Chapter 10
Surgery for Pancreatic Neuroendocrine Neoplasms (pNENs)

Thomas Clerici and Bruno Schmied

pNENs

Hallmarks

- Are rare (incidence of 1/100,000; represent 1–2 % of all pancreatic neoplasms)
- Can be functional or nonfunctional in regard to hormonal hypersecretion
- Can be single or multiple
- Are often (10–20 %) associated with hereditary syndromes like multiple endocrine neoplasia type 1 (MEN1) or von Hippel-Lindau syndrome (VHL)

Presentation to the Surgeon

- Referral to surgery with a complete biochemical and imaging work-up, mostly for a specific hormonal syndrome caused by a pNEN
- Referral for the resection of a pancreatic mass of unknown origin with incomplete work-up
- As an "incidental" finding on CT or MR imaging for other pathology

T. Clerici, MD (✉) • B. Schmied, MD
Department of Surgery, Kantonsspital St. Gallen,
Rorschacherstrasse, St. Gallen CH-9007, Switzerland
e-mail: thomas.clerici@kssg.ch

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Classification

- According to WHO 2010[1] and TNM[2] criteria

General Preoperative Considerations

- The family history regarding the possibility of multiple endocrine neoplasia type 1 (MEN1) and von Hippel-Lindau disease (VHL) is of utmost importance.
- The complex nature of pNEN requires multiple medical specialities for diagnostic work-up, therapy, and follow-up; thus, the indication for surgery and the type of surgery should be discussed preoperatively in a multidisciplinary meeting.
- Some patients with pNEN might require therapy with a somatostatin analogue late after the initial surgical procedure to stabilize progression or to control hormonal excesses in metastasized disease. Because of its side effect of inducing gallstone development, cholecystectomy should be proposed to patients at the time of the initial surgery (exception: benign insulinoma).

Pre- and Perioperative Management (General Aspects)

- To avoid specific post-splenectomy infections, patients who undergo splenectomy must be vaccinated with Meningitec® and Pneumovax® at discharge or 2 weeks after the operation at the latest. If splenectomy is planned as part of the surgical procedure needed to remove pNEN, these vaccinations can be given at least 2 weeks preoperatively.
- Some studies have shown that perioperative treatment with a somatostatin analogue (e.g., 2–4 subcutaneous injections of 0.1–0.2 mg) reduces pancreatic fistula after pancreatic resection. Evidence of the effectiveness of this measure in regard to overall morbidity and mortality remains controversial; therefore, it cannot be recommended as a general rule. Its use will depend on personal preference, experience, and sometimes intraoperative conditions.

Insulin-Producing pNEN (Insulinoma)

Hallmarks

- Most insulinomas are small (<2 cm).
- Most insulinomas are benign (90 %).

[1] Bosman FT. WHO classification of tumors of the digestive system. Lyon: IARC Press; 2010.

[2] UICC. TNM classification of malignant tumours. 7th ed. New York: Wiley; 2011.

- Incidence: 2–4 patients/1,000,000 per year.
- 10–15 % are MEN1 associated.
- Represent approximately 25 % of pNEN.

Work-Up

Insist on:

- A properly taken family history concerning MEN1
- A proper biochemical work-up with
  - Documented neuroglycopenic symptoms during a 72-h fast test (see Chap. 8)
  - Compiled biochemical criteria obtained during the fast test: glucose ≤2.2 mmol/l; insulin ≥36 pmol/l, C-peptide ≥200 pmol/l, proinsulin ≥5 pmol/l
  - Exclusion of factitious hyperinsulinism, medication with oral sulfonylurea antidiabetics
- Preoperative localization work-up (see Chap. 9)

Pre- and Perioperative Management

- Patients with severe tendency to clinically manifest hypoglycemia should be hospitalized the day before scheduled surgery and given on a glucose infusion in order to avoid hypoglycemia during preoperative fasting.
- Preoperative information and patient consent must include all classical types of pancreatic resection (partial pancreatoduodenectomy, distal pancreatic resection, depending on preoperative localization) because the exact extent of the procedure cannot be anticipated. Even if preoperative planning suggests the possibility of a resection by "simple" enucleation, there is a possibility of intraoperative diagnosis of malignant disease or major lesion of the pancreatic duct.

Intraoperative Prerequisites

- Intraoperative ultrasound – to localize the insulinoma and ascertain its relation to the pancreatic duct and splenic vessels.
- Frozen section – to prove the resection of a neuroendocrine tumor using histopathological criteria.
- Consider using insulin monitoring (if available) and/or glucose monitoring during surgery to biochemically verify resection of the insulin-producing tumor.

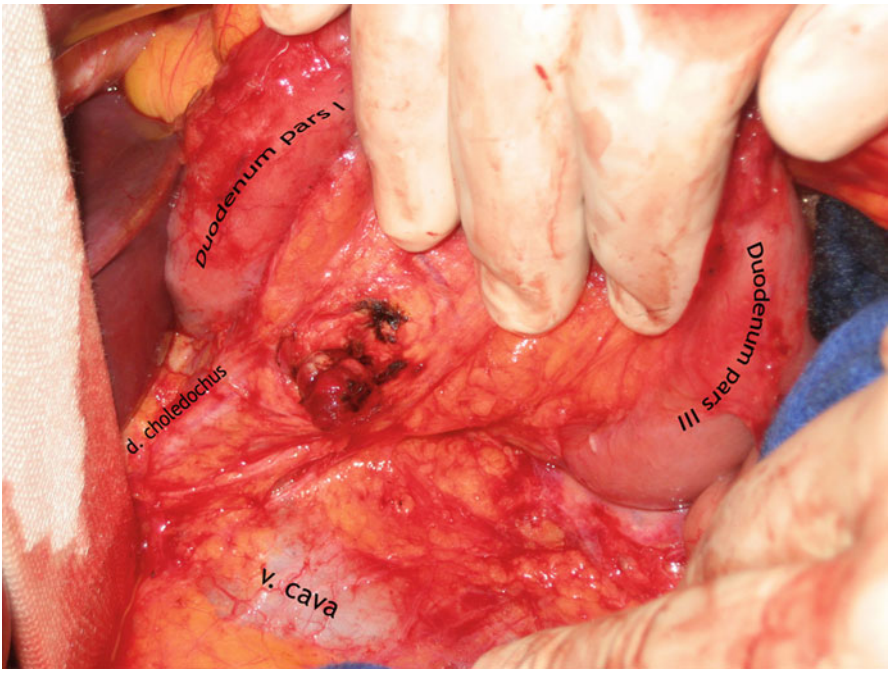

Fig. 10.1 Enucleation of a 1.5 cm insulinoma on the posterior surface of the pancreatic head in a adult

Surgical Technique

- Exposure and mobilization of head (Kocher's maneuver) and/or tail of the pancreas according to the result of the preoperative localizations studies.
- Palpation and IOUS should enable localization of the insulinoma in up to 95 % of cases.
- Enucleation
  - A simple enucleation is the procedure of choice if one can stay clear of the pancreatic duct during resection (Figs. 10.1 and 10.2).
  - Consider intraoperative secretin stimulation (2 units of secretin per kg body weight, as single intravenous bolus dose) if you are not sure whether there is a relevant lesion to the pancreatic duct or to a related contributing duct.
  - If a leak of pancreatic juice occurs on stimulation, cover the defect with a Roux-en-Y (side-to-side pancreatojejunostomy) or pursue a standard pancreatic resection (e.g., distal spleen-preserving pancreatic resection).
- If there is intraoperative suspicion of malignancy, attempt verification by frozen section and revert to an oncological resection type (right: pylorus-preserving partial pancreatoduodenectomy (PPPD), left: distal pancreatectomy).
- Never resort to "blind" resections. If you do not identify the insulinoma, close the abdomen and reevaluate diagnosis and imaging. Consider regionalization of the insulin-producing source with ASVS if not yet done.

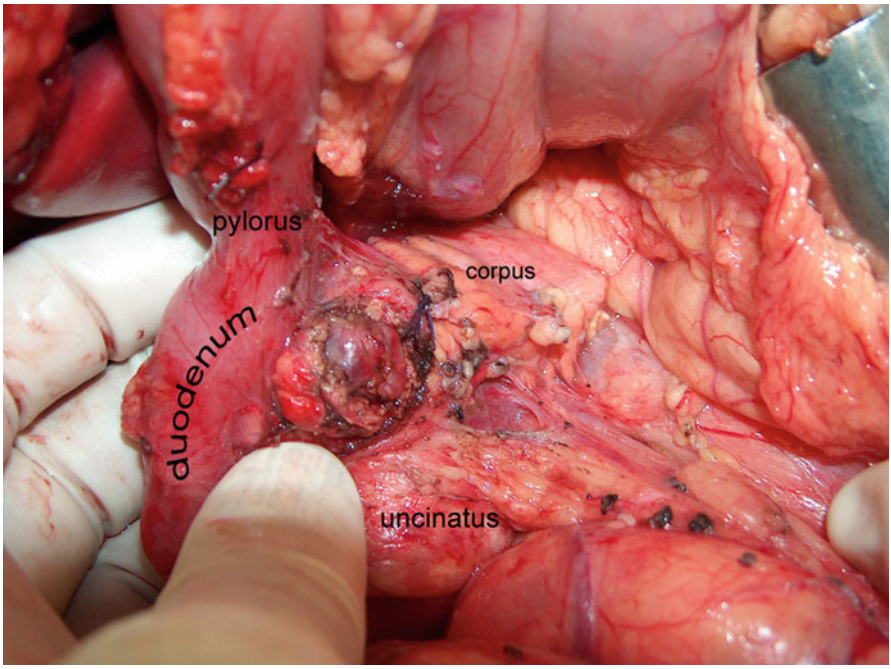

Fig. 10.2 Enucleation of a 1.5 cm insulinoma on the anterior surface of the pancreatic head in a 9-year-old child

- Laparoscopic surgery
  - Since palpation is not available, intraoperative ultrasound with a laparoscopic probe is mandatory for precise tumor localization and its topographical relation to the pancreatic duct.
  - Laparoscopic enucleation may be considered for superficially localized insulinomas that are mainly of the body and tail of the pancreas and that lack contact with major vessels or the pancreatic duct.
  - If the insulinoma lies in the tail and cannot be reasonably enucleated laparoscopically, laparoscopic distal spleen-preserving pancreatectomy may be an appropriate option.

Insulinoma (MEN1 Related)

- May be multifocal
- May be present in addition to other functioning or nonfunctioning pNEN, therefore:
  - Insist on preoperative regionalization (ASVS test, Imamura test) to ascertain the NEN responsible for hyperinsulinemia
  - In presence of multiple pNEN
- Insist on a complete biochemical work-up, including gastrin, glucagon, somatostatin, pancreatic polypeptide (PP), and chromogranin A (CrA);

include vasoactive intestinal polypeptide (VIP) only in cases with specific typical clinical symptoms.
- Plan for a resection type that meets the requirements of multiple MEN1-related NEN (usually spleen-preserving distal pancreatectomy, eventually combined with enucleation in the head).

Gastrin-Producing NEN of the Duodenum/Pancreas (Gastrinoma): Zollinger-Ellison Syndrome (ZES)

Hallmarks

- Most gastrinomas are small and located in the duodenum or pancreatic head ("gastrinoma triangle") (see Chap. 9).
- The clinical manifestations comprise recurrent (often complicated) peptic ulcer disease, chronic secretory diarrhea, and peptic esophagitis.
- All gastrinomas should be considered malignant.
- Up to 45 % of patients have lymph node involvement at diagnosis and 10 % present with liver metastasis.
- Hypergastrinemia leads to ECL-cell hyperplasia in the stomach that can cause the development of ECL-omas (type II).
- 20–30 % of gastrinomas are MEN1 associated.
- Gastrinomas represent approximately 15 % of pNEN.

Work-Up

Insist on:

- A properly taken family history concerning MEN1
- A proper clinical and biochemical work-up (see Chap. 8)
  - Evaluation for typically elevated fasting gastrin
  - Exclusion of other conditions leading to high gastrin levels:
    - Medication with proton pump inhibitors (PPIs)
    - Chronic atrophic gastritis (CAG)
    - Chronic renal insufficiency
    - *Helicobacter pylori* infection
    - Short bowel syndrome
    - Gastric outlet obstruction
  - Secretin stimulation test (see Chap. 8)
  - Biochemical screening for other potential MEN1-associated diseases
- Preoperative localization work-up (see Chap. 9)

Intraoperative Prerequisites

- Intraoperative ultrasound – to localize the gastrinoma within the pancreas
- Frozen section – to prove the resection of a neuroendocrine tumor and safe resection margins based on histopathological criteria
- Intraoperative gastroduodenoscopy – for transillumination to detect gastrinomas in the duodenal wall

Indication for Surgery

- There is general agreement that all patients with sporadic gastrinoma without evidence of hepatic metastasis and no relevant comorbidities should undergo explorative surgery with the intention to cure.
  - Arguments:
    - Up to 95 % of gastrinomas are localized intraoperatively.
    - Biochemical cure is achieved in up to 60 %.
    - Surgery prolongs disease-free survival and reduces the development of hepatic metastasis.
- Even in situations without positive localization in imaging studies, but with positive regionalization by ASVS to the duodenum/head of the pancreas, patients should be operated upon because they are very likely to have a small, resectable gastrinoma of the duodenum.

Surgical Technique

- Gastrinomas in the body or tail of the pancreas: distal pancreatectomy with splenectomy and clearance of the regional lymph nodes.
- Gastrinomas in the head of the pancreas: if locally appropriate, plan an enucleation with regional lymph node clearance and lymphadenectomy along the hepatoduodenal ligament. However, consider pylorus-preserving partial pancreatoduodenectomy (PPPPD) as an alternative.
- Proven or suspected gastrinomas of the duodenum: after complete Kocher's maneuver, localize gastrinomas by palpation and/or transillumination. Small gastrinomas can be resected in their mucosal layer after longitudinal duodenotomy in the second part of the duodenum. Larger tumors (>5 mm) should be removed with a full-thickness resection of the duodenal wall. Regional lymph node clearance and lymphadenectomy along the hepatoduodenal ligament are mandatory.

Gastrinomas (MEN1 Related)

Indication for Surgery

- This issue is and has been the topic of many discussions, with controversial attitudes on how to surgically treat MEN1 patients with ZES without evidence of a hepatic spread.
- Facts:
  - Most MEN1-associated gastrinomas are small, multiple, and located in the duodenum.
  - MEN1-associated gastrinomas tend to have a much more benign disease course than sporadic ones; this has to be carefully balanced against the morbidity of any surgical intervention.
  - After conservative surgical management (duodenotomy, local resection, and regional lymph node clearance), few patients will be biochemically cured, and a relevant part will recur since the underlying pathology in MEN1 patients is a G-cell hyperplasia in the duodenum.
  - Proponents of a Whipple procedure or PPPPD for MEN1 patients with ZES report high biochemical cure rates (>75 %).
- Attitudes in regard to indication for surgery:
  - Conservative approach: operative exploration is proposed when a localized, gastrin-producing pNEN reaches a diameter of 2 cm (higher risk of development of liver metastasis).
  - Proactive approach: operative exploration is proposed in all patients with biochemically proven ZES.

Type of Surgery

- In the absence of any randomized trials, this aspect is managed differently in different centers with great experience in endocrine surgery.
  - Conservative approach: duodenotomy, local resection of evident duodenal tumors, and regional lymph node clearance
  - Proactive approach: pylorus-preserving partial pancreatoduodenectomy (PPPPD)
- Author's comment: The final decision on extent and type of surgery will depend mainly on local skills and talent. In centers with a great experience in pancreatic surgery and low morbidity, a more radical approach may well be justified; on the other hand, in less experienced hands, a more conservative approach would be prudent.

Other Aspects

- Since hypercalcemia simulates gastrin secretion, concomitant primary hyperparathyroidism in MEN1 patients with ZES should also be addressed surgically.

Nonfunctioning pNEN

Hallmarks

- Up to 50 % of all pNEN are nonfunctioning.
- They are considered "silent" or "nonfunctioning" because they lack clinical symptoms based on a hormone excess.
- May nevertheless produce:
  - Excessive hormones that cause no overt clinical symptoms
  - Clinically relevant hormones but at levels too low to become clinically manifest
- Develop in up to 40–60 % of patients with MEN1.
- Are mostly located in pancreatic head.
- Are mostly diagnosed "incidentally" in abdominal imaging, in a work-up for unspecific abdominal discomfort, or occasionally because of obstructive symptoms (e.g., jaundice) in non-MEN1 situations.

Work-Up

- Biochemistry: CrA and pancreatic polypeptide (PP) are usually elevated.
- Fine needle aspiration (FNA) can prove the neuroendocrine character of a tumor of unknown origin.
- Biopsy can provide information concerning the differentiation and aggressiveness of the tumor (Ki67 proliferation index).
- Gastroduodenoscopy and EUS eventually combined with endoscopic FNA.

Preoperative Imaging Work-Up (See Chap. 9)

- CT/MRI for local extension and assessment of hepatic spread (usually a hypervascularized lesion) (Fig. 10.3)
- Somatostatin receptor scintigraphy (Octreoscan) (mostly positive)

Indication for Surgery

- For a non-MEN1-associated, nonfunctioning pNEN without evidence of metastasis, the treatment of choice is a standard pancreatic resection with the aim of an R0 resection. However, recent publications suggest that an observational strategy or limited resection (e.g., laparoscopic spleen-preserving distal pancreatectomy or conventional central pancreatic resection with regional lymphadenectomy)

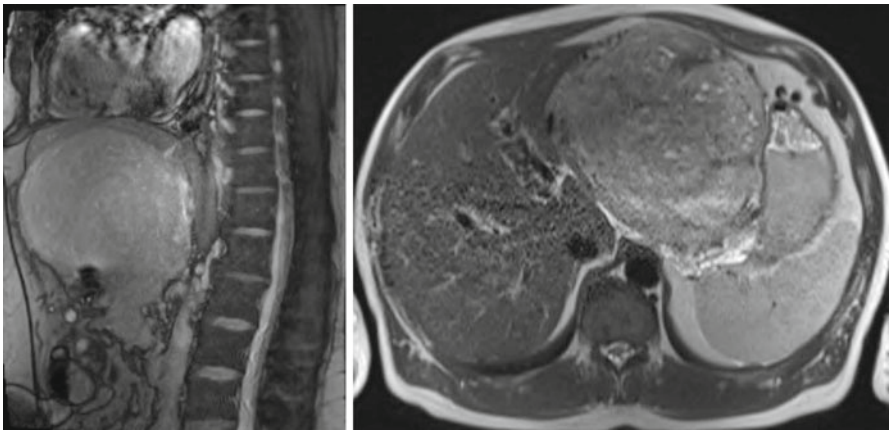

Fig. 10.3 Huge, non-functioning, well-differentiated pNEN of the pancreatic tail in a 46-year-old man with moderate, non-specific symptoms in the upper abdomen

may be justified in patients with incidentally discovered sporadic pNEN of <2 cm in size.

- Metastatic G1 or G2 pNEN (according to the 2010 WHO classification) usually show a slow disease progression, not comparable with the course of a metastatic pancreatic adenocarcinoma. In this situation, resection of the primary tumor and surgical treatment of hepatic metastases (by resection or, e.g., radiofrequency ablation) may be justified in absence of extrahepatic disease. Such an indication should be well discussed as part of an interdisciplinary plan with oncologists and nuclear medicine specialists.
- In presence of a G3 tumor (Ki67 proliferation rate of >20 %) with a very poor prognosis, the indication for any surgical procedure should handled very restrictively.

Type of Surgery

- In non-metastatic disease, R0 resection should be attempted by classical partial pancreatoduodenectomy or distal splenopancreatectomy, depending on the localization of the tumor. Rarely, central pancreatectomy or even a total pancreatectomy might be indicated.
- In a metastatic situation with hepatic spread, the type of resection used to remove the primary tumor will also correspond to a partial pancreatoduodenectomy or distal splenopancreatectomy. Hepatic metastasis will be approached by atypical or standard types of hepatic resection or radiofrequency ablation (RFA).
- Palliative procedures could also include gastrojejunostomy to treat gastric outlet obstruction or hepatic jejunostomy to manage obstructive jaundice in cases where intraluminal stenting is impossible.

Nonfunctioning pNEN (MEN1 Related)

Hallmarks

- More than 50 % of MEN1 gene mutation carriers will develop one or more nonfunctioning pNEN during their lifetime.
- Nonfunctioning pNEN are a significant cause of death in MEN1 patients, accounting for approximately 15 % of the overall mortality.
- Studies have shown that surgery for nonfunctioning pNEN <2 cm in MEN1 patients is not beneficial and suggest that these patients should be followed up regularly.

Indication for Surgery

- MEN1 patients should undergo surgery in case of:
  - Nonfunctioning pNEN >2 cm
  - Nonfunctioning pNEN < 2 cm with possible radiological signs of malignancy
  - Nonfunctioning pNEN <2 cm with documented increase in diameter of >5 mm in 1 year

Types of Surgery

- Regarding the extent of resection, one should take into account that these patients may develop new pNEN during their lifetime and require further resections over time.
- For small, isolated, nonfunctioning pNEN enucleation or parenchyma, sparing distal pancreatic resection can be an option.
- For selected patients, laparoscopic spleen-preserving distal pancreatectomy can represent a valuable option.
- In case of multiple pNEN, classic distal pancreatic with or without spleen preservation represents the procedure of choice.

Very Rare Functioning pNEN (VIPoma, Glucagonoma, Somatostatinoma, PPoma)

- Are mostly malignant.
- May also secrete: serotonin, adrenocorticotropic hormone (ACTH), calcitonin, and growth hormone-releasing hormone (GHRH).

- In non-overtly metastatic disease, radical surgery (R0) should be attempted by standard oncologic pancreatic resection.
- Debulking operations to reduce the tumor load or the hormonal load should include >90 % of the tumor to be beneficial.

Complications in Pancreatic Surgery

Early Complications

- Systemic inflammatory response syndrome (SIRS)
  - Requires surveillance in an intermediate care unit or intensive care unit for 24–48 h, and eventually treatment
- Early postoperative hemorrhage
  - Intra-abdominal: generally requires operative revision
  - Intraluminal: consider endoscopic hemostasis for anastomotic bleeding (e.g., from the gastrojejunostomy)

Midterm Complications

- Delayed gastric emptying
  - Usually requires a nasogastric tube, eventually prokinetic drugs (e.g., erythromycin), and patience
  - Can be a manifestation of other intra-abdominal complications (pancreatic leak, abscess)
- Pancreatic fistula (insufficiency of a pancreatojejunostomy or of the pancreatic stump closure in distal pancreatectomy)
  - Monitor quality and quantity of the fluids drained every day.
  - Regularly measure amylase and bilirubin in the fluids.
  - In manifest fistula:
    - Keep drainages in place.
    - Fasting, somatostatin analogue, and parenteral nutrition.
    - Interventional percutaneous drainage of insufficiently drained intra-abdominal fluid collections.
    - Very rarely, total pancreatectomy might be needed in cases of progressive multiorgan failure.
- Secondary intra-abdominal hemorrhage from pseudoaneurysms of major visceral vessels (mostly from the stump of the gastroduodenal artery or the hepatic arteries)

  - Usually a consequence of pancreatic fistula
  - Has a high mortality
  - Be alarmed by a "sentinel bleed" in the drain fluid and investigate immediately with contrast-enhanced CT
  - Preferably consider early interventional coiling or stenting
  - If not possible, operative revision
- Bile leakage from bilioenteric anastomosis
  - If early postoperative (<48 h), consider operative revision.
  - If later in the postoperative course:
    - Keep drains in place.
    - Evaluate temporary percutaneous transhepatic drainage/stenting.

Pearls and Pitfalls
Pearls

- pNENs are a fascinating tumor group; every single tumor has a unique clinical presentation and requires an individualized work-up and a "custom-tailored" therapeutic approach
- An incomplete preoperative biochemical work-up lacking specific preoperative marker levels may compromise the postoperative oncologic follow-up

Pitfalls

- No medical discipline can treat pNEN single-handedly! pNEN treatment requires multidisciplinary team work at its best! Diagnostic work-up, therapy, and follow-up involve endocrinologists, surgeons, radiologists, nuclear medicine specialists, histopathologists, and oncologists; therefore, the indication for surgery and the type of procedure should be discussed preoperatively as part of a coherent treatment plan by an interdisciplinary board
- An inappropriate work-up concerning MEN1 can be a missed chance to recognize other MEN1-related diseases in a patient and a whole kindred

Further Reading

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