Surgical Therapy of Sporadic Pancreatic Neuroendocrine Neoplasias G1/G2

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Keywords

Neuroendocrine tumors of the pancreas · Insulinoma · Gastrinoma · Non-functional pancreatic tumors · Liver metastases · Surgical therapy

Summary

Background: Pancreatic neuroendocrine neoplasias (pNENs) are uncommon but fascinating tumors with an annual incidence of 1 per 100,000 people. pNENs present either as functional tumors, causing specific hormonal syndromes like Zollinger-Ellison syndrome (ZES) or organic hyperinsulinism, or as non-functional pancreatic tumors (NF-pNENs). The natural history of pNENs is highly variable. 90% of all insulinomas or small NF-pNENs are readily curable by surgical resection. Most other functional and late detected NF-pNENs have a less favorable chance for cure. **Methods:** A systematic review of the literature was performed to identify the current state of the art with regard to the key issues of surgery in pNEN G1/G2. **Results:** This article provides a comprehensive review of the current literature addressing the current challenges in pNEN surgery. **Conclusion:** Patients with completely resected tumors generally have a good prognosis, and an aggressive surgical approach combined with conservative treatment options in patients with advanced disease rarely provides cure but often results in long-term survival.

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Introduction

Pancreatic neuroendocrine neoplasias (pNENs) represent an important subset of pancreatic neoplasms (table 1). They account for 2–4% of all clinically detected pancreatic tumors. pNENs are rare tumors, but are detected more and more often [1, 2]. pNENs show no significant gender predilection and occur at all ages. They consist of single or multiple neoplasias and are associated in 10–20% with multiple endocrine neoplasia type 1 (MEN1). pNENs present either as functional tumors, causing specific hormonal syndromes like Zollinger-Ellison syndrome (ZES) or organic hyperinsulinism, or as non-functional pNENs (NF-pNENs) with symptoms similar to pancreatic adenocarcinoma [1]. This article focuses on the surgical management of sporadic pNENs G1/G2 and their liver metastases (LM).

Short Overview of Clinical Characteristics of Pancreatic Neuroendocrine Neoplasias

Insulinomas

Insulinomas are the most frequent of all functioning pNENs. Virtually all insulinomas are located in the pancreas. Approximately 90% of insulinomas are solitary; the remaining 10% are multiple and are associated with MEN1 syndrome [3]. Most insulinomas are small. 40% are less than 1 cm, 66% are less than 1.5 cm, and 90% are less than 2 cm in diameter. Only 10% of the tumors are malignant at the time of diagnosis.

Insulinomas are characterized by fasting hypoglycemia and neuroglycopenic symptoms, and occasionally sympathoadrenal autonomic symptoms [3]. Whipple developed a symptom triad bearing his name to identify patients with insulinoma more accurately. These symptoms include signs and symptoms of hypoglycemia after fasting or exercise, blood glucose of less than 45 mg/dl when symptomatic, and symptoms relieved by intravenous or oral glu-

Table 1. Neuro-endocrine neoplasias of the pancreas

Tumor (syndrome)	Incidence, %	Presentation
Insulinoma	70–80	weakness, sweating, tremulousness, tachycardia, anxiety, fatigue, headache, dizziness, disorientation, seizures, and unconsciousness
Gastrinoma	20–25	intractable or recurrent peptic ulcer disease (hemorrhage, perforation), complications of peptic ulcer, diarrhea
VIPoma	4	profuse watery diarrhea, hypotension, abdominal pain
Glucagonoma	4	migratory, necrolytic skin rash, glossitis, stomatitis, angular cheilitis, diabetes, severe weight loss, diarrhea
Somatostatinoma	<5	weight loss, cholelithiasis, diarrhea, neurofibromatosis
Carcinoid	<1	flushing, sweating, diarrhea, edema, wheezing
ACTHoma	<1	Cushing's syndrome
GRFoma	<1	acromegaly
PTH-like-oma	<1	hypercalcemia, bone pain
Neurotensinoma	<1	hypotension, tachycardia, malabsorption
Non-functional tumors	30–50	obstructive jaundice, pancreatitis, epigastric pain, duodenal obstruction, weight loss, fatigue

VIP = Vasoactive intestinal peptide; ACTH = adrenocorticotropin hormone; GRF = growth hormone-releasing factor; PTH = parathyroid hormone.

cose. These symptoms usually occur when serum glucose is less than 40 mg/dl [4]. A fasting test that may last up to 72 h is regarded as the most sensitive test. About 80% of insulinomas are diagnosed by this test, most of them in the first 24 h [5].

Non-Functioning pNENs

Clinically, NF-pNENs produce no or insufficient quantities of hormones, such as pancreatic polypeptide, that do not cause any hormonal symptoms [6]. Because of modern imaging modalities, they have been diagnosed more frequently and now represent at least 50% of pNENs. At operation these tumors are generally larger than their functional counterparts and are equally located throughout the pancreas. Patients usually present late owing to the lack of a clinical/hormonal marker of the tumor's activity. Therefore, in contrast to functioning pNENs, patients with NF-pNENs present with either various non-specific symptoms, such as abdominal pain and weight loss, or pancreatitis. Nowadays, however, more and more asymptomatic NF-pNENs are detected incidentally during an imaging procedure for other reasons.

Measurement of detectable serum or plasma levels of various hormones can establish the diagnosis of an NF-pNEN. Chromogranin A (CgA) is considered the best tumor marker currently available for the evaluation and follow-up of patients with NF-pNENs, as these tumors do not reliably produce any other suitable marker. Plasma CgA is elevated in 60–100% of patients with NF-pNENs. Furthermore, up to 75% of NF-pNENs are associated with increased serum levels of pancreatic polypeptide [6].

Gastrinomas (Zollinger-Ellison Syndrome)

Gastrinomas were first described in 1955 when Zollinger and Ellison, of the Ohio State University Medical School, reported on

2 patients with islet cell tumors associated with atypical peptic ulceration of the jejunum [7]. Approximately 0.1% of patients with duodenal ulcers show evidence of ZES. The reported incidence is between 0.5 and 4/1,000,000/year. The anatomical area harboring the vast majority of these tumors comprise the head of the pancreas, the superior and descending portion of the duodenum, and the relevant lymph nodes and has been termed the 'gastrinoma triangle' [8].

In patients with ZES abdominal pain is the most frequent complaint either alone or with diarrhea, followed by heartburn, nausea, or bleeding. The abdominal pain is primarily due to peptic ulcer disease or gastroesophageal reflux disease and is indistinguishable in character from that seen in ordinary ulcer patients [9].

If the patient presents a gastric pH below 4.0 and a serum gastrin concentration above 1,000 pg/ml (normal <100 pg/ml), then the diagnosis of ZES is confirmed.

Rare Functioning pNENs

Vipomas

Vasointestinal peptide-secreting tumors, also called VIPomas, Verner-Morrison syndrome, or WDHA (watery diarrhea, hypokalemia, and acidosis), account for fewer than 5% of islet cell tumors [1]. The 2 patients described by Verner and Morrison died from dehydration and renal failure in spite of attempted intravenous hydration. The VIP directly inhibits gastric acid secretion, causing achlorhydria. Sporadic VIPomas are solitary tumors and arise from the VIP-secreting cells that are usually located in the region of the pancreatic tail and body [1]. More than 90% of these tumors are <2 cm in size as well as malignant and metastasize to the lymph nodes, liver, and bone. The secretory diarrhea ranges between 0.5 and 15 l/24 h and is usually the most prominent symptom at presentation. It results in severe loss of potassium and bicarbonate, which in turn leads to metabolic acidosis and dehydration. The 5-year survival

rate is 60% for patients with metastases and over 90% for patients without distant metastases [1].

Glucagonomas

Glucagonomas arise from the glucagon-producing α -cells of the pancreas. Around 60% of patients already have LM at the time of diagnosis [1]. Tumors that produce excessive glucagon cause a specific syndrome of diabetes mellitus, a skin rash (necrolytic migratory erythema), hypoaminoacidemia, and a tendency for deep venous thrombosis. Patients often also have stomatitis, glossitis, and cheilosis associated with the skin rash. The syndrome is diagnosed by elevated plasma levels of glucagon. Levels greater than 1,000 pg/ml are diagnostic of the syndrome. Once the syndrome is diagnosed, surgical resection of the tumor is indicated whenever possible. Preoperatively a management with somatostatin analogs and nutritional supplementation is indicated to correct the nutritional deficiency and to resolve the rash [10].

Current Surgical Treatment Strategies for Sporadic Pancreatic Neuroendocrine Neoplasias

Insulinoma

Surgical cure rates in patients with the biochemical diagnosis of insulinoma range from 77 to 100% [3]. At surgical exploration, the abdomen is initially explored for evidence of metastatic disease. Then a meticulous surgical exploration, i.e. an extended Kocher maneuver to be able to palpate the head, as well as the mobilization of the distal pancreas and the spleen should follow to explore the body and tail of the gland to examine the distal pancreas carefully and completely. Intraoperative ultrasonography (IOUS) should then be used to confirm the presence of the insulinoma or to detect non-palpable lesions and also to discern the relation of the tumor to the pancreatic duct. Identification of the pancreatic duct and determination of its proximity to the insulinoma can guide safe enucleation of the tumor. This approach can minimize the likelihood of a postoperative pancreatic fistula. Tumor enucleation, when feasible, is the technique of choice. If the tumor is located in the pancreatic tail, a distal spleen-preserving pancreatic resection might be the procedure of choice. In order to be considered malignant, these tumors must show evidence of either local invasion into surrounding soft tissue or verification of lymph node or LM. Malignant insulinomas account for only about 5–10% of all insulinomas. Aggressive attempts for resection are indicated, since there is no effective medical treatment option to control hypoglycemia. Malignant insulinomas located in the body or tail of the pancreas are effectively treated by distal pancreatectomy with splenectomy and lymphadenectomy. For tumors located in the head of the gland, resection requires partial pancreaticoduodenectomy (PPD) [11].

Recent advances in laparoscopic technique and instrumentation have enabled surgeons to approach complex procedures laparoscopically. This is also true for insulinomas [12–14]. The patient is placed in a half-lateral position with the left side up for tumors lo-

Fig. 1. Laparoscopic operation for pancreatic neuroendocrine neoplasias. The patient is placed in a half-lateral decubitus position with the left side uppermost for tumors in the body/tail of the pancreas. The surgeon and the assistant stand on the left of the patient, while the cameraman and the scrub nurse are on the opposite side. Two monitors are used. Typical port sites for resection of lesions in the body/tail of the pancreas are shown.

Fig. 2. Laparoscopic ultrasound.

cated in the body or tail of the pancreas or with the right side up for tumors in the head of the gland, and in the reverse Trendelenburg position. Four 10–12 mm trocars are inserted in the abdominal wall: 3–4 cm above the umbilicus, in the xiphoid area, subcostal on the midaxillary line, and in the subcostal midclavicular line (fig. 1). The pancreas is exposed after opening the lesser sac after mobilizing its head. Laparoscopic ultrasound should be used to identify non-visible tumors and to determine the relationship of the lesion to surrounding veins and the pancreatic duct (fig. 2). Laparoscopic ultrasound can be particularly helpful in identifying lesions in the tail that are often missed by endoscopic ultrasound. For superficial ventral tumors, laparoscopic enucleation is undertaken with electrocautery or laparoscopic vessel sealing shears. Small pancreatic vessels can be clipped and cut. Tumors located deep in the body or tail of the pancreas and those in close proximity to the pancreatic duct (<3 mm distance) require distal pancreatectomy. In cases where visualization and ultrasound fail, a hand port can be used to allow palpation of the gland. Tumors situated very distally near the splenic hilum are especially difficult to identify. It is worthwhile preserving the spleen during this procedure, if

it can be safely accomplished. The pancreatic tail and/or body should be meticulously dissected from the splenic vessels, or these vessels may be resected together with the pancreas, leaving the spleen vascularized by the short gastric vessels [15].

Postoperatively, blood sugar levels begin to rise in most patients within the first hours after the removal of an insulinoma (reactive hyperglycemia). To preserve pancreatic function and to reduce the risk of iatrogenic diabetes mellitus, patients in whom tumor identification is not successful at operation should not undergo blind resection.

Non-Functioning pNENs

According to the classification of the World Health Organization, the size of the endocrine tumor correlates with malignant growth. Therefore, in localized tumors larger than 2 cm, aggressive surgery and, if required, resection of adjacent organs (stomach, colon, kidney, adrenal gland) and/or major venous resection is indicated [16]. At the present time, most would advocate an aggressive surgical approach for the management of malignant NF-pNENs even in the presence of localized metastases [11, 16]. The major goal is a potentially curative R0 resection by either partial pancreatoduodenectomy or distal splenopancreatectomy depending on the localization of the tumor. As lymph node metastases are frequently encountered, regional lymphadenectomy with en bloc resection of the primary tumor is the goal [11, 16]. In contrast, only few data exist with respect to a positive effect of surgery on overall survival in small (<2 cm), possibly benign or intermediate-risk pancreatic endocrine tumors. In a very recent study, Partelli et al. [17] analyzed five retrospective studies with a total of 540 patients. Of these, 327 patients underwent active surveillance and 213 had surgery. The median length of follow-up ranged from 28 to 45 months. Measurable tumor growth was observed in 0–51% of patients. Overall, 46 patients (14%) underwent pancreatic resection after initial conservative treatment. In most patients the reason was an increase in tumor size (19 of 46). There were no disease-related deaths in the active surveillance group in any of the studies. This systematic review suggests that active surveillance of patients affected by sporadic, small, asymptomatic NF-pNENs may be a good alternative to surgical treatment. There are some criteria to opt for surgery even if the tumor is <2 cm: the wish of the patient to end a lifelong surveillance, a progression of 20% of the tumor in 12 months, or suspicious lymph nodes. However, the possibility of surgical cure has to be weighed against the operative morbidity, mortality, and long-term complications associated with pancreatic surgery [16].

Laparoscopic and Robotic Surgery for Insulinomas and Non-Functioning pNENs

As already mentioned, most patients with insulinomas are ideal candidates for a minimally invasive approach, because these tu-

mors are small, solitary, and benign. The first successful laparoscopic resection was reported by Gagner in 1996 [18]. As mentioned earlier, the most sensitive method of localization is intraoperative palpation and IOUS. In laparoscopic surgery, palpation is not possible. We and others have reported that preoperative localization, mainly by endoscopic ultrasonography, is crucial for the decision to operate laparoscopically [19, 20] and that minimally invasive surgery for pNENs should be undertaken only if laparoscopic ultrasound is available. Laparoscopic ultrasound helps the surgeon to decide whether to use enucleation or resection, a decision that will depend on the proximity to the main pancreatic duct or large blood vessels.

Laparoscopic enucleation is reserved for tumors less than 2 cm in diameter located on, or near, the surface of the pancreas, and not in contact with splenic vessels, the portal vein, or the main pancreatic duct. If these criteria are not met, laparoscopic spleen-preserving distal pancreatectomy should be the preferred choice. Recent small-scale retrospective studies have shown that the rate of spleen and vessel preservation is higher with the robotic approach than with the conventional laparoscopic approach for distal resections [21, 22].

Gastrinomas are not yet considered as candidates for a laparoscopic approach for two reasons. First, most gastrinomas are usually located in the duodenum, and bidigital palpation after duodenotomy (DUODX) is essential to identify the small tumor. Second, most pancreatic gastrinomas are over 2 cm in diameter at diagnosis and reveal metastases in up to 70% of patients, thus requiring a meticulous lymphadenectomy, which is not ideal for a laparoscopic approach. The same holds true for rare functioning pNENs [11].

Given the current data, minimally invasive enucleation or resection of insulinoma and most NF-pNENs is feasible and safe so that it is considered the procedure of choice for selected insulinomas [1, 12–14]. Nevertheless, it seems clear that such a treatment should only be offered by surgeons who are experienced in both endocrine pancreatic operations and advanced laparoscopic surgery. The same is true for robotic surgery, which emerged in the last years as a new technical possibility [22, 23]. As technology advances and experience with robotic-assisted surgery will increase, it is likely to become an alternative method of pancreatic resection for pNENs (fig. 3, 4).

Gastrinoma

As with all pNENs, the only chance for cure of gastrinoma is complete surgical resection, which is achieved in 26–100% of patients. A study compared 160 patients with ZES undergoing resection with 35 patients who had a similar stage of disease but did not undergo surgical exploration [24]. After a follow-up of 12 years, 41% of patients were cured with surgery and significantly more patients developed LM with conservative treatment (29 vs. 5%; $p < 0.001$). The 15-year disease-related survival was 98% after surgery and 74% after medical treatment ($p < 0.001$). These results demonstrate that routine surgical exploration increases survival in pa-

Fig. 3. Robotic-assisted setup for enucleation of a pancreatic neuroendocrine neoplasia.

tients with sporadic ZES by increasing disease-related survival and reducing the rate of advanced disease. Therefore, routine surgical exploration should be performed in all patients with sporadic gastrinomas without evidence of diffuse hepatic metastases and in those who are fit for surgery.

Duodenal Gastrinomas

DUODX should be routinely performed for all patients with ZES. Recently, Norton et al. [25] underlined the importance of DUODX in patients with ZES. They performed DUODX in 79 patients, and no DUODX was performed in 64 patients. Gastrinoma was found in 98% with DUODX compared with 76% with no DUODX. They could show that the use of routine DUODX increases the short- and long-term cure rate. Duodenal exploration is undertaken via longitudinal DUODX in the descending part of the duodenum. Small tumors can be identified by palpation. Duodenal tumors smaller than 5 mm can be enucleated with the overlying mucosa (fig. 4); larger tumors are excised with full thickness excision of the duodenal wall. After completion of this exploration the DUODX is cautiously sutured longitudinally.

Because of the high incidence of lymph node metastases associated with duodenal gastrinomas, prophylactic lymph node dissection should be performed [1]. Bartsch et al. [26] could demonstrate in 41 patients who underwent potentially curative surgery that systematic lymphadenectomy with excision of more than 10 lymph nodes resulted in a higher rate of biochemical cure after surgery than no or selective lymphadenectomy (13 of 13 vs. 18 of 28 patients; $p = 0.017$), and a reduced risk of death (0 of 13 vs. 7 of 24 patients; $p = 0.037$). Another study analyzed the distribution of lymph node metastases found at the time of operation in 38 patients with sporadic duodenal gastrinomas by mapping their location in relation to the duodenal primary [27]. Patients who had primary duodenal tumors located above the ampulla of Vater generally harbored positive lymph nodes in the superior periduodenal area, celiac axis, or periportal area. Those with primary tumors in

Fig. 4. Robotic-assisted enucleation of a pancreatic neuroendocrine neoplasia.

the third and fourth portions of the duodenum had positive lymph nodes located most commonly in the superior mesenteric artery or inferior periduodenal areas. Lymph nodes were found close to the primary tumor in most cases.

Pancreatic Gastrinomas

The role of operative exploration in patients with sporadic gastrinomas is relatively well defined. Most of these non-MEN1 gastrinomas are solitary, identifiable at laparotomy, and resectable with simple enucleation. Formal pancreatic resections are typically reserved for patients with local tumor invasion. In practice, this leads to distal pancreatic resection, splenectomy, and peripancreatic lymph node dissection for gastrinomas in the pancreatic body or tail. Most of the pancreatic gastrinomas are located in the head of the gland or uncinus process. An enucleation with peripancreatic lymph node dissection is the procedure of choice in gastrinomas of the pancreatic head. For large pancreatic head gastrinomas a partial PPD is justified [11].

Treatment of Rare Functioning pNENs

Curative surgery is always recommended whenever feasible after careful symptomatic control of the clinical syndrome; the latter may be achieved by medical or locoregional treatments [1]. Curative surgery should include an oncological pancreatic resection with lymphadenectomy. Laparoscopic resection is generally not recommended because of the need for lymphadenectomy and careful inspection for invasion/metastases [1, 11].

Management of Liver Metastases

LM frequently develop during the natural history of pNENs, with an incident rate of liver involvement between 28 and 78% [28]. In metastatic pNENs, 5-year survival rates are around 40–60% [16]. Patients with gastrinoma and no metastatic disease have a 20-year survival rate of 95% whilst a 10-year survival of only 15% is reported when diffuse metastatic liver disease is present [29]. Whenever possible, R0 resection of LM is still considered as the

gold standard, although several different options to treat LM have become available in the last years, including biotherapy, chemotherapy, targeted treatments (everolimus, sunitinib), local ablative treatments with transarterial embolization/transarterial chemoembolization, radiofrequency ablation (RFA), irreversible electroporation (IRE) or peptide receptor radionuclide therapy (PRRT), and selective internal radiation therapy (SIRT).

Surgery for Liver Metastases

The interdisciplinary decision to perform liver surgery is based on a multifactorial assessment, taking into account tumor grading, the presence of extrahepatic metastases, and the presence of symptoms [29]. Only 20–30% of patients with metastatic disease are suitable for radical intent at presentation. Debulking surgery (R2) in incompletely resectable metastatic disease is not universally accepted, but particularly in symptomatic patients it may improve the quality of life when medical treatment failed [29]. For surgery with curative intent, the European Neuroendocrine Tumor Society (ENETS) has proposed the following criteria: (i) resectable G1–G2 liver disease with acceptable morbidity and less than 5% mortality, (ii) absence of right heart insufficiency, (iii) absence of unresectable lymph node and extra-abdominal metastases, and (iv) absence of diffuse or unresectable peritoneal carcinomatosis [28]. The overall survival after hepatic resection is 46–86% at 5 years and 35–79% at 10 years [16]. In referral centers, the 5-year survival for hepatic resections of patients with NET (neuroendocrine tumor) LM commonly exceeds 60%. Preselection biases due to better performance status or less advanced disease are likely to influence such differences in favor of the outcomes associated with surgery. Nevertheless, resection is associated with a low mortality rate (0–5%) and an acceptable morbidity (30%). Analysis of histopathology specimens revealed that the disease burden in the liver is often underestimated, with almost half the number of LM from NETs being undetectable on preoperative imaging [16].

In the last 20 years, non-surgical novel techniques such as RFA, IRE, SIRT, and PPRT have become available and gained popularity mainly as complementary treatment options. The lack of randomized data makes the comparison with a surgical approach in terms of survival benefit and symptomatic relief difficult.

Liver Transplantation for Metastatic NETs

In selected cases, liver transplantation (LT) has been used to treat LM from NENs. However, considerable controversy exists due to the absence of adequate available data comparing transplantation for unresectable LM to other treatment modalities [30]. In addition, in Germany, there is a serious lack of donor organs for

this indication so that only about 1% of patients with diffuse metastatic pNEN liver disease will receive a liver transplant. However, LT has been advocated in patients with bilateral unresectable LM that are refractory to other treatment. Only a few multicenter studies and several single-center retrospective studies with a small number of patients are available which evaluate the survival benefits of LT for the treatment of NEN metastases [30]. Recent evidence suggests that the 5-year survival after LT for unresectable LM can be as good as 60–80% in selected patients. Given an expected survival rate of 20–30% in untreated cases with diffuse LM, it seems that LT may play a role in highly selected patients [30].

Peritoneal Carcinomatosis

Peritoneal metastases are considered a serious event in virtually all malignancies and usually lead to a poor prognosis. In NEN, they are the direct cause of death in 40% of patients [31]. In the largest study so far, which included NENs from different origins, 41 patients underwent cytoreductive peritonectomy with or without hyperthermic intraperitoneal chemotherapy (HIPEC). LM were treated during the same operative procedure in 66% of the patients. Elias et al. [32] reported an overall survival at 5 and 10 years of 69 and 52%, respectively. Overall survival was not different between patients treated with or without HIPEC, but the disease-free survival was greater in the HIPEC group ($p = 0.018$). The authors concluded that resection of peritoneal metastases from a NEN is feasible in most of the patients and seems to increase survival rates, without proving whether the addition of HIPEC had a positive or a negative impact [32].

Conclusions

pNENs are rare but fascinating tumors. Biochemical diagnosis justifies laparotomy in patients with insulinomas and gastrinomas, even if a tumor is not detected preoperatively. Whereas patients with insulinomas are usually cured, a significant surgical cure rate can also be achieved in patients with gastrinoma. The prognosis of pNENs is much better than that of pancreatic adenocarcinoma, even though patients are frequently diagnosed with metastatic disease. Therefore, an aggressive surgical approach leads to long-term survival even in patients with malignant pNENs. Although long-term cure can only be realized in a small proportion of patients, significant long-term palliation can be achieved.

Disclosure Statement

The authors do not have a conflict of interest to declare.

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