Surgical Management of Pancreatic Neuroendocrine Tumors

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KEYWORDS

• Neuroendocrine • Pancreas • Pancreatectomy • Surgery • Enucleation

KEY POINTS

- Pancreatic neuroendocrine tumors are relatively rare and make up approximately 1% to 2% of all solid pancreatic tumors.
- They include a diverse group of neoplasms, with clinical behavior ranging from small indolent tumors to widely metastatic disease.
- A minority are associated with hormone secretion and syndromes of hormone excess.
- Surgery is the treatment of choice for localized disease and may include formal pancreatic resection or parenchyma-preserving enucleation in some cases.
- Surgical care must be individualized to tumor characteristics and clinical symptoms.

Pancreatic neuroendocrine tumors (PNETs) are relatively rare, constituting approximately 1% to 2% of all pancreatic neoplasms and with an overall incidence of approximately 5 cases per million annually.[1] Despite sharing histologic characteristics with neuroendocrine tumors from other sites, PNETs have unique biology and clinical behavior from other neuroendocrine neoplasms.[2] These tumors include a heterogeneous group of neoplasms that have long been held in unique fascination by physicians and surgeons because of the ability of some tumors to secrete specific hormones and their association with well-described clinical syndromes. Most PNETs, however, do not secrete specific hormones and are often referred to as nonfunctioning PNET. Recent years have seen an increased understanding of the origin[3] and biological basis of PNETs[2] as well as in new targeted therapies for advanced PET.[4–6] Surgical resection remains the mainstay of therapy for localized and occasionally metastatic disease.

Disclosure Statement: The author has nothing to disclose.
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Hematol Oncol Clin N Am 30 (2016) 103–118
http://dx.doi.org/10.1016/j.hoc.2015.09.004 **hemonc.theclinics.com**
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In addition to their relatively rare incidence and diverse clinical manifestations, PNETs have a wide range of biological behavior and associated prognosis. Although many PNETs are relatively slow growing and have a favorable long-term prognosis,[7] others may present with locally invasive or metastatic disease.[8] Furthermore, some PNETs may present in association with genetic syndromes, such as multiple endocrine neoplasia type I (MEN1),[9] that will influence rates of recurrence. This variability in biological behavior and recurrence risk precludes a unified treatment strategy for all PNETs. Unique surgical considerations for functioning and nonfunctioning PNETs, both localized and metastatic, are considered.

CLINICAL PRESENTATION AND DIAGNOSIS

Functioning Pancreatic Neuroendocrine Tumors

PNETs are classified as functional based on secretion of one of a variety of hormones, including insulin, gastrin, glucagon, vasoactive intestinal peptide (VIP), and rarely somatostatin.[10] The clinical presentation and evaluation of these are specific to each type of tumor.

Insulinoma

Given the unregulated production of insulin, patients with insulinoma will typically present with signs and symptoms of hypoglycemia, including neuroglycopenic or sympathetic effects. Neuroglycopenic symptoms may include headaches, blurred vision, forgetfulness, and difficulties with speech. Activation of the sympathetic nervous system can result in sweating, tachycardia, tremors, and weakness. Both neuroglycopenic and sympathetic symptoms may be relieved with eating. Excess caloric intake coupled with the anabolic effects of insulin often leads to weight gain in these patients.

Diagnosis of insulinoma is traditionally suspected based on the combination of clinical signs, known as Whipple's triad in recognition of the original description of these tumors by Whipple and Frantz[11] in 1935. This triad consists of the presence of symptomatic hypoglycemia with fasting, documented plasma glucose of less than 50 mg/dL with symptoms, and the relief of symptoms with glucose administration. Diagnosis is confirmed by assessment of serum insulin, proinsulin, C-peptide, and glucose to establish hyperinsulinism[12]; the absence of ketosis or sulfonylurea metabolites in blood or urine is important to rule out factitious hyperinsulinism. Within 48 hours of an observed fast, between 90% and 95% of patients will develop hypoglycemia, with a diagnostic insulin-to-glucose ration of more than 0.4. Although far less common than insulinoma, adult nesidioblastosis or beta cell hyperplasia will occasionally present with similar laboratory and clinical findings.[13] This syndrome has been described in a population of patients after bariatric surgery.[14,15]

In the absence of a clinical syndrome such as MEN1, most insulinomas occur as small, solitary, benign lesions.[16] Although tumors may range in size, most are less than 2 cm in size and can be found with relatively equal distribution throughout the pancreas.[17] Very few patients with insulinoma develop metastatic spread, with a rate of less than 10%, far less than other pancreatic islet cell tumors.[18]

Although selective pancreatic angiography with calcium stimulation and hepatic venous sampling was traditionally used to detect these small lesions,[19] contrast-enhanced computed tomography (CT) can localize most lesions[20] (**Fig. 1**). Endoscopic ultrasound (EUS) is quite sensitive for the detection of insulinoma, and the combination of EUS with CT can identify nearly all lesions.[21] Conventional MRI is similarly sensitive in this setting.[22] The use of somatostatin receptor scintigraphy is limited given the low expression of type 2 somatostatin receptors on insulinomas.[23]

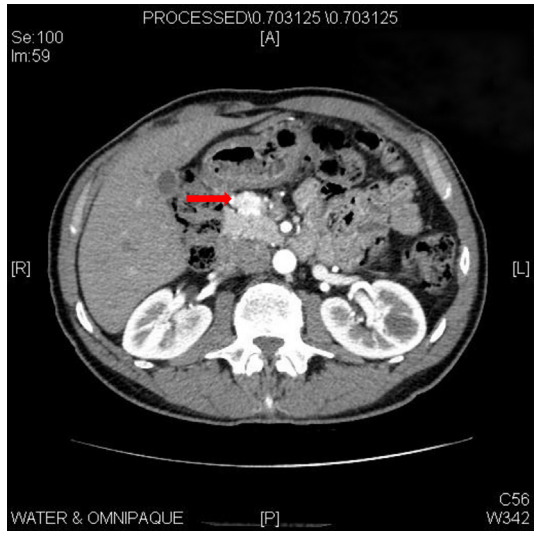

Fig. 1. Contrast-enhanced CT scan of insulinoma in pancreatic head (*arrow*). Tumor demonstrates arterial enhancement and is thereby distinguished from the remaining pancreatic parenchyma.

Gastrinoma

The identification of patients with severe ulcer disease and associated non–insulin-producing islet cell tumors led to the description of gastrinomas by Zollinger and Ellison[24] in 1955. Gastrinomas are associated with MEN1 in approximately 25% of cases[25] and develop metastatic disease in 60% to 90%.[26,27] Patients may present with disabling pain, diarrhea, reflux, and duodenal ulcers.

Hypergastrinemia in the setting of excess gastric acid secretion is important to rule out atrophic gastritis or proton pump inhibitor use. Secretin stimulation causes a paradoxic increase in serum gastrin in the setting of a gastrinoma, which can be used to diagnose the tumors.[28]

Gastrinomas are frequently multifocal, with a higher propensity for local or distant spread than insulinoma. Most are localized in an area referred to as the gastrinoma triangle, delineated by the junction of the cystic duct and common bile duct, the body and neck of the pancreas, and the second and third portion of the duodenum.[29] Localization of tumors may be challenging with traditional cross-sectional imaging, though somatostatin receptor scintigraphy has a sensitivity of approximately 60%.[30] In some cases, operative exploration can be required to identify lesions using palpation, intraoperative ultrasound, duodenotomy, and transillumination of the duodenum[31] (**Fig. 2**).

Glucagonoma

Glucagonoma is a rare functioning pancreatic neuroendocrine tumor associated with a range of signs, most characteristically a rash known as necrolytic migratory erythema, a vesicular, erythematous necrotic dermatitis. Patients present with diabetes, glossitis, weight loss, and weakness. Deep vein thrombosis can occur in 30% of patients, and patients present with anemia and a decreased level of amino acids due to gluoneogensis.[32] These tumors are often large at diagnosis, and contrast-enhanced CT scan is often sufficient for localization. Patients often present with advanced and metastatic disease.

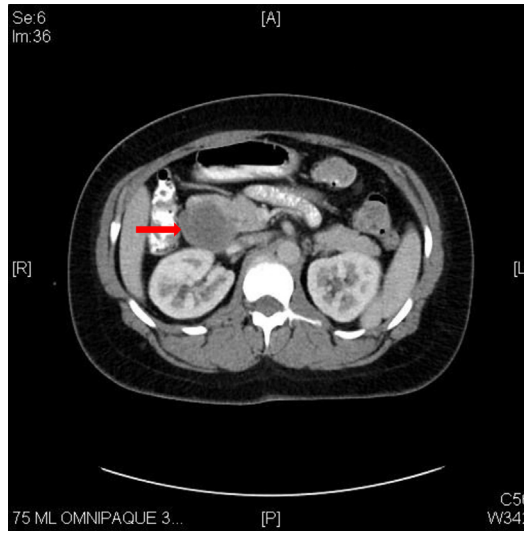

Fig. 2. Contrast-enhanced CT scan of a patient with metastatic gastrinoma to the periduodenal space. A 5-cm lesion adjacent to the duodenum was identified (*arrow*); biopsy was consistent with neuroendocrine tumor, and the lesion was the only site localized on octreotide scan. On surgical exploration, a primary tumor measuring 5 mm was identified in the duodenal wall.

VIPoma

Vasoactive intestinal peptide (VIPoma) are exceedingly rare tumors associated with secretion of the hormone VIP. The syndrome of copious watery diarrhea, hypokalemia, and achlorhydria is also described as pancreatic cholera. These tumors are characteristically large and are often metastatic to the liver at the time of diagnosis. Most are easily visualized by contrast-enhanced CT or somatostatin receptor scintigraphy.

Nonfunctioning Pancreatic Neuroendocrine Tumors

Approximately 70% of PNETs do not secrete a specific hormone and are not associated with specific clinical syndromes. These tumors are often asymptomatic in the absence of vague abdominal pain. Although symptoms may include abdominal pain, jaundice, pancreatic insufficiency, a palpable mass, and anorexia, tumors are often detected before symptoms as incidental finding on imaging studies performed for an unrelated indication.[33] In one 20-year cohort of nonfunctioning PNET, 35% of patients were asymptomatic with an incidental diagnosis.[34] Patients with advanced disease may present with locally advanced disease involving the mesenteric vessels or with widespread metastases.

PNETs typically appear as hypervascular lesions on CT, as opposed to the often hypovascular appearance of adenocarcinoma. MRI has a comparable sensitivity and specificity (**Fig. 3**). Somatostatin-receptor scintigraphy has excellent sensitivity and specificity and is particularly important for evaluating the presence of occult metastatic disease.[35] Definitive diagnosis can often be obtained with EUS-guided fine-needle aspiration. Serum chromogranin A is a valuable tumor marker in the management of well-differentiated PNETS, and levels can be used in determining response to therapy and for serial follow-up of patients.

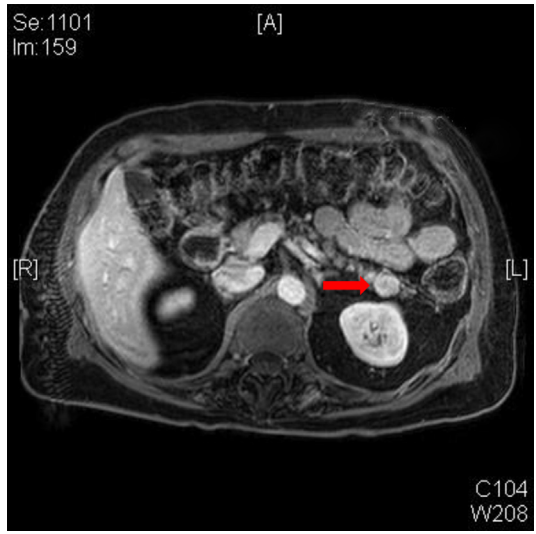

Fig. 3. MRI demonstrates a 2-cm enhancing mass in the pancreatic tail (*arrow*). Resection confirmed PNET.

STAGING

The World Health Organization classifies neuroendocrine tumors into different grades based on histologic characteristics. Well-differentiated tumors include low-grade (G1) tumors with a low mitotic count and Ki-67 proliferative index of less than 3% as well as intermediate-grade (G2) tumors with mitotic counts of 2 to 20 per high-power field (HPF) and Ki-67 rate of 3% to 20%. Poorly differentiated tumors or high-grade (G3) tumors have mitotic rates more than 2 per 10 HPF and Ki-67 rate of greater than 20%.[36] High-grade tumors, often referred to as neuroendocrine carcinomas, display more aggressive clinical behavior[10] and unlike, well-differentiated tumors, are generally not candidates for surgical resection.

Staging systems include variants proposed by the American Joint Committee on Cancer and a second promoted by the European Neuroendocrine Tumor Society.[37,38] Both systems are useful for predicting survival, with overall survival ranging from 90% to 100% at 5 years for stage I tumors to approximately 60% for stage IV tumors.[7,39]

SURGICAL MANAGEMENT

Functioning Pancreatic Neuroendocrine Tumors

Insulinoma

Although surgical resection of localized disease is the mainstay of therapy for all PNETs, insulinomas are unique in their relative lack of metastases and potential for treatment with pancreas-sparing procedures. Unlike formal pancreatic surgery, such as distal pancreatectomy, central pancreatectomy, or pancreaticoduodenectomy, enucleation involves removal of just the tumor and associated capsule, sparing otherwise normal pancreatic parenchyma (**Fig. 4**). In a systematic review of case series with a total of more than 6200 insulinoma patients, Mehrabi and colleagues[17] describe enucleation as the procedure of choice in more than half of insulinomas.

Enucleation is particularly applicable to small, benign, superficial tumors.[40] Tumors closer to the main pancreatic duct will have a higher risk of postoperative pancreatic

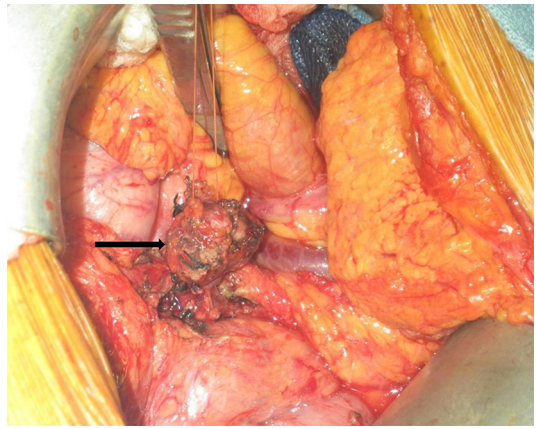

Fig. 4. Enucleation, pancreatic head insulinoma (*arrow*). Patient in Fig. 1 was taken to the operating room for symptomatic insulinoma. Enucleation was possible as the mass was greater than 3 mm from the pancreatic duct.

fistula after enucleation. Tumors located deeper in the parenchyma, larger tumors, or tumors with any suspicion of malignancy are more appropriately treated with formal resection. Enucleation is also well described using minimally invasive or laparoscopic techniques.[41] The use of intraoperative ultrasound should be routine in either open or laparoscopic cases to identify the distance between the tumor and the main pancreatic duct and to exclude multiple tumors.[42] Given the benign behavior of most insulinomas, lymph node dissection is not required as part of the procedure.[43]

In rare instances, a thorough evaluation has failed to identify the location of an insulinoma; it was thought that blind distal pancreatectomy would remove most occult lesions. This procedure is now rarely performed because of improved localization techniques. In cases of truly undetected lesions, it is more appropriate to stop the operation and seek more accurate localization.[44]

Surgery for insulinoma in the presence of MEN1 is aimed at controlling all excess insulin secretion by removing all possible tumor burden. Preoperative localization is essential given the propensity for multifocal disease (**Box 1**).

Gastrinoma

Although the historical surgical treatment of gastrinoma was total gastrectomy to remove all acid-producing tissue, symptoms are now much more easily managed

Box 1
Insulinoma: surgical considerations

- Enucleation preferred for tumors distant (>2–3 mm) from pancreatic duct
- Formal resection indicated if enucleation not possible
- Lymph node dissection not needed
- Laparoscopic resection beneficial
- No indication for blind distal pancreatectomy
- Role for surgery in MEN1 to remove tumor burden

with acid-reducing agents, such as histamine type-2 blockers and proton pump inhibitors. The identification of a causative tumor offers the possibility of biochemical cure, prevention of disease progression, and prolongation of survival. As noted earlier, surgical resection may require operative exploration with ultrasound, direct palpation, duodenal transillumination, or duodenotomy. Surgical resection of the primary tumor and involved lymph nodes is the only potentially curative treatment.[45] Based on the high incidence of lymph node metastases in sporadic gastrinomas and the prognostic importance of nodal metastases, most investigators recommend routine systematic lymph node dissection in the peripancreatic, periduodenal, and pancreaticoduodenal area during surgery for sporadic gastrinoma.[46]

Resection in sporadic cases of gastrinoma may lead to long-term cure in approximately one-third of patients, with disease-specific survival at 10 years of 95%.[25] Enucleation may be applicable for tumors with an adequate margin to the pancreatic duct (3 mm), particularly in pancreatic head tumors in order to avoid pancreaticoduodenectomy, whereas distal pancreatectomy may be required for tumors of the pancreatic body or tail. Tumors larger than 2 cm or involving the pancreatic duct may require pancreaticoduodenectomy. Given the often-difficult localization of duodenal gastrinoma, requiring direct palpation, laparoscopic resection is controversial.

Unlike insulinoma, surgery for gastrinoma in the setting of MEN1 has an extremely high rate of recurrence. Although patients with hyperparathyroidism and gastrinoma with MEN1 require subtotal parathyroidectomy to remove stimulation of gastric acid from hypercalcemia, surgery for the gastrinoma itself is more controversial. Given the favorable prognosis with small (<2 cm) gastrinomas and the multifocal nature of the disease, nonoperative management is generally recommended for small tumors in the setting of MEN1. Surgery to prevent malignant transformation has been recommended by some investigators for larger tumors.[47] More radical surgery to remove the field defect of MEN1 with pancreaticoduodenectomy or total pancreatectomy is supported by some investigators.[48] Given the high recurrence rate and often slow-growing nature of disease, a more targeted surgical approach in MEN1 is advocated.[49] Incomplete resection is not beneficial, and surgery is not indicated with extensive metastases (**Box 2**).

Other functional pancreatic neuroendocrine tumors

Potentially curative surgical resection is recommended if feasible. Glucagonomas frequently present as large tumors and at an advanced stage, precluding safe resection. As most tumors arise in the body and tail, distal pancreatectomy is often possible if resection is feasible. Enucleation is rarely possible and not indicated. Similarly, laparoscopic resection may not be feasible because of the large size of lesions and propensity for liver metastases.[50] VIPomas are very rare and frequently occur in the

Box 2
Gastrinoma: surgical considerations

- Enucleation possible in some patients
- Surgical exploration required to identify tumors in the gastrinoma triangle (delineated by cystic duct, junction of body/neck of pancreas), and
- Lymph node dissection indicated
- Laparoscopic resection suboptimal because of difficulty with identification of tumors
- Smaller tumors observed in MEN1; resection of larger tumors controversial

pancreatic tail. Large and metastatic lesions are common, making curative resection challenging. For these and other rare functional PNETs, cytoreductive surgery may be indicated to improve hormonal control; surgery for liver metastases may be performed at the same time as resection of the primary tumor, if possible[51] (**Box 3**).

Nonfunctioning Pancreatic Neuroendocrine Tumors

Unlike functional PNETs, the primary goal of surgical management of nonfunctional PNETs is to prevent metastases and improve long-term survival.[52,53] Surgical resection typically consists of formal anatomic resection of the pancreatic head (pancreaticoduodenectomy) or body/tail (distal pancreatectomy with or without splenectomy). Local invasion of nearby organs or vascular structures is not a contraindication to potentially curative resection if all macroscopic disease can be removed.[54,55] Controversies in operative management include the role of conservative management in small incidentally detected PNETs (<2 cm), the role of pancreas-sparing operations for small PNETs, and the role of resection in MEN1.

Small nonfunctioning pancreatic neuroendocrine tumors

Studies have demonstrated a direct relationship between tumor size and risk of metastases.[56] With increased utilization and improved accuracy of cross-sectional imaging, an increasing number of incidental, small (<2.0 cm) PNETs are now identified.[57,58] Given that only 6% of nonfunctional PNETs less than 2 cm in size will be metastatic at diagnosis, some suggests a conservative strategy; the optimal management of these more indolent neoplasms is debated.

Support for an expectant management approach is supported by 2 recent studies. Gajoux and colleagues[59] described an observational study of 46 patients with small PNETs, with a median follow-up of 34 months. Eight patients underwent surgery for patient preference or for growth of tumors under observation. In the remaining 38 patients, there was no evidence of spread to lymph nodes or distant sites; most patients showed no growth. Lee and colleagues[60] described a series of 133 patients win incidental PNETs; in a group of 77 patients with a median tumor size of 1.0 cm and mean follow-up of 45 months, no patient showed significant growth or disease progression. Based on these data, serial imaging of PNETs less than 2.0 cm in size with MRI every 6 months for 2 years and annually afterward might be considered, with surgery reserved for growth or evidence of nodal metastases.[61]

Other data, however, suggest a more aggressive approach to even small incidental tumors. A retrospective group of 139 incidentally discovered PNETs included 39 patients with tumors 2.0 cm or smaller; in this group, 7.7% had late metastases or recurrence.[62] In a 20-year analysis of the Surveillance, Epidemiology, and End Results database, disease-specific survival at 5, 10, and 15 years for PNETs smaller than 2 cm was 91.5, 84.0, and 76.8%.[57] In a multi-institutional cohort of nonfunctioning PNET who underwent surgery, 3 of 56 patients with tumors less than 2 cm developed distant metastases, with 2 disease-related deaths. The investigators concluded that

Box 3
Additional functioning PNETs: surgical considerations

- Tumors usually present as large lesions, and metastases are common.
- Curative resection is rarely possible.
- Enucleation is not indicated.

the decision to proceed to surgical resection should not merely be based on size but also include tumor characteristics, such as grade.[63] In a recent review of 136 surgical patients, Hashim and colleagues[64] suggested a metastatic rate of 8% in tumors as small as 1.5 cm. Given this risk and the inability to accurately predict metastatic potential, resection was advised for small tumors.

Extent of surgery

The extent of surgery required when resecting small lesions is also a matter of debate. Enucleation is proposed for small lesions to avoid pancreatic insufficiency.[65] Tumor recurrence after enucleation is one potential concern; one series demonstrated an 8% risk of recurrence after enucleation of small incidental PNETs with a median follow-up less than 5 years.[66] The precise size threshold whereby enucleation may be safely performed for nonfunctional PNETs is unclear.

Furthermore, enucleation is typically performed at the expense of accurate nodal sampling. Individual series have shown a risk of nodal metastases in tumors smaller than 2 cm between 7.7% and 26.0%.[62,67,68] Although debate exists regarding the value of lymphadenectomy with surgery for PNETs, several large single-institution studies suggest a correlation between nodal metastases and outcome.[64,69,70] Conversely, a review of PNETs in the National Cancer Data Base suggested that tumor grade but not size or nodal metastases was associated with long-term survival.[71] Similarly, the largest single-institutional experience of nonfunctional PNETs reported that overall survival is predicted by tumor grade as determined by the Ki-67 index, without input of tumor size or nodal involvement.[72] The therapeutic value of lymphadenectomy is undefined, though potential prognostic information is gained from nodal sampling. Until the role of lymphadenectomy is better defined, the National Comprehensive Cancer Network's guidelines recommend consideration of lymph node resection for PNETs between 1 and 2 cm in size.[73]

Nonfunctioning pancreatic neuroendocrine tumors in multiple endocrine neoplasia type 1

Management of PNETs in the setting of MEN1 is complicated by the multifocal nature of small tumors, which almost universally behave in an indolent manner. Although the precise incidence of PNETs in MEN1 is unclear, data suggest that, when EUS is used for diagnosis, PNETs are found in between 54% and 93% of asymptomatic patients with MEN1, with most tumors less than 1 cm in size.[74] Evidence suggests that lesions smaller than 1 cm act in an indolent manner, with risk of malignancy increased as tumors exceed 2.0 cm.[75,76] Surveillance data for asymptomatic small PNETs in MEN1 suggest that most small lesions remain stable or decrease in size with a median follow-up of 6 years, though other tumors may develop on surveillance and may grow at a rate faster than earlier lesions.[77] Surgery, when indicated, can include parenchyma-sparing operations to total pancreatectomy with intraoperative ultrasound guidance to avoid leaving occult tumors behind (**Box 4**).[9]

Surgery for Metastatic Pancreatic Neuroendocrine Tumors

Neuroendocrine liver metastases (NELM) may occur in up to half of all patients with PNETs, and metastatic disease has a significant impact on prognosis.[1,70] Liver-directed treatment of NELM can include several modalities, such as surgery, tumor ablation, and transarterial embolization. In addition, new systemic approaches have proven beneficial specifically in metastatic neuroendocrine tumors from the pancreas.[4–6] Although a comprehensive review of NELM is beyond the scope of this article, several salient points about surgical management of liver metastases are relevant for functional and nonfunctional tumors (**Box 5**).

Box 4
Nonfunctioning PNETs: surgical considerations

- All tumors greater than 2 cm should be resected, typically with formal anatomic resection (pancreaticoduodenectomy, distal pancreatectomy) including negative margins and regional lymph nodes.
- Evidence suggests incidental tumors less than 1 cm can be followed with surveillance.
- Some studies with short-term follow-up suggest that all nonfunctioning PNET less than 2 cm might be followed with surveillance, with resection for growth.
- Pancreatic enucleation is most appropriate for small PNETs; lymph node resection should be considered for tumors 1 to 2 cm in size.
- MEN1 is associated with small, multifocal tumors, most of which have a low risk of progression. Surgery is reserved for tumors greater than 1 to 2 cm in size.

Functional pancreatic neuroendocrine tumors

Surgical therapy for metastatic disease in functional PNETs may be considered not only for potential oncologic benefit for control of hormone excess. Cytoreductive surgery including nonanatomic or formal hepatectomy may be considered for metastatic disease if most tumor burden can be removed. Debulking or cytoreductive surgery is potentially beneficial if more than 90% of the tumor burden can be removed,[43,51,78] though the precise means of estimating tumor volume are not clear.[79] Regardless of the potential oncologic benefits, reducing the tumor burden can improve symptom control in many patients with hormonally active tumors if tumors develop resistance to medical therapy.[80] Synchronous resection of primary pancreatic tumors and liver metastases must be undertaken with caution given the increased morbidity of the combined procedures.[81,82]

Nonfunctional pancreatic neuroendocrine tumors

Unlike functional tumors, metastatic nonfunctional PNETs do not lead to symptoms of hormonal excess; surgery is only indicated for potential oncologic benefit. Data supporting metastasectomy with nonfunctional pancreatic primary tumors are often retrospective and nonrandomized, allowing for the strong possibility of selection bias. Numerous single-institutional and retrospective studies suggest a survival benefit to surgical resection of NELM from intestinal or pancreatic primary tumors,[83,84] a benefit confirmed in pooled multi-institutional data as well.[85] This potential benefit is confirmed in studies limited to nonfunctional PNETs.[81,86] In a review of 72 patients, complete resection of all liver metastases led to a 5-year overall survival of 60%, compared with 45% in patients unable to have disease resected.[81]

Box 5
Metastatic PNETs: surgical considerations

- Cytoreductive surgery may be beneficial in metastatic functional PNETs to relieve symptoms of hormonal excess.
- Resection may offer improved overall survival in metastatic nonfunctional PNETs in low-grade or well-differentiated tumors if all disease can be removed or treated.
- Recurrence rates are near universal, with a high rate of occult metastases in the clinically normal liver.

Despite favorable survival data in these series, recurrence rates after metastasectomy are nearly universal, even with microscopically negative resection. Of note, data from a prospective cohort of patients with NELM show that careful thin-slice examination of the liver after resection of NELM reveals a high rate of occult disease.[87] CT scan had only 38% accuracy in determining the extent of disease, with most NELM only detected on the pathology examination. This finding suggests that most potentially curative resections for NELM are actually cytoreductive. In the absence of randomized data, surgery to remove liver metastases can be recommended primarily in low-grade tumors, with metastases limited to the liver, and if all disease can be feasibly resected.[88,89]

SUMMARY

PNETs include a diverse group of neoplasms, including functional and nonfunctional disease. Surgical resection is the mainstay of therapy for localized disease, and precise surgical techniques and goals should be tailored to clinical presentation and biological behavior. Complete surgical resection has an oncologic benefit in localized disease and a potential palliative benefit for any functional tumor as well.

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