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Review Article

Updated Surgical Management of Pancreatic Neuroendocrine Tumors

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Abstract

The incidence of Pancreatic Neuroendocrine Tumors (PNETs) is growing, related in part to the increased incidental diagnosis of small asymptomatic non-functional tumors. Arisen from the uncontrolled proliferation of neuroendocrine cells with genetic alterations inducing hormone secretion, the PNETs are majorly sporadic, non-functional, and associated with genetic syndromes, mainly Multiple Endocrines Neoplasm type 1 (MEN1) in up to 5% to 10% of cases. Because of the very high heterogeneity, optimizing management and standardizing therapeutic strategies for PNETs remains a challenge for surgeons, requiring a multidisciplinary collaboration. Surgery for PNETs has evolved varying from radical resection to parenchyma sparing surgery and even now selective conservative management. This review work aims to provide an update regarding the surgical treatment for PNETs, in the light of the recently published reports.

Keywords: Pancreatic neuroendocrine tumor; Surgical management; Pancreatic surgery; Sparing parenchyma resection; Follow-up

Introduction

Pancreatic Neuroendocrine Tumors (PNETs) is an uncontrolled proliferation of neuroendocrine cell associated with further genetic alterations and induced hormonal secretion including glucagon/insulin/gastrin/VIP. The significant increase in PNETs incidence during the past decades is in part related to the widespread use of cross-sectional imaging resulting in an increased diagnosis of small asymptomatic non-functional PNETs or "incidentalomas" [1]. Currently, the PNETs represent approximately 3% to 5% of all diagnosed pancreatic tumors with an annual incidence of 0.8 per 100.000 persons [1,2]. In addition, however, the vast majority of the PNETs are sporadic. Optimal management with standardized therapeutic strategies remains difficult because of the very high heterogeneity of PNETs. Surgery for PNETs has evolved varying from extended radical surgery to parenchyma sparing resection and even now conservative management or "wait-and-see" strategy [3-6]. This review work aims to provide an update regarding the surgical treatment for PNETs, in the light of the recently published reports.

Overview of PNETs

Physiopathology

Physiopathology Developed from the uncontrolled proliferation of the neuroendocrine cells, up to 5% to 10% of PNETs frequently arise from genetic syndromes including Multiple Endocrine Neoplasm type 1 (MEN-1); Von Hippel-Lindau syndrome (VHL); Neurofibromatosis type I (NF1). About 70% to 80% of patients with MEN-1 will develop PNETs [7,8], so, MEN-1 is the most common genetic syndrome associated with PNETs. Non-Functional (NF)-PNETs represent 60% to 85% of PNETs [9]. PNETs vary from indolent well-differentiated to poorly differentiated tumors with biological and molecular heterogeneity [10]. Understanding of disease and pathogenesis of PENTs have been well improved [11]. Genetic alterations have been identified leading to defining a subset of patients with more aggressive tumors and poor oncological outcomes [12-14].

Clinical and biological diagnostic

Mostly small and indolent, the diagnosis of PNETs is usually delayed and up to 50% of PNETs are discovered incidentally in surgical series [15]. Approximately, metastasizes are present in half of the patients at the time of diagnosis [16]. Majorly non-functional (80% to 90%), the clinical pattern of Non-Functional PNETs (NF-PNETs) is poor with unspecific symptoms such as abdominal pains or bowel disorder. Depending on location, the NF-PNETs can be revealed by jaundice (17% to 50%), acute pancreatitis (45%), weight loss (20% to 35%), or palpable mass related to a locally advanced disease [17]. Instead of NF-PNETs, the clinical symptoms of Functional PNETs (F-PNETs) are related to specific hormone hypersecretion. In decreasing order insulin, glucagon, gastrin, VIP, and somatostatin are the most frequent secreted hormones. Mainly sporadic, Insulinomas account for 30% to 40% of F-PNETs. Also, gastrinomas are the most frequent F-PNETs in MEN-1 syndrome (54%) [18]. Biologically, about 80% of PNETs have an increased plasma Chromogranin A (CgA) level, and CgA is widely used as a biomarker for PNETs, and it correlated to tumor burden and liver metastasis, specifically in well-differentiated tumor [19]. However, many clinical conditions may be associated with increased CgA including Helicobacter pylori infection, Biermer's disease, atrophic gastritis, drugs, etc. CgA is a useful biological marker for response and recurrence after treatment, and it also has a prognostic value. However, a high level of CgA should be taken into consideration only with a normal plasmatic gastrin level. Specific hormones as insulin, gastrin, glucagon, VIP, should be only performed according to the clinical symptoms.

Pathological diagnostic

The confirmation of the pathological diagnosis of PNETs is done if at least two markers among CgA, Synaptophysin or CD56 are expressed in immunohistochemistry. The histoprognostic

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classification of PNETs is based on a proliferative activity defined by the Ki67 index and the mitotic count (number of mitoses per 10 high power fields). The revised World Health Organization (WHO) classification (2017) included the following modifications, the cut-off Ki-67 raised to 3% for G2 tumors, the Grade-3 PNETs was divided into the well-differentiated neuroendocrine tumor of high-grade NET-G3 and poorly differentiated NEC NEC-G3. Up to 20% of G3 tumors was NET-G3 with a Ki-67 index varying from 20% to 50% and should be managed as a G2 tumor (Table 1). The Tumor-Node-Metastasis classification (TNM) is also recommended for defining a prognostic subset of the tumor. New criteria and modifications on T-stage and M-status have been introduced in the 8th AJCC edition (2017) and asserted by the European Neuroendocrine Tumor Society (ENTS; Table 2). As reported by studies, this new classification is more accurate than the previous 7th AJCC edition in defining the prognosis of patients with PNETs.

Table 1: 2017 WHO histoprognostic classifications of pancreatic neuroendocrine neoplasms.

Grade	Mitotic index	KI67%	Differentiation
G1-PNET	<2	<3%	Well differentiated
G2-PNET	2-20	3% to 20%	Well differentiated
G3-PNET	>20	>20%	Well differentiated
G3-PNEC	>20	>20%	Poorly differentiated
MINEN	Mixed neuroendocrine–non-neuroendocrine neoplasm (minor component > 30%)		

WHO: World Health Organization; PNET: Pancreatic Neuroendocrine Tumor; PNEC: Pancreatic Neuroendocrine Carcinoma; MINEN: Mixed Neuroendocrine-nonneuroendocrine Neoplasm

Table 2: AJCC 8th TNM staging classification.

	AJCC 8th edition for pancreatic neuroendocrine tumors
T1	Tumor limited to the pancreas of <2 cm
T2	Tumor limited to the pancreas of >2 cm to <4 cm
T3	Tumor limited to the pancreas of >4 cm or invading duodenum or common bile duct
T4	Tumor invades adjacent structures or vessels (CA or SMA)
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M0	No distant metastasis
M1	
M1	a Metastasis confined to liver
M1	b Metastasis in at least one extrahepatic site[a]
M1	c Both hepatic and extrahepatic metastases

AJCC: American Joint Committee on Cancer; TNM: Tumor-Node-Metastasis; SMA: Superior Mesenteric Artery; CA: Celiac Artery
[a]Non-regional lymph node, lung, ovary, peritoneum, bone, brain.

Morphological imaging

Radiology: The PNETs are usually hypervascularized with the tendency of easier identification from the surrounding pancreatic parenchyma in the delayed arterial phase (30s) enhancement, and "washout" in the portal venous phase (60-90s). Therefore, Multiple Detectors Computed Tomography (MDCT) scan is the first imaging modality used to detect PNETs with including delayed arterial (30s) and portal venous (60-90s) phases to increase the detection rate. The sensitivity and specificity of MDCT are 82% and 96%, respectively [20]. MDCT allows to detect F-NETs in an earlier stage with small size and to assess the local extension, vascular involvement, and distant metastases. In addition, Magnetic Resonance Imaging (MRI) with gadolinium-enhanced and diffusion-weighted sequences is the more accurate modality to detect small tumors and liver metastases [21]. Also, it was more accurate than SRS for the detection of distant metastasis, especially small liver metastasis [22]. Contrast-enhanced Endoscopic Ultrasonography (EUS) has a higher sensitivity in detecting small tumors (<20 mm) and regional Lymph Node (LN) metastasis [23]. Also, it is more interesting to evaluate vascular invasion, determine distance separating main pancreatic duct and tumor when sparing surgery is considered, and allow biopsy for diagnostic certainty.

Nuclear medicine imaging: The radiometabolic Somatostatin Analog (SA) is used to uptake the somatostatin receptor (SR) that reportedly was present in about 70% of PNETs, especially in well-differentiated tumors. This functional imaging allows assessing tumor stage, metastasis and SR expression in a bite to select patients for Peptide Receptor Radiometabolic Treatment (PRRT). The Somatostatin Receptor Scintigraphy (SRS) also called Octreoscan has a respective sensibility and specificity of 90% and 80% in diagnosing well-differentiated PNETs larger than 1 cm. However, SRS has a limited diagnostic value for NF-small NET of <1 cm. Positron Emission Tomography (PET)/CT associated with 68Gallium-Labeled Somatostatin Analog (68GA-SA-PET/CT) has sensitivity up to 97% in detecting gastro-pancreatic NETs. Also 68GA-SA-PET/CT sensitivity in detecting LN metastases and distant metastases (liver, peritoneum, and bone) was higher than Octreoscan [24]. 68GA-DOTATOC; 68GA-DOTATOTE, 68GA-DOTANOC are the current available SAs, which have a higher affinity for SR than Octreoscan but without superiority of one SA over others in detecting PNETs [25]. For poorly differentiated NETs with low expression of SR, NEC or well-differentiated PNETs with Ki67>10%, Fluorodeoxyglucose (FDG)-PET/TDM is more suitable with better sensitivity in this setting [24]. It can also be used as a prognostic tool.

Surgical Treatment

The natural history and biological behavior of the PNETs have been better studied and understood leading to substantial progress in the surgical management of PNETs during the last decade. Therefore; conservative treatment can be supported in selected patients with indolent and small tumors. In bite to define the best suitable strategy for PNETs management, treatment decisions should be made after a multidisciplinary discussion.

Surgical strategy

When surgery is considered, two strategies can be discussed, including standard pancreatic resection with lymphadenectomy, and conservative surgery or Parenchyma Sparing Surgery (PSS) with LN picking. As known, node involvement is a strong prognostic factor of survival, so, pancreaticoduodenectomy and distal pancreatectomy should be indicated for PNETs with a high risk of nodal involvement [26]. Distal pancreatectomy with spleen preservation can be considered for small left-sided PNETs with benignity presumption [27]. Parenchyma Sparing Surgery (PSS) includes enucleation and central pancreatectomy and can be considered for small- and low-grade tumors [28,29]. However, LN picking should be performed to assess node invasion. Enucleation may be indicated for a small low-grade or benign PNETs located further than 2 mm to 3 mm from the main pancreatic duct. So, preoperative assessment using echo endoscopy and MRI, and/or intraoperative evaluation by echography is highly recommended to refine the tumor location when the tumor is closer to the main pancreatic duct. Central pancreatectomy for tumors of the pancreatic neck and the first part of the body is associated with significant morbidity especially pancreatic fistula, and

so, this surgical procedure is rarely performed for such tumor location. Regarding postoperative pancreatic function, PSSs are only associated with 5% of postoperative exocrine and endocrine insufficiency, and excellent overall and recurrence-free 5-year survival of >95% in selected PNETs. Pancreatic parenchyma sparing is associated with 5% of postoperative exocrine and endocrine insufficiency and excellent overall and recurrence-free 5-year survival (>95%) in selected PNETs.

Minimally invasive approach versus open approach

The open surgery remains the standard of care for pancreatic resection, and nowadays, indications for the minimally invasive approach are not based on clear consensus. Laparoscopic pancreaticoduodenectomy did not show any advantage over the open approach [30]. In addition, and due to increased mortality in the laparoscopic arm, a Dutch trial comparing the minimally invasive approach to open pancreaticoduodenectomy has been prematurely stopped [31]. Differently, the safety and effectiveness of laparoscopic distal pancreatectomy were clearly reported by several studies and meta-analysis; also, it was associated with decreased morbidity rate and shorter length stay [30,31]. Regarding robotic pancreatic surgery, the reported preliminary results of robot-assisted pancreatectomy are encouraging [32,33], however, further trials are required to better evaluate the role of robotic approach in pancreatic surgery especially in pancreaticoduodenectomy that might improve the postoperative outcome.

Surgical indication

The indication of surgery should be balanced with morbidity, mortality and impaired functional results after pancreatectomy. Surgery is clearly indicated for symptomatic NF-PNETs, NF-PNETs greater than 2 cm or 3 cm, NF-PNETs with main pancreatic duct dilatation on imaging. Also, functional PNETs including insulinomas, sporadic gastrinomas, VIPomas, somatostatinomas must be absolutely operated. Recently, a better understanding of the natural history of small sporadic NF-PNETs has led to consider surgery for this category of PNETs [34,35]. Asymptomatic sporadic NF-PNETs<2 cm or "incidentalomas", and MEN-1 NF-PNETs can be managed conservatively, however, active serial imaging follow-up and well-established PNETs diagnosis are required [3,4]. The diagnostic certainty can be confirmed using somatostatin-receptor imaging and/or ideally with EUS-Fine-Needle Aspiration (FNA). The major convenient of this conservative strategy is to undertreating about 10% of patients who might have nodal metastatic involvement [36].

Oncological results

The oncological results varied widely depending on multiple factors including tumor grade, size, and stages. A year disease-specific survival superior to 90% has been reported in resected patients without synchronous liver metastasis [37], and median overall survival ranging from 12years to less than one year for G1-PNETs and G3 tumors has been reported respectively by data from Surveillance, Epidemiology, and End Results (SEER) [2]. Although, overall survival remains mostly excellent, and recurrence incidence after curative surgery varies from 27% to 40% within 3 to 5 years respectively [38]. A Recurrence Risk Score (RRS) has been recently (2019) proposed to tailoring follow-up strategies [39]. This score included independent prognostic factors: tumor, size >2 cm, Ki67 of 20%, and positive LN. The patients were stratified into three groups, low (0-2), moderate (3-5), and high (6-10) risk with a 2-year recurrence rate of 2%, 14%, and 33%, respectively. Postoperative exocrine and endocrine pancreatic insufficiencies vary from 9% to 30% and 5% to 25%, respectively [40]. However, it decreases below 5% after sparing pancreatic surgery [40].

Follow-up following surgery

The main objective of the follow-up is to detect early recurrence by proposing an effective and curative treatment. The secondary resection rate varies from 10% to 25% and less than 10% of the patients develop metastases [41,42]. The routine follow-up for PNETs includes clinical exams, biomarkers, and imaging. The follow-up time should be adapted to tumor aggressivity assessed by using multiple factors including tumor grade, stage, quality of the initial surgery, and patient's health status. Nevertheless, the follow-up frequency varies widely according to the published guidelines [43]. According to published guidelines, several situations have been defined:

1) The Commonwealth Neuroendocrine Tumor Collaboration (CommNETS) [44], recommended using biomarkers only for functional PNET and according to recurrence risk; two groups of patients were identified. Low recurrence risk without requiring follow-up includes G1-PNETs, node-negative, tumors smaller than 2 cm; complete resection of insulinomas of any size with negative LN. High-risk recurrence with requiring follow-up includes tumors with Ki-67 index>5% and positive LNs. The follow-up should be performed every 6 to 12 months for 3 years, then every 1 to 2 years for at least 10 years.

2) The National Comprehensive Cancer Network (NCCN) guidelines [45], recommended performing a clinical examination, biomarkers and CT/MRI every 3 to 12 months after surgery and then every 6 to 12 months for a maximum of 10 years. However, G3-PNETs must be reviewed every 3 months.

3) For European Neuroendocrine Tumor Society (ENETS) guidelines [46], a follow-up with clinical exams, biomarkers and conventional imaging (CT and/or MRI) should be performed every 3 to 9 months for G1 or G2-PNETs. However, follow-up intervals can be increased in the case of "indolent" G1-PNET which is defined as well-differentiated tumors with Ki67<3%. If positive, SR imaging should be repeated every 2 years or earlier when progression is suspected. Resected G3-PNET with R0/ localized R1 should be followed up every 3 months during the first 2 to 3 years, and every 6 to12 months up to 5 years following surgery. The advanced disease should be followed up every 2 to 3 months if active therapy, with performing clinical exams and conventional imaging. The Biomarkers are recommended if they were positive initially [47].

4) The European Society for Medical Oncology (ESMO) guidelines [48], recommend following up, the resected G1 or G2-PNETs with R0/R1 and G3-PNET every 3 to 6 months and 2 to 3 months respectively. Biomarkers CgA first or NSE, CT or MRI should be used, and if positive, SR imaging should be performed after 18 to 24 months. The absence of an international consensus with an excessive risk of radiation exposure and the financial burden of follow-up has anticipated developing a prognostic score for disease recurrence to guide individually tailored surveillance strategies [39,49-51].

Recently, a recurrence risk score (RRS) has been established including prognostic factors: tumors, size, Ki-67 index and lymph nodes [39]. This RRS ranges from 0 to 10 and patients with non-functional, non-metastatic well/moderately differentiated PNET who underwent curative-intent surgery into three groups: low (RRS=0-2), intermediate (RRS=3-5), or high (RRS=6-10) risk group. The

recurrence risk at 2 years was 2%, 14%, and 33% for low, intermediate and high-risk groups respectively. Based on RRS, a proposed follow-up interval was 12, 6, and 3 months for low, intermediate, and high-risk recurrence, respectively [48]. Well known as a prognostic factor, the perineural invasion is not included in previously described RRS [39], however, it was used specifically for G1/G2-PNETs [52].

Another RRS has been described by Fisher et al. [49], including CgA (>5 upper limit of normal), grade (2 or 3), tumor size (≥ 4.0 cm) and surgery for tumor recurrence. According to this score, three groups were identified: low (score=0), intermediate (score=1), and high (score ≥ 2) risks. The 5-year Recurrence-Free Survival (RFS) rate was 39%, 63%, and 96%, respectively. Also, tumor size (>20 mm), LN metastasis, and Ki-67>5% or Mitotic Index (MI) >2 have been used as risk factors, a significantly lower 5-year disease-specific survival was observed in patients with two factors, compared to low-risk patients (70% *vs.* 100%).

Based on tumor localization (distal=1, proximal=4) and Ki-67 (<3%=1, ≥ 3=3), A new lymph node risk score has been described categorizing patients into three groups: low (LNRS 1-2), intermediate (LNRS 3-4), and high (LNRS 5-7) risks with lymph recurrence of 3.2%, 13.8%, and 20.5%, respectively. This lymph node risk score has been designed for PNETs of <2 cm, for which many studies have proposed observation. However, all previously described scores can be used after curative surgery for PNETs.

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