormality

3. Classification and staging

The WHO 2010 classification (7, 45) distinguishes between well- or moderately-differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas (NEC) of small or large cell type. This classification is mainly constructed on a grading scheme based on mitotic count or Ki67 index. pNENs are then classified into three categories: NET-G1 (with a mitotic count < 2 per 10 high-power fields (HPF) and/or < 2% Ki67 index), NET-G2 (with a mitotic count 2–20 per 10 HPF and/or 3–20% Ki67 index) and NEC-G3 (with a mitotic count > 20 per 10 HPF and/or > 20% Ki67 index) **(Table 1)**.

The grading requires mitotic count in at least 50 HPFs (1 HPF = 2mm) and Ki67 index using the Dako MIB-1 antibody as a percentage of 500-2000 cells counted in areas of strongest nuclear labeling (“hot spots”) **(Figure 1)**. If grade differs for mitotic count compared with Ki67 index, it is suggested that the higher grade must be assumed (45).

The tumor-node-metastasis (TNM) system, proposed by the European Neuroendocrine Tumor Society (ENETS), is based on the evaluation of the following parameters: size, extra pancreatic invasion, lymph-node and liver metastasis. In this classification, pT1tumors are < 2 cm, pT2 are between 2 cm and 4 cm and pT3 are > 4cm (44). In 2009 an additional TNM staging classification for pNET was suggested in the seventh edition of the AJCC/UICC TNM classification (47). The AJCC/UICC and ENETS classifications differ in the definitions of the T stages although a cut-off of 2 cm to distinguish pT1 from pT2 is used in both. On the contrary, the AJCC/UICC system requires recognition of peripancreatic soft tissue invasion in order to distinguish pT2 from pT3 whereas the ENETS classification based this distinction on tumor size using a cut-off of 4 cm. **(Table 2)**.

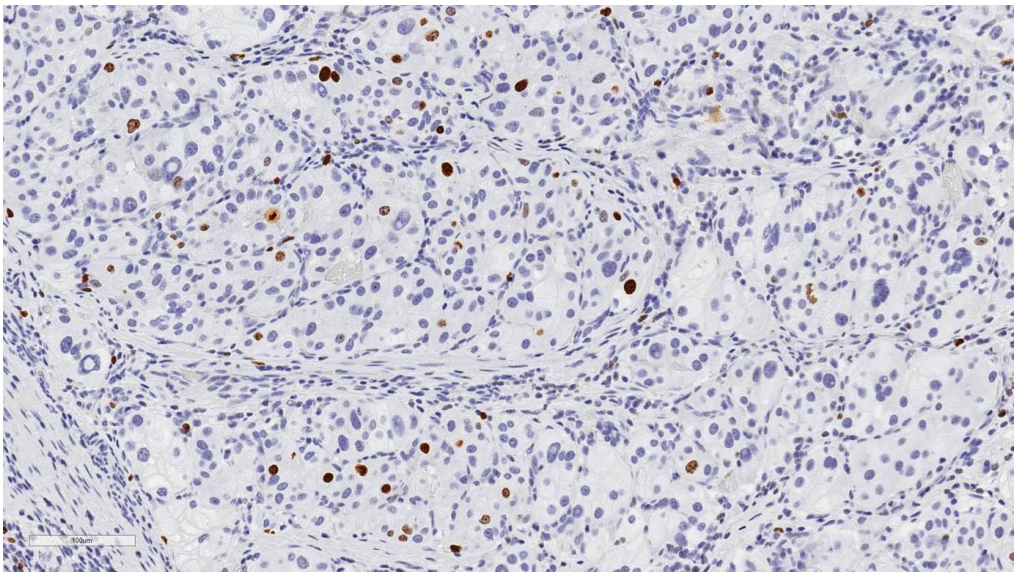

Figure 1. Non-functioning pNET: well-differentiated solid tumor cell nests with immunostaining for Ki67 (Ki-67: 6%)

Table 2. Comparison of TNM system proposed by ENETS (44) and AJCC/UICC (47)

	ENETS TNM	AJCC/UICC TNM
T1	Confined to pancreas, < 2 cm	Confined to pancreas, <2 cm
T2	Confined to pancreas, 2-4 cm	Confined to pancreas, >2 cm
T3	Confined to pancreas, > 4 cm, or invasion of duodenum or bile duct	Peripancreatic spread, but without major vascular invasion (celiac trunk, SMA)
T4	Invasion of adjacent organs or major vessels	Major vascular invasion

SMA: superior mesenteric artery

A large retrospective multi-institutional study that included 1072 patients affected by pNENs demonstrated that the ENETS TNM staging system is superior to the AJCC/UICC 2010 TNM staging system (43).

4. Pathology

pNENs are usually solitary and solid masses with rounded borders. The most common pNEN is rich in small vessels and has little fibrotic stroma. Evident features of malignancy after macroscopic examination include involvement of perivisceral fat, invasion of duodenal wall or adjacent organs (2). Microscopically, the majority of pNENs are well-differentiated tumors, which grow as solid nests or arranged on trabecular patterns **(Figure 2)**.

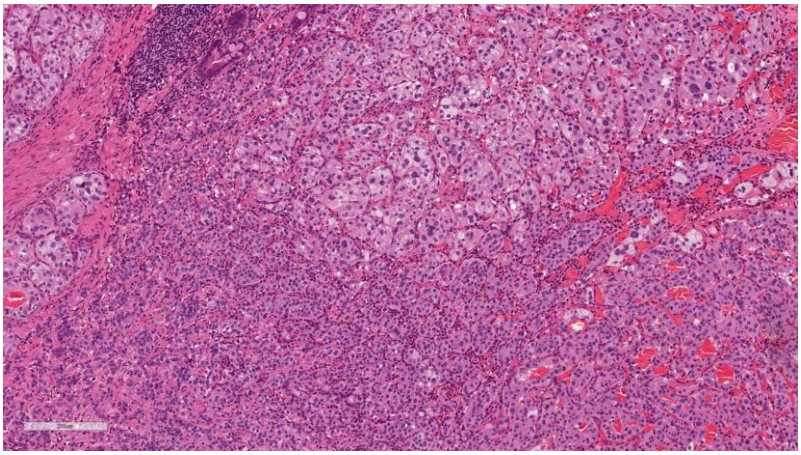

Figure 2. Example of the most common form of a pNEN, a well differentiated tumor. Architectural patterns included nesting and micro trabecular, with numerous small vessels. Nuclear features show the coarsely clumped, "salt and pepper" chromatin pattern.

Glandular, acinar and cribriform features are also observed. A rich vascularization is typical. Immunohistochemistry is used to differentiate a pNEN from other neoplasms using antibodies to at least one general endocrine marker such as synaptophysin or chromogranin A (CgA). pNEN may express normally produced pancreatic hormones (i.e. insulin, glucagon, somatostatin, pancreatic polypeptide), hormones of ectopic origin (i.e. gastrin, vasoactive intestinal polypeptide, adrenocorticotrophic hormone) and bioamines (i.e. serotonin).

5. Diagnosis

Clinical findings

Clinical suspect of PNEN should be considered in one of the following conditions:

1. presence of a clinical endocrine syndrome, which pushes the patient to seek medical care. In this case, diagnosis is considered “early” and allows the identification of the endocrine neoplasm when it is still small;
2. presence of clinical symptoms related to the growth of the neoplasm or to the presence of pain related to retroperitoneal infiltration. Those cases usually involve a non-functioning pNEN (NF-pNEN) and do not lead to early symptoms, also they are diagnosed by symptoms caused by the increase in tumoral mass;
3. incidental diagnosis of a pancreatic mass, which is the most common way these lesions are diagnosed.

If patients have symptoms, the most common presenting symptoms are abdominal pain (35-78%), weight loss (20-35%), anorexia and nausea (45%). Less frequent signs are intra-abdominal haemorrhage (4-20%), jaundice (17-50%), or a palpable mass (7-40%) (10, 11, 27, 29, 54).

Laboratory

There are generally two types of laboratory analyses. First, measurement of specific hormones in the case of functioning-pNEN, which include glucagon, somatostatin, serotonin, gastrin, insulin, etc. in baseline conditions and after stimulation using respective clinical-laboratory tests (12, 48). Secondly, dosage of generic neuroendocrine markers such as chromogranin A (CgA) and neuron-specific enolase (NSE). The former is a glycoprotein localized inside secretory vesicles of endocrine cells as well as neuronal cells of the central and peripheral nervous system. It is the most important generic neuroendocrine marker with sensitivity between 60-90% (39). Nevertheless, plasma levels of CgA can be falsely positive in the presence of altered renal function, atrophic chronic gastritis, and during therapy with

proton pump inhibitors. The latter (NSE) is found at the cytoplasmic level in endocrine cells and neurons (37).

Imaging

Radiological examinations such as abdominal computed tomography (CT) and ultrasound, especially with contrast medium, are able to localize the neoplasm and obtain complete preoperative assessment in about 60% of cases (46). Hyper vascularization of endocrine tumors, present in 60-70% of patients (30, 35), can be observed by both CT **(Figure 3)** and ultrasound with contrast medium, and can localize the lesion and provide other information regarding its nature. Recently, there has been a dramatic technical improvement in MRI assessment of pancreatic disease using diffusion-weighted imaging (DWI) (14). DWI has been used for years in brain MRI but it has only recently been extended to abdominal imaging. Recent reports have suggested that high *b*-value DWI may be helpful in the detection and characterization of pancreatic tumors (25, 28).

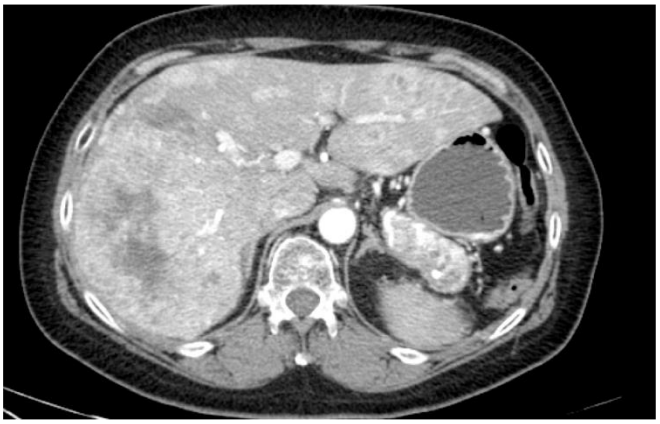

Figure 3. CT scan demonstrating a hypervascularized lesion of the pancreatic tail associated with multiple liver metastases

It has been reported that a reduced apparent diffusion coefficient (ADC) is observed in most malignant lesions related to the histopathological features of the tumor (33). Endoscopic ultrasound (EUS) can be useful when it is difficult to localize the neoplasm as well as other techniques such as venous sampling during angiography. As EUS offers excellent visualization of the pancreas from the duodenum or stomach and can produce high-resolution images of the pancreas. It has been considered one of the most accurate methods for the detection of a pancreatic focal lesion, especially in patients with small tumors of 3 cm or less, but is operator dependant (41, 53). EUS also has the unique ability to obtain specimens for histopathological diagnosis using EUS-guided fine-needle tissue acquisition (EUS-FNTA). Ki-67 determination can be assessed in the 87% of patients with a concordance of 83% with postoperative Ki-67 (22).

Nuclear Medicine

The presence of prominent molecular biomarkers makes pNENs attractive for functional imaging with PET and SPECT. Over the past few years the gold standard for functional imaging of pNENs has been somatostatin receptor scintigraphy (SRS) with ^{111}In-diethylenetriaminepentaacetic acid octreotide (6). More recently the introduction of ^{68}Ga-DOTA-peptide PET/CT has significantly improved the diagnostic work-up in the evaluation of pNENs (3) **(Figure 4)**. In comparison to scintigraphy, positron emission tomography (PET) has a 2- to 3-fold higher spatial resolution (3–6 vs. 10–15 mm) and facilities quantification of tracer uptake.

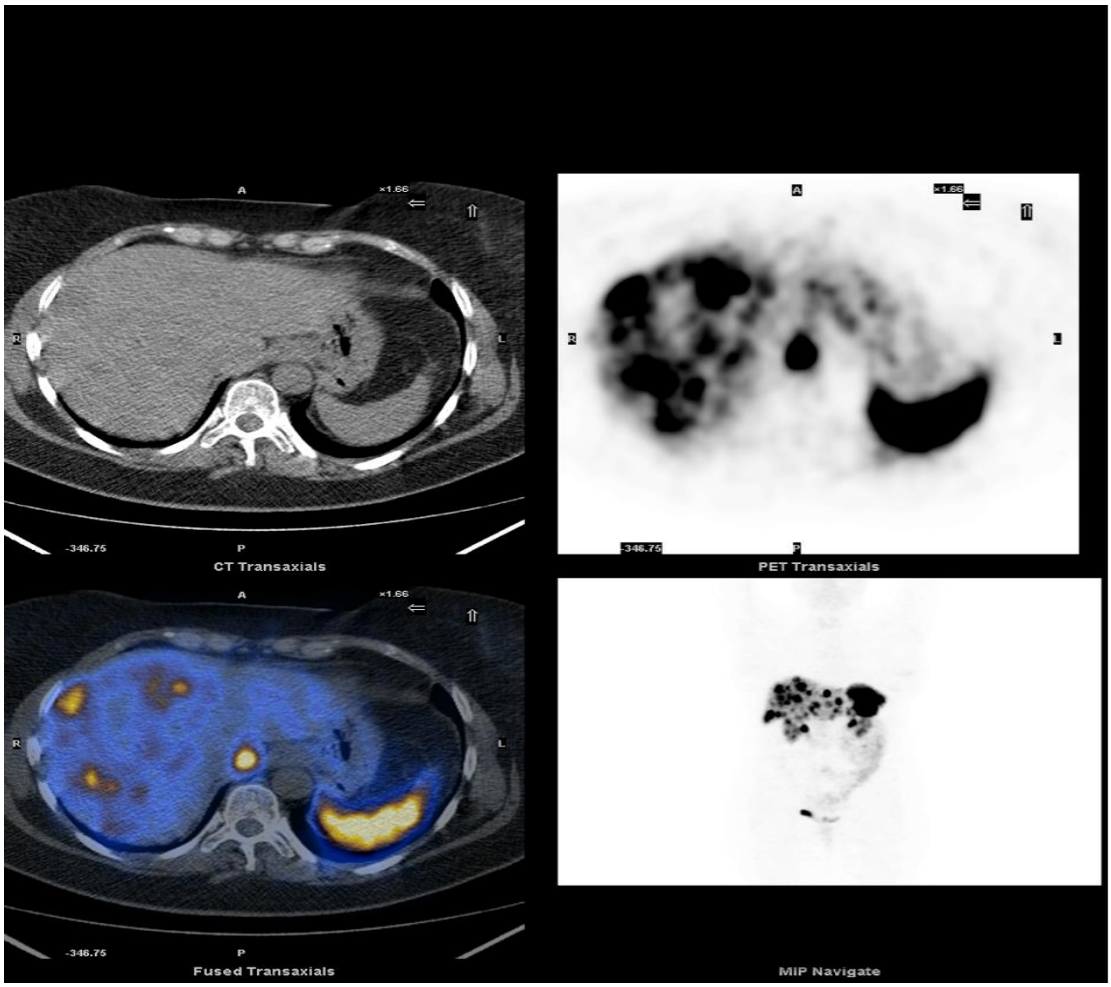

Figure 4. ^{68}Gallium PET/CT of a pNET with liver metastases

Several different DOTA-peptides (DOTATOC, DOTANOC, and DOTATATE) have been used in the clinical setting for both pNENs diagnosis and peptide receptor radionuclide therapy (PRRT). The major difference among these compounds relies on a slightly different affinity to somatostatin receptor subtypes (3). The sensitivity and specificity of ^{68}Ga PET/CT in detecting NET is 93 and 91%, respectively (49). Moreover, this technique provides relevant information for pNET patients' clinical management (3). ^{18}F-FDG PET/CT is of value for tumors with a high proliferation index (pNEC), whereas the diagnostic sensitivity seems to be low for pNETs with a low proliferation index, slow growth rate, and low glucose consumption (6). Usually, ^{18}F-FDG PET/CT had a sensitivity of 92% for tumors with a proliferation index of above 15% (6). Dual tracer PET/CT can be performed on a single day owing to the short half-life of ^{68}Ga and can be superior to histopathology by demonstrating tumor heterogeneity especially for patients with multiple metastases (18).

6. Treatment

Surgery

Incidental diagnosis of pancreatic NENs is associated with a significantly better survival after curative resection, compared to patients with symptoms (9). Moreover, Bettini et al. (4) demonstrated that patients with an incidental diagnosis associated with a tumor size < 2 cm, had a 5-year overall survival of 100% with a minimal risk of recurrence. On the basis of these experiences, the European Neuroendocrine Tumor

Society (ENETS) guidelines now recommend a *wait and see* policy in selected patients with asymptomatic sporadic pancreatic NENs, when the possibility of surgical cure has to be weighed against the operative morbidity, mortality and long-term complications associated with pancreatic surgery (15). Preliminary reports have demonstrated the safety of this conservative approach (9, 17, 24). On the other hand, surgery still represents the treatment of choice for pancreatic NENs > 2 cm and/or for symptomatic forms. Pancreatic resections differ according to tumor site: lesions of the pancreatic head are treated with a pancreaticoduodenectomy while lesions of the body and tail with a distal pancreatectomy. Role of lymphadenectomy for patients with a pancreatic NEN is still unclear (40). Lymph node metastases occur only in the 30% of patients affected by these tumors (40) but the association between node metastases and poorer survival is still debated (5). Laparoscopic procedures play an important role in the treatment of pancreatic endocrine tumors. It was demonstrated that laparoscopic distal pancreatectomy and enucleation are safe and feasible in patients with pancreatic endocrine tumors (16). Whenever a resection leaves no residual disease, an aggressive approach, including liver resection, is recommended. The conditions that have to be assessed preoperatively are (23) the absence of extra-abdominal disease, (30) the presence of a low proliferative index (Ki67), and (34) the existence of somatostatin receptors in order to deliver radiolabelled therapies, as they have been effective after cytoreductive surgery (15). The type of hepatic resection depends on the number of liver metastases, site and hepatic reserve itself. It can range from simple enucleation to segmental resection or to hepatectomy. In those patients with bilobar metastases or more than 75% of liver involvement, radical surgery can be rarely performed. In this light, medical, ablative and embolizing techniques can be provided in order to allow radical resection. There are valid palliative options in patients with pancreatic NETs with liver metastases which are not candidates for surgical resection. These mainly include trans arterial embolization (TAE), trans arterial chemo-embolization (TACE) and radiofrequency ablation (RFA). Such procedures can be used as loco-regional ablative therapy per se or as an adjunct to palliative surgery. Liver transplantation may be an option in a patient without extrahepatic metastases, and low proliferation rate when all other therapeutic options have failed (15).

Anti-tumoral treatments

A number of potential therapeutic targets have been identified and investigated for treating advanced pNENs. Recently, three large randomized clinical trials have been published **(Table 3)**.

The mTOR pathway

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that stimulated cell growth, proliferation, and angiogenesis. Autocrine activation of the mTOR signaling pathway mediated through insulin-like growth factor 1, has been implicated in the proliferation of pancreatic neuroendocrine tumor cells. Consistently with this observation is the finding that inhibition of mTOR has a significant antiproliferative effect on PNET (56).

RADIANT-3 compared the efficacy of daily everolimus 10 mg versus placebo in 410 patients with advanced low- or intermediate-grade PNET (56). Everolimus significantly increased median PFS (progression-free survival) by 6.4 months compared with placebo (11 vs. 4.6 months, respectively; HR 0.35; 95% CI 0.27-0.45, $p<0.001$).

Table 3. Recent phase III studies on antitumoral treatment of advanced pNENs

Regimen	*n*	Median PFS	HR	95% CI	*P*	Ref
Sunitinib	86	11.4	0.42	0.26-0.66	<0.001	42
Placebo	85	5.5				
Everolimus	207	11.0	0.35	0.27-0.45	<0.001	56
Placebo	203	4.6				
Lanreotide	42	n.r.	0.58	0.32-1.04	n.r.	8
Placebo	49	n.r.				

n.r: not reported

VEGF pathway

Vascular endothelial growth factor (VEGF) is a key driver of angiogenesis in PNET. Tissue from pancreatic neuroendocrine tumors shows widespread expression of platelet-derived growth factor receptors (PDGFRs) α and β, stem-cell factor receptor (c-kit), and VEGF receptor (VEGFR)-2 and VEGFR-3 (42). Sunitinib malate inhibits these kinases. In a phase III, double-blind, placebo-controlled trial, sunitinib was compared with placebo in patients with advanced, well-differentiated PNET (42). Patients in the sunitinib group (37.5 mg/d) had a median PFS of 11.4 months compared with 5.5 months for the placebo group (HR 0.42; 95% CI 0.26-0.66; np<0.001).

Somatostatin Receptor Pathway

Somatostatin is a hormone that targets transmembrane G-protein-coupled somatostatin receptors. There are 5 known types of somatostatin receptors (SST1, SST2, SST3, SST4, and SST5). The use of somatostatin analogues (SSAs) in the treatment of patients with neuroendocrine neoplasms is a well-established practice (38). SSAs include octreotide/octreotide LAR, Lanreotide, and Pasireotide. Lanreotide was compared with placebo in a recent randomized, double-blind, multinational study (8). This study included neuroendocrine tumors originating in the pancreas, midgut, or hindgut or of unknown origin. Lanreotide, as compared with placebo, was associated with significantly prolonged PFS (HR 0.47; 95% CI 0.30-0.73, P<0.001). Nevertheless, therapeutic effect in the subgroup of PNET was not demonstrated (HR 0.58; 95% CI 0.32-1.04) (8). Peptide receptor radionuclide therapy (PRRT) is a new modality that uses radiolabelled peptides for treating unresectable or metastasized NENs. The rationale for such therapy is to convey radioactivity inside the tumor cells, where the sensitive targets, such as DNA, can be hit as a result of internalization of the somatostatin receptor and radiolabelled analogue complex (21). However, the exact role of this treatment in the management of NET remains to be defined. One trial comparing PRRT with high-dose SSA therapy has been launched (1).

Chemotherapy

Chemotherapy is recommended in PNET-G2 when other treatments failed and in PNEC-G3 (15). Most important regimens include the combination of streptozotocin (STZ) + doxorubicin or 5-fluorouracil (5-FU), cisplatin + etoposide and dacarbazine (13).

The main indication for the use of cisplatin+etoposide is treatment of poorly differentiated neuroendocrine tumors. The combination has been reported to produce objective response in about 50% of anaplastic or poorly differentiated neuroendocrine tumors (31).

7. Functioning PNET

Insulinoma

Insulinomas are the most common functional pNETs with an incidence of 4 cases in one million people per year. Insulinoma should be suspected in the presence of Whipple's triad (symptoms or signs consistent with hypoglycemia; glucose level <50 mg/dL; relief of symptoms after administration of glucose). Insulinomas usually appear as small neoplasms, and are smaller than 1 cm in about 85% of cases (51); in 10-20% of cases they cannot be localized. In the majority of cases, however, ultrasound with contrast medium, abdominal CT and EUS are sufficient to localize the neoplasm. Surgery is the treatment of choice for localized lesions. A laparotomy is preferable because it allows meticulous manual exploration of the pancreas (36).

Gastrinoma

Gastrinomas are the second most frequent functioning endocrine tumor of the pancreatic area. Gastrinomas are malignant in 60-90% of cases and have a very aggressive behaviour in about 25% of cases. Similar to other functioning endocrine neoplasms, a gastrinoma is suspected when patients exhibit clinical symptoms, known as Zollinger-Ellison syndrome. The diagnosis is confirmed based on laboratory tests of acid secretion and gastrin levels before and after secretin stimulation. Gastrinomas are generally malignant tumors and are often associated with unrecognized nodal metastases (52). A pancreaticoduodenectomy is the treatment of choice (26).

8. Conclusion

PNENs are rare neoplasms of the pancreas with a disease course considerably different from pancreatic ductal adenocarcinoma. Aggressive and extensive surgery may be an option for some patients suffering from locally advanced and even metastatic disease. In select cases this may involve resection of multiple organs to achieve a significant reduction of the tumor mass. The multidisciplinary approach is always mandatory in the management of these lesions. Since most pNENs exhibit indolent behavior, both the preservation of quality of life of the patient and the personalization of the therapy according to tumor's and patient's features are needed.

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