Resection Versus Chemotherapy for Metastatic Neuroendocrine Tumors of the Pancreas

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Abstract

Pancreatic neuroendocrine tumors (PNET) represent a broad spectrum of disease with behavior ranging from benign to highly malignant. Treatment strategies are quite variable and frequently lack consensus. This chapter focuses on the debate between surgery and chemotherapy for metastatic PNET. We summarize the evidence for both strategies including which treatment is appropriate in each clinical setting.

Keywords

Pancreatic neuroendocrine tumor · Neuroendocrine carcinoma · Ki67 · mTOR inhibitors · MGMT

Introduction

Pancreatic neuroendocrine tumors (PNET) account for only 1–4% of all clinically apparent pancreatic tumors [1–3]. The majority are sporadic in inheritance, although 10% may be part of inherited disorders such as neurofibromatosis, tuberous sclerosis, multiple endocrine neoplasia (MEN) type 1 or von Hippel-Lindau (VHL) syndrome. PNETs arise from islet cells of the pancreas and may or may not secrete functionally active hormones (classified as functional versus nonfunctional

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Table 36.1 PICO table

*P*opulation	Patients with metastatic PNET
*I*ntervention	Surgical resection
*C*omparator	Medical management
*O*utcomes	Survival, recurrence, complications, QOL

[majority]). In 2010, the World Health Organization developed another clinically relevant classification based on tumor grade (G) and Ki-67 index. A G1 tumor was defined as having a mitotic count <2/10 high powered fields (hpf) and a Ki-67 index <3%. G2 tumors were defined as having a mitotic count of 2–20/10 hpf and a Ki-67 of 3–20%. G3 tumors were defined as having a mitotic count of >20/10 hpf and/or a Ki-67 index >20%. In general, well differentiated PNETs are either low or intermediate grade (G1 or G2), whereas poorly differentiated PNETS are high grade (G3) and considered carcinomas [4]. The older literature references to high-grade neuroendocrine carcinoma, small cell carcinoma, undifferentiated carcinoma, anaplastic carcinoma and large cell neuroendocrine carcinoma are all included in the current nomenclature of poorly differentiated PNET [5]. This terminology can be confusing since all well differentiated PNETs have malignant potential (defined as the ability to metastasize to regional lymph nodes and/or distant organs). The exception is small, nonmetastatic insulinomas which in general, carry no risk for metachronous distant organ recurrence. Tumor grade has significant prognostic value and is particularly important for treatment decisions because well differentiated PNETs are managed very differently relative to poorly differentiated tumors [5–10]. All patients with a PNET who have advanced disease should undergo a biopsy of their tumor and have proper histologic assessment (Ki-67/mitotic index) in order to classify the tumor as a guide for further therapy.

Surgical resection of PNETs remains the only curative therapy for this disease and represents the current standard of care [11–16]. A complete resection of all visible disease controls tumor growth, reduces excess hormone production in patients with liver metastases and provides a 5-year overall survival exceeding 60% [17–19]. This chapter summarizes the current literature in the debate of surgery versus systemic therapy for the treatment of metastatic PNET (Table 36.1).

Search Strategy

We conducted a focused review of current guidelines related to the surgical and medical management of metastatic PNET. The PubMed database was searched for the past 20 years for the following key words: pancreatic neuroendocrine tumor, pancreatic neuroendocrine carcinoma, chemotherapy, pancreatectomy, resection, enucleation, transplantation, mTOR inhibitors, somatostatin analogues, and tyrosine kinase inhibitors. Emphasis was placed on national and international guidelines and recommendations.

Surgical Resection of PNET

Patients with well-differentiated PNETs or those "tumors" that are G1 or G2 with Ki67 < 20% should be treated differently from patients with poorly differentiated "neuroendocrine carcinomas" that are grade G3 and have Ki67 indices >20% [5, 8, 20, 21]. Poorly differentiated PNETs have a high rate of metastatic spread even in patients that appear to have localized disease and therefore surgical resection is rarely curative [5, 22]. Surgical resection is, however, generally recommended if all or >90% of the imageable disease can be removed [11, 13, 16, 19, 23]. In general, surgery is not recommended where resection cannot be complete or results in removal of >90% of the metastatic tumor as this does not improve survival [11, 13, 16]. Less than a complete resection (debulking) is considered in patients with functional tumors where hormone secretion is causing significant symptoms; we rarely consider surgery for nonfunctional PNETs if a complete gross resection of all disease cannot be accomplished.

Minimal Resection for Early Disease

Benign biologic behavior is exhibited in 10–40% of PNETs and is uniformly seen in nonmetastatic insulinomas [24]. Solitary PNETs located >2–3 mm from the pancreatic duct are frequently enucleated, as opposed to resected with a margin of normal pancreas [11, 25]. For tumors in the pancreatic neck or proximal body of the pancreas, parenchymal preservation in the form of middle segment pancreatectomy is an option when enucleation is not feasible due to ductal proximity [26]. The disadvantage of any operation which requires transection of the pancreatic duct is the risk of a pancreatic fistula [27]. Pancreatic endocrine and exocrine function is preserved with any operation that is able to preserve pancreatic parenchyma, which is very important in young patients [27]. Minimally invasive approaches are ideal for tumors that are small, benign and located in the pancreatic body or tail [28, 29]. More recently, robotic-assisted minimally invasive pancreatic resections have been advocated as superior to laparoscopic approaches due to decreased rates of conversion to open laparotomy (0% vs 16%) without adding increased morbidity [30].

Lymph Node Resection

With the exception of sporadic nonmetastatic insulinoma, positive regional lymph nodes are found in up to 23% of patients with low risk PNETs and result in a significantly shorter disease-free survival than in patients who are node negative (4.5 vs 14.6 years; $P < 0.0001$) [31]. Node positivity occurs more frequently in tumors with the following characteristics: >15 mm in size, located in the pancreatic head, G3 and exhibiting lymphatic invasion [31, 32]. Although Partelli and colleagues

attempted to develop predictive models of risk for lymph node involvement, preoperative variables did not reliably predict the probability of nodal involvement to the extent that surgeons could omit regional lymphadenectomy at the time of pancreatic resection for PNET [33, 34]. Clearly, there is a huge selection bias in this literature as lymph nodes cannot be assessed for the presence of metastases unless they are both surgically excised and pathologically assessed. It is perhaps best to conclude that all PNETs, except for small insulinomas, are associated with a significant risk of regional lymph node metastases and these nodes should be removed at the time of surgery whenever possible. This surgical practice prevents a metachronous recurrence in regional nodes which could have been removed at the first operation.

High Risk/Malignant Disease

In the setting of neuroendocrine carcinoma, surgery is superior to conservative therapies in extending survival and controlling local and metastatic disease [34]. A retrospective study utilizing the Surveillance, Epidemiology and End Results (SEER) database demonstrated a survival benefit of 79 months for resected patients compared to those who were recommended to undergo surgery but were not resected (114 months vs 35 months; $P < 0.0001$) [35]. This survival advantage held true for the subgroup of patients with distant metastases (60 vs 31 months; $P = 0.01$) [35]. In addition, surgical resection reduced the risk of metachronous liver metastases in patients with gastrinoma (5% vs 29%) [36]. In patients with more advanced/larger local disease, aggressive resection when possible, in carefully selected patients, offers optimal disease control [37]. Interestingly, in some reports, a margin-positive resection in patients with large, regionally advanced PNETs had a similar overall survival benefit compared to a margin negative resection [38]. This finding clearly reflects the more indolent biology of this disease compared to pancreatic adenocarcinoma.

Liver Metastases

Liver metastases are present in up to 60% of patients with PNET at the time of initial diagnosis and such synchronous liver metastases are not a contraindication to surgical treatment [19, 39, 40]. However, it remains controversial as to whether the primary tumor should be removed in the setting of unresectable metastatic disease. Some reports conclude that removal of the primary tumor in the setting of unresectable distant disease does not improve survival compared to the use of nonsurgical therapies [41, 42]. In contrast, if the liver metastases are able to be completely resected, a much higher 5 year survival (72 vs 25%) and longer median survival (96 vs 20 months) is observed compared to patients treated nonoperatively [43]. Extended liver resections for metastatic disease can be performed safely with acceptable morbidity (21%) and mortality (5% or less) [44–48]. In sharp contrast to most other solid tumors, 5-year survival is both possible and probable after

resection of PNET liver metastases; one series reported a 5-year survival of 66% [44]. The European Neuroendocrine Tumor Society (ENETs) guidelines take the role for surgery even further and extend it to patients with liver metastases who may not be eligible for complete resection and can undergo surgical debulking of >90% of liver metastases [13, 49, 50]. The authors of this review are not comfortable with this recommendation in most situations and largely limit elective liver resections to those patients who can receive a complete gross resection of all image positive disease. Surgical resection may be complemented by ablation or transarterial chemoembolization (TACE) [12, 43].

Extended Resections of the Primary

Major vascular involvement (portal/superior mesenteric vein, superior mesenteric artery, inferior vena cava) does not preclude resection and may result in 30% of patients with PNETs being disease-free at 5 years [37, 51, 52]. This is particularly important for PNETs involving the splenic vein (SV) or portal vein/superior mesenteric vein (PV/SMV) resulting in extrahepatic portal hypertension with resultant gastroesophageal varices and gastrointestinal bleeding, as the bleeding resolves with resection of the PNET and the spleen [37, 53, 54]. Current evidence stems from retrospective nonrandomized studies as ethical and feasibility considerations preclude realization of a prospectively controlled randomized trial. PNETs with a Ki-67 index >5%, positive lymph nodes, and a size >4 cm have a significantly higher risk of metachronous disease recurrence [55, 56].

Liver Transplantation

Liver transplantation is an option, but evidence is limited, oncologic outcome is uncertain and its use is controversial [12, 57–59]. A recent study of 17 patients who underwent liver transplantation for metastatic PNET reported a 1-, 5-, and 10-year survival of 89%, 80% and 50% respectively which may not be much better than other forms of therapy. However, these patients may have had very large tumor burdens and the highly selected nature of these results makes further interpretation very difficult [13, 49, 60, 61]. Risk factors for a poor prognosis after transplantation include: extrahepatic disease at the time of transplant; abdominal exenteration or multivisceral transplant at the time of the liver transplant; metastatic PNET (as opposed to gastrointestinal carcinoid); age > 50; >50% of the liver involved; Ki 67 > 10%; and, aberrant E-cadherin staining [12, 14, 58, 59, 62]. ENETs 2012 consensus guidelines therefore, recommend liver transplantation only for patients with life-threatening hormonal disturbances refractory to other treatments, or for patients with nonfunctional PNET with diffuse liver metastases refractory to all other treatments [12]. PNET liver metastases are not considered a standard exception that would yield more points by Eurotransplant or UNOS criteria.

High Grade Pancreatic Neuroendocrine Carcinomas

Patients with a high Ki-67 index have increased risk of recurrence and metastatic disease with resultant poor survival. In patients with poorly differentiated carcinomas with a high Ki-67, surgery should only be undertaken if an R0 resection is possible; there is no role for cytoreductive (<R0) surgery in these patients [13, 55]. Conventional systemic chemotherapy and less frequently, targeted systemic therapies such as multityrosine kinase inhibitors and mTOR inhibitors are the standard in these settings [34].

Summary of Recommendations

The biology of PNETs is different based on tumor grade and Ki 67 index and therefore tumor biopsy at the time of diagnosis is critically important. Surgical resection is the only curative treatment modality and is the current standard of care for patients who appear eligible for a complete gross resection of all local and distant disease. Resection of PNETs with low malignant potential should be done with the goal of parenchymal preservation (enucleation or limited resection) and with minimally invasive surgery if possible (robotically or laparoscopically). Lymph node metastases are present in up to one fourth of PNETs and regional lymphadenectomy is recommended for all diagnoses other than sporadic insulinoma. In the setting of well to moderately differentiated (G1 or G2) PNETs, surgery when feasible, is superior to nonoperative therapies in extending survival and controlling local and metastatic disease. In addition, surgery is often the optimal treatment for large G1 or G2 PNETs with local extension requiring vascular resection and reconstruction; in such situations, the role of pre-operative/adjunctive systemic therapies should be explored in a multidisciplinary setting. Liver transplantation is reserved for those patients with life-threatening hormonal imbalances or nonfunctional PNETs refractory to all other treatments. High grade, poorly differentiated tumors should not be treated with surgical resection unless an R0 status can be achieved.

Medical Management of Metastatic PNET

Chemotherapy for PNETs

Cytotoxic chemotherapy continues to play an important role in patients with advanced metastatic PNET. The regimens utilized differ based on several factors, most notably, the degree of differentiation of the neuroendocrine carcinoma [5, 12, 14, 63–65]. Chemotherapy is usually reserved for palliative intent treatment of patients with inoperable disease. Currently, there is no defined role for systemic therapy in the adjuvant setting (post resection of PNETs) outside of clinical trials, however, it is increasingly used in a neoadjuvant fashion to (1) assess tumor biology in patients that present with synchronous metastatic disease prior to offering them

a resection and (2) to induce response in patients with a large tumor burden if they require a complex operation for removal of the primary tumor with or without concomitant liver resection [12, 14, 64–66]. Because of significant treatment-related toxicities, cytotoxic chemotherapy is recommended for PNETs in the following situations: (1) metastatic poorly differentiated PNETS (G3, Ki 67 index > 20%), (2) unresectable G1 or G2 PNETS (Ki 67 < 20%) after failure of biotherapy and/or targeted systemic therapy, (3) neoadjuvant therapy for G1 or G2 PNETS that present with synchronous metastatic disease or bulky primary tumors mandating complex surgery/vascular reconstruction to assess tumor biology and/or to induce a response prior to offering resection [12, 14, 67–69].

In G1–G2 (Ki67 < 3 or 3–20%) well differentiated metastatic PNETs, the combination of streptozotocin and 5-fluorouracil (FU) with/without doxorubicin has an objective response rate of 20–45%. Responses can be relatively short lived (6–20 months), and patients may experience side effects including but not limited to nausea and emesis (70–100%) and renal toxicity (15–40%) [12, 14, 65, 70]. A relatively new combination of temozolomide and capecitabine has shown efficacy with improved response rates and less toxicity based on early non-randomized data. A retrospective study of 30 patients with metastatic well differentiated PNETs treated with capecitabine and temazolomide demonstrated a partial response rate of 70% with a median PFS of 18 months, a 2 year survival of 92%, and only 13% developed grade three or four adverse events [71–74]. The ongoing randomized, phase II, Eastern Cooperative Oncology Group (ECOG) 2211 trial evaluates the efficacy of temozolimide with or without capecitabine in patients with G1 or G2 metastatic PNETs, with progression free survival (PFS) being the primary endpoint.

Kulke et al. showed that low levels of the DNA repair enzyme 06-methylguanine DNA methyltransferase (MGMT) in the tumor were associated with response to alkylating agents such as temozolomide [74]. This correlation between low tumoral expression of MGMT by immunohistochemistry and response to temozolomide has been noted in glioblastoma as well, but MGMT has thus far not been prospectively validated as a predictive biomarker for temozolomide therapy.

Both ENETS 2012 and the North American Neuroendocrine Tumor Society (NANETS) 2010 guidelines recommend chemotherapy in selected patients with advanced, metastatic, inoperable, well-differentiated (G1 or G2) PNETs—especially if rapidly growing, symptomatic, or if a large volume of disease is present [12, 16].

Biotherapy for Advanced/Metastatic PNETs

Somatostatin Analogues

Somatostatin analogues (SSAs) help control the hormone-excess state in functional PNETs and also have anti-tumor growth effects [12, 14, 16, 75–78]. PNETS overexpress one or more of the five subtypes of somatostatin receptors (SSTR 1–5) in 70–100% of patients [14, 75–78]. The PROMID study, which included patients ($N = 85$, 74% octreoscan positive, 39% with carcinoid syndrome) with well

differentiated metastatic midgut NETs tumors (but did not include patients with PNETs), demonstrated that octreotide LAR extended time to tumor progression (14.3 vs 6 months, $p < 0.000072$) resulting in 67% of treated patients having stable disease at 6 months compared to 37% of controls ($p = 0.0079$) [79]. Tumor response was significant only in patients with low hepatic tumor burden (<10%) and was more favorable in the setting of a resected primary tumor. Objective decrease in tumor size was uncommon (<10%) but tumor stabilization was frequent (40–80%) [12, 14, 16, 75, 77, 78]. Another SSA (lanreotide) was investigated in the phase III, CLARINET trial that compared lanreotide versus placebo in patients with advanced, well to moderately differentiated (Ki-67 < 10%), non-functioning, gastroenteropancreatic NETs [80]. Notably, the majority of the patients (96%) had no tumor progression in 3–6 months prior to randomization and a third of the patients had hepatic tumor burden >25%. Lanreotide when compared to placebo, was associated with a significantly prolonged median PFS (median not reached vs. 18.0 months, hazard ratio (HR) 0.47, 95% confidence interval (CI) 0.30–0.73, $p < 0.01$). The estimated rate of PFS at 2 years in the lanreotide arm was 65% (95% CI, 54.0–74.1%) compared to 33% (95% CI, 23.0–43.3%) in the placebo group. While there were some key differences between the patient populations evaluated in the PROMID and CLARINET trials that were reflected in the outcomes noted in the placebo and interventional arms, these two trials unequivocally established a therapeutic role for SSAs in treatment of patients with well to moderately differentiated gastroenteropancreatic NETs.

National Comprehensive Cancer Network (NCCN) guidelines state that somatostatin analogues should be considered (level 2A evidence) for local-regional, unresectable, and/or metastatic well-moderately differentiated PNETs [81, 82]. ENETS 2012 guidelines support somatostatin if tumors are G1 and NANETS 2010 uses somatostatin analogues for antiproliferative effects and their low side effect profile [12, 81, 82]. Both octreotide and lanreotide have high affinity for somatostatin receptor subtypes two and five, however PNETS frequently possess other subtypes [14, 76, 83]. Pasireotide has high affinity for somatostatin receptors one, two, three and five and is being evaluated for enhanced anti-growth effects on neuroendocrine tumors and for its antisecretory effects [84–86]. However, Pasireotide is currently not recommended for treatment of well-moderately differentiated PNETs outside of a clinical trial.

Targeted Therapy

mTOR Inhibitors (Everolimus)

Everolimus is an oral mTOR inhibitor with efficacy demonstrated in several recent trials evaluating patients with metastatic PNETs, including the pivotal phase III RADIANT-3 trial [86–89]. In this report, 410 patients with low to intermediate grade metastatic PNETs were assigned to everolimus (10 mg, orally, once daily) or placebo, both in conjunction with best supportive care. Patients treated with everolimus, compared to placebo, showed a significant improvement in PFS (11 vs 4.6 months, HR 0.35, 95% CI, 0.27–0.45, $p < 0.0001$) and PFS rate at 18 months

(34%, 95% CI 26–43% vs 9%, 95% CI, 4–16%). The significant improvement in PFS and low rate of grade 3 or 4 adverse events (stomatitis 7%, anemia 6% and hyperglycemia 5%) led to everolimus being approved in Europe and the United States for use in patients with low to intermediate grade metastatic PNETs. This strategy is endorsed by both ENETS and NCCN.

Tyrosine Kinase Inhibitors (Sunitinib)

Tyrosine kinase receptors are a family of receptors (20 members) which include epidermal growth factor, platelet derived growth factor, hepatocyte growth factor (c-MET), stem cell factor (c-KIT) and VEGFRs among others. These receptors function as tyrosine kinases when activated and downstream effects include mediation of growth-related cascades, angiogenesis, apoptosis and cellular differentiation [90, 91]. PNETs frequently possess a number of tyrosine kinase receptors [91–95]. Sunitinib is an oral inhibitor of tyrosine kinase activity of PDGFRs, VEGFR-1, VEGFR-2, c-KIT and FLT3 [91]. An international, double-blind, multicenter Phase III study randomly assigned 171 patients with metastatic well differentiated PNETs to Sunitinib (37.5 mg/day, orally) or placebo in conjunction with SSA (at the investigator's discretion, in both arms). The primary end point (median PFS) was significantly improved in the Sunitinib arm compared to the placebo arm (11.4 vs. 5.5 months, HR 0.42, 95% CI, 0.26–0.66, $p < 0.001$). This study was discontinued early, after an independent data and safety monitoring committee observed more serious adverse events in the placebo group and a favorable PFS in the Sunitinib group. The demonstrated efficacy and relative paucity of grade 3 or 4 adverse events (neutropenia 12%, hypertension 10%, and palmar-plantar erythro-dysesthesia 6%) resulted in approval for the use of Sutent in both Europe and the United States, in patients with metastatic well-differentiated PNETS. This was subsequently endorsed by both ENETS and NCCN. In addition to sunitinib, numerous tyrosine kinase inhibitors have demonstrated activity in NETS (imatinib, sorafenib, vatalanib, pazopanib) [90, 91, 95–97] but none of these agents are recommended for use outside of clinical trials.

Summary of Targeted Therapy

For patients with metastatic low to intermediate grade PNETs, the authors recommend initiation of therapy with either a SSA or combination of SSA and everolimus/sunitinib based on disease burden and symptomatology. Patients with bulky disease and/or symptoms from their low-intermediate grade metastatic PNETs may benefit from combining SSA with either a targeted agent or cytotoxic chemotherapy, at presentation, based on the rapidity of response desired.

While the addition of these targeted therapies have led to significant improvements in the overall survival of patients with low-intermediate grade PNETs, there is a crucial need for newer therapeutic strategies to further the oncologic outcome in these patients. Disease progression while on these agents occurs either due to

development of resistance to therapy and/or intolerance to the side effects. Strategies that attempt to overcome acquired/intrinsic resistance to available therapies and explore new therapeutic opportunities based on our evolving understanding of the development and progression of PNETs are being evaluated in clinical trials. These efforts include both individual and combined strategies aimed at targeting candidate genes/proteins involved in alternate tumor survival pathways.

Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin (PRRT)

This treatment is based on the over/ectopic expression of somatostatin receptors by 60–100% of PNETs which in turn, allows for targeting of the tumor by cytotoxic, radiolabeled somatostatin analogues [14, 83, 98, 99]. Two different radiolabels are commonly used in combination with SSAs (1) ^{90}Y which strongly emit beta particles or (2) ^{177}Lu which emit B particles and gamma rays. A number of different somatostatin analogues and attached chelators (to allow binding of the radioisotope) have been used in various studies (DTPA, DOTA and peptide-chelator combinations DOTATATE, DOTATOC). Although a number of reports support the role of PRRT in the treatment of metastatic low-intermediate grade PNETs (European Studies), it is still considered investigational in the United States [99–101].

Treatment of Metastatic Poorly Differentiated PNETs

Poorly differentiated PNETs account for <1% of all malignant PNETS and 2–3% of all PNETS [5]. They have histologic and radiologic/clinical features of aggressive growth (G3, Ki 67 > 20% but usually 50–90%, necrosis, nuclear atypia), and carry a poor prognosis [5, 7, 20, 102]. Poorly differentiated PNETs have low densities of (or absent) somatostatin receptors and thus somatostatin scintigraphy is rarely useful and somatostatin analogues are not clinically effective. Most patients have regional or distant metastases at the time of presentation and surgery is rarely curative [5, 7]. Systemic chemotherapy is the treatment of choice and commonly used drugs include various combinations of platinum agents (Cisplatin, Carboplatin), Etoposide, topoisomerase inhibitors (Irinotecan, Topotecan) and Paclitaxel. Such treatments induce response in 14–80% of patients with a mean duration of response of <12 months [5, 20, 21, 64, 103]. Major toxicity can occur including myelosuppression and nausea/emesis [21, 11, 104].

Summary of Recommendations for Medical Management

Somatostatin analogues are commonly used at the time of initial diagnosis for patients with unresectable and/or metastatic PNETs to control the hormone excess state and for their antiproliferative effects. Octreotide and lanreotide have the most data in support of their use however, newer agents with higher affinity for other

somatostatin receptors are currently being evaluated. NCCN guidelines recommend targeted therapy with mTOR inhibitors (Everolimus) or tyrosine kinase inhibitors (Sunitinib), either as first-line treatment for unresectable and/or metastatic well-moderately differentiated PNETs in combination with SSAs or sequentially following progression on SSAs.

Cytotoxic chemotherapy is recommended for use in patients with well-moderately differentiated metastatic/unresectable PNETs due to (1) failure of SSAs and/or targeted therapy and (2) presentation with initial bulky or symptomatic disease mandating disease response to facilitate cytoreduction or symptom control. The use of Streptozotocin, 5FU, and doxorubicin (FAS) as well as the combination of capecitabine and temozolomide are supported by non-randomized data. Peptide receptor radionuclide therapy while promising, remains in the experimental realm to date. Metastatic high grade/poorly differentiated PNETs are treated with cytotoxic chemotherapy alone.

Personal View of the Data/How We Do It

Initial Evaluation

Patients with functional PNETs usually present with symptoms caused by hormone hypersecretion. Patients with nonfunctional PNETs may present with vague abdominal complaints or have no symptoms whatsoever, having their tumors incidentally discovered on cross-sectional imaging obtained for unrelated conditions. If there is no evidence of metastatic disease, workup includes endoscopic ultrasound (EUS) with fine needle aspiration (FNA) for tissue diagnosis and assessment of Ki-67/mitotic index. If the patient has metastatic disease, a metastatic lesion may be targeted for biopsy, if readily accessible. Multiphasic cross-sectional imaging (computed tomography or magnetic resonance imaging) with emphasis on an early arterial phase is critical to assess the lesion(s) and to rule out metastatic disease. Laboratory evaluation should include serum levels of chromogranin A, neuron specific enolase, gastrin, human pancreatic polypeptide, serotonin, calcium and possibly others, if a particular symptom complex related to hormonal hypersecretion is present (i.e. insulinoma, gastrinoma, VIPoma among others). The Chromogranin A suppression test is also frequently performed, especially if metastatic disease is discovered, as a guide to the use of octreotide or lanreotide [105]. Finally, an octreotide scan is completed to assess otreotide avidity of the primary and assess metastatic disease burden. This is particularly helpful for surveillance after resection.

Single Small Pancreatic PNET

In the setting of a single tumor confined to the pancreas, we prefer a minimally invasive, parenchymal-sparing approach to resection. Our preferred technique is laparoscopic or robotic resection either by enucleation (if eccentric, away from the pancreatic duct) or a limited parenchyma-sparing resection (margin negative,

spleen-preserving). The advantages of 3-D, high magnification vision, wristed motion and precision in limited space makes the robotic platform quite attractive in this patient population and certainly in those patients with small volume disease. As the patients are frequently younger and the disease course is often measured in many years, parenchyma preservation is very important to minimize the risk of insulin dependence.

Larger Volume Tumors with Vascular Involvement and/or Metastatic Disease

As most of these patients will survive for years (not months), even in the absence of surgery, it is critically important that the treatment not worsen survival and/or cause undue morbidity; the treatment should not be worse than the disease itself. For patients with large tumors and/or metastatic PNETs at diagnosis, the disease has either been indolent for years and progressed slowly until mass effect has occurred, or is highly aggressive and has spread rapidly. This reality underscores the need for biopsy with assessment of tumor differentiation and Ki-67/mitotic index. Patients with a resectable primary and somewhat limited metastatic disease, with moderate or well differentiated tumors (GI/G2, Ki-67 < 20%) are frequently taken to the operating room for a combined liver/pancreas resection. If both the liver and the pancreas require an extensive operation (for example, a formal lobectomy or more in the liver, or a Whipple procedure with vascular resection/reconstruction in the pancreas) we may two-stage the operation based on the surgical risk and technical complexity of the procedure. If a biliary-enteric anastomosis is required/anticipated for resection of the primary pancreatic tumor, we may treat the liver first (with liver directed therapies, if mandated by multidisciplinary evaluation/discussion) to avoid the risk of liver abscess from biliary contamination.

In contrast, patients with moderate to poorly differentiated (Ki-67 > 20%) will be assessed for cytotoxic therapy with capecitabine/temozolomide (based on MGMT status), or other agents if MGMT is not deficient. In situations where the liver is diffusely involved and the patient is unlikely to ever be taken for surgical resection, transarterial chemoembolization (TACE) or yttrium90 is attractive early in the treatment course to control hepatic disease progression, especially in those patients with hormone secretion as their major symptom.

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