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Review

The Role of Surgery for Pancreatic Neuroendocrine Tumors

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Abstract. *Pancreatic neuroendocrine tumors (PNETs) arise from endocrine pancreatic cells and comprise 3-5% of pancreatic cancers. Surgical resection is the only potentially curative option for PNETs. Surgical candidates should be carefully selected according to tumor functionality, size, location, grade, and stage. Current guidelines state that patients with neuroendocrine carcinoma may not be surgical candidates due to aggressive tumor behavior and poor prognosis, while in cases of PNET with unresectable metastatic disease, resection may be of benefit in certain patients. The current guidelines recommend resection of any size of functional PNETs and of non-functional PNETs >2 cm. Watchful waiting is recommended for patients with non-functional PNETs <1 cm. Further evidence is needed to determine whether surgery for non-functional PNETs of 1-2 cm would be of benefit or if surgery should be individualized. This review aimed to discuss the current literature on the management of PNETs and highlight the utility of surgery in treatment.*

Pancreatic neuroendocrine tumors (PNETs) arise from hormone-producing cells of the pancreas (1) and account for 3-5% of all pancreatic malignancies (2). Functional PNETs can secrete a variety of peptide hormones, however, the majority of PNETs are non-functional (3, 4). Due to the increasing use and improved accuracy of cross-sectional imaging (5), PNETs have an increasing incidence (6, 7). This leads to more frequent consultations with general surgeons and surgical oncologists. Despite the increasing availability of options for the management of PNETs, including somatostatin analogs, temozolomide-based chemotherapy, targeted therapies (*e.g.*, sunitinib, everolimus), peptide receptor radionuclide therapy (PRRT), and immunotherapy (8-10), surgery is the only option that can be potentially curative. Therefore, determining timing of surgical management for these patients is crucial. There are several factors that determine the applicability of surgical treatment for PNETs, which include tumor staging, differentiation, size, functionality, and location. The aim of this review is to summarize these considerations and discuss when surgery is indicated for PNETs.

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Diagnostic Approach

The optimal diagnostic modality for accurately diagnosing PNETs is a pancreatic protocol computed tomographic (CT) scan. This helps characterize vascular involvement, staging, aberrant arterial anatomy, pancreatic and biliary duct abnormalities, and adjacent organ involvement (11). Even though diffusion-weighted imaging with magnetic resonance imaging (MRI) can contribute to PNET detection and provide some information about tumor grading (*i.e.* high-grade tumors have more restricted diffusion) (12), pathological examination of biopsies most commonly obtained using endoscopic ultrasound (EUS) is the gold standard (13).

Since 40-80% of patients with PNET have metastatic disease at presentation, most commonly to the liver (40-93%), proper evaluation of the patient for hepatic metastasis is crucial (14, 15). One distinct advantage of the pancreatic protocol CT scan is that it does not interfere with this crucial assessment of liver metastases, since the arterial and portal venous phases match those recommended for liver imaging (16). The arterial phase is particularly important since PNET liver metastases predominantly receive blood from the hepatic arteries (11). However, the optimal imaging study for

Table I. *Classification and grading criteria for pancreatic neuroendocrine tumors (23).*

Terminology	Differentiation	Grade	Mitotic rate (mitoses/2 mm^2)	Ki-67 index
NET, G1	Well-differentiated	Low	<2	<3%
NET, G2		Intermediate	2-20	3-20%
NET, G3		High	>20	>20%
NEC, small-cell type	Poorly differentiated	High	>20	>20%
NEC, large-cell type				
MiNEN	Well or poorly differentiated*	Variable*	Variable*	Variable*

MiNEN: Mixed neuroendocrine non-neuroendocrine neoplasm; NEC: neuroendocrine carcinoma; NET: neuroendocrine tumor. *In most MiNENs, both the neuroendocrine and non-neuroendocrine components are poorly differentiated, and the neuroendocrine component has proliferation indices in the same range as other NECs, but this conceptual category allows for the possibility that one or both components may be well-differentiated; when feasible, each component should therefore be graded separately.

the assessment of liver metastases is a hepatobiliary-phase MRI with gadoxetate disodium because of its high measurement consistency and detection sensitivity (17-19).

Evaluation of lymph node involvement is also important for patients with PNET. A study of 326 patients undergoing PNET resection at the National Institutes of Health and Stanford University Hospital showed that 52% had lymph node involvement at the time of surgery (20). Both CT and MRI can detect lymph node involvement but are dependent on size criteria for characterization. Somatostatin receptor (SSTR)-based positron-emission tomography (PET) scan has revolutionized the diagnostic approach for PNETs and should be obtained if concerning lymph nodes are identified on conventional imaging studies. A chest CT scan should be obtained if SSTR-PET is not obtained at the time of initial presentation (11).

PNET Grading

One of the most important factors determining PNET management is tumor grade, which is determined using measures of tumor proliferation (mitotic index and Ki-67). Prior to 2017, well-differentiated PNETs were subdivided into low-grade (grade 1; Ki-67 index <3%) and intermediate-grade (grade 2; Ki-67 index 3-20%), while poorly differentiated were classified as high-grade: grade 3; Ki-67 index >20%. However, over time, researchers identified that some grade 3 PNETs are well-differentiated with a relatively good prognosis and response to platinum-based chemotherapy (21, 22). Realizing that not all grade 3 PNETs behave poorly, the World Health Organization decided to revisit this grading system.

PNET classification is based on the 2017 and 2019 World Health Organization neuroendocrine tumors classification (Table I) (23). Yang *et al*. published a study of 480 patients with PNETs who underwent resection between 2002-2018 and reported that the 5-year overall survival for those with grade 1 PNETs was 75.8%, grade 2 PNETs was 58.4%, grade 3 PNETs was 35.1%, and grade 3 pancreatic neuroendocrine carcinoma (NEC) was 11.1% (23). According to the North American Neuroendocrine Tumor Society (NANETS) guidelines, patients with poorly differentiated NEC should not be considered as surgical candidates due to the aggressive disease biology and poor prognosis of NECs (11). In contrast, patients with localized, well-differentiated grade 3 PNETs can be considered for resection in the context of multimodal treatment, such as neoadjuvant therapy (11). In particular, further research of the operative and non-operative options for grade 3 PNETs is warranted.

PNET Staging

Another equally important factor involved in the decision-making process of PNET management is tumor staging. Despite the prior differences between Europe and the United States, the most recent and widely used staging system is the Tumor, Node, Metastasis (TNM) classification of the American Joint Committee on Cancer/Union for International Cancer Control staging system (8th edition, 2017) (Table II) (24). This staging system is based on the definitions proposed by the European Neuroendocrine Tumor Society (ENETS) (24) and is prognostic for survival (2, 25, 26). In 2018, Li *et al*. performed a Surveillance, Epidemiology, and End Results database analysis of 2,350 patients who underwent oncological resection between 2004-2014 (2). They showed that the 5-year overall survival rate for patients with stage I PNETs was 89.9%, for stage II PNETs was 82.6%, for stage III PNETs was 75.8%, and for stage IV PNETs was 56.9% (2). Although no definitive consensus was reached among the experts in the NANETS guidelines, the majority deemed there to be a benefit of primary tumor resection in cases with unresectable metastatic disease (11). Furthermore, they identified the most important factors to take into account during the decision-making process as tumor functionality, location (pancreatic head lesion resection is associated with greater morbidity and recovery time than resection of body or tail tumors), patient age (younger patients are better surgical candidates than older patients), comorbidities, potential local complications, and the possibility to improve response to other therapies (*e.g*., PRRT) (11).

Table II. *American Joint Committee on Cancer/Union for International Cancer Control Tumor, Node, Metastasis Staging of pancreatic neuroendocrine tumors eighth edition (24).*

Primary tumor (T)			
TX	Tumor cannot be assessed		
T1	Tumor limited to the pancreas, <2 cm		
T2	Tumor limited to the pancreas 2-4 cm		
T3	Tumor limited to the pancreas, >4 cm; or tumor invading the duodenum or common bile duct		
T4	Tumor invading adjacent organs (*e.g.*, stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery)		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node involvement		
N1	Regional lymph node involvement		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastases		
M1a	Metastasis confined to liver		
M1b	Metastases in at least one extrahepatic site (*e.g.*, lung, ovary, nonregional lymph node, peritoneum, bone)		
M1c	Both hepatic and extrahepatic metastases		
Prognostic stage groups			
Stage I	T1	N0	M0
Stage II	T2/T3	N0	M0
Stage III	T4	N0	M0
Stage III	Any T	N1	M0
Stage IV	Any T	Any N	M1

Functional PNET

The nomenclature of PNETs can be further influenced by the functionality of the tumor. Around 10-40% of PNETs are functional in that they secrete a predominant hormone, resulting in a clinical syndrome (5, 27). Functional PNETs are also typically well-differentiated. The surgical management for functional lesions relies on two main pillars: Symptom control and improved survival by limiting disease progression (11). Once the PNET is properly classified, graded and staged, and the presence of multiple endocrine neoplasia type 1 (MEN1) and distant metastases are excluded, the next step is to localize the PNET. If the biochemical diagnosis or localization is challenging, then referral to a specialized center is indicated for further evaluation. As previously mentioned, this evaluation might include upper gastrointestinal endoscopy with EUS, pancreatic protocol CT scan, or MRI. If these modalities are still unrevealing, venous sampling or intra-arterial simulation testing may be useful (28, 29). SSTR-PET may also be considered for non-insulinoma PNETs. This has a reported sensitivity of 100% [95% confidence interval (CI)=93-100%], specificity of 57.1% (95% CI=18.4-90.1%), and accuracy of 94.8% for non-insulinoma PNETs, and a reported sensitivity of 22.2% (95% CI=8.6-42.2), specificity of 33.3% (95% CI=0.8-90.5), and accuracy of 23.3% for insulinomas (30). If the PNET is still not localized, surgical exploration with intraoperative ultrasound should be considered at an experienced center (11). Once the functional PNET is adequately localized, surgical resection is indicated according to both the NANETS and the ENETS guidelines (11). Insulinomas have a 5-10% risk of malignancy (31). However, there is a markedly increased risk of 60-90% malignancy for PNETs secreting glucagon, gastrin, vasoactive intestinal peptide, parathyroid hormone-related protein, or ectopic adrenocorticotrophic hormone (5, 11, 27, 32). The biochemical cure rate for resected localized insulinoma is 93-100% and the risk of recurrence is 7.2% (5, 33). On the other hand, the biochemical cure rate for resected gastrinomas is 30-50%, with a 15-year disease-related survival of 98% (34-38). Unfortunately, the cure rates for more aggressive PNETs, including glucagonoma, and those secreting vasoactive intestinal peptide, parathyroid hormone-related protein, or ectopic adrenocorticotrophic hormone are significantly lower (11, 39). Although mostly investigated in the setting of non-functional PNET, regional lymphadenectomy can be considered during surgical resection since evidence from resected gastrinomas suggests an increase in the chance for biochemical cure and improved survival (20, 40).

Non-functional PNET

The majority of PNETs (75-90%) do not secrete a hormone and are therefore categorized as non-functional (3, 4). Because of their association with few symptoms, most non-functional PNETs have an indolent natural history and are diagnosed at more advanced stages, either incidentally or during workup for

pain or compression symptoms (1, 39). Since non-functional PNETs >2 cm are associated with a higher probability of lymph node involvement, poor tumor differentiation, metastasis, and worse outcomes (41, 42), both the NANETS and the ENETS guidelines recommend surgical resection. This holds true even if that means a radical operation with resection of adjacent organs and vascular reconstruction (43). On the other hand, the management of non-functional PNETs <2 cm is more controversial. The NANETS guidelines recommend observation for non-functional PNETs <1 cm and a patient-oriented management for those 1-2 cm depending on age, comorbidities, grade, growth, extent of the required operation, and patient preference (11). The ENETS (5) and the National Comprehensive Cancer Network guidelines (44) state that observation of non-functional PNETs ≤2 cm with EUS, MRI, or CT scan, every 6-12 months is a reasonable option.

However, the argument for resecting non-functional PNETs <2 cm is becoming more supported by a growing body of evidence that shows a relative risk of disease progression and nodal disease. Haynes and colleagues identified that 7.7% (n=3/39) of patients who underwent resection of incidental non-functional PNETs <2 cm developed late metastases or recurrence (45). Furthermore, a National Cancer Database analysis of patients diagnosed with PNETs <2 cm between 1998 and 2006 comparing 309 who underwent resection and 71 observation showed an increased risk of death for the observation group in both univariate analysis (5-year overall survival: 34.3% *vs*. 82.2%) and multivariate analysis (adjusted hazard ratio=2.80, 95% CI=1.28-6.16, p=0.01) (46). Similarly, a meta-analysis of 11 studies demonstrated an increased risk of overall mortality in patients with PNETs ≤2 cm who were observed compared with those who underwent resection at 3 years (risk ratio=1.70, 95% CI=1.27-2.26, p<0.001) and 5 years (risk ratio=2.21, 95% CI=1.75-2.79, p<0.001) (47). Moreover, another National Cancer Database analysis on localized, well-differentiated, non-functional PNETs diagnosed in the United States between 2004-2015 showed that surgery was associated with improved overall survival for patients with tumors 1-2 cm and >2 cm but not for those with tumors <1 cm, when adjusted for covariates (48). Dong *et al*. used international multi-institutional data and reported that patients with PNETs measuring 1.5-2 cm had a higher incidence of lymph node metastases (17.9% *vs*. 8.7%), higher Ki-67 index (>3%: 35.9% *vs*. 18.8%), worse tumor grade (grade 2: 29.2% *vs*. 13.9%), and higher recurrence risk (8.0% *vs*. 4.5%) following curative-intent resection compared with patients with PNETs measuring <1.5 cm. Therefore, they suggested that patients with non-functional PNETs measuring 1.5-2 cm should be strongly considered for surgical resection (49). Notably, another multi-institutional study from France showed that the cutoff of 2 cm used for malignancy for non-functional PNETs might need to be reduced to 1.7 cm to ensure more accurate patient selection (50). Overall, there are numerous studies suggesting benefit in resecting non-functional PNETs <2 cm.

On the contrary, there is also evidence supporting the non-operative management of small non-functional PNETs. Lee *et al*. compared 77 observed *vs*. 56 resected cases with PNETs <4 cm and reported no disease-specific progression or mortality in either group, while 46% of the resected cases had at least one postoperative complication (51). Sadot *et al*. also compared 104 observed *versus* 77 resected cases with PNETs <3 cm and showed that at a median of 30 months, 26 (25%) of the observed patients required resection (65% by patient or physician preference, 31% due to increased tumor size), and none of the 26 patients died or developed metastases after a median follow-up of 6.6 years (52). Similarly, a systematic review of five studies comparing 327 observed *versus* 213 resected cases reported that 46 (14.1%) of the observed patients required resection, with the most common reason being an increase in tumor size (n=19/46), while no disease-related mortality or distant metastasis was reported in the observed group in any of the five studies; the median length of follow-up ranged from 28 to 45 months (53). A 2021 interim analysis of a prospective PANDORA study from the Dutch Pancreatic Cancer Group demonstrated that 89% (n=68/76) of patients with a non-functional PNET ≤2 cm had no disease progression at a median follow-up of 17 months during watchful waiting (54). Although four mortalities were reported, all of them were unrelated to PNET, suggesting that well-selected patients with a non-functional PNET <2 cm can be safely managed with observation (54). Despite the growing evidence for resection of non-functional PNETs <2 cm, there are still several studies suggesting a watchful waiting approach.

Although further evidence is required to definitively determine the appropriateness of observation *versus* surgical resection for small non-functional PNETs, conducting a randomized clinical trial would be particularly difficult since survival is long in these patients, requiring protracted follow-up. Nevertheless, a prospective observational study by ENETS is currently recruiting patients at IRCCS San Raffaele Hospital, Italy (NCT03084770). Patients will undergo active surveillance with MRI, CT scan, 68Ga-labeled PET/CT scan, and/or EUS every 6 months for 2 years, followed by annual imaging for 5 years. This surveillance group will be compared with patients undergoing surgical resection for asymptomatic small pancreatic endocrine neoplasms (ASPEN trial) ≤2 cm. The primary outcome of this study is disease-free survival, while the secondary outcomes include morbidity and mortality after surgical resection, number of patients requiring surgery, type of surgery, PNET evolution and growth, and quality of life. Given the observational nature of the study, the findings of the ASPEN trial may be subject to potential selection bias but will still provide further insight into the argument of

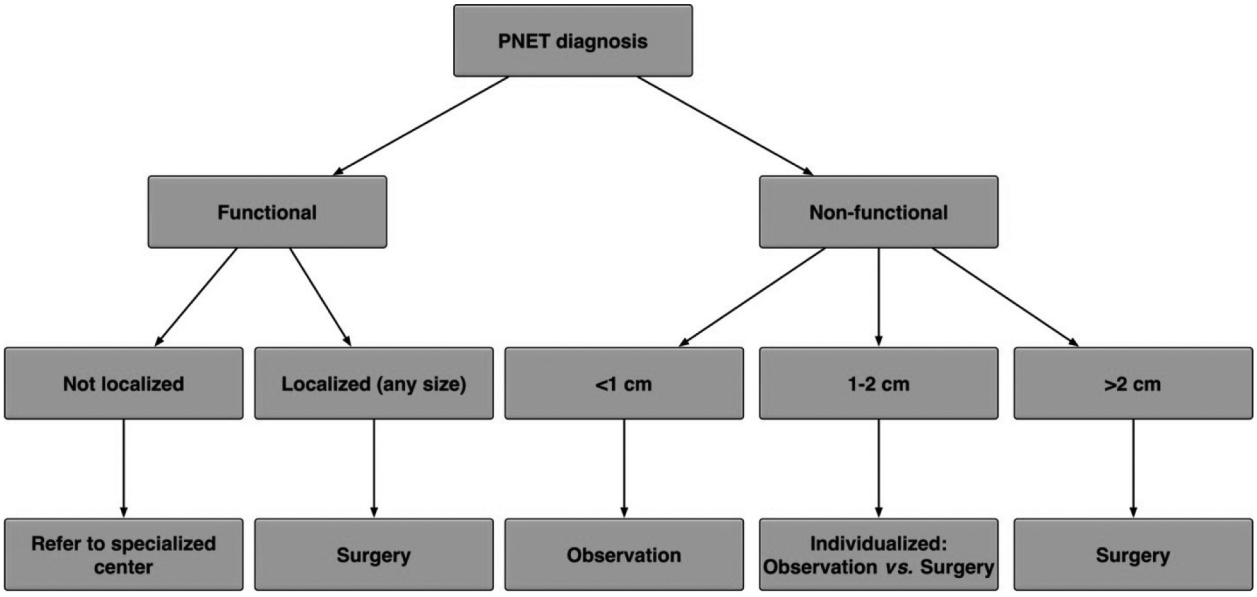

Figure 1. *Proposed treatment algorithm for pancreatic neuroendocrine tumors (PNETs).*

surgery *versus* observation for non-functional PNETs <2 cm. Until then, the proposed management algorithm is provided in Figure 1.

PNET in MEN1

Although MEN1 is seen in 20-60% of patients with Zollinger–Ellison syndrome, more than 60% of patients with MEN1 have either Zollinger–Ellison syndrome or asymptomatic hypergastrinemia (55). In addition, radiographically confirmed, non-functional PNETs and gastrinomas have a prevalence of 30-80% in patients with MEN1 (56-59). In fact, the DutchMEN Study Group evaluated MEN1 patients using pancreatic imaging in a population-based cohort and demonstrated that five out of 350 patients developed clinically significant non-functional PNETs before entering adulthood and the actual risk was 1% at a median of 9.5 years (95% CI=6.5-12.7), 2.5% at a median of 13.5 years (95% CI=10.2-16.9), and 5% at a median of 17.8 years (95% CI=14.3-21.4) (60). Therefore, the authors recommended starting active surveillance with annual EUS, CT, MRI scans for non-functional PNETs with pancreatic imaging at the age of 13-14 years in patients with MEN1 (60).

Low-risk patients with MEN1 and functional PNETs should generally undergo surgical resection according to tumor size and disease extent. However, given the frequent multiplicity of PNETs in these patients, determining definitively that the identified PNET is the actual source of hormone overproduction may be challenging (11). That is particularly challenging for gastrinomas since hypergastrinemia in patients with MEN1 is more likely to arise from duodenal gastrinomas rather than from PNETs. Therefore, medical *versus*. surgical management of patients with MEN1 with hypergastrinemia has been controversial since gastrinomas in these patients are typically small, multiple, and difficult to image. In addition, controlling hypergastrinemia with surgery has been challenging to achieve (36, 61). In fact, the NANETS guidelines recommend the use of EUS to determine the presence of multifocal disease in patients with MEN1 (11). Surgery is a reasonable option for those with MEN1 with hypergastrinemia and lymph node metastasis, poorly controlled symptoms, and PNET-dominant disease (11). For those with non-functional PNETs, the NANETS guidelines recommend resection of tumors >2 cm and observation of tumors <1 cm. Management of non-functional PNETs 1-2 cm in size should be individualized based on symptoms, tumor grade, growth rate or radiographic progression, family history, and comorbid conditions (11).

Extent of Surgery for PNET and Postoperative Outcomes

Surgical resection for PNETs can range from parenchyma-sparing operations, such as enucleation and central pancreatectomy, to major demolitive operations, such as pancreaticoduodenectomy, distal pancreatectomy, or even total pancreatectomy (Figure 2) (62). The decision on the extent of surgery is based on tumor location, size, grade, and

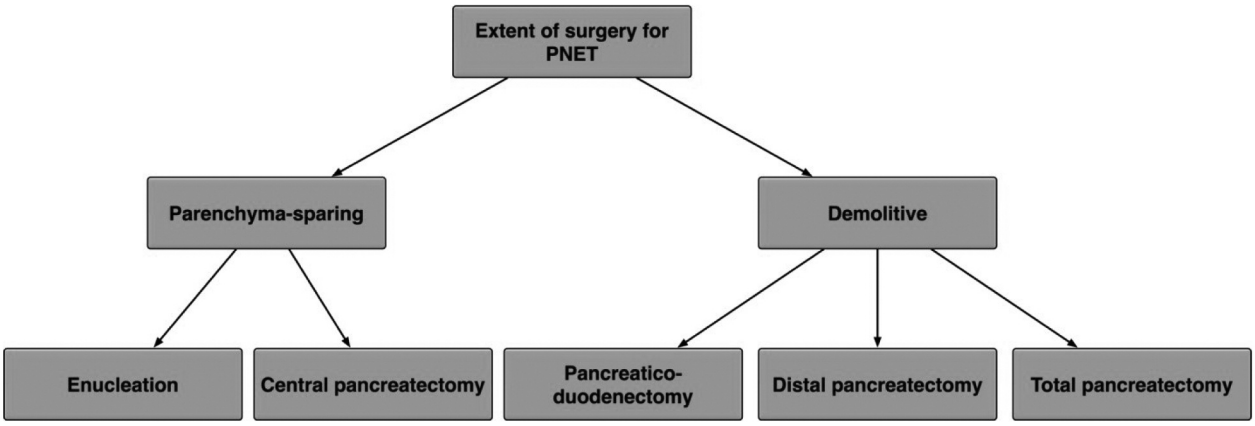

Figure 2. *Extent of pancreatic surgery for pancreatic neuroendocrine tumors (PNETs).*

risk of nodal involvement (63). Parenchyma-sparing surgery can be an option for small, low-grade PNETs (*e.g.*, non-functional PNETs <2 cm or insulinomas), while for patients with large or high-grade PNETs or with increased risk of nodal involvement, demolitive surgery with regional lymphadenectomy should be preferred (11). For PNETs at the body or tail of the pancreas, spleen-preserving distal pancreatectomy may be considered for small presumably benign tumors, depending on the association of the PNET with the splenic vasculature and hilum (63).

Overall, no major difference in postoperative morbidity has been reported after enucleation *versus* central pancreatectomy for PNETs (64-67). Although parenchyma-preserving resections and demolitive resections for PNETs have similar reported rates of postoperative hemorrhage and delayed gastric emptying, the rate of postoperative pancreatic fistula is higher after parenchyma-preserving resections, and particularly after enucleation (66-69). On the other hand, demolitive operations, particularly pancreaticoduodenectomy and total pancreatectomy, are associated with increased rates of diabetes mellitus and exocrine pancreatic insufficiency compared with parenchyma-sparing resections (67, 69).

A multicenter study from the United States showed that the extent of curative pancreatic resection for PNETs was not associated with the status of surgical margins in that all types of pancreatic surgery had similar R1 rates. The authors concluded that parenchyma-sparing resections of PNETs with minimal margins may be appropriate in well-selected patients (70). In fact, similar survival outcomes have been reported in several studies between parenchyma-sparing pancreatic surgery and more aggressive oncologic resections for PNETs (65, 66, 71). However, the importance of lymph node sampling during parenchyma-sparing resections should be emphasized to avoid understaging (64). Of note, the NANETS guidelines recommend parenchyma-sparing surgery particularly for patients with familial PNETs to preserve pancreatic endocrine and exocrine functions (11).

Minimally Invasive Surgery for PNET

The introduction of minimally invasive surgical approaches in the operative management of hepato-pancreato-biliary neoplasms has also emerged for PNETs. Specifically, several series worldwide have demonstrated the safety and feasibility of laparoscopic distal pancreatectomy and enucleation for insulinomas (72-74), even in patients with MEN1 (75). A growing body of evidence has demonstrated favorable outcomes of minimally invasive pancreatic surgery compared with the conventional open approach for PNETs in terms of shorter operative time, reduced blood loss, and shorter hospital stay, with equivalent or even lower complication rates and incidence of recurrence (76-78). Notably, robotic pancreatic surgery is also being implemented more and more frequently for the resection of PNETs, ranging from enucleation of PNETs of the uncinate process (79) to total pancreatectomy for diffuse PNET in the head, body, and tail (80) or even multivisceral resection for PNET with synchronous liver metastasis (81).

PNET with Liver Metastases

Depending on the presentation and extent of metastatic disease to the liver, different surgical or medical treatment options may be utilized (14). Evidence has shown that cytoreduction of PNET liver metastases can lead to improved symptoms and survival (82-84). Cytoreduction is more likely offered to patients with favorable or limited disease and it can delay the cause of death in patients with liver metastases, which is liver failure secondary to liver replacement by the tumor. Initially, it was thought that more than 90% cytoreduction is required to achieve a favorable outcome but more recent data from both

Table III. *Liver transplantation criteria for patients with pancreatic neuroendocrine tumors with liver metastases (90).*

Milan-NET criteria	UNOS recommendations
Absolute • Histological grade 1 or 2 • Portal drainage of the primary tumor • Hepatic tumor invasion <50% • Pre-transplant curative resection of all extrahepatic lesions • Duration of stable disease >6 months Relative • Age <60 years	Criteria common to Milan-NET • Histological grade 1 or 2 • Tumors of gastro-entero-pancreatic origin with portal system drainage • Tumor replacement <50% of the liver volume • Resection of primary and extra-hepatic disease without recurrence >6 months • Recipient age <60 years Additional criteria • Unresectable liver metastases • Radiographic characteristics of NET of the liver lesions • Negative metastatic workup by PET scan • Lack of extrahepatic tumor recurrence during the previous 3 months • In the presence of positive findings for lymph node metastases by PET scan, the finding should become negative for 6 months before re-listing • In the presence of extrahepatic solid organ metastases (*i.e.*, lungs or bones), the case will be permanently delisted

NET: Neuroendocrine tumor; PET: positron-emission tomography; UNOS: United Network for Organ Sharing.

gastrointestinal neuroendocrine tumors and PNETs have demonstrated that little benefit is achieved once 70% of the PNET liver metastases are cytoreduced (85-87). Although the current level of evidence is still low, most experts believe that a patient-oriented approach should be adopted according to the number and distribution of lesions, age, comorbidities, grade, and rate of progression, and that 70% cytoreduction can improve symptom control and survival (11). For patients who are not candidates for cytoreduction, medical management has shown significant progress and options include somatostatin analogs, molecularly targeted therapy (*e.g.*, everolimus or sunitinib), cytotoxic chemotherapy (*e.g.*, capecitabine and temozolomide), immunotherapy, and PRRT (14, 88, 89).

Liver transplantation may also be an option for well-selected patients with PNETs and unresectable liver metastases (Table III) (90). Although the overall survival outcomes post-transplant are favorable, with a 5-year rate of 47-71%, the main issue is the high rate of recurrence post-transplant (31-57%) which warrants further research to identify prognostic factors and optimize patient selection (90-92).

Conclusion

Overall, according to the current body of evidence, surgical resection is a reasonable option for well-selected patients with functional PNETs of any size or non-functional PNETs >2 cm. For patients with non-functional PNETs 1-2 cm, a patient-oriented approach should be used based upon age, comorbidities, tumor location, differentiation, and staging. Ongoing research will give further insight into how better to select surgical candidates for PNET resection, to determine whether observation or resection is appropriate for non-functional PNETs 1-2 cm, and to improve patient outcomes and quality of life.

Conflicts of Interest

No conflicts of interest.

Authors' Contributions

IA Ziogas, R Schmitz, D Moris, and CJ Vatsaas conceived and designed the study, acquired, analyzed, and interpreted the data, drafted, and critically revised the article, and approved the final version of the article.

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