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The Treatment of Pancreatic Neuroendocrine Tumors – A Retrospective Single-Centre Study

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Rezumat

Tratamentul tumorilor neuroendocrine pancreatice - studiu retrospectiv într-un singur centru

Introducere: Tumorile neuroendocrine pancreatice (TNEP) sunt tumori maligne rare, însă incidența generală pare să fie în creştere, probabil ca urmare a creşterii recunoaşterii în contextul îmbunătățirii calității imagisticii.
Material şi Metode: Acest studiu constă într-o analiză retrospectivă a pacienților cu TNEP tratați în Clinica I Chirurgie Oncologică pe o perioadă de 10 ani. Au fost evaluate dosarele pacienților şi au fost luați în considerare următorii parametri: sexul, vârsta, localizarea tumorii primare, extensia bolii, localizările metastatice, abordarea terapeutică, tipul de intervenție chirurgicală, rezultatele histopatologice, mortalitatea şi morbiditatea postoperatorie.
Rezultate: Pe parcursul a 10 ani au fost 16 pacienți diagnosticați cu TNEP. Intervențiile chirurgicale au constat în: duodeno-pancreatectomie cefalică cu prezervarea pilorului în 5 cazuri, splenopancreatectomie distală în 3 cazuri, enucleerea tumorii în 4 cazuri, biopsie hepatică la 3 pacienți şi un caz la care s-a impus o coledoco-duodeno-anastomoza şi o biopsie hepatică. Durata medie a şederii în spital a fost de 10,6 zile. În grupul de studiu au existat 4 cazuri care au prezentat complicații de gradul I-II (Clavien-Dindo). Nu a existat niciun caz de mortalitate postoperatorie sau la 30 de zile.
Concluzii: Acest studiu conturează managementul chirurgical şi constatările clinico-patologice ale TNEP. Terapia chirurgicală trebuie să fie adaptată la caracteristicile tumorale şi clinice.

Cuvinte cheie: tumori neuroendocrine pancreatice, chimioterapie, terapie targhetată, tratament chirugical

Abstract

Introduction: Pancreatic neuroendocrine tumors (PNETs) are uncommon cancers, but their overall incidence seems to be on the rise, possibly due to better detection with advancements in cross-sectional imaging techniques.

Methods: This study consists of a retrospective analysis of PNET patients treated in the First Surgical Oncology Clinic over a period of 10 years. The patient files were evaluated, and the following parameters were taken into consideration: gender, age, primary tumor site, extension of the disease, metastatic sites, the therapeutic approach, type of surgery, histopathological results, postoperative mortality, and morbidity.
Results: Over the course of 10 years, there were 16 patients diagnosed with PNETs. Surgical interventions consisted in: pylorus-preserving pancreaticoduodenectomy in 5 cases, distal pancreatectomy in 3 cases, enucleation of the tumor in 4 cases, liver biopsy in 3 patients and one case in which choledochoduodenostomy and a liver biopsy were the treatment option. Mean length of stay was 10.6 days. In the study group, there were 4 cases that presented grade I-II complications (Clavien-Dindo). There was no case of postoperative or 30 days mortality.
Conclusion: This study outlines the surgical management and clinicopathological findings of PNETs. Surgical therapy must be tailored to tumor and clinical characteristics.

Key words: pancreatic neuroendocrine tumor, chemotherapy, targeted therapy, surgical treatment

Introduction

Pancreatic neuroendocrine tumors (PNETs) are uncommon cancers that arise from the endocrine tissues of the pancreas. They account for approximately 2% of all pancreatic tumors, but their overall incidence seems to be on the rise (1). In fact, diagnoses of PNETs have increased four to seven times in recent years. Moreover, the size of these tumors on diagnosis has notably decreased, with tumors smaller than 2 cm being detected in 26% to 61% of cases (2). For sporadic non-functional pancreatic neuro-endocrine tumors (NF-PNETs) measuring less than 2 cm, both current North American Neuroendocrine Tumor Society Consensus and European Neuroendocrine Tumor Society (ENETS) guidelines recommend active surveillance (3).

The purpose of this retrospective study was to evaluate the surgical treatment options for pancreatic neuroendocrine tumors, histopathological results, and morbidity. In our study, the main surgical procedure was pylorus-preserving pancreaticoduodenectomy, although enucleation of the tumor seems to be an effective option in selected cases.

The clinical outcomes for these cases vary significantly based on multiple factors, such as the primary tumor location, grading, and staging, which can be correlated to evaluate the prognosis of the tumor. Of these characteristics, tumor grading is generally recognized as the most significant prognostic indicator, capable of predicting the response to medical treatments, the likelihood of recurrence following radical surgery, and overall survival rates (4).

In 2017, based primarily on established histopathological criteria to enhance predictions of tumor grade and biological behavior, the WHO officially categorized pancreatic neuroendocrine neoplasms into two main groups in its updated grading classification: well-differentiated PNETs which consist of G1 PNETs (<2 mitoses per 10 HPFs and a Ki-67 < 3%), G2 PNETs (between 2 and 20 mitoses per 10 HPFs or a Ki-67 between 3 and 20%) and G3 PNETs (>20 mitoses per 10 HPFs or a Ki-67 >20% without poorly-differentiated pathological features), and poorly-differentiated pancreatic neuroendocrine carcinoma which referred to G3 p-NECs having >20 mitoses per 10 HPFs or a Ki-67 >20% with poorly-differentiated small cell or large cell features (5). PNETs are staged according to the 8th edition of the AJCC Cancer Staging Manual, which is shown in *Table 1.*

Table 1. American Joint Committee on Cancer (AJCC). TNM Staging System for Well-Diferentiated Neuroendocrine Tumors of the Pancreas (NET G1, G2, and G3) (Version 9, 2023) (42)

Stage	Details
T1	Tumor limited to the pancreas,* ≤ 2 cm in greatest dimension
T2	Tumor limited to the pancreas,* >2 cm but ≤ 4 cm in greatest dimension
T3	Tumor limited to the pancreas,* > 4 cm in greatest dimension; or tumor invading the duodenum, ampulla of Vater, or common bile duct
T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery/vein, splenic artery/ vein, gastroduodenal artery/vein, portal vein)
N0	No tumor involvement of regional lymph node(s)
N1	Tumor involvement of regional lymph node(s)
M0	No distant metastasis
cM1	Distant metastasis
cM2	Microscopic confirmation of distant metastasis

Although most PNETs are sporadic, approximately 10% are due to an inherited syndrome, which include multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 4 (MEN4), von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF1), and tuberous sclerosis complex (TSC) (6).

PNETs can be divided into functional and nonfunctional tumors. Functional tumors manifest symptoms, and nonfunctional tumors are usually asymptomatic. The former produce hormones, which are responsible for their clinical manifestations. Some examples of functional tumors are insulinoma and glucagonoma, which have highly variable presentations (7). Functional pancreatic neuroendocrine tumors (F-PNETs) comprehend insulinomas manifesting with the classical Whipple's triad, gastrinomas with the Zollinger-Ellison syndrome, glucagonomas with the "4D syndrome" (dermatitis, diabetes, deep vein thrombosis, and depression), and VIPomas related to the Verner-Morrison syndrome (watery diarrhea, achlorhydria, and hypokalemia). Somatostatinomas are associated with a range of symptoms, including diabetes, diarrhea, steatorrhea, anemia, and weight loss (2).

Four insulinoma characteristics are associated with the "90%" rate: 90% occur in the pancreas, 90% are benign, 90% are solitary, 90% are less than 2 cm in diameter (8). Malignant insulinoma is an uncommon tumor, accounting for about 10% of all insulinoma cases. A definitive sign of malignancy, which helps differentiate between benign and malignant insulinomas, is the presence of metastases-mostly in the liver - at the time of diagnosis. Unfortunately, certain benign insulinomas can evolve over the course of the disease, and recent studies indicate that malignant tumors can also emerge from non-functioning pancreatic neuroendocrine tumors (PNETs) (7).

Identifying the primary tumor location and accurately staging the detected lesion, along with obtaining an accurate histological diagnosis, carry significant prognostic implications. This information helps to estimate disease progression and the risk of recurrence following attempts at curative resection (9).

Imaging is essential for diagnosing and assessing PNETs. Traditional methods, such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are commonly employed for initial detection. Additionally, PET/CT (Fluorine-18 fluoro-deoxyglucose positron emission tomography) techniques combined with innovative radiotracers have shown remarkable effectiveness in identifying and classifying these tumors.

CT is frequently used for the initial evaluation of suspected PNETs. Due to its high spatial resolution, CT delivers outstanding diagnostic insights for detecting and characterizing the primary tumor while also assessing local vascular involvement and distant metastasis. A standard CT protocol includes multiphasic imaging, starting with pre-contrast acquisition followed by arterial, pancreatic, and venous phase imaging after contrast administration (10).

The MRI protocol should consist of T1-weighted (T1W) and T2-weighted (T2W) sequences, along with a dynamic three-dimensional (3D) sequence taken before and after the intravenous injection of a gadolinium chelate. This should include multi-arterial, venous, and delayed acquisitions (more than 5 minutes), as well as diffusion-weighted imaging (DWI) sequences. Diffusion-weighted images increase the sensitivity for the detection of the primary pancreatic tumor as well as associated liver metastases (11).

EUS (endoscopic ultrasound) delivers high-resolution images of the pancreas and is considered one of the most reliable methods for diagnosing pancreatic diseases, with a sensitivity that ranges from 57% to 94% (9). EUS-tissue acquisition is a safe and highly precise method for obtaining cytohistological diagnoses of PNETs. Additionally, preoperative EUS-guided fine needle tattooing or placement of fiducial markers can aid surgeons in locating small, deep tumors, allowing them to perform parenchymal-sparing surgery instead of formal pancreatic resections (9).

Over the years, nuclear medicine has been pivotal in diagnosing neuroendocrine neoplasms. The discovery of somatostatin (SST) in 1973, followed by the identification of the five subtypes of somatostatin receptors (SSTR1 to SSTR5) in the early 1990s, has opened up valuable diagnostic and therapeutic avenues. Somatostatin receptors are broadly found in healthy tissues, with varying levels of expression throughout the body. Notably, their expression is significantly elevated in many human solid tumors, often appearing alone or in different combinations, particularly in gastro-entero-pancreatic neuroendocrine tumors (12). Somatostatin receptors are expressed by 80–100% of PNETs, with the exception of insulinomas for which the rate of expression is 50–70% (13). Functional imaging techniques include indium-111 somatostatin receptor scintigraphy (111In-SRS, Octreoscan) and gallium-68 positron emission tomography (68Ga-PET, Netspot), both of which

use radiolabeled somatostatin analogs to localize neuroendocrine tumors. 111 In- SRS predates 68Ga-PET and has been more widely available; however, due to its quicker acquisition and superior sensitivity, 68Ga-PET is rapidly becoming the functional imaging modality of choice (13).

Surgical resection is the gold standard treatment for localized insulinomas. Nodal sampling might be performed in order to decrease the risk of tumour understaging. Tumour size, location, and relationship with the main pancreatic duct should guide the surgical decision-making in patients with benign insulinomas. Enucleation can be proposed to patients with insulinomas smaller than 2-3 cm and located at ≥ 3 mm from the main pancreatic duct. EUS-guided radio-frequency ablation (EUS-RFA) is a novel technique able to induce necrosis of small pancreatic lesions (14).

Enucleation is a suitable method if the tumor is located in the head of the pancreas and also for tumors of the body and tail of the pancreas. Enucleation can cause injury to the main pancreatic duct if the distance to the tumor is small, and suturing of the pancreatic parenchyma after enucleation can cause stenosis of the main pancreatic duct. In such cases, spleen-preserving distal pancreatectomy with conservation of the splenic artery and vein (Kimura's method) can be performed. These procedures are performed for relatively small tumors of less than 2 cm, without liver or lymph node metastasis, especially for insulinomas (1).

Titan AL et al. conducted a study indicating that patients with locally advanced PNETs, who do not have liver or distant metastases, can safely undergo tumor excision with acceptable rates of disease-free progression and mortality. The study consisted of 99 patients with T3/T4 tumors and no distant metastatic disease. Most patients underwent a distal or subtotal pancreatectomy; but there were also patients who underwent pancreaticoduodenectomy, total pancreatectomy and other pancreatic procedures. In 86 patients, concurrent resection of additional organs was necessary. The majority of these cases involved the resection of the superior mesenteric vein/portal vein confluence, while four patients underwent resection of the celiac axis or superior mesenteric artery. The five-year disease-free survival rate was 61% (61 patients), and the five-year overall survival rate was 91% (91 patients) (15).

Surgical resection of the primary site of disease, as well as resection of metastatic disease results in significant increase in survival, benefits for patients with stage IV PNET. Resection of the primary tumor with pancreaticoduodenectomy or metastasectomy significantly improved overall survival time compared with performing no resection in patients with metastatic disease (16).

The aim of our study was to observe the outcomes of patients treated in our surgical unit over a period of 10 years.

Material and Methods

This study is a retrospective analysis of patients with PNETs treated in our unit over a period of 10 years (2013-2022). The patient files were evaluated and the following parameters were taken into consideration: gender, age, primary tumor site, extension of the disease (localized vs. disseminated), metastatic sites (if any), hormone- related symptoms, the therapeutic approach, tumor localization, type of surgery, histopathological results, postoperative mortality, and morbidity. Postoperative mortality was defined as death occurring in the first 30 postoperative days or prior to discharge from the hospital. The occurrences of Delayed Gastric Emptying (DGE) and Postoperative Pancreatic Fistula (POPF) were evaluated in accordance with the International Study Group of Pancreatic Surgery (ISGPS) classification system (17,18). Complications were defined as any adverse event from the normal postoperative course in the first 30 days after surgery. Major complications that required endoscopic, radiologic or surgical intervention were defined as class 3 or higher according to Clavien classification system (19). Histopathological tumors were evaluated according to WHO classification.

Written informed consent was obtained from all patients.

Results

Baseline Characteristics

Over the course of 10 years, there were 16 patients diagnosed with and treated for PNETs. The median age was 59 years, with a minimum of 18 and a maximum of 76 years. Six men with pancreatic neuroendocrine tumors and 10 women were found in the study group. The preoperative work-up consisted of imaging and laboratory investigations. Imaging evaluation consisted of computed tomography (CT), magnetic resonance imaging (MRI) and in selected cases, angio-computed tomography. Tumor markers CA19-9, ACE and AFP were also tested. Insulin and

C-peptide values were interpreted in relation to the glucose level at the same time point. The localization of neuroendocrine tumors was found in the head of the pancreas in 10 patients, and in 6 patients in the tail or pancreatic body. Four patients presented with functional PNETs. The presence of metastatic disease was confirmed in 4 patients.

Surgical interventions consisted of: pylorus-preserving pancreaticoduodenectomy in 5 cases, distal pancreatectomy in 3 cases, enucleation of tumor in 4 cases, liver biopsy in 3 patients and one case which required a choledocho-duodenostomy and a liver biopsy (*Table 2*). In our series, preoperative biliary stenting was limited to one case, in which this was the treatment option due to severe cholestasis and impaired liver functional tests.

For patients with PNETs confined to the pancreas and regional lymph nodes, treatment options included pancreatico-duodenectomy or distal pancreatectomy. Pancreaticoduodenectomy was performed for tumors of the pancreatic head. Two patients had a preoperative diagnostic of neuroendocrine tumor, 2 patients with pancreatic adenocarcinoma biopsy, and 1 patient who underwent surgery without biopsy. All patients were staged by CT and MRI. The tumor size varied between 2.1 and 4.8 cm.

All patients with enucleation had a pre-operative diagnosis of sporadic insulinoma, based on imaging (CT or MRI), laboratory investigations and clinical symptoms (episodes of severe hypo-glycemia, sweating, dizziness). The localization of neuroendocrine tumors was found in the head of the pancreas in 3 patients, and in one patient in the pancreatic body. Tumor size varied between 1.7 and 2.7 cm for patients with enucleation.

Distal pancreatectomy along with resection of the spleen was performed according to pre-operative CT/MRI imaging and based on intra-operative findings. No metastases were found in these patients.

One particular case was of a patient in whom intraoperative exploration revealed locallyad-vanced pancreatic tumor with vascular invasion, liver metastasis, but also signs of peritoneal involvement. The surgical intervention consisted of peritoneal node excision, liver biopsy and choledochoduodenostomy. It is worth mentioning that during the preoperative staging of this patient, no peritoneal carcinomatosis was suspected.

Three patients with multiple bilobar hepatic metastases and tumors of the pancreatic body and tail (large tumors with local invasion) were found in our study group. An exploratory laparoscopy was performed with the aim of obtaining tissue specimens to confirm a histological diagnosis.

Table 2. Baseline characteristics

Characteristics	n
Age	
<60	6
>60	10
Male	6
Female	10
Localization of tumor	
Head	10
Body/ tail	6
F-PNETs	4
NF-PNETs	12
Metastatic disease at diagnosis	4
Radical surgery	12
Pylorus-preserving pancreaticoduodenectomy	5
Distal pancreatectomy	3
Enucleation of tumor	4
Palliative surgery	1
Liver biopsy	3

Postoperative Outcomes

Outcomes after surgery are summarized in *Table 3*. Mean length of stay was 10.6 days. In the study group there were 4 cases that presented grade I-II complications (Clavien-Dindo). There were no cases of postoperative or 30 days mortality. Five cases underwent pylorus-preserving pancreatico-duodenectomy. In all cases a duct-to-mucosa anastomosis was performed, with pancreatic duct stenting. A feeding jejunostomy was inserted for postoperative nutritional support and a nasogastric tube for gastric evacuation was inserted. The nasogastric tube was held in

Table 3. Postoperative outcomes

Mean length of in hospital stay	10.6 (3-25)
Grade I-II complications (Clavien-Dindo)	4
Grade III-V complications (Clavien-Dindo)	0
Pancreatic fistula	1
Delayed gastric emptying	1
Postpancreatectomy hemorrhage	0
Other infections	2
Reoperation	0
In hospital mortality	0
30 day mortality	0

position for a mean of 5 days. Postoperative care included routine administration of octreotide analogues, early enteral feeding using jejunostomy, continuous proton pump inhibitors. Delayed gastric emptying occurred in one case mandating only the necessity to reinsert the nasogastric tube, but under conservative treatment the further evolution was favourable.

In one patient with enucleation of the tumor, a grade I pancreatic fistula occurred on the 5th postoperative day, but the evolution was simple and the patient was discharged. Three months later the patient underwent a CT-scan in the context of a dyspeptic syndrome, which revealed a peripancreatic cystic mass in contact with the pancreas and gastric body about 10 centimeters in size. Surgical intervention was decided, performing cysto-gastro-anastomosis, with successful outcome.

Other postoperative complications included cholangitis in 2 cases successfully treated with antibiotics.

Table 4. Histopathological results

Histopathological features	n
NET G1	8
NET G2	6
NET G3	1
NEC	1
Mixed Tumors	
Coexistence of neuroendocrine Tumor (G1) and Adenocarcinoma of the Pancreas	1
Coexistence of pancreatic neuroendocrine tumor (G1) and adenocarcinoma of the ampulla of Vater	1
Nesidioblastosis + micro neuroendocrine tumor (G1)	1
Neuroendocrine Tumor (G1) + retroperitoneal leiomyosarcoma	1
Multifocal neuroendocrine tumors	1

Table 5. Staging

American Joint Committee on Cancer (AJCC) staging	n
Stage I	7
Stage II	2
Stage III	3
Stage IV	4

Histopathological Characteristics

Immunohistochemistry was performed in all patients, testing chromogranin, synaptophysin, CD56, Ki67 and number of mitoses/10 HPF and in selected cases CDX2, CK 20, CK7, TTF1 (*Fig. 1 A, B*). Relying mainly on established histopathologic criteria, the results show well differentiated PNET in 8 cases, G2 PNET in 6 cases, G3 PNET in 2 cases, and one neuroendocrine carcinoma. Of these, 4 patients had mixed tumors, and one patient with multifocal neuroendocrine tumors (*Table 4*).

Regarding the staging of the PNETs according to AJCC, most of them were classified as stage I (n=7), followed by stage IV(n=4) (*Table 5*). In our cohort of patients diagnosed with PNETs, the decision to administer chemotherapy was guided by the presence of negative prognostic factors and advanced tumor staging. Patients in stages III and IV, with locally advanced disease or distant metastases, were considered eligible for adjuvant treatment in accordance with current literature recommendations. Additionally, tumor aggressiveness-defined by high ki-67 prolifera-

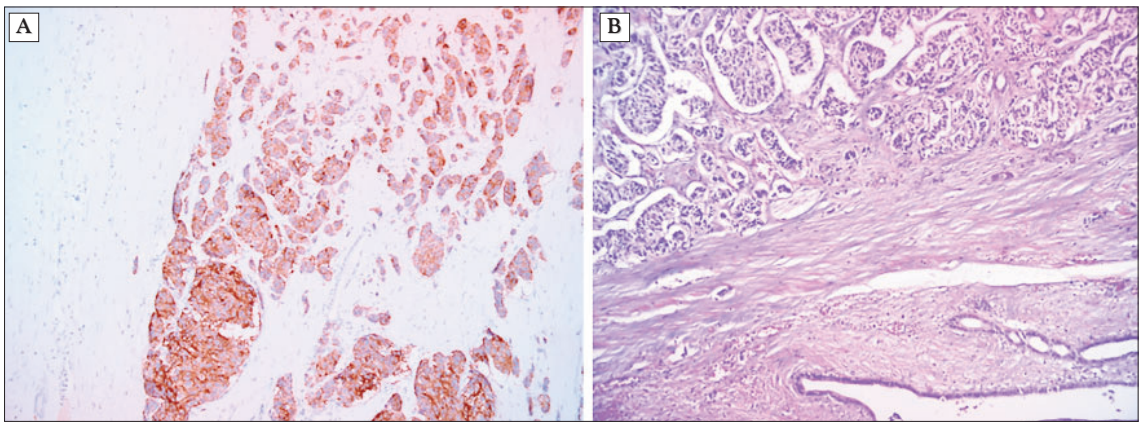

Figure 1. **(A)** Synaptophysin positive in neuroendocrine cells. **(B)** CD56 positive in neuroendocrine cells

tion index, histological grade G2-G3, and the presence of vascular or perineural invasion was also taken into account. The median follow-up period was 37.7 months. Of the 16 patients, 6 died, 4 patients with stage IV and 2 patients with stage III.

Discussions

Histological grading systems and TNM staging classifications as outlined by the World Health Organization (WHO), European Neuroendocrine Tumor Society and American Joint Committee on Cancer are now of established value in prediction of prognosis and are now routinely used in the real clinical practice worldwide (4), but no specific criteria have yet been established to definitively and unequivocally predict the behaviour of PNETs. As a consequence, the heterogeneous and often unpredictable behaviour of PNETs leads to difficult management of these patients (2). The significant rise in the number of incidentally discovered pancreatic neuroendocrine tumors (PNETs) aligns with another development: the growing capability to achieve a preoperative histological diagnosis in increasingly smaller pancreatic tumors using endoscopic ultrasonography combined with needle aspiration (20).

Pancreatic NETs are definitively diagnosed by immunohistochemistry (IHC) and histological examination of the tumor. Tissue may be obtained via EUS and FNA (fine needle aspiration) of the pancreatic tumor, by percutaneous core needle biopsy of a liver metastasis, or by surgical resection, although every effort should be made to obtain a tissue sample prior to operation (13). Due to the limited amount of material obtained by FNA, biopsies taken using this technique may be more prone to sampling error and tend to underestimate tumor grade (21).

Somatostatin receptor scintigraphy is often used, but PET scan with 68-Ga DOTATATE has been approved recently by the FDA and has improved sensitivity (22). Although tumor stage is based on the American Joint Committee on Cancer (AJCC) TNM staging system, the primary prognostic factor for PNETs is tumor grade, which is assessed through immunohistochemical analysis of biopsy samples (23). From a curative standpoint, all patients diagnosed with functional PNETs should be assessed for surgical intervention (2).

The main weakness of this study is the small number of cases that only enables for a descriptive study. However, it is a retrospective study, based on the experience of our clinic, with a homogenous treatment plan for all patients. We must also consider the fact that since the beginning of the study, new therapies have been identified as effective for patients with pancreatic neuroendocrine tumors.

Enucleation, a procedure designed to protect pancreatic tissue, has gained popularity in various studies. This trend likely reflects a heightened priority on preserving pancreatic function and decreasing the invasiveness of surgery. It is especially advantageous for small, well-defined tumors, as it allows for their removal while keeping the surrounding pancreatic parenchyma intact (24).

In this study, pancreatic enucleation was performed on small, superficial neuroendocrine tumors that were not connected to or closely related to the pancreatic duct, with the goal of avoiding any damage to the duct. This decision was based on preoperative imaging (CT or MRI) and intraoperative assessments of the size of the tumor, superficial location, and proximity to the pancreatic duct. All 4 female patients with enucleation had a preoperative diagnosis of sporadic insulinoma, based on imaging, laboratory investigations, and clinical symptoms (episodes of severe hypoglycemia, sweating, dizziness). The localization of neuroendocrine tumors was found in the head of the pancreas in 3 patients, and in one patient in the pancreatic body. All patients underwent an open approach, with an R0 (no residual tumor) resection.

One factor in the surgical management of insulinomas that has been debated is tumor size, with tumors $\leq$ 2.5 cm suggested to be safe for enucleation, but Naples et al. published the results of a single center experience with sporadic pancreatic insulinoma where there were no tumor size criteria for enucleation cases, and there were two patients undergoing an open enucleation with tumors > 2.5 cm (25). In our study the tumor size varied between 1.7 and 2.7 cm for patients with enucleation.

In general, PNETs are approached via laparotomy to facilitate adequate inspection of the abdomen and debulking of nodal or distant metastases. In our study group, the procedures were performed by open approach, except for the three patients with laparoscopic liver biopsy. However, for patients with small, localized tumors, distal pancreatectomy or enucleation may be performed laparoscopically with similar outcomes. In tumors that are located in the body or the tail of the pancreas and are not suitable for enucleation,

laparoscopic distal pancreatectomy is the treatment of choice. This surgery can be further divided into three different entities: spleen-preserving distal pancreatectomy with splenic vessel preservation, spleen-preserving distal pancreatectomy without splenic vessel preservation, and distal pancreatectomy with splenectomy (26).

In recent years, laparoscopic pancreaticoduodenectomy is also performed more often for benign and malignant lesions, because its feasibility, safety, and good oncological outcomes. However, this procedure is not yet widely performed or accepted as the gold standard treatment for PNETs (27).

Peritoneal carcinomatosis in patients with gastro-entero-pancreatic neuroendocrine tumors is another topic of discussion because it represents a clinical challenge, as there is a lack of comprehensive data to guide management approaches. Surgical options, such as cytoreductive surgery, have demonstrated potential for enhancing symptom management and overall survival, especially when a 70% reduction of tumor burden can be attained (28). In our study group, there was only one patient with peritoneal carcinomatosis, hepatic metastases, and locally advanced pancreatic tumor, for whom the surgery consisted of peritoneal node excision, liver biopsy, and choledochoduodenostomy. The histopathological result revealed large cell neuroendocrine carcinoma. Clinical management was discussed at interdisciplinary tumor board meetings, not only for him, but also for all the patients. The cases were discussed before the surgery, but also after the final histopathological results.

In terms of postoperative outcomes, Beane et al. compared outcomes between enucleation and resection, and the results showed a higher pancreaticoduodenectomy or distal pancreatectomy mortality rate than enucleation ($p = 0.016$). In the same study, the rates of serious morbidities, lengths of stay, and surgical site infections were lower for both distal pancreatectomy and enucleation than pancreaticoduodenectomy (29). Jilesen et al. reported that the postoperative morbidity following enucleation of PNETs is similar to that associated with pancreaticoduodenectomy or distal pancreatectomy, indicating that enucleation should be regarded as a high-risk procedure (30). In our study group, there were 4 cases that presented grade I-II complications (Clavien-Dindo): one delayed gastric emptying, two cholangitis after pancreaticoduodenectomy, and one postoperative pancreatic fistula after enucleation.

The increasing diagnosis of small PNETs presents numerous challenging clinical decisions. While these tumors are generally indolent, a notable percentage (up to 39%) may exhibit aggressive behavior despite their small size (2). Complete resection for NF-PNET is associated with 5-year survival rates of 70-80%. It has now been established that not all localized NF-PNETs have the same biology (31).

The results of a multicenter prospective observational study from the Netherlands (PANDORA study) indicate that watchful waiting appears to be a safe alternative to upfront surgery in patients with NF-PNET not exceeding 2 cm, although longer follow-up is required (32).

ENETS has promoted another larger prospective, observational study (ASPEN study) that involves more than 40 institutions worldwide, and is currently enrolling 1000 patients affected by asymptomatic NF-PNET ≤ 2 cm. The ASPEN study is designed to investigate if an active surveillance of asymptomatic NF-PNEN $\leq$ 2 cm is safe as compared to surgical approach (33). The management of patients with NF-PNET >1 cm and ≤ 2 cm, without dilation of the main pancreatic duct, should be personalized according to the type of needed surgical resection as well as to patients' comorbidities Surgery is strongly recommended for all NF-PNET associated with main pancreatic duct dilation and/or larger > 2 cm (31).

Detailed information on the simultaneous coexistence of adenocarcinoma and NET, as well as their relationship, is rare because the occurrence of these two pathological entities together is extremely uncommon. In the literature, very few cases have been described concerning NET with adenocarcinoma of the pancreas (34). In large series studies, the incidence of combined neoplasms ranged from 0.06 to 0.2% of all pancreatic tumors. In most cases, the coexistence of both tumors was an incidental discovery after the examination of the surgical specimen (35). The same conclusions can be drawn in the case of the patient with coexistence of pancreatic neuro-endocrine tumor (G1) and pancreatic adenocarcinoma.

PNETs in patients with hereditary cancer syndromes are typically multifocal (36). When tumors are multifocal, achieving complete resection becomes challenging, and an extensive surgical approach might increase the risk of complications (3). Because many PNETs may have an indolent disease course, the optimal time to initiate treatment with somatostatin analogs in asymptomatic patients is blurred. The guidelines

by the ENETS, NCCN, and North American Neuroendocrine Society (NANETS) suggest initiation of somatostatin analog treatment in asymptomatic patients with high burden of well-differentiated, unresectable PNET (23).

Research has explored targeted therapies for treating PNETs. In a phase 3 clinical trial, sunitinib, a tyrosine kinase inhibitor used as adjuvant therapy, showed a median progression-free survival of 11.4 months, compared to just 5.5 months in patients with well-differentiated PNETs. Both everolimus and sunitinib demonstrate antiproliferative effects that extend progression-free survival in patients with unresectable or metastatic insulinoma. If these therapies fail, a chemotherapy regimen should be considered for malignant insulinoma (8). These treatments typically lead to disease stabilization, but only for a limited duration. In the RADIANT-3 trial, everolimus resulted in a progression-free survival (PFS) of 11 months for PNET (38). In our descriptive study, all stage III and IV patients received adjuvant chemotherapy (cisplatin and etoposide protocol) and somatostatin analogs. For these patients, chemotherapy was indicated to reduce the risk of tumor progression and improve overall survival, particularly in cases with unresectable metastases.

Promising data have been obtained on peptide receptor-targeted radiotherapy (PRRT) in the treatment of NETs with liver metastases using Dotatoc (Edotreotide) or Dotatate (Oxodreotide) labeled with 90Yttrium and Lutetium-177 (Lu-177). The initial key prospective clinical trial, NETTER-1, focused on G1 and G2 gastro-enteric (GE) NETs, comparing the radiolabeled peptide Lu-177-Dotatate with the somatostatin analogue Octreotide-LAR (39).

Based on the data from the study of Baron, a retrospective analysis was made for patients with advanced PNETs, previously treated with one or several lines of chemotherapy, of whom 90% had progressive disease and the majority had grade 2 tumors, undergoing peptide receptor radionuclide therapy (PRRT) with 177Lu-Dotatate, with good indicators (40). Phase 3 trial, NETTER-2 recently published the first end point of the study, and the results are promising. First-line 177Lu-Dotatate plus octreotide LAR significantly extended median progression-free survival (by 14 months) in patients with grade 2 or 3 advanced gastroenteropancreatic neuroendocrine tumor (41). PRRT can be considered in functional and non-functional NETs with positive somatostatin receptor scintigraphy results regardless of localization.

Conclusion

This study outlines the surgical management and clinicopathological findings of PNETs. There are various surgical options, such as enucleation of the tumor, distal pancreatectomy with splenectomy, pancreaticoduodenectomy. Surgical resection is the mainstay of therapy, particularly for localized disease. Surgical therapy must be tailored to tumor and clinical characteristics. Consideration to disease extent and location, tumor grade, performance status, symptoms, comorbidities, and patient preference should all be considered and re-evaluated at each treatment decision point. Patients were evaluated for adjuvant treatment based on negative prognostic factors, stage, histological grade, and ki-67 proliferation index. Of the16 patients, 6 died during follow-up, all of whom were in advanced stages (III-IV) at the time of diagnosis. These findings highlight the significant impact of tumor staging on patient, but the small sample size limits the ability to draw general conclusions.

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Author's Contributions

Conception, design, collection of data, interpretation: MMG, IH, DVS, BF, MGA, IR, VS. Drafting the manuscript: MMG, DVS. All authors participated and approve the content of the manuscript.

Conflict of Interest

The authors declare no conflicts of interests.

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