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Evaluation and Management of Neuroendocrine Tumors of the Pancreas

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INTRODUCTION

Neuroendocrine tumors (NETs) are a diverse group of neoplasms arising from cells in the diffuse neuroendocrine system. At least 17 different types of neuroendocrine cells are found in the pancreas and gastrointestinal tract.[1] In the pancreas, they are located in the islets of Langerhans, which were first described by their namesake in 1869.[2] There are five well-defined pancreatic islet cell types which produce biologically active peptides including insulin, glucagon, somatostatin, pancreatic polypeptide, and ghrelin.[3] Pancreatic neuroendocrine tumors (PNETs) are also capable of hormone production and are believed to arise from islet cells or, more likely, their precursors.[1,4] Tumors that overproduce hormones may be associated with distinct clinical syndromes and are referred to as functional; those that do not secrete hormones, secrete them in minimal quantities, or secrete peptides that do not result in an obvious syndrome (e.g. pancreatic polypeptide) are termed non-functional. PNETS may produce multiple hormones[5] and are referred to by the name of the hormone whose effects dominate the clinical picture appended with “-oma”, as in insulinoma or gastrinoma.

History

The first report of a PNET was by Albert Nicholls, who described an adenoma arising from the islets of Langerhans in 1902.[6] The term *karzinoide* (carcinoid) was introduced in 1907 by Siegfried Oberndorfer to describe small tumors of the distal ileum resembling carcinoma,

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but with less malignant potential.[7] Although the term originally referred specifically to ileal tumors, over the next half century the definition would be expanded until nearly any NET could be referred to as a carcinoid, regardless of its primary site.[8] In 1924, Seale Harris described several patients with symptoms of hypoglycemia, which the authors attributed to hypersecretion of insulin by the pancreas.[9] Convincing evidence of insulinoma was first presented by Wilder et al. in 1927, who reported a patient with recurrent hypoglycemic episodes who was found at exploratory surgery to have an unresectable distal pancreatic mass. Autopsy of the same patient revealed nodal and liver metastases, and the tumor cells were noted to bear a “striking” resemblance to islets of Langerhans. Further evidence that the tumor was an insulinoma was provided when the effect of tumor extract injected in rabbits mimicked that of insulin.[10] Two years after this report, Roscoe Graham enucleated a 1.5 cm insulinoma from the pancreas of a patient suffering from recurrent hypoglycemic episodes, successfully curing her disease.[11] In the decades following the initial reports of hyperinsulinism and insulinoma, syndromes associated with oversecretion of various other peptides by islet cell tumors were described, although the responsible hormone was not always correctly identified until later: serotonin in 1931, glucagon in 1942, adrenocorticotropic hormone (ACTH) in 1950, gastrin in 1955, vasoactive intestinal peptide (VIP) in 1958, parathyroid hormone-related peptide (PTHrP) in 1973, somatostatin in 1977, growth hormone releasing factor (GRF) in 1978, neurotensin in 1981, and cholecystokinin (CCK) in 2013.[12–23]

Epidemiology

Pancreatic NETs have an approximate incidence of 0.5 per 100,000 persons per year and account for fewer than 10% of all NETs.[24,25] The mean age at diagnosis is 57–58 years, and the peak incidence is in the seventh decade.[26–29] At least 70% of these tumors are non-functional, and the most common functional PNETs are insulinomas, followed by gastrinomas.[29–32] Together, these three subtypes account for the large majority of PNETs. The incidence of other tumors, such as VlPomas, glucagonomas and somatostatinomas, is not well defined, but they are significantly rarer.[31,32] Most PNETs are malignant, and upwards of 60% of patients will have metastatic disease at the time of diagnosis.[1,26,27] Insulinomas, which are benign in 90% of cases, are the exception to this rule; as a consequence, their incidence is frequently underestimated in population-based studies which use data from cancer registries, such as the SEER database.[24,29,31,32] The majority of PNETs are sporadic, but as many as 10–20% are associated with inherited cancer syndromes such as multiple endocrine neoplasia type 1 (MEN1), Von Hippel-Lindau syndrome (VHL), tuberous sclerosis complex (TSC), neurofibromatosis type 1 (NF1), or glucagon cell hyperplasia and neoplasia.[32–37] Of these, MEN1 is the most frequently associated with PNETs.

Despite the high frequency of metastases, the prognosis of patients with PNETs is favorable, particularly when comped to pancreatic adenocarcinoma. The median overall survival for patients in the SEER database diagnosed with PNETs between 1973 and 2012 was 3.6 years. However, over this time period there has been significant improvement in survival, particularly for patients with advanced stage disease.[24,26] The median overall survival for

patients with metastatic PNETs is now 5 years, and for patients with surgically resected, non-metastatic tumors the 20-year disease specific survival is just over 50%.[24,38]

PRESENTATION

The presentation of PNETs varies considerably. When present, the symptoms of non-functional tumors are generally non-specific and related to tumor mass effect, but these tumors are increasingly being detected incidentally on imaging prior to developing symptoms.[39,40] In contrast, functional tumors are frequently associated with dramatic hormonal syndromes leading to an earlier diagnosis and improved prognosis.[28] The clinical presentations of PNET subtypes are summarized in table 1.[18,29–32,41–46] Despite the stark differences in presentation, the diagnostic workup and treatment of functional and non-functional tumors is largely similar.[1,5,45] While the majority of PNETs occur sporadically, they may also arise in association with several hereditary cancer syndromes, the characteristics of which are shown in table 2.[33,34,36,47–52]

DIAGNOSIS

The diagnosis of PNET ultimately depends on immunohistochemical examination of tumor tissue for confirmation; however, serum markers and imaging also play a critical role in the workup of these tumors. The diagnostic sequence will vary from patient to patient, depending on the presentation; those that present with hormonal symptoms may initially undergo blood testing, while those with non-functional tumors are frequently discovered incidentally on imaging. Regardless of whether biochemical testing precedes imaging or vice versa, patients with PNETs will usually undergo both as part of their diagnostic workup.[45,53–55]

Biochemical

Laboratory testing involves the use of both biomarkers which are common to most PNETs as well as specific hormones which are secreted by functional PNETs and responsible for the associated syndromes. Chromogranin A (CgA) is an acidic glycoprotein which is found in the secretory granules of all neuroendocrine cells and is among the most widely studied biomarkers for NETs. Serum CgA is elevated in patients with PNETs and is correlated with both disease burden and survival.[56,57] A recent meta-analysis on CgA for the diagnosis of NETs reported that the pooled sensitivity and specificity were 73% and 95% respectively; however, these values will vary depending on the specific assay and diagnostic thresholds employed.[58] Moreover, clinicians should be aware that elevated CgA may be associated with hypertension, renal dysfunction, treatment with proton-pump inhibitors, and a variety of other benign and malignant diseases unrelated to NETs.[59] Pancreastatin, a protein derived from CgA, is another potential biomarker. Although pancreastatin is less sensitive for the diagnosis of NETs than CgA, it is also less susceptible to non-specific elevation, and has been shown to correlate with survival in surgical patients.[56,57,60] Other biomarkers which are variably elevated in patients with PNETs include neuron-specific enolase, chromogranin B, and pancreatic polypeptide, though none of these are as widely validated as CgA.[56,57] Given the limitations of the available biomarkers, a 51-gene, PCR-based assay (NETest) has recently been developed for the diagnosis and surveillance of NETs. The NETest has

superior sensitivity and specificity (94 and 96%, respectively) for PNETs when compared to CgA; however, the test is significantly more expensive than serum testing for other makers.[61]

Biochemical testing for functional PNETs is directed by symptoms of hormone excess (table 1). Insulinomas present with inappropriately high insulin levels in the setting of hypoglycemia, characterized by Whipple's triad: hypoglycemic symptoms, low plasma glucose, and resolution of symptoms with administration of glucose. The diagnosis should be confirmed by measurement of elevated insulin, pro-insulin and C-peptide during a hypoglycemic episode, which is often induced by a supervised 72-hour fast. In patients with refractory peptic ulcer disease, the presence of a gastrinoma may be confirmed by serum gastrin > 10 times the upper limit of normal in the setting of gastric pH ≤ 2, or moderately elevated gastrin with a positive secretin or glucagon stimulation test. Proton pump inhibitors should be discontinued for 1–2 weeks prior to measurement of the fasting serum gastrin, during which time acid suppression may be maintained with histamine type 2 blockers. Biochemical testing can help support the diagnosis for other functional PNETs, but given their rarity, there are no universally accepted diagnostic thresholds.[46,56,57]

Imaging

Imaging studies play a vital role in the diagnosis and workup of PNETs. Computed tomography (CT) is the most commonly used modality, and it has several favorable characteristics when compared to other studies: it is quick, widely available, and provides excellent anatomic definition of the pancreas, and of lymph node or liver metastases (Figures 1, 2). The mean sensitivity of CT for PNETs is 82%.[62,63] Magnetic resonance imaging (MRI) has a similar mean sensitivity of 79% for primary PNETs, but is significantly more sensitive than CT for the detection of liver metastases, particularly when hepatocyte specific contrast agents are used (e.g. Eovist).[63–65] Because of this, MRI is primarily used to evaluate liver tumor burden, particularly in patients for whom hepatic debulking is being considered.[53,54]

Somatostatin receptors are expressed by 80–100% of PNETs, with the exception of insulinomas for which the rate of expression is 50–70%.[66] Functional imaging techniques include indium-111 somatostatin receptor scintigraphy (^{111}In-SRS, Octreoscan) and gallium-68 positron emission tomography (^{68}Ga-PET, Netspot), both of which use radiolabeled somatostatin analogs to localize neuroendocrine tumors (Figures 1, 3). ^{111}In-SRS predates ^{68}Ga-PET and has been more widely available; however, due to its quicker acquisition and superior sensitivity, ^{68}Ga-PET is rapidly becoming the functional imaging modality of choice.[62,63] A recent meta-analysis found the pooled sensitivity and specificity of ^{68}Ga-PET for the diagnosis of NETs were 93% and 91%, respectively.[67] Somatostatin-receptor based imaging will often clearly show distant metastases that are not apparent on conventional imaging, and is very useful for evaluating the entire body in a single scan, or for equivocal lesions on CT or MRI. Although the spatial resolution of ^{68}Ga-PET is superior to that of ^{111}In-SRS, the non-contrasted CT scan which accompanies it does not provide adequate anatomic definition for surgical planning, and a contrast enhanced CT and/or MRI is still required for this purpose. Finally, while fluorodeoxyglucose positron emission

tomography (FDG-PET) is widely used to image other malignancies, well-differentiated PNETs are comparatively slow growing and frequently do not show avid glucose uptake. FDG-PET may be used for imaging poorly differentiated tumors, which are also less likely to express somatostatin receptors, and thus less likely to show up well on ^{68}Ga-PET or ^{111}In-SRS.[68]

Patients who present with liver metastases can have symptoms mimicking biliary pathology, in which case the first evidence of a NET may be a liver mass seen on right upper quadrant ultrasound. In these patients, ultrasound guided biopsy of the metastases will confirm the diagnosis. For patients with localized disease, or for those with biochemical evidence of a PNET but no imaging findings (usually small insulinomas or gastrinomas), endoscopic ultrasound (EUS) should be used to visualize the tumor. EUS is the most sensitive test for localizing small PNETs, and it also allows for biopsy via fine needle aspiration (FNA) to confirm the diagnosis.[69–71]

Pathology

Pancreatic NETs are definitively diagnosed by immunohistochemistry (IHC) and histologic examination of the tumor.[45,72,73] Tissue may be obtained via EUS and FNA 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 diagnosis prior to operation. Immunohistochemical examination of the tumor should include staining for general NET markers, commonly chromogranin and synaptophysin, as well as markers for the site of origin which is particularly important for NET liver metastases of unknown origin. First line IHC markers for this purpose include PAX6 (paired box 6), PAX8 (paired box 8), ISL1 (islet 1), CDX2 (caudal type homeobox 2) and TTF1 (thyroid transcription factor 1). Of these, PAX6, PAX8 and ISL1 serve as pancreatic markers, while CDX2 positivity suggests a small bowel NET and TTF1 indicates a lung NET.[72,73] Once the neuroendocrine nature of the tumor has been established, the tumor should be graded by the Ki-67 index (proliferative index) and mitotic rate according to 2017 WHO classification (Table 3).[35] Due to the limited amount of material returned by FNA, biopsies obtained using this technique may be more prone to sampling error, and tend to underestimate tumor grade.[71,74] PNETs are staged according to the 8th edition of the AJCC Cancer Staging Manual, which is shown in table 4, or the ENETS system, which is largely similar.[75] A study comparing validity of these two staging systems found them to be equally valid, and that a model which employed the Ki-67 index as a continuous variable was more prognostic than either.[76]

MANAGEMENT

The treatment of PNETs is a multidisciplinary effort, incorporating surgery, somatostatin analogs (SSAs), targeted therapy, and cytotoxic chemotherapy. A number of recent trials have significantly expanded the therapeutic options, and guidelines for treatment continue to evolve.

Surgery

Surgery is the mainstay of treatment for PNETs.[31,45,53–55] For patients with localized disease, resection is frequently curative, and even those with distant metastases may derive significant benefit in terms of both symptom control and survival from surgical debulking.[77,78] The surgical approach to PNETs depends on the size and location of the tumor, functional status, and presence or absence of distant metastases. Resection of PNETs may be accomplished by pancreaticoduodenectomy (Whipple procedure) or distal pancreatectomy; however, the high morbidity associated with major pancreatic resection combined with the indolent growth of well-differentiated PNETs has led to the adoption of more conservative strategies for small tumors, including enucleation or careful observation.[79]

Localized Disease

For patients with PNETs confined to the pancreas and regional lymph nodes, treatment options include distal pancreatectomy, pancreaticoduodenectomy, central pancreatectomy, enucleation or observation. All PNETs larger than 2 cm and functional tumors, irrespective of size, should be resected.[31,45,53–55] Incidentally discovered PNETs less than 2 cm in size generally exhibit benign behavior,[80] and the increasingly frequent diagnosis of small, non-functional PNETs has heightened the controversy over how these tumors should be managed. Single-institutional studies have shown that a nonoperative approach to PNETs smaller than 2 cm is feasible and safe: with an average follow-up of 3 to 4 years, no patients under observation developed metastases and there was no disease specific mortality.[81,82] The risks of observation must be balanced against the complication rate for patients undergoing resection of PNETs, which is roughly 30%, and as high as 45% in patients undergoing pancreaticoduodenectomy or total pancreatectomy.[83] In an effort to avoid these complications, close observation rather than resection may be considered for well-differentiated PNETs less than 2 cm, particularly those confirmed to be low grade by biopsy.[46,54] However, recommendations for conservative management should be interpreted with caution: reviews of the SEER and NCDB databases have found that nearly 30% of PNETs under 2 cm had nodal involvement, clearly demonstrating the malignant potential of these tumors, and studies supporting the safety of observation had relatively short follow-up.[81,82,84,85] Additionally, a meta-analysis of studies comparing resection to nonsurgical management found that surgery was associated with a significant overall survival benefit, even for PNETs less than 2 cm.[79]

When the decision to resect is made, enucleation can be considered for tumors which are well-circumscribed, small, well-differentiated, not in close proximity to the pancreatic duct, and without evidence of nodal or distant metastases (Figure 3).[45,54,55] The primary advantage of enucleation versus standard pancreatic resection is that the former is associated with a lower rate of postoperative pancreatic insufficiency,[55] although this advantage may primarily apply only to pancreatic head masses.[86] Additionally, pancreatic enucleation is associated with a similar rate of overall complications, and a higher rate of postoperative pancreatic fistula when compared to standard resection.[79,86] Small tumors located in the pancreatic body that are too close to the duct to allow for enucleation may be resected via central pancreatectomy.[31,55]

Formal pancreatic resection should be performed for tumors that are larger than 2–3 cm, abutting the pancreatic duct, intermediate or high grade, or suspicious for lymph node involvement.[31,54,55] Pancreaticoduodenectomy is performed for tumors of the pancreatic head, while tumors in the body or tail are resected via distal pancreatectomy, with or without splenic preservation. Regional lymphadenectomy should be performed as a matter of course with pancreatic resection, as more than 50% of tumors larger than 2 cm will have nodal metastases.[46,54,84,87] Recurrence is common even following R0 resection, and is significantly more likely in patients with nodal metastases.[46,87]

Although several factors, including tumor size greater than 3 to 4 cm, lymph node involvement, tumor vascularity as assessed by CT, and Ki-67 index greater than 5% are associated with an increased likelihood of recurrence,[87–89] the optimal frequency and duration of follow-up has not been conclusively established. Surveillance should include imaging with CT or MRI and monitoring of serum markers, particularly if these were elevated preoperatively. Follow-up is initially at 3 to 6 months, and then every 6 to 12 months in the absence of recurrence, but this may be more frequent for high-grade tumors. Given the risk of late recurrence, surveillance should be continued for at least seven years following resection. ^{68}Ga-PET may be used to evaluate equivocal evidence of disease recurrence.[53,55]

Metastatic Disease

Although patients with distant metastases have generally passed the point at which curative resection may be hoped for, surgery continues to play a central role in their treatment.[45,54,55,77,78,90–92] The liver is the overwhelmingly favored site of metastasis for PNETs, accounting for roughly 80% of all metastases, but metastases to the bone, distant lymph nodes, and peritoneal cavity (by direct invasion) are also frequent.[93] Significant hepatic replacement by tumor is common, and among patients with metastatic disease, liver failure is the most common cause of death. In contrast to surgery for metastatic adenocarcinoma, the importance of margin status is de-emphasized, and there is a proportionally greater emphasis on preservation of normal hepatic parenchyma. There appears to be minimal benefit associated with R0/R1 resection compared to R2, and even when R0 margins are achieved, eventual disease recurrence is nearly universal.[90,91] Numerous surgical series have shown that cytoreductive surgery improves survival and symptomatic control, and historically this has been attempted when 90% cytoreduction was deemed feasible. While a significant majority of patients will be considered unresectable at this threshold, recent studies have shown similar results may be achieved using a lower cutoff of 70% debulking. In order to achieve adequate cytoreduction in patients with numerous, bilobar liver metastases, parenchyma sparing techniques including enucleation and intraoperative, ultrasound-guided ablation are employed (Figure 2), with similar results compared to formal hepatectomy.[77,78,92]

Cytoreductive surgery is largely accepted as a standard treatment for PNET liver metastases,[45,54,55] but precise indications and contraindication for surgery continue to be defined. Broadly, patients should be considered for debulking if they have well-differentiated, grade 1 or 2, metastatic PNETs with less than 50% hepatic replacement (preferably <25%) with a

surgically amenable distribution (i.e. not miliary), normal or near-normal liver function, and no evidence of carcinoid heart disease or other major comorbidities. Extra-hepatic metastases should not be considered a contraindication to hepatic debulking, and peritoneal tumor deposits may be resected concurrently.[77,92] For patients with extensive liver involvement who are ineligible for hepatic debulking, but are otherwise well-suited for surgery and have no evidence of extra-hepatic disease, liver transplantation appears to offer improved survival.[94,95] However, the potential benefits of transplant must be carefully weighed against the scarcity of available grafts and the prospect of lifelong immunosuppression. Moreover, the indications for transplant, as defined by the Milan-NET criteria,[95] are very similar to those for hepatic debulking, further complicating patient selection.

Primary tumor resection should be considered in patients with metastatic disease to avoid obstructive complications from the pancreatic mass and further metastatic seeding. In most cases this may be performed simultaneously; the primary exception is for pancreaticoduodenectomy and hepatic ablation, which should be performed in a staged fashion to avoid the theoretical risk of hepatic abscess formation. Even in the case of unresectable metastatic disease, there may be a survival advantage associated with resection of the primary tumor,[96] but studies showing a benefit may be prone to selection bias.

Patients with metastatic PNETs are usually treated long-term with somatostatin analogs (SSAs) such as octreotide long-acting-repeatable (octreotide LAR) or lanreotide. The incidence of gallstones in these patients is roughly 50%, significantly higher than the general population. Because the rate of symptomatic biliary disease remains low, prophylactic cholecystectomy is not recommended as a separate operation. However, the risk of developing complications from gallstones is sufficiently elevated to warrant cholecystectomy for patients undergoing primary resection or hepatic cytoreduction, particularly since laparoscopic cholecystectomy may be more difficult after liver surgery.[97]

Patients with distant metastases should be assumed to have residual tumor following surgery, and should undergo routine biochemical and radiographic surveillance.[53,55,90] Patients should be seen in 3 to 6 months following surgery, and then every 6–12 months thereafter. Rapid progression or high-grade disease warrants more frequent surveillance.[53,55]

Surgical Approach

In general, PNETs are approached via laparotomy to facilitate adequate inspection of the abdomen and debulking of nodal or distant metastases. However, for patients with small localized tumors, distal pancreatectomy or enucleation may be performed laparoscopically with similar outcomes.[54,55,98] The role of laparoscopy for metastatic disease is significantly more limited. For patients with PNETs and liver dominant disease, laparoscopic hepatic ablation offers a less invasive alternative to open surgery, with equivalent rates of symptomatic improvement, significantly less morbidity, and a much shorter hospital course.[99]

Hereditary Syndromes

Many of the principles of management are common between sporadic and inherited PNETs, but there are some special considerations for patients with hereditary syndromes such as MEN-1 and VHL. The surgical management of MEN-1 is covered in Colleen M Kiernan and Elizabeth G Grubbs' article "Surgical Management of MEN-1 and MEN-2," in this issue, and this effort will not be duplicated here. The most common pancreatic manifestations of VHL are multiple cysts or serous cystadenomas; however, PNETs are also seen in approximately 10 to 20% of these patients.[48,52,55,100] PNETs associated with VHL are frequently multiple and usually non-functional. They are also significantly more likely to be benign than sporadic tumors, and have longer recurrence-free survival following resection.[52,100] The risk of progression for PNETs less than 1.5 cm in patients with VHL appears to be very low, and this observation, coupled with the high incidence of multifocal tumors, has led to recommendations against routine resection of asymptomatic PNETs smaller than 1.5 cm.[100] Tumors over 3 cm in size, with doubling time less than 500 days, or exon 3 mutations are significantly more likely to metastasize, and therefore, these are indications for resection in VHL patients.[101]

Liver Directed Therapy

For patients with PNET liver metastases, percutaneous ablation and hepatic artery embolization (HAE) are less invasive options for hepatic cytoreduction compared to surgery. Percutaneous ablation of liver metastases may be performed using radio-frequency ablation (RFA), microwave ablation (MWA), or cryoablation.[45,54,55,102,103] Direct comparison of each modality for the treatment of PNET liver metastases is difficult due to the limited data in the literature, but extrapolation from the treatment of hepatocellular cancer suggests that outcomes are similar.[104,105] MWA has several theoretical advantages over RFA, including faster ablation time and higher intertumoral temperature, and may be superior for larger lesions.[104,106] Reported rates of symptomatic improvement and complete ablation are both greater than 90%.[103,106] Percutaneous ablation is a reasonable option for the treatment of one or only a few metastases, particularly in patients who are not candidates for surgical resection.[45]

Hepatic artery embolization takes advantage of the fact that liver metastases are preferentially supplied by the hepatic artery, in contrast to the normal liver parenchyma, which receives much of its blood supply from the portal vein. A catheter is introduced into the hepatic artery and used to deliver therapy locally to the metastatic lesions rather than systemically. Bland HAE is performed using polyvinyl alcohol particles which occlude blood flow to the metastases, inducing hypoxic necrosis. Chemotherapy or radioactive microspheres may also be delivered via the catheter, (chemoembolization and radioembolization, respectively) but at this time no one method has been shown to be definitively superior.[107] Patients are admitted following embolization for the management of a constellation of symptoms referred to as post-embolization syndrome. This self-limited syndrome is characterized by fever, abdominal pain, nausea and vomiting and occurs in up to 90% of patients following the procedure.[108] HAE is indicated for patients with liver dominant disease and a patent portal vein who are not candidates for operative hepatic debulking.[45,54,55]

Medical Therapy

For patients with localized PNETs, resection is often curative, and no further treatment is needed in the absence of recurrence. For patients with metastases, a number of systemic therapies are available for disease control and symptom palliation. Streptozocin was one of the first agents to show activity against PNETs, but significant side effects and the more recent introduction of less toxic therapies have limited its use.[109,110] The antiproliferative properties of SSAs were demonstrated by the CLARINET trial, and due to their favorable side effect profile and inhibition of hormone secretion, long acting SSAs are considered first line therapy for metastatic PNETs.[45,54,55,111,112] The tyrosine kinase inhibitor sunitinib and the mTOR inhibitor everolimus are second line treatments which are generally well tolerated and are associated with modest improvements in progression-free survival.[113,114] Although previous chemotherapeutic regimens have provided only moderate survival benefits and substantial toxicity, the combination of capecitabine and temozolomide (CAPTEM) has been introduced as a promising new regimen with high objective response rates, improved survival and superior tolerability.[115,116] Finally, peptide receptor radionuclide therapy (PRRT) was recently shown to significantly increase progression-free survival in patients with metastatic NETs in the NETTER-1 trial. Although this trial enrolled only patients with midgut NETs, other non-randomized trials have shown similar results in NETs arising from other sites, and PRRT was recently FDA approved for the treatment of all NETs.[117] A summary of selected randomized controlled trials for the treatment of PNETs are presented in table 5.

High Grade Pancreatic Neuroendocrine Tumors

Until recently, all high-grade PNETs, defined by a Ki-67 index over 20%, were classified as neuroendocrine carcinoma (NEC); as of the latest WHO classification, they are now divided into high-grade well-differentiated NETs and poorly differentiated NEC (Table 3).[35] NEC may be further subdivided into small-cell and large-cell types, but it is unclear how this may affect prognosis or treatment.[118,119] With a median survival of 5 to 21 months, these tumors are significantly rarer and more aggressive than well-differentiated, grade 1 and 2 PNETs, and their management is distinct in several respects.[118–120] High-grade PNETs are more metabolically active and less likely to express somatostatin receptors. Thus, they are more likely to be detected by FDG-PET and less likely to show uptake on somatostatin receptor based imaging when compared to low-grade tumors.[68] On immunohistochemical exam, high-grade tumors are less likely to stain positively for chromogranin, and the typical markers used to assign a site of origin cannot be reliably applied.[72,118,119]

Surgical resection should be considered for localized, high-grade PNETs and should involve formal oncologic resection (pancreaticoduodenectomy or distal pancreatectomy with lymphadenectomy) rather than enucleation.[53,54,118] Patients with metastases derive minimal benefit from cytoreduction, and should not be considered for debulking surgery.[78] Adjuvant chemotherapy and every 3 month follow-up after resection is recommended due to the high risk of recurrence.[53,118] Standard first line chemotherapy for high-grade PNETs consists of cisplatin or carboplatin plus etoposide or irinotecan.[53,54,110,118]. A number of other agents have been suggested as second line therapy, but none are well validated.[53,54,110,118] Among high-grade PNETs, those with a Ki-67 index between 20 and 55% were less likely to

respond to platinum based chemotherapy, but were associated with better survival than those with a Ki-67 index over 55%.[119] This may reflect the difference between well-differentiated, high-grade PNETs, which typically have Ki-67 indices closer to 20%, and poorly differentiated NECs, which typically have much higher Ki-67 indices. SSAs, everolimus and sunitinib play a limited role in the treatment of high-grade PNETs.

SUMMARY

Pancreatic neuroendocrine tumors are rare malignancies characterized by indolent growth and a propensity to metastasize. The heterogeneity of PNETs is striking: they may present with debilitating hormonal syndromes, diffuse liver metastases, or as asymptomatic, incidentally discovered masses. Similarly, their prognosis runs the gamut from extremely favorable, as is the case with the majority of insulinomas, to dismal for poorly differentiated NEC. Once a PNET is suspected, the diagnostic workup should consist of biochemical testing for NET markers and thorough imaging, which may include CT, MRI, EUS and ^{68}Ga-PET. The diagnosis is confirmed by verifying IHC positivity for NET markers, at which point the tumor is graded according to the WHO classification. Pancreatic tumors which are low-grade, non-functional, stable in size and smaller than 2 cm may be safely observed, while those that do not meet these criteria are indicated for resection. Standard resections include pancreaticoduodenectomy for head masses and central or distal pancreatectomy for body and tail masses. Enucleation is an option for selected tumors smaller than 3 cm which are not abutting the pancreatic duct. Patients with well-differentiated, metastatic PNETs should be considered for surgical debulking, with or without concurrent primary resection, in order to improve survival and symptomatic control. Other options for hepatic cytoreduction include percutaneous ablation, HAE and liver transplant in highly selected patients. A wide variety of systemic therapies are now available for the treatment of metastatic disease including SSAs, everolimus, sunitinib, PRRT and CAPTEM. High grade PNETs carry a grave prognosis and are treated primarily with platinum-based chemotherapy. Formal oncologic resection may be considered for localized disease but does not play a role for metastatic, high-grade tumors.

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KEY POINTS

- Pancreatic neuroendocrine tumors (PNETs) arise from islet cells or their precursors and may cause symptoms from mass effect or hormone production.
- The standard treatment for localized PNETs is pancreaticoduodenectomy or distal pancreatectomy, but enucleation or observation may be considered for small tumors.
- Approximately 60% of PNETs will present with metastases, most commonly to the liver.
- The treatment for metastatic PNETs is multimodal and includes primary resection, surgical debulking, liver directed therapy, and a variety of systemic treatments.
- PNETs carry a significantly more favorable prognosis when compared to pancreatic adenocarcinoma.

SYNOPSIS

Pancreatic neuroendocrine tumors (PNETs) are a diverse group of neoplasms with a generally favorable prognosis. Although they exhibit indolent growth, metastases are seen in roughly 60% of patients. PNETs may produce a wide variety of hormones which are associated with dramatic symptoms, but the majority are non-functional. The diagnosis and treatment of these tumors is a multidisciplinary effort, and management guidelines continue to evolve. This review provides a concise summary of the presentation, diagnosis, surgical management, and systemic treatment of PNETs.

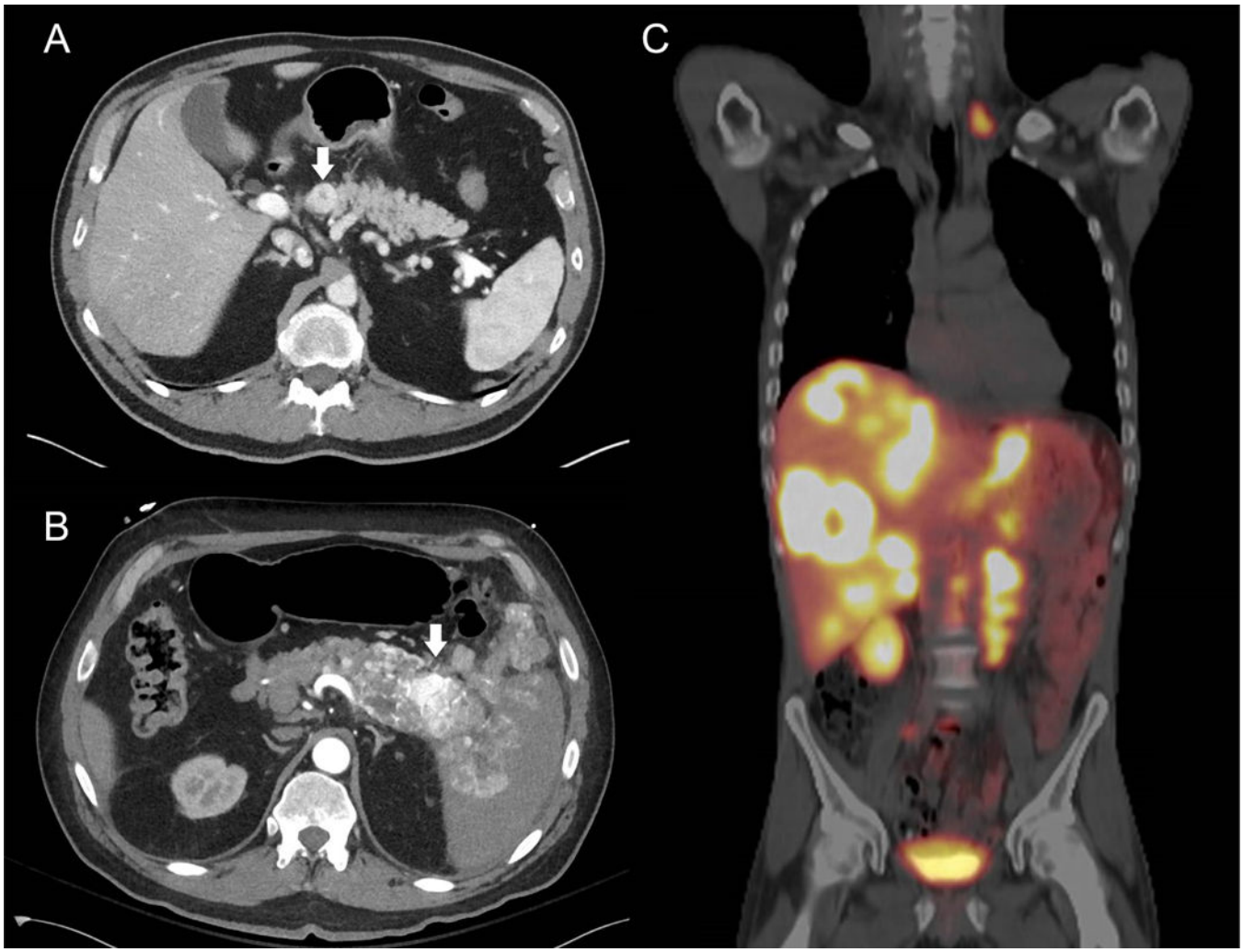

Figure 1:

(A) Arterial phase CT showing a well-circumscribed, enhancing PNET (arrow). (B) Arterial phase CT showing an enhancing PNET (arrow) which is directly invading the spleen and peritoneal cavity. (C) ^{68}Ga-PET allows the entire body to be imaged in a single study. In this patient, who had previously undergone primary PNET resection, extensive metastases are seen in the liver, paraaortic lymph nodes, and left supraclavicular lymph nodes.

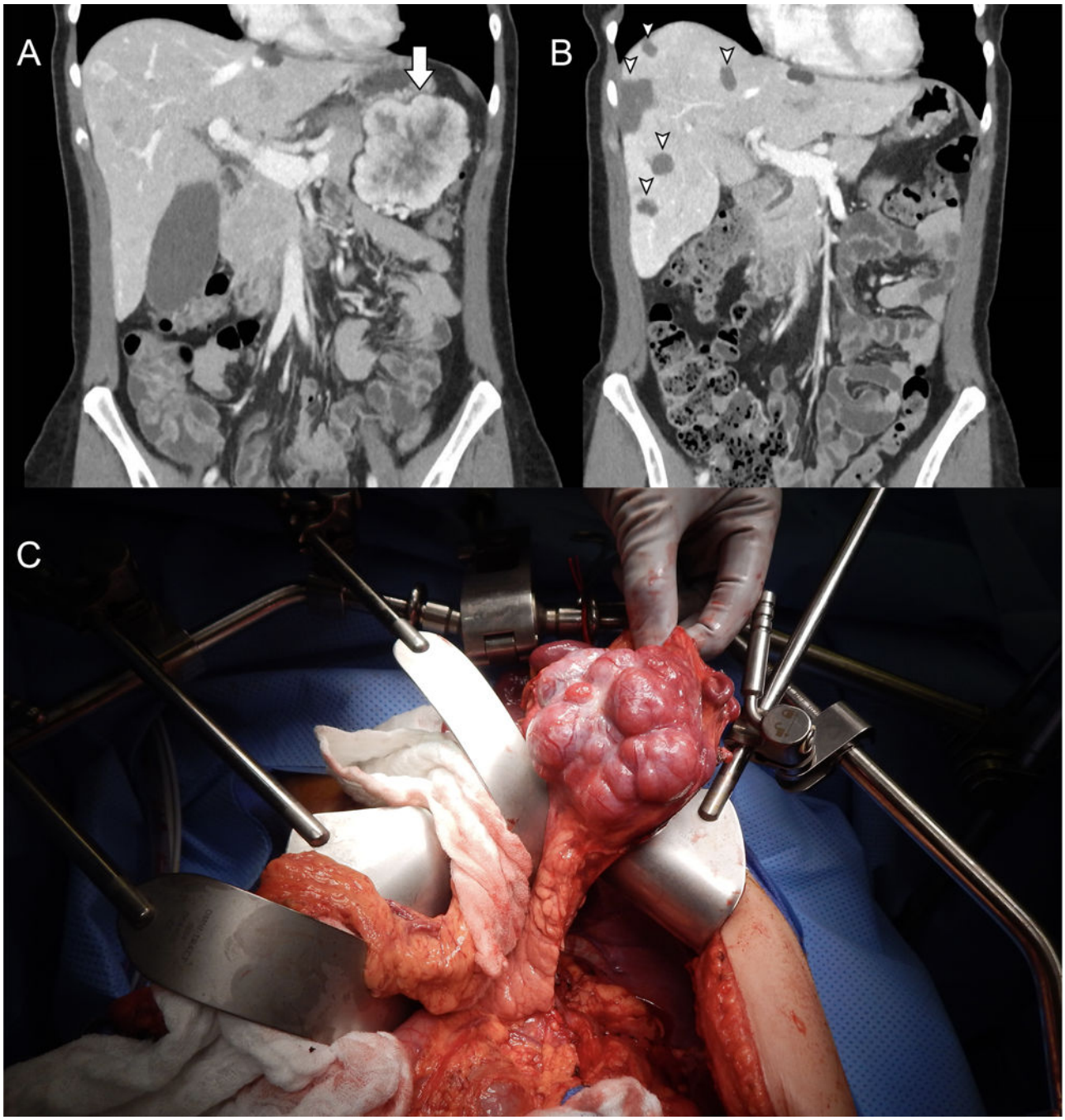

Figure 2:
(A) A large, peripherally enhancing PNET in the tail of the pancreas (arrow), and faintly hyper-and hypoenhancing hepatic metastases are seen on venous phase CT. (B) The postoperative venous phase CT from the same patient following distal pancreatectomy, cholecystectomy and multiple ultrasound-guided, microwave ablations of the liver (arrow heads). (C) Intraoperative appearance of the PNET, within the tail of the pancreas.

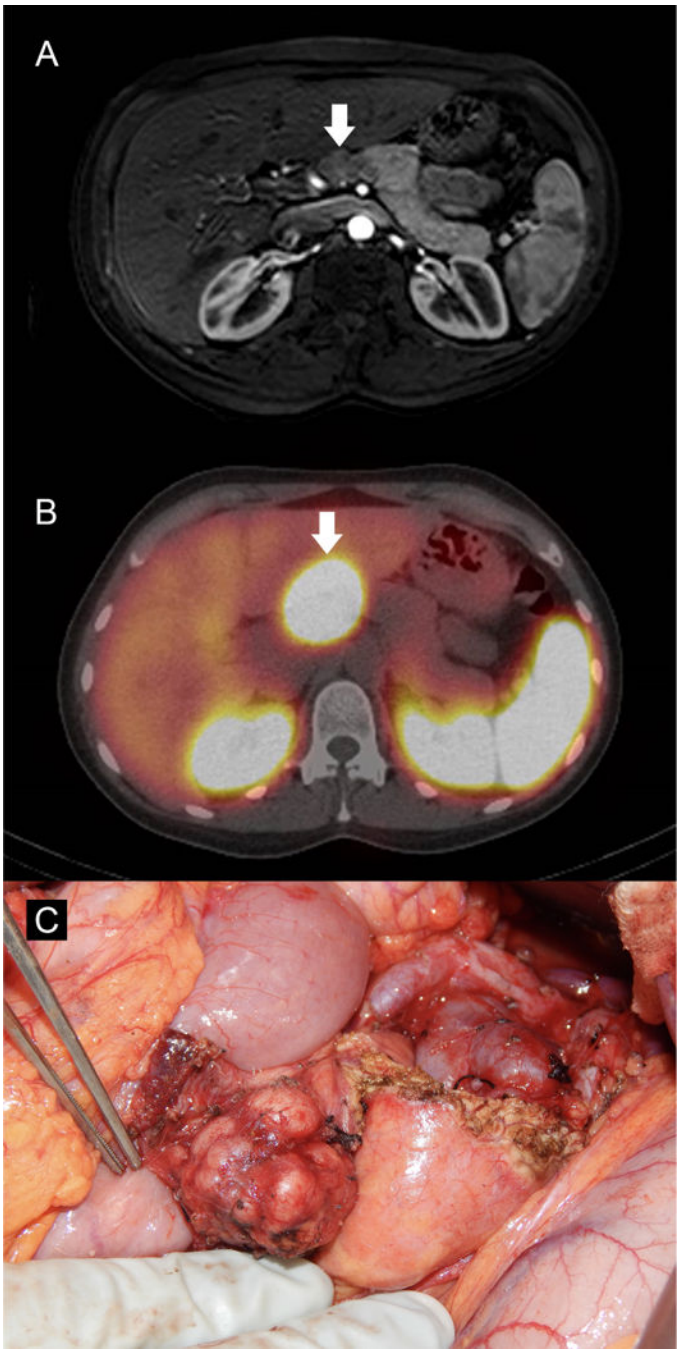

Figure 3:
(A) Hypoenhancing pancreatic neck mass shown on contrast enhanced, T1 weighted MRI (arrow). (B) The same mass shows intense uptake on ^{111}In-SRS (arrow). (C) The mass was well encapsulated and not near the pancreatic duct, thus enucleation and lymphadenectomy were performed.

Table 1:

Clinical presentation of various PNET subtypes Data from references 18, 29-32, 41-46.

Clinical Presentation of PNET Subtypes		
Tumor	**Hormone**	**Symptoms**
Nonfunctional PNET	Varies (Pancreatic polypeptide, chromogranin A, others in small quantities)	Asymptomatic, abdominal/back pain, nausea/vomiting, pancreatitis, obstructive jaundice
Insulinoma	Insulin	Hypoglycemic symptoms (tremor, palpitations, anxiety, hunger, cognitive impairment, seizure, coma), fasting hypoglycemia, rapid correction with glucose (Whipple's triad)
Gastrinoma	Gastrin	Severe, medically refractory peptic ulcer disease, gastroesophageal reflux, diarrhea (Zollinger Ellison-Syndrome)
VIPoma	Vasoactive intestinal peptide (VIP)	Watery diarrhea, hypokalemia, achlorhydria (WDHA syndrome, pancreatic cholera or Verner Morrison Syndrome)
Glucagonoma	Glucagon	Necrolytic migratory erythema, weight loss, diabetes mellitus, diarrhea, venous thrombosis
Somatostatinoma	Somatostatin	Diabetes, gallstones, steatorrhea, weight loss
Pancreatic Carcinoid	Serotonin, tachykinins	Flushing, diarrhea, bronchospasm, valvular heart disease (carcinoid syndrome)
ACTHoma	Adrenocorticotropic hormone (ACTH)	Obesity, facial plethora, round face (moon facies), hirsutism, hypertension, bruising, fatigue, depression, dorsal fat pad, glucose intolerance, stria, proximal weakness, menstrual irregularities, decreased fertility (Cushing's syndrome)
GRFoma	Growth hormone-releasing factor (GRF or GHRF)	Coarse facial features, enlarged hands and feet, macroglossia, deepening voice, skin thickening, sleep apnea, arthritis, cardiovascular disease, insulin resistance, fatigue, weakness (Acromegaly)
PTHrPoma	Parathyroid hormone-related protein (PTHrP)	Nephrolithiasis, weakness, bone pain, nausea, constipation, polyuria, depression (Hypercalcemia)

Table 2:

Characteristics of hereditary cancer syndromes associated with PNETs. Data from references 33, 34, 36, 47-52.

Hereditary Cancer Syndromes Associated with PNETs				
Syndrome	**Gene**	**Inheritance**	**Incidence of PNETs**	**Other Characteristics**
Multiple endocrine neoplasia type 1	*MEN1*	Autosomal Dominant	20–70% symptomatic PNET, nonfunctional most common followed by gastrinoma, nearly 100% develop multiple pancreatic microadenomas	Parathyroid hyperplasia (95–100%), pituitary tumors (30–50%), angiofibromas (85%), adrenal adenoma (30–40%), Gastric NETs (10–35%)
Von Hippel-Lindau syndrome	*VHL*	Autosomal Dominant	10–20%, almost all nonfunctional	Retinal and CNS hemangioblastoma (60–80%), renal cell carcinoma (25–70%), pheochromocytoma (10–20%), pancreatic cysts (35–80%), epididymal cystadenoma (25–60%)
Neurofibromatosis type 1	*NF1*	Autosomal Dominant	0–10%, characteristically ampullary/duodenal somatostatinomas	Café-au-lait macules (99%), neurofibromas (99%), skin fold freckling (85%), Lisch nodules (95%), optic pathway glioma (15%), learning problems (60%) skeletal abnormalities, pheochromcytomas, malignant peripheral nerve sheath tumors
Tuberous sclerosis complex	*TSC1, TSC2*	Autosomal Dominant	Rare, may be functional or nonfunctional	Variable presentation: hamartomas affecting brain, skin, kidneys, and eyes; clasically seizures, developmental delay, and angiofibromas
Glucagon cell hyperplasia and neoplasia (Mahvash Syndrome)	*GCCR*	Autosomal Recessive	100%, micro- and macro-glucagonomas	Background of glucagon cell hyperplasia

Table 3:

2017 WHO classification of PNETs. From Lloyd RV, Osamura RY, Klöppel G, Rosai J. *WHO classification of tumours of endocrine organs.* 4th Edition ed. Lyon, France: International Agency for Research on Cancer; 2017, with permission.

WHO Classification of Pancreatic Neuroendocrine Tumors		
Classification/grade	Ki-67 Proliferative index	Mitotic index (per 10 HPF)
Well-differentiated NET		
Grade 1	<3%	<2
Grade 2	3–20%	2–20
Grade 3	>20%	>20
Poorly differentiated NEC		
Grade 3	>20%	>20

Table 4:

AJCC Staging of Pancreatic Neuroendocrine Tumors. From Amin MB, Edge S, Greene F, et al., eds. *AJCC Cancer Staging Manual.* 8th Edition ed. New York, NY: Springer International Publishing; 2017, with permission.

AJCC Staging of Pancreatic Neuroendocrine Tumors	
Primary Tumor (T)	**Description**
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 (stomach, spleen, colon, adrenal) or the wall of large vessels (celiac axis, or the superior mesenteric artery)
(m) suffix	Multiple tumors, if the number is known use T(#), if unavailable or too numerous use T(m)
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Regional lymph node involvement
(sn) suffix	Indicates nodal metastasis identified by sentinal node biopsy only
(f) suffix	Indicates nodal metastasis identified by FNA or core needle biopsy only
Distant Metastasis (M)	
M0	No distant metastases
M1a	Metastases confined to the liver
M1b	Metastases in at least 1 extrahepatic site
M1c	Both hepatic and extrahepatic metastases
Stage	
I	T1, N0, M0
II	T2-T3, N0, M0
III	T4, N0, M0, OR Any T, N1, M0
IV	Any T, Any N, M1

Table 5:

Selected Randomized Controlled Trials for the Treatment of Pancreatic Neuroendocrine Tumors. Data from references 53, 109, 112-114, 117.

Selected Randomized Controlled Trials for the Treatment of Pancreatic Neuroendocrine Tumors							
Trial	**Year**	**Enrollment**	**Patients Enrolled**	**Intervention**	**Comparator**	**Progression Free Survival**	**Response rate**
Moertel et al.	1980	Unresectable, metastatic PNETs	84	STZ 500mg/m^2 + FU 400mg/m^2 daily × 5 days, q6w	STZ 500mg/m^2 daily × 5 days, q6w	Not reported	63% vs 36% (p<0.01)
Raymond et al.	2011	Well-differentiated, progressive, unresectable PNETs	171	Sunitinib 37.5mg daily	Placebo	11.4 vs 5.5 months (p<0.001)	9.3% vs 0% (p=0.007)
RADIANT-3	2011	Low or intermediate-grade, unresectable, progressive PNETs	410	Everolimus 10mg daily	Placebo	11.0 vs 4.6 months (p<0.001)	5% vs 2% (p<0.001)
CLARINET	2014	Nonfunctioning enteropancreatic NETs or Gastrinoma, SSR+, Unresectable, Ki-67 <10%, 96% stable disease	204 (45% PNETs)	Lanreotide 120mg q28d	Placebo	65.1% vs 33.0% at 24 months (p<0.001)	Not reported
NETTER-1	2017	Well-differentiated, unresectable, progressive midgut NETs, SSR+, Ki-67 <20%	229	177Lu-Dotatate PRRT 7.4 GBq q8w + Octreotide LAR 30mg q4w	Octreotide LAR 60mg q4w	65.2% vs 10.8% at 20 months (p<0.001)	18% vs 3% (p<0.001)
E2211	2018	Low or intermediate-grade, unresectable, progressive PNETs	144	CAP 750 mg/m^2 daily × 14 days + TMZ 200 mg/m^2 daily × 5 days	TMZ 200 mg/m^2 daily × 5 days	22.7 vs 14.4 months (p=0.023)	Not reported