

Minimally Invasive Techniques for Resection of Pancreatic Neuroendocrine Tumors



Gustavo G. Fernandez Ranvier, MD^a, Daniel Shouhed, MD^a,
William B. Inabnet III, MD^{b,*}

KEYWORDS

- Pancreatic neuroendocrine tumors • Insulinoma • Gastrinoma
- Laparoscopic pancreas resection • Robotic pancreas resection

KEY POINTS

- Surgical resection is the only curative treatment of pancreatic neuroendocrine tumors (PNETs).
- Minimally invasive procedures are a safe modality for the surgical treatment of PNETs.
- Laparoscopy does not compromise oncologic resection, and is associated with decreased postoperative pain, better cosmetic results, a shorter hospital stay, and a shorter postoperative recovery period.
- The overall 5-year and 10-year survival rates for all PNETs are approximately 65% and 45%, respectively.

INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs) are a heterogeneous group of neoplasms that have an incidence of 1 per 100,000 individuals per year, and account for 1% to 2% of all pancreatic neoplasms.^{1,2} PNETs can develop at any age, but they are more frequently seen in patients between the fourth and sixth decades of life. Although most tumors are considered sporadic, about 10% to 30% of cases present in patients with familial syndromes such as multiple endocrine neoplasia type 1 (MEN1), von

Disclosures: The authors have nothing to disclose.

^a Division of Metabolic, Endocrine and Minimally Invasive Surgery, Department of Surgery, Mount Sinai Hospital, Icahn School of Medicine at Mount Sinai, 5 East 98 street, box 1259, New York, NY 10029, USA; ^b Department of Surgery, Mount Sinai Beth Israel, Icahn School of Medicine at Mount Sinai, First Ave at 16th street, Baird Hall, Suite 16BH20, New York, NY 10003, USA

* Corresponding author.

E-mail address: william.inabnet@mountsinai.org

Surg Oncol Clin N Am 25 (2016) 195–215

<http://dx.doi.org/10.1016/j.soc.2015.08.009>

surgonc.theclinics.com

1055-3207/16/\$ – see front matter © 2016 Elsevier Inc. All rights reserved.

Hippel-Lindau, neurofibromatosis type 1, and tuberous sclerosis, among other more rare syndromes.³ PNETs can be classified into functional and nonfunctional tumors. Functional tumors are usually detected early because of the symptoms caused by hormonal production. Nonfunctional tumors are more common, but given the absence of hormonal symptoms these tumors are found incidentally or in more advanced stages of the disease, with larger tumors causing mass effect, invading surrounding tissues or presenting with metastatic disease.^{4,5}

Surgical resection of the primary tumor remains the treatment of choice for PNETs, because it is associated with increased survival.⁴ With the advancement of minimally invasive techniques, an increasing number of laparoscopic surgical resections for pancreatic neuroendocrine tumors are currently performed.⁶ Low-risk PNETs in the body and the tail of the pancreas are suitable for minimally invasive surgery, with enough evidence in the literature supporting better outcomes of the laparoscopic approach compared with open surgery.^{6,7} However, minimally invasive pancreatic surgery has not yet been widely accepted as the gold standard for all pancreatic resections. Most recently, robotic surgical techniques across different specialties have slowly gained popularity, although the existing experience is only based on reports of small series.^{8–12} This article provides an insight into well-established minimally invasive procedures and also those that slowly have gained popularity over the last few years. It also reviews and discusses the different minimally invasive surgical techniques with their benefits and limitations.

DIAGNOSIS

Insulinoma

Insulinomas are the most common functional neuroendocrine tumors of the pancreas as well as the most common cause of hypoglycemia related to endogenous hyperinsulinemia. Most insulinomas are benign, small (<2 cm) tumors with only 10% of cases usually presenting as malignant lesions. They are typically solitary lesions distributed evenly throughout pancreas, except in association with MEN1 syndrome, when they tend to be multifocal. The clinical signs and symptoms of insulinomas are divided into 2 categories. Neuroglycopenic symptoms, which are a direct result of hypoglycemia, may include weakness, confusion, visual disturbances, and in extreme cases seizures and comas. Autonomic symptoms, which are a consequence of catecholamine release from hypoglycemia, include diaphoresis, palpitations, anxiety, and tremor.^{13,14}

Establishing a diagnosis of insulinoma has classically relied on satisfying the criteria of the Whipple triad: (1) hypoglycemia (plasma glucose level <50 mg/dL), (2) neuroglycopenic symptoms, and (3) prompt resolution of symptoms following administration of glucose.¹⁵ At present, biochemical measurement of plasma glucose, insulin, C peptide, and proinsulin levels during a 72-hour fast can detect up to 99% of insulinomas and has become the gold standard of diagnosis.¹⁶ However, in more than 97% of cases, biochemical testing in conjunction with a supervised 48-hour fast is sufficient to diagnose an insulinoma.¹⁷ Other conditions, such as the factitious use of insulin or oral hypoglycemic agents, can be ruled out through the measurements of plasma proinsulin, C peptide, and sulfonylurea.

Gastrinoma

Gastrinomas, along with insulinomas, account for most functional PNETs. Most of these tumors are found sporadically, although 20% to 30% are found in conjunction with MEN1. They are the most common pancreatic tumor found in patients with MEN1.¹⁸ Gastrinoma syndrome, also known as Zollinger-Ellison syndrome, has a

slight male preponderance and is most commonly diagnosed in the fifth decade of life.¹⁹ Patients most often present with peptic ulcer disease, particularly multiple ulcers and ulcers that are resistant to medical treatment. Up to 75% of patients present with diarrhea, and occasionally this is the chief complaint. Most (up to 60%–90%) of these lesions are malignant, with up to 20% to 30% presenting with liver metastasis at the time of diagnosis. Ninety percent of gastrinomas are found within the gastrinoma triangle, which is formed by the borders of the second and third portions of the duodenum inferiorly, the junction of the cystic and common bile duct superiorly, and the junction between the neck and body of the pancreas medially.²⁰

The biochemical diagnosis of gastrinomas can be difficult because many conditions can cause hypersecretion of gastrin, such as the use of proton pump inhibitors, renal failure, and gastric outlet obstruction.²¹ Nonetheless, initial testing should be targeted at measuring serum gastrin levels. Increased fasting serum gastrin levels (>500 pg/mL) should prompt further testing, whereas levels greater than 1000 pg/mL are highly suspicious for gastrinoma. A finding of normal gastrin levels is often sufficient to rule out the syndrome. A high fasting serum gastrin level should prompt provocative testing to confirm the diagnosis, most commonly using secretin or calcium gluconate infusion. Secretin does not stimulate the secretion of gastrin from G cells of the stomach; however, it does lead to hypersecretion of gastrin from gastrinomas. An increase in fasting serum gastrin levels to more than 200 pg/mL is assumed to be diagnostic.²²

Glucagonoma

Glucagonomas, the alpha-cell counterparts of insulinomas, are rare tumors of the pancreas. Unlike insulinomas, these tumors are typically bulky, large malignant lesions, often localized to the body and tail of the pancreas. The most common presenting symptoms include mild glucose intolerance manifesting as diabetes mellitus, weight loss, normocytic anemia, and a distinct skin rash, referred to as necrolytic migratory erythema.²³ Biochemical diagnosis is established through the serum measurement of glucagon, with levels greater than 500 pg/mL characteristic of glucagonomas.

Vasoactive Intestinal Peptideoma

Vasoactive intestinal peptideomas (VIPomas) are exceedingly rare tumors, with an estimated incidence of only 1 in 10 million per year.²⁴ Approximately 70% of patients present with malignant tumors, as shown by hepatic, distant, or lymph node metastasis.²⁵ Most tumors are at least 3 cm, with a mean of about 5 cm at initial presentation. Most tumors are found primarily in the body and tail of the pancreas; however, tumors can be identified in the head as well as outside the pancreas. Nearly all patients present with watery diarrhea, with most patients also presenting with hypokalemia and achlorhydria, hence the designation of WDHA syndrome. The diagnosis is established through the measurement of increased fasting serum vasoactive intestinal peptide levels (75–150 pg/mL) in the setting of secretory diarrhea.²⁶

Somatostatinoma

Neuroendocrine tumors of the pancreas secreting somatostatin are the rarest of the PNETs, with an incidence of only 1 in 40 million people per year.¹ Most tumors are located in the head of the pancreas; however, it is common to find a lesion within the tail or outside the pancreas. At initial presentation, tumors are large (>5 cm) and nearly half are malignant. Somatostatinomas may lead to diarrhea and/or steatorrhea, cholelithiasis, and diabetes mellitus. However, most commonly patients typically present with signs or symptoms directly related to the tumor, such as abdominal pain, weight

loss, or intestinal obstruction.²⁷ The diagnosis is established through measurement of fasting plasma somatostatin levels, with a level greater than 160 pg/mL strongly suggestive of a somatostatinoma, particularly in the presence of a mass seen on imaging.²⁷

PREOPERATIVE EVALUATION

Localization

Management of PNETs depends heavily on a thorough preoperative evaluation. Various imaging studies, including MRI, computed tomography (CT), PET, endoscopic ultrasonography (EUS), and octreotide scans play an important role in localizing the primary tumor and identifying potential sites of metastases. Imaging is also important to assess response to treatment and as a screening tool for recurrence. The utility of each imaging modality differs based on the tumor type.

CT scanning is the most widely accepted and used imaging modality for localizing and staging PNETs. Compared with nonfunctional PNETs, functional PNETs are typically small at the time of diagnosis, creating more of a challenge for proper identification. These smaller tumors seldom alter the contour of the pancreas; therefore obtaining thinly sliced images enhances the ability to detect smaller tumors and should be used routinely. Fidler and colleagues²⁸ showed that multiphasic imaging with early and late arterial phases as well as portal venous-phase CT had a higher sensitivity for detecting islet cell tumors. The classic CT findings of islet cell tumors are an isodense lesion during the precontrast phase and a hyperattenuating mass in both the arterial and portal venous phases (**Fig. 1**). Depending on the biology and characteristics of the tumor, they may be more apparent during either phase.²⁹

Insulinomas are typically small on presentation and particularly difficult to diagnose. Up to 10% to 20% of these lesions are not identifiable during surgical exploration, which emphasizes the importance of preoperative localization of these tumors. With the use of more advanced helical, thinly sliced, multidimensional CT scanning, insulinomas are diagnosed with a sensitivity of 94%; combined with EUS, the sensitivity of identifying insulinomas in one study was 100%.³⁰ Gastrinomas, like insulinomas, tend to be small at presentation and are more difficult to find when they are present in extrapancreatic locations. They often do not alter the contour of the pancreas. As described earlier, 90% of gastrinomas are found within the gastrinoma triangle and careful attention should be given to this area during imaging review.²⁹ Other functioning tumors, namely VIPomas, somatostatinomas, and glucagonomas, as well as nonfunctioning neuroendocrine tumors of the pancreas, are often easier to identify because they

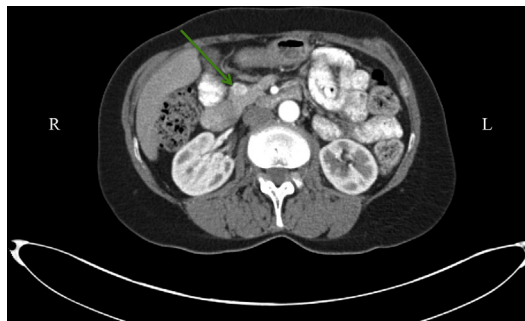


Fig. 1. CT of the abdomen showing a 1-cm arterially enhancing lesion in the head of the pancreas consistent with a PNET (green arrow).

commonly present as large, malignant lesions. They tend to show central necrosis, discrete nodular calcifications, and cystic areas.³¹ Unlike pancreatic adenocarcinomas, PNETs are hypervascular tumors and rarely cause ductal obstruction.³²

MRI can play a complimentary role to CT imaging, particularly for small tumors. Relative to the pancreas, PNETs frequently present as low-intensity lesions on T1-weighted sequences and high-intensity lesions on T2-weighted sequences (**Fig. 2**). MRI has been effective at identifying PNETs with a sensitivity of about 93% (range, 85%–100%) and a specificity of about 88% (range, 75%–100%) among 7 studies.³³ Magnetic resonance cholangiopancreatography can be included for the local assessment of PNETs to evaluate the relation of the tumor to the pancreatic and main bile duct.³⁴

EUS should be performed in every patient in whom minimally invasive surgery is recommended. EUS provides useful anatomic information that may influence the operative plan, especially pertaining to the pancreatic ductal and vascular anatomy. Fine-needle aspiration can be readily performed if indicated to assist with PNET diagnosis; this is especially helpful in the setting of multifocal disease. Similar to MRI, one of the benefits of EUS is the lack of patient exposure to radiation. Ultrasonography can now be performed with intravenous contrast enhancement using microbubbles, which can be highly effective in depicting smaller tumors, and provides a method to perform needle biopsies for diagnosis, if needed.³⁵ The first study to report the efficacy of EUS in localizing PNETs was done in 1992 by Rösch and colleagues,³⁶ showing a sensitivity and specificity of 82% and 92%, respectively, among 50 patients. EUS is particularly useful for identification of small pancreatic tumors as small as 2 to 5 mm, particularly insulinomas and gastrinomas.³⁶ Despite the various benefits of EUS, it is a more invasive form of imaging study than the other modalities already listed and is highly operator sensitive.

PET imaging has been gaining popularity but may be difficult to obtain because most third party payers do not reimburse for PET scanning. Although the use of PET imaging is controversial, there is emerging evidence that increased intensity, and therefore glucose metabolism, in PNETs indicates a higher likelihood of tumor invasion and metastasis, and poorer prognosis.³⁴ One study showed that most patients with PET-positive lesions also had early progressive disease.³⁴ Although not yet conclusive, PET imaging may play an important role in the future in predicting outcomes and management of PNETs.

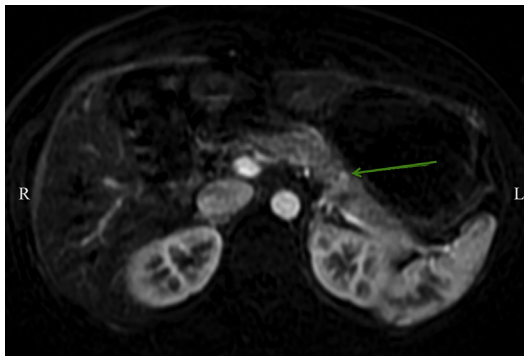


Fig. 2. Gadolinium-enhanced T2-weighted MRI showing a 3.2-cm subtle hypervascular lesion with focal area of enhancement in the body of the pancreas consistent with an insulinoma (*green arrow*).

Patient Selection and Choice of Procedure

Surgical resection is the only curative treatment of patients with PNETs. Surgery may also alleviate symptoms from hormonal production of functioning tumors or symptoms caused by the mass effect frequently seen with nonfunctioning tumors. The planned surgical procedure is mainly mandated by the preoperative localization studies, but it may change according to intraoperative findings. No consensus has been established regarding the indications of minimally invasive surgery for the treatment of PNETs; however, the presence of a malignant PNET could represent a relative contraindication for a minimally invasive approach.³⁷ Laparoscopic surgery for small and solitary PNETs is feasible and safe.³⁸ Laparoscopic enucleation is generally recommended in well-circumscribed lesions smaller than 3 cm, with noninvasive features and a peripheral location without involvement of the main pancreatic duct.^{38,39} If the tumor is in close proximity to the main pancreatic duct, enucleation is not recommended in light of its high incidence of pancreatic fistula.⁴⁰

Solitary insulinomas are particularly amenable to laparoscopic enucleation because of their small size and benign nature. Intraoperative laparoscopic ultrasonography is routinely performed to confirm tumor location and its relationship to the pancreatic duct and peripancreatic vessels, in order to plan the margin of resection before enucleation³⁷ (Fig. 3). If enucleation is not possible, a formal pancreatic resection is recommended.⁶ In tumors involving the head of the pancreas, pancreaticoduodenectomy is indicated. Pancreaticoduodenectomy has proved to be among the most complex procedures in general surgery, with high rates of morbidity and mortality.⁴¹ However, many studies have shown the effectiveness and safety of this procedure when performed through minimally invasive techniques in high-volume institutions by experienced surgeons.^{42–45}

In tumors that are located in the body or tail of the pancreas, which are not amenable for enucleation, laparoscopic distal pancreatectomy (LDP) is the procedure of choice. There are 3 variations of the distal pancreatectomy: spleen-preserving distal pancreatectomy with splenic vessel preservation, spleen-preserving distal pancreatectomy

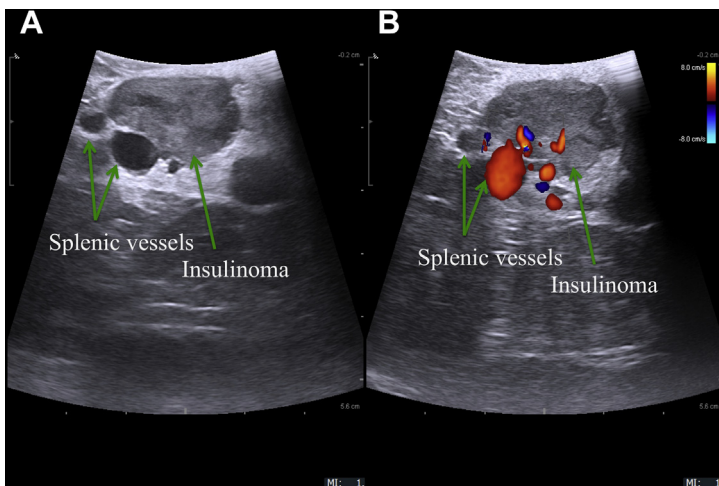


Fig. 3. Intraoperative sonographic appearance of a 3-cm insulinoma involving the pancreatic body and its anatomic relationship to the splenic vessels (A) without Doppler effect, (B) with Doppler effect.

without splenic vessel preservation, and distal pancreatectomy with splenectomy.^{46,47} The anatomic relationship between the tumor within the pancreatic body or tail and the splenic vessels and hilum are factors that determine the appropriate procedure to perform. In addition, the presence or suspicion of a malignant tumor favors a more aggressive approach.

SURGICAL TECHNIQUE

Enucleation (Head)

Once the laparoscopic ports have been placed, exposure of the pancreas is accomplished by opening the gastrocolic ligament, thereby gaining access to the lesser sac. Subsequently, intraoperative laparoscopic ultrasonography is performed to help accurately localize the tumor, rule out the presence of additional lesions, and to identify the exact location of the tumor and its relation to the pancreatic duct and major vessels. Special care is taken to avoid injury to the pancreatic duct and the mesenteric/splenic vessels during the dissection. The use of a combination of blunt dissection, electrocautery, and high-energy cautery devices are recommended to perform the enucleation. Bleeding is common during enucleation (**Fig. 4**). A drain is almost routinely left in the surgical bed.

Enucleation (Body and Tail)

Laparoscopic ports are placed and laparoscopic ultrasonography is performed for tumor localization and its relationship with surrounding structures. The spleen is mobilized superiorly and laterally while the splenic flexure is taken down inferiorly. When the tumor is located anteriorly, an opening is created in the anterior visceral peritoneum of the pancreas and careful dissection is performed between the tumor and the normal pancreatic parenchyma until successful enucleation of the mass is accomplished. For tumors located in the posterior aspect of the pancreatic body or the tail, the inferior margin of the pancreas is dissected and the pancreas is mobilized and lifted up, allowing exposure of the posterior pancreatic surface (**Fig. 5**). After enucleation, the tumor bed must be examined for any evidence of pancreatic duct injury. Tumors located in the distal portion of the tail of the pancreas are in close proximity to the pancreatic duct. Therefore, if in doubt about potential ductal injury, a distal pancreatectomy should be performed.

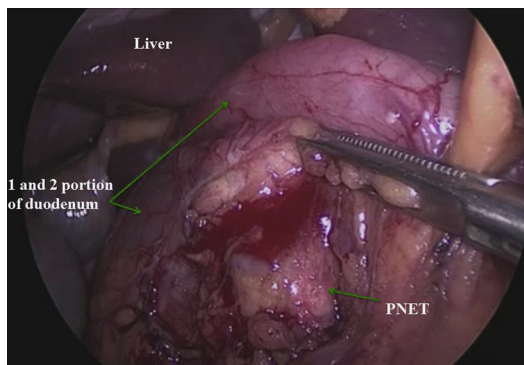


Fig. 4. Intraoperative complication of bleeding during laparoscopic enucleation of a PNET in the head of the pancreas.

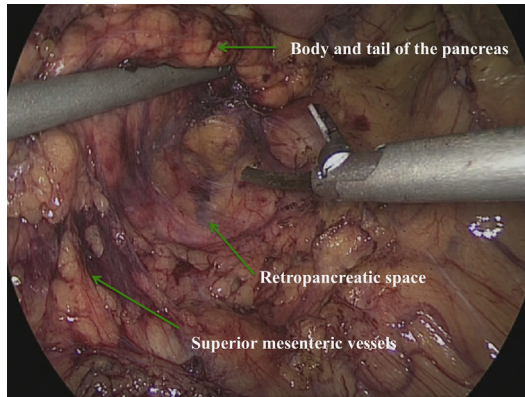


Fig. 5. Laparoscopic exposure of the retropancreatic space with visualization of the tail of the pancreas and the anatomic location of the superior mesenteric vessels.

Laparoscopic Distal Pancreatectomy (Spleen-preserving with Splenic Vessel Preservation)

When possible, spleen-preserving distal pancreatectomy with splenic vessel preservation is performed for distal tumors; however, this procedure requires more advanced technical expertise, with separation of the splenic vessels from the pancreatic parenchyma (see [Fig. 5](#)), and division of the branching vessels supplying the pancreas. As a result, this procedure is associated with a longer operating time.^{48,49} The pancreatic tail is exposed as described earlier. Special care is taken to preserve the short gastric and the left gastroepiploic vessels. After mobilizing the inferior margin of the pancreas, the pancreas is mobilized and lifted up, allowing exposure of the posterior pancreatic surface (see [Fig. 5](#)).

At this time, the superior mesenteric vein (SMV) and the splenic vein can be identified forming the portal vein ([Fig. 6](#)). Blunt dissection around the splenic vein is performed, with ligation of the small tributaries coming from the pancreas. After identification and preservation of the splenic artery, the pancreas is divided to the

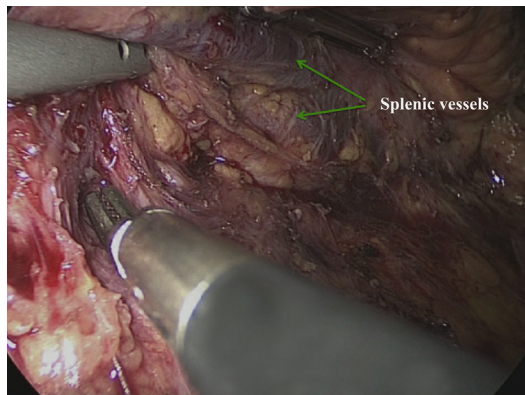


Fig. 6. Laparoscopic exposure of the retropancreatic space. The body and tail of the pancreas has been lifted, allowing exposure and visualization of the splenic vessels.

left of the SMV using an endoscopic stapler device. The body/tail of the pancreas is then anteriorly retracted, allowing separation of remaining small bridging vessels between the pancreas and the splenic vessels. The resection is completed after reaching the splenic hilum. A surgical drain is left in the surgical bed in proximity to the pancreatic stump.

Laparoscopic Distal Pancreatectomy (Spleen-preserving Distal Pancreatectomy Without Splenic Vessel Preservation)

This procedure follows the same course mentioned earlier until obtaining visualization of the posterior aspect of the pancreas and the confluence of the splenic vein and SMV.

At this time, the splenic vein and artery are clipped and ligated. The pancreas is then divided with an endoscopic stapler. The pancreatic body and tail are retracted upwards (along with the attached splenic artery and vein), and the vessels between the pancreatic tail and the splenic hilum are clipped and divided. Blood supply to the spleen depends on the short gastric and left gastroepiploic vessels; therefore, special care is taken to preserve these vessels; this is crucial for the success of this procedure.

Laparoscopic Distal Pancreatectomy with Splenectomy

This procedure is similar to the previous technique (spleen-preserving distal pancreatectomy without splenic vessel preservation) with a few exceptions. Unlike in spleen-preserving procedures, the short gastric and left gastroepiploic vessels can be ligated. In addition to mobilizing the splenic flexure, the lateral attachments of the spleen are divided up to the left crus of the diaphragm, allowing medialization of the spleen. The splenic vessels can be divided separately if an easy plane of dissection is encountered or along with the pancreas if separation of the vessels is difficult. The specimens are removed en bloc from the abdominal cavity in an endoscopic specimen bag. A surgical drain is left in the surgical bed in proximity to the pancreatic stump.

Laparoscopic Central Pancreatectomy

The initial dissection is performed laparoscopically through 5 trocars. Once the anterior surface of the gland is cleared from the head distal to the lesion, a tunnel over the portal vein is created. The lesion is resected with an endoscopic stapler on the proximal margin and cautery on the distal margin with care to avoid thermal injury to the duct. The reconstruction is then performed via a pancreaticogastrostomy or with Roux-en-Y pancreaticojejunostomy reconstruction.

Laparoscopic Pancreaticoduodenectomy

One of the largest series of laparoscopic pylorus-preserving pancreaticoduodenectomy comes from 100 consecutive cases performed in Korea.⁴² In their first 10 cases, reconstruction was partially performed extracorporeally, whereas the last 90 cases were performed completely intracorporeally. The patient was positioned supine with the surgeon on the patient's right and the assistant and scrub technician on the left. The operator ports were placed in the right flank area and 1 near the umbilicus with a camera placed in between in the right lower quadrant. Assistant ports were placed in the left flank area.

After evaluation of the abdomen, the gastrocolic omentum was dissected to allow entry into the lesser sac. The hepatic flexure was mobilized and the duodenum was kocherized. The pancreatic dissection began at the inferior border and was continued over the retropancreatic portal vein. The duodenum was mobilized to the ligament of

Treitz and the duodenum was transected 2 cm distal to the pylorus. Next, the common bile duct was isolated within the hepatoduodenal ligament. A cholecystectomy was performed separately. The common bile duct was divided and the common hepatic artery was dissected from the pancreas. The gastroduodenal and right gastric arteries were transected with 2 titanium clips and the pancreas was divided at the neck with an endoscopic linear stapler or Harmonic scalpel. With retraction of the pancreatic head toward the right side of the patient, the intrapancreatic portal vein was dissected. The jejunum was divided 10 to 15 cm distal to the ligament of Treitz with another load of the endoscopic stapler. An endoscopic linear stapler or ultrasonic shears was used to divide the soft tissue and arterial branches between the superior mesenteric artery and the uncinate process to complete the resection.

For totally intracorporeal laparoscopic pancreaticoduodenectomy (LPD), a pancreaticojejunostomy was performed using the double-layered, end-to-side dunking method in normal-sized ducts or using the duct-to-mucosa method in dilated pancreatic ducts. An intracorporeal laparoscopic choledochojejunostomy was performed using interrupted absorbable sutures and an extracorporeal knot pusher in the initial cases and continuous suturing for later cases, except for very small ducts. An internal stent was used if the diameter of the common bile duct was too small. Duodenojejunostomies and jejunojejunostomies were performed intracorporeally or extracorporeally using the specimen extraction site from the umbilical port site. Closed suction drains were placed near the pancreaticojejunostomy and choledochojejunostomy sites.

Robotic Surgery

Robotic systems were first introduced in the late 1990s, and since then the popularity and number of robotic procedures has increased exponentially.^{10,11} Since its first reported application in 2003, the appeal of robotic pancreatic surgery has increased.⁹ The most popular robotic-assisted minimally invasive surgical platform (da Vinci system, Intuitive Surgical, Sunnyvale, CA) offers multiple advantages, such as, a three-dimensional high-definition view with significant magnification of the surgical field; elimination of tremor with improved dexterity, particularly with the use of articulating instruments that provide 540° range of motion; stereotactic binocular visualization; and improved surgeon comfort.⁵⁰

Most series reporting their experience of robotic surgery describe similar techniques to those listed earlier through the laparoscopic technique. Zeh and colleagues⁵¹ reported their series of 51 robotic-assisted pancreaticoduodenectomies performed at the University of Pittsburgh, 9 of which were performed for neuroendocrine tumors. They emphasized the importance of teamwork in obtaining a successful outcome. They also admitted to several limitations of robotic surgery compared with standard laparoscopic surgery, including the difficulty of working in multiple abdominal quadrants with the robot; frequent collisions between the arms of the robot caused by their large size and suboptimal positioning; the inability to change the position of the table once the robot is docked, preventing gravity from being used as a retractor of viscera; and the lack of tactile feedback. Future generations will potentially address some of these issues, thus improving the flow of robotic-assisted surgery.

Radiofrequency Ablation for Pancreatic Neuroendocrine Tumors

With the goal of developing less invasive techniques, the use of radiofrequency ablation (RFA) has been proposed for the treatment of PNETs, because it has been applied for the treatment of adenocarcinomas of the pancreas.^{52–56} More specifically, the use of RFA has been proposed in those patients with PNETs who are ineligible for surgical

resection.⁵⁷ Radiofrequency ablation can be performed percutaneously under ultrasonography guidance or intraoperatively. The available experience on this procedure is limited and the evidence has been documented in a recent study.⁵⁷ The use of RFA is associated with known adverse effects, which include thermal-induced pancreatitis as well as potential injuries to surrounding tumor structures such as the duodenum, pancreatic duct, and major blood vessels.

In the only prospective pilot study currently available, the use of RFA in selective PNETs has shown encouraging results.⁵⁷ The study included 10 patients (7 women and 3 men) aged 38 to 75 years old, with 3 functioning PNETs (1 gastrinoma and 2 insulinomas) and 7 nonfunctioning PNETs. Tumor size ranged from 0.9 to 2.9 cm in diameter. Selective criteria to receive treatment with RFA included patients with pathologically confirmed PNETs, those patients ineligible for or who refused surgery, single tumors less than or equal to 3 cm in diameter, and tumor location greater than 1 cm from the wall of the stomach, intestine, or bile ducts. The ultrasonography-guided RFA was performed percutaneously in 7 cases, endoscopically in 1, and intraoperatively in 2 patients.

Endoscopic Ultrasonography-directed Alcohol Ablation

Ethanol ablation has also been used as a treatment modality for PNETs. Ethanol has gained interest as an ablative agent because it is inexpensive and readily available. Alcohol ablation works by causing coagulation necrosis of the tumor as a result of cellular dehydration, protein denaturation, and vascular occlusion.^{58,59} Major limitations of alcohol ablation include the possibility of late recurrence, incomplete ablation, and risk of progression during follow-up. As with RFA, ethanol ablation has the potential to cause acute pancreatitis. In a pilot study performed on 11 patients with 14 tumors by a group in Korea, 3 patients developed postoperative pancreatitis. Seven (54%) of the 13 tumors responded to treatment, with the remainder showing residual viable enhancing tissue at 3-month radiologic imaging follow-up.⁶⁰

OUTCOMES

Laparoscopic Pancreatic Resections

Minimally invasive surgery continues to gain popularity as surgeons become more comfortable with and realize the benefits of such techniques. Laparoscopic and robotic surgeries for pancreatic resections are among the slowest to evolve given the complexity of these procedures and fear of suboptimal oncologic resection. Although surgeons continue to extend the limits of what is possible, only a limited number of reported series exist within the literature for minimally invasive pancreatic surgery, particularly for neuroendocrine tumors. Clinicians have yet to reach a consensus on the efficacy and safety of minimally invasive techniques for PNETs; however, several studies describing the outcomes of these operations currently exist and are discussed here.

LDP was first performed in 1994 by Cuschieri⁶¹ in a case of benign disease. Gagner and colleagues⁶² subsequently reported on their experience with LDP for the specific treatment of islet cell tumors. Since these initial studies, several series have been reported, with only a few involving more than 30 patients and even a smaller number of malignant cases described.^{63–65} The first LPD was reported in 1994 by Gagner and Pomp.⁶⁶ Since then, more than 285 cases have been reported in the literature, including hand-assisted and robotic-assisted cases.⁶⁷

LDP seems to be more popular than LPD, perhaps because of the lack of anastomoses and the ability to more easily control major sources of intraoperative

hemorrhage, if encountered. Published data, although limited, show that the LDP might be performed with superior results to the open approach in patients with benign disease, resulting in shorter hospital stays, reduced blood loss, and equivalent rates of complications.^{68–70} At present, almost all surgical resections for PNETs of the body or tail of the pancreas are performed laparoscopically or through other minimally invasive techniques.^{38,40,71,72}

An early report on 17 cases of laparoscopically treated PNETs showed a perioperative complication rate of 23%, and a postoperative pancreatic fistula (POPF) rate of 15.3%. No mortality or recurrence was seen, although this series did not include patients with malignant neuroendocrine tumors.⁴⁶ In the same study the investigators reviewed the literature and reported the outcomes on an additional 93 reported cases of laparoscopically managed PNETs, showing an overall perioperative complication rate of 28% and a POPF rate of 17.9%. Following enucleation, the fistula rate was higher than that following distal pancreatectomy (30.7% vs 5.1%, respectively). No mortality was observed in this study.⁴⁶

A group from the University of Barcelona reported their series in 2008. Among 49 patients undergoing laparoscopic surgery for PNETs, a higher perioperative complication rate was seen in patients undergoing laparoscopic enucleation compared with those who underwent LDP (42.8% vs 22%, respectively; $P < .001$).⁷² The main complication was POPF, which also occurred more frequently in the enucleation group (38% vs 8.7%; $P < .001$). However, all fistulas following enucleation were successfully managed conservatively. No perioperative mortality was shown.

DiNorcia and colleagues⁷ reported on a total 85 open and 45 laparoscopic procedures for PNETs performed at the same institution. This study showed no statistically significant difference in overall morbidity, mortality, or survival rate between the two groups. However, complications were more prevalent in the open surgery group (11.1% vs 28.2%; $P = .03$). No perioperative mortality was seen in the laparoscopic group, whereas in patients who underwent open surgery, the perioperative mortality was 3.5% ($P = .55$). Length of hospital stay was shorter in the laparoscopic group (6 days vs 9 days; $P = .01$). Within the 25.4-month follow-up period, a 4.4% (2 patients) recurrence rate was seen in the laparoscopic group, compared with a 15.3% (13 patients) recurrence rate after a median follow-up of 42.7 months in the open surgery group. Nonetheless, a statistically significant difference was observed with regard to pathologic characteristics of the tumors, with the laparoscopically operated group having smaller, lower-grade tumors, with less local and lymph node invasion.

In a recently published series, 75 laparoscopic procedures for PNETs were documented, of which 65 pancreatic resections or enucleations were performed.³⁸ The most common operation performed was distal pancreatectomy with splenectomy ($n = 28$), followed by distal pancreatectomy without splenectomy ($n = 23$). Enucleation of a PNET of the head was performed in 7 cases, and of the body or tail in another 7 patients. The most common surgical complication was POPF, occurring in 21% of patients. This complication was more common in patients undergoing enucleation (7 of 14 [50%]), with a reported incidence of 13% to 50% following enucleation.^{38,40,71} Other nonfistula surgical complications had an incidence of 21%, but no perioperative mortality was shown. In this study, the 5-year disease-specific survival was 90%.

Laparoscopic central pancreatectomy has not been studied extensively, probably because of 2 main factors: first, dual pancreatic transected surfaces could be at an increased risk of leak if handled laparoscopically; and second, lesions of the pancreatic neck that do not require distal pancreatectomy are rare. However, the potential

benefits of decreasing or avoiding the incidence of surgically induced diabetes and exocrine insufficiency attributable to loss of pancreatic parenchyma added to the possible benefits of laparoscopy have led to a small number of reports on the subject.⁷³ Sa Cunha and colleagues⁷⁴ and Rotellar and colleagues⁷⁵ reported on the 2 largest series of 6 and 9 patients, respectively.^{74,75} Experience was fairly similar between the two groups, with median blood loss of 125 mL and less than 100 mL respectively. The median operating times were 225 minutes and 435 minutes; this large discrepancy is probably related to the difference in pancreatic anastomoses, because the first group performed a pancreaticogastrostomy, whereas the second performed a Roux-en-Y reconstruction with a sutured pancreaticojejunostomy and stapled jejunojejunostomy. Median hospital length of stay (LOS) was 13 and 18 days, and the fistula rates were 33% and 22%, respectively.^{74,75}

Robotic Pancreaticoduodenectomy

The first reported case of a robotic-assisted pancreatic resection of a PNET was described in 2003 by Melvin and colleagues.⁹ One of the earliest series included 8 patients who underwent robotic pancreaticoduodenectomy (RAPD),⁷⁶ and outcomes were compared with open operations at the same institution. The robotic operations took considerably more time (mean, 718 minutes vs 420 min minutes) but the blood loss was less, with a mean of 153 mL versus 210 mL. The R0 resection was 100% in their small series. Fistulas occurred in 2 patients and there were no perioperative deaths. LOS was higher than average at 16 days. No short-term or long-term survival data were described.

Buchs and Giulianotti and colleagues^{77–80} evaluated important facets of pancreatic surgery, including robotic versus open outcomes, surgery in the elderly, and the feasibility of the robotic approach in cases of vascular involvement. Buchs and colleagues⁷⁷ performed 44 RAPDs and compared these patients with a group who underwent open surgery ($n = 39$). Patients within the robotic group were older, had higher body mass indices (BMIs), and higher American Society of Anesthesiologists (ASA) scores than patients in the open group. The robotic group had a significantly shorter operative time (444 minutes vs 559 minutes), less blood loss (387 mL vs 827 mL), and a higher number of lymph nodes harvested (16.8 vs 11) than the open group. No difference was found between the 2 groups in terms of complications, perioperative mortality, or LOS.

In the series by Giulianotti and colleagues,⁸⁰ the rate of conversion of robotic to open surgery was 7.7% to 18.3%. The overall fistula rate was 36.5%. Mean LOS was 21.8 days in the Italian group and ranged from 9.3 days to 14.3 days in the US cohorts. The mortality at 90 days was 4.5%. Oncologic outcomes were similar to those of large open studies: R0 resection of 90% to 92% with 14 to 21 lymph nodes harvested. In patients with adenocarcinoma of the pancreatic head ($n = 27$), 2 patients died in the perioperative period, 8 were lost to follow-up, 5 died within 2 years, 3 were alive with recurrences at 1 year, and 9 patients were disease free at a mean follow-up of 16.8 months. Fifteen patients with ampullary carcinoma were followed up for a mean of 50 months. Three patients died within 3 years, but only 1 as a result of disease recurrence. The other 10 patients were disease free at follow-up. These follow-up data preclude meaningful conclusions on long-term outcomes after RAPD because of the small numbers of patients. The group also compared RAPD performed in patients greater than 70 years of age ($n = 15$) with RAPD performed in younger patients ($n = 26$). Perioperative complications, morbidity, and mortality were equivalent, suggesting that elderly patients can safely undergo complex robotic procedures.⁷⁷

The University of Pittsburgh has also published its experience on robotic pancreatectomies.^{51,81–83} In a series of 50 RAPDs for periampullary lesions, the patients included had a mean age of 68 years, an average BMI of 27% and 56%, and a mean ASA score of 3. The operating time was higher than in the Giulianotti experience,⁸⁰ with a median operative duration of 568 minutes. Median blood loss was 350 mL. Of the RAPDs, 16% were converted to an open procedure. The fistula rate was 22% with a preponderance of soft glands (73%), and a median pancreatic duct diameter of 3 mm. LOS was 10 days and 90-day mortality was 2% (1 patient). The series showed an 87% R0 resection rate with a median of 18 lymph nodes resected, compared with the Johns Hopkins R0 resection rate of 58%. Of 15 patients who qualified for adjuvant chemotherapy, 11 (73%) received this treatment within 11 weeks of surgery. Long-term outcomes are pending.

In conclusion, both of the large RAPD series discussed earlier compare well with reported laparoscopic and open data. RAPD does not seem to result in increased morbidity or mortality, or compromise short-term oncologic outcomes of margin-negative resection and lymph node harvest. However, these data awaits long-term survival follow-up. It is important to highlight that reported fistula rates for laparoscopic and robotic resections seem to be considerably higher than the rates reported by the group from Johns Hopkins. This finding might reflect heightened awareness by surgeons in detecting leaks (via consistent assessment of drain output and amylase levels) with these new platforms. Moreover, it was only in 2005 that a consensus was reached on stringent guidelines for defining and detecting postoperative fistulas.⁸⁴ It is also noteworthy that there is probably a selection bias within the fistula data presented. For example, there were a disproportionate number of soft glands with smaller duct size reported within their series. Furthermore, this leak rate might represent the learning curve for robotic-assisted pancreatic anastomoses. The long operative times will probably improve with newer generations of the robotic platform, providing a reticulating ligation energy device and reticulating stapler, which will enable reduced dissection times.

Robotic Distal Pancreatectomies

The data for robotic distal pancreatectomy (RDP) are also limited.^{79,80,85–88} Waters and colleagues⁸⁸ evaluated their series of 77 distal pancreatectomies between 2008 and 2009 for both outcome and cost, comparing open distal pancreatectomy (ODP; n = 32) with LDP (n = 28) and RADP (n = 17). The operative times were longer in the RADP group, with a mean of 298 minutes versus 245 minutes in the ODP cohort and 222 minutes in the LDP cohort. Blood loss was less in the RADP group, with a mean of 279 mL versus 681 mL and 661 mL in the ODP and LDP groups, respectively, although this value was not statistically significant. The spleen was preserved in 65% of RADP procedures versus only 29% in the LDP group and 12% in the ODP group. No fistulas were found in the patients who underwent RADP versus 11% in the LDP group and 18% in the ODP cohort. LOS was significantly less in the RADP group, with an average hospital stay of 4 days versus 8 days and 6 days in the LDP and ODP groups, respectively. Oncologic outcomes were similar, with R0 resection in 100%, 82%, and 100% of patients in the RADP, LDP, and ODP groups, respectively. Note that the differences in mean lymph node harvest approached statistical significance, with fewer harvested in the robotic cohort than in the LDP or ODP groups (5 vs 14 and 11). The potential major confounder in this study was that the RADP group had much smaller lesions and no invasive cancers compared with patients treated with the other techniques; patients who underwent LDP resection similarly had smaller

lesions than those who underwent ODP (3 cm vs 5 cm and 2 cm for LDP, ODP, and RADP, respectively).

Giulianotti and colleagues⁸⁰ published a series of 46 patients undergoing RADP. Their results showed that 6.3% of operations were converted to an open procedure and fistulas occurred in 20% of patients. Thirty nine percent of patients underwent RADP for malignancy, with 6 of these for adenocarcinoma. Other, smaller case reports have shown similar results to the series mentioned earlier regarding duration of operation, blood loss, and short-term oncologic outcomes (R0 resection and lymph node harvest) with longer operative duration seen in malignant cases.⁹

In a retrospective review of 45 patients who underwent laparoscopic or robotic-assisted surgery at Yonsei University, Seoul, South Korea, from 2006 to 2010, Kang and colleagues⁸⁷ identified 20 patients who underwent RADP and 25 who underwent LDP.⁸⁶ Mean operation length was greater in the RADP group than in the LDP group (258 minutes vs 348 min), which was statistically significant. Mean blood loss was greater in the LDP group than in the RADP group (420 mL vs 372 mL) but did not reach significance, and LOS was the same. Neither fistula rate nor details of the complications were given, and the cumulative mortality was zero in both groups. The investigators did note a superior splenic conservation rate of 95% (19 of 20) in the robotic cohort compared with 64% (16 of 25) in the laparoscopic group ($P = .027$). Operative time was longer for RADP than for LDP, and the LOS reported by Kang and colleagues⁸⁷ was longer than that reported by Waters and colleagues.⁸⁸

Investigators from the University of Pittsburgh compared their experience in the first 30 cases of RADP (performed between 2008 and 2011) with a historical control group of 94 laparoscopic cases (2004–2007).⁸⁵ The length of hospital stay after surgery and rates of pancreatic fistula, blood transfusion, and readmission were not significantly different. The mean time to complete RADP (including time to dock the robot) was significantly shorter than for LDP (293 minutes vs 371 minutes; $P < .01$). No conversions to open surgery occurred in the RADP group compared with 16% in the LDP group ($P < .05$). More pancreatic ductal adenocarcinomas were approached robotically than laparoscopically (43% vs 15%; $P < .05$). Oncologic outcomes were superior for the RADP group compared with the LDP group, with higher rates of margin-negative resection and improved lymph node yield for both benign and malignant lesions ($P < .01$). RADP was equivalent to LDP in nearly all measures of outcome and safety but significantly reduced the risk of conversion to open resection despite a statistically greater probability of malignancy in the robotic cohort.

In conclusion, RADP seems to have similar results to LDP in the short term. The robotic approach seems to have lower blood loss and higher splenic preservation, although the operative time is higher. Similar to RAPD, limited data are available on long-term follow-up.

Robotic Central Pancreatectomies

Very limited data are available to date on robotic central pancreatectomy (RCP) for PNETs. Giulianotti and colleagues⁸⁹ presented their experience in 3 cases. The mean operating time was 320 minutes with 233 mL of blood loss. One patient developed a fistula. Mean LOS was 15 days with no perioperative mortalities. R0 resection was obtained in all 3 patients. The patients showed neither endocrine nor exocrine deficiencies during a mean follow-up of 44 months. In the largest published series, which included 5 patients, Kang and colleagues⁹⁰ report a mean operating time of 480 minutes with blood loss of 200 mL. One patient developed a fistula. Mean LOS was 12 days. No patients reported endocrine dysfunction during the follow-up period of almost 2 years. The investigators compared this experience with 10 open central

pancreatectomies that were performed at their institution. Within this small series comparison, tumors were significantly larger and blood loss significantly greater in the open cohort; however, operating times were significantly longer in the robotic group.

Overall Prognosis

The 5-year and 10-year survival rates for all PNETs are about 65% and 45%, respectively.^{91,92} The 5-year survival rate for functioning PNETs is about 80%, whereas the 5-year and 10-year survival rates for nonfunctioning PNETs are about 60% and 30%, respectively.^{92,93} Curative surgical resection of the primary tumor, absence of liver metastases, metachronous liver metastases, and aggressive treatment of the liver metastases are all favorable effect factors of long-term survival in patients with PNETs.⁹⁴

SUMMARY

Minimally invasive procedures are a safe modality for the surgical treatment of PNETs. Multiple studies have shown a lower overall complication rate among benign, small tumors (<2 cm) undergoing minimally invasive surgery compared with the open technique. In malignant PNETs, laparoscopy, although requiring advanced surgical skills, is not associated with a compromise in terms of oncologic resection, and provides the benefits of decreased postoperative pain, better cosmetic results, shorter hospital stay, and a shorter postoperative recovery period. Further prospective, multi-center, randomized trials are required for the analysis of these minimally invasive surgical techniques for the treatment of PNETs and their comparison with traditional open pancreatic surgery.

REFERENCES

1. Milan SA, Yeo CJ. Neuroendocrine tumors of the pancreas. *Curr Opin Oncol* 2012;24(1):46–55.
2. Yao JC, Hassan M, Phan A, et al. One hundred years after “carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008;26(18):3063–72.
3. Panzuto F, Nasoni S, Falconi M, et al. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. *Endocr Relat Cancer* 2005;12(4):1083–92.
4. Hill JS, McPhee JT, McDade TP, et al. Pancreatic neuroendocrine tumors: the impact of surgical resection on survival. *Cancer* 2009;115(4):741–51.
5. D’Haese JG, Tosolini C, Ceyhan GO, et al. Update on surgical treatment of pancreatic neuroendocrine neoplasms. *World J Gastroenterol* 2014;20(38):13893–8.
6. Drymoussis P, Raptis DA, Spalding D, et al. Laparoscopic versus open pancreas resection for pancreatic neuroendocrine tumours: a systematic review and meta-analysis. *HPB* 2014;16(5):397–406.
7. DiNorcia J, Lee MK, Reavey PL, et al. One hundred thirty resections for pancreatic neuroendocrine tumor: evaluating the impact of minimally invasive and parenchyma-sparing techniques. *J Gastrointest Surg* 2010;14(10):1536–46.
8. Giulianotti PC, Coratti A, Angelini M, et al. Robotics in general surgery: personal experience in a large community hospital. *Arch Surg Chicago, IL* 1960 2003;138(7):777–84.

9. Melvin WS, Needleman BJ, Krause KR, et al. Robotic resection of pancreatic neuroendocrine tumor. *J Laparoendosc Adv Surg Tech A* 2003;13(1):33–6.
10. Wayne M, Steele J, Iskandar M, et al. Robotic pancreatic surgery is no substitute for experience and clinical judgment: an initial experience and literature review. *World J Surg Oncol* 2013;11:160.
11. Winer J, Can MF, Bartlett DL, et al. The current state of robotic-assisted pancreatic surgery. *Nat Rev Gastroenterol Hepatol* 2012;9(8):468–76.
12. Abood GJ, Can MF, Daouadi M, et al. Robotic-assisted minimally invasive central pancreatectomy: technique and outcomes. *J Gastrointest Surg* 2013;17(5):1002–8.
13. Dizon AM, Kowalyk S, Hoogwerf BJ. Neuroglycopenic and other symptoms in patients with insulinomas. *Am J Med* 1999;106(3):307–10.
14. Service FJ, McMahon MM, O'Brien PC, et al. Functioning insulinoma—incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clin Proc* 1991;66(7):711–9.
15. Rostambeigi N, Thompson GB. What should be done in an operating room when an insulinoma cannot be found? *Clin Endocrinol (Oxf)* 2009;70(4):512–5.
16. Service FJ, Natt N. The prolonged fast. *J Clin Endocrinol Metab* 2000;85(11):3973–4.
17. Hirshberg B, Livi A, Bartlett DL, et al. Forty-eight-hour fast: the diagnostic test for insulinoma. *J Clin Endocrinol Metab* 2000;85(9):3222–6.
18. Gibril F, Jensen RT. Zollinger-Ellison syndrome revisited: diagnosis, biologic markers, associated inherited disorders, and acid hypersecretion. *Curr Gastroenterol Rep* 2004;6(6):454–63.
19. Cameron AJ, Hoffman HN. Zollinger-Ellison syndrome. Clinical features and long-term follow-up. *Mayo Clin Proc* 1974;49(1):44–51.
20. Norton JA, Jensen RT. Current surgical management of Zollinger-Ellison syndrome (ZES) in patients without multiple endocrine neoplasia-type 1 (MEN1). *Surg Oncol* 2003;12(2):145–51.
21. Berna MJ, Hoffmann KM, Serrano J, et al. Serum gastrin in Zollinger-Ellison syndrome: I. Prospective study of fasting serum gastrin in 309 patients from the National Institutes of Health and comparison with 2229 cases from the literature. *Medicine (Baltimore)* 2006;85(6):295–330.
22. Berna MJ, Hoffmann KM, Long SH, et al. Serum gastrin in Zollinger-Ellison syndrome: II. Prospective study of gastrin provocative testing in 293 patients from the National Institutes of Health and comparison with 537 cases from the literature. Evaluation of diagnostic criteria, proposal of new criteria, and correlations with clinical and tumoral features. *Medicine (Baltimore)* 2006;85(6):331–64.
23. Wermers RA, Fatourehchi V, Wynne AG, et al. The glucagonoma syndrome. Clinical and pathologic features in 21 patients. *Medicine (Baltimore)* 1996;75(2):53–63.
24. Friesen SR. Update on the diagnosis and treatment of rare neuroendocrine tumors. *Surg Clin North Am* 1987;67(2):379–93.
25. Mekhjian HS, O'Dorisio TM. VIPoma syndrome. *Semin Oncol* 1987;14(3):282–91.
26. Adam N, Lim SS, Ananda V, et al. VIPoma syndrome: challenges in management. *Singapore Med J* 2010;51(7):e129–32.
27. House MG, Yeo CJ, Schulick RD. Periampullary pancreatic somatostatinoma. *Ann Surg Oncol* 2002;9(9):869–74.
28. Fidler JL, Fletcher JG, Reading CC, et al. Preoperative detection of pancreatic insulinomas on multiphasic helical CT. *AJR Am J Roentgenol* 2003;181(3):775–80.

29. Sheth S, Hruban RK, Fishman EK. Helical CT of islet cell tumors of the pancreas: typical and atypical manifestations. *AJR Am J Roentgenol* 2002;179(3):725–30.
30. Gouya H, Vignaux O, Augui J, et al. CT, endoscopic sonography, and a combined protocol for preoperative evaluation of pancreatic insulinomas. *AJR Am J Roentgenol* 2003;181(4):987–92.
31. Buetow PC, Parrino TV, Buck JL, et al. Islet cell tumors of the pancreas: pathologic-imaging correlation among size, necrosis and cysts, calcification, malignant behavior, and functional status. *AJR Am J Roentgenol* 1995;165(5):1175–9.
32. Stark DD, Moss AA, Goldberg HI, et al. CT of pancreatic islet cell tumors. *Radiology* 1984;150(2):491–4.
33. Sundin A, Vullierme M-P, Kaltsas G, et al. Mallorca Consensus Conference participants, European Neuroendocrine Tumor Society. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological examinations. *Neuroendocrinology* 2009;90(2):167–83.
34. Lopez Hänninen E, Amthauer H, Hosten N, et al. Prospective evaluation of pancreatic tumors: accuracy of MR imaging with MR cholangiopancreatography and MR angiography. *Radiology* 2002;224(1):34–41.
35. Kim MK. Endoscopic ultrasound in gastroenteropancreatic neuroendocrine tumors. *Gut Liver* 2012;6(4):405–10.
36. Rösch T, Lightdale CJ, Botet JF, et al. Localization of pancreatic endocrine tumors by endoscopic ultrasonography. *N Engl J Med* 1992;326(26):1721–6.
37. Patterson EJ, Gagner M, Salky B, et al. Laparoscopic pancreatic resection: single-institution experience of 19 patients. *J Am Coll Surg* 2001;193(3):281–7.
38. Haugvik S-P, Marangos IP, Røsok BI, et al. Long-term outcome of laparoscopic surgery for pancreatic neuroendocrine tumors. *World J Surg* 2013;37(3):582–90.
39. Al-Kurd A, Chapchay K, Grozinsky-Glasberg S, et al. Laparoscopic resection of pancreatic neuroendocrine tumors. *World J Gastroenterol* 2014;20(17):4908–16.
40. Crippa S, Bassi C, Salvia R, et al. Enucleation of pancreatic neoplasms. *Br J Surg* 2007;94(10):1254–9.
41. Whipple AO, Parsons WB, Mullins CR. Treatment of carcinoma of the ampulla of Vater. *Ann Surg* 1935;102(4):763–79.
42. Kim SC, Song KB, Jung YS, et al. Short-term clinical outcomes for 100 consecutive cases of laparoscopic pylorus-preserving pancreaticoduodenectomy: improvement with surgical experience. *Surg Endosc* 2013;27(1):95–103.
43. Keck T, Wellner U, Küsters S, et al. Laparoscopic resection of the pancreatic head. Feasibility and perioperative results. *Chirurg* 2011;82(8):691–7 [in German].
44. Jacobs MJ, Kamyab A. Total laparoscopic pancreaticoduodenectomy. *JSLs* 2013;17:188–93.
45. Lai ECH, Yang GPC, Tang CN. Robot-assisted laparoscopic pancreaticoduodenectomy versus open pancreaticoduodenectomy—a comparative study. *Int J Surg* 2012;10(9):475–9.
46. Assalia A, Gagner M. Laparoscopic pancreatic surgery for islet cell tumors of the pancreas. *World J Surg* 2004;28(12):1239–47.
47. Fernández-Cruz L. Distal pancreatic resection: technical differences between open and laparoscopic approaches. *HPB* 2006;8(1):49–56.
48. Fernández-Cruz L, Sáenz A, Astudillo E, et al. Outcome of laparoscopic pancreatic surgery: endocrine and nonendocrine tumors. *World J Surg* 2002;26(8):1057–65.
49. Tagaya N, Kasama K, Suzuki N, et al. Laparoscopic resection of the pancreas and review of the literature. *Surg Endosc* 2003;17(2):201–6.

50. Hanly EJ, Talamini MA. Robotic abdominal surgery. *Am J Surg* 2004;188(4A Suppl):19S–26S.
51. Zeh HJ, Bartlett DL, Moser AJ. Robotic-assisted major pancreatic resection. *Adv Surg* 2011;45:323–40.
52. Bown SG, Rogowska AZ, Whitelaw DE, et al. Photodynamic therapy for cancer of the pancreas. *Gut* 2002;50(4):549–57.
53. Wu Y, Tang Z, Fang H, et al. High operative risk of cool-tip radiofrequency ablation for unresectable pancreatic head cancer. *J Surg Oncol* 2006;94(5):392–5.
54. Varshney S, Sewkani A, Sharma S, et al. Radiofrequency ablation of unresectable pancreatic carcinoma: feasibility, efficacy and safety. *JOP* 2006;7(1):74–8.
55. Spiliotis JD, Datsis AC, Michalopoulos NV, et al. Radiofrequency ablation combined with palliative surgery may prolong survival of patients with advanced cancer of the pancreas. *Langenbecks Arch Surg* 2007;392(1):55–60.
56. Girelli R, Frigerio I, Salvia R, et al. Feasibility and safety of radiofrequency ablation for locally advanced pancreatic cancer. *Br J Surg* 2010;97(2):220–5.
57. Rossi S, Viera FT, Ghittoni G, et al. Radiofrequency ablation of pancreatic neuroendocrine tumors: a pilot study of feasibility, efficacy, and safety. *Pancreas* 2014;43(6):938–45.
58. Zhang W-Y, Li Z-S, Jin Z-D. Endoscopic ultrasound-guided ethanol ablation therapy for tumors. *World J Gastroenterol* 2013;19(22):3397–403.
59. Gelczer RK, Charboneau JW, Hussain S, et al. Complications of percutaneous ethanol ablation. *J Ultrasound Med* 1998;17(8):531–3.
60. Park DH, Choi J-H, Oh D, et al. Endoscopic ultrasonography-guided ethanol ablation for small pancreatic neuroendocrine tumors: results of a pilot study. *Clin Endosc* 2015;48(2):158–64.
61. Cuschieri A. Laparoscopic surgery of the pancreas. *J R Coll Surg Edinb* 1994;39(3):178–84.
62. Gagner M, Pomp A, Herrera MF. Early experience with laparoscopic resections of islet cell tumors. *Surgery* 1996;120(6):1051–4.
63. Fernández-Cruz L, Cosa R, Blanco L, et al. Curative laparoscopic resection for pancreatic neoplasms: a critical analysis from a single institution. *J Gastrointest Surg* 2007;11(12):1607–21 [discussion: 1621–2].
64. Kooby DA, Hawkins WG, Schmidt CM, et al. A multicenter analysis of distal pancreatectomy for adenocarcinoma: is laparoscopic resection appropriate? *J Am Coll Surg* 2010;210(5):779–85, 786–7.
65. Jayaraman S, Gonen M, Brennan MF, et al. Laparoscopic distal pancreatectomy: evolution of a technique at a single institution. *J Am Coll Surg* 2010;211(4):503–9.
66. Gagner M, Pomp A. Laparoscopic pylorus-preserving pancreatoduodenectomy. *Surg Endosc* 1994;8(5):408–10.
67. Gumbs AA, Rodriguez Rivera AM, Milone L, et al. Laparoscopic pancreatoduodenectomy: a review of 285 published cases. *Ann Surg Oncol* 2011;18(5):1335–41.
68. Kim SC, Park KT, Hwang JW, et al. Comparative analysis of clinical outcomes for laparoscopic distal pancreatic resection and open distal pancreatic resection at a single institution. *Surg Endosc* 2008;22(10):2261–8.
69. Borja-Cacho D, Al-Refaie WB, Vickers SM, et al. Laparoscopic distal pancreatectomy. *J Am Coll Surg* 2009;209(6):758–65 [quiz: 800].
70. Nigri GR, Rosman AS, Petrucciani N, et al. Metaanalysis of trials comparing minimally invasive and open distal pancreatectomies. *Surg Endosc* 2011;25(5):1642–51.

71. Dedieu A, Rault A, Collet D, et al. Laparoscopic enucleation of pancreatic neoplasm. *Surg Endosc* 2011;25(2):572–6.
72. Fernández-Cruz L, Blanco L, Cosa R, et al. Is laparoscopic resection adequate in patients with neuroendocrine pancreatic tumors? *World J Surg* 2008;32(5):904–17.
73. Speicher JE, Traverso LW. Pancreatic exocrine function is preserved after distal pancreatectomy. *J Gastrointest Surg* 2010;14(6):1006–11.
74. Sa Cunha A, Rault A, Beau C, et al. Laparoscopic central pancreatectomy: single institution experience of 6 patients. *Surgery* 2007;142(3):405–9.
75. Rotellar F, Pardo F, Montiel C, et al. Totally laparoscopic Roux-en-Y duct-to-mucosa pancreaticojejunostomy after middle pancreatectomy: a consecutive nine-case series at a single institution. *Ann Surg* 2008;247(6):938–44.
76. Zhou N, Chen J, Liu Q, et al. Outcomes of pancreatoduodenectomy with robotic surgery versus open surgery. *Int J Med Robot* 2011;7(2):131–7.
77. Buchs NC, Addeo P, Bianco FM, et al. Outcomes of robot-assisted pancreaticoduodenectomy in patients older than 70 years: a comparative study. *World J Surg* 2010;34(9):2109–14.
78. Buchs NC, Addeo P, Bianco FM, et al. Robotic versus open pancreaticoduodenectomy: a comparative study at a single institution. *World J Surg* 2011;35(12):2739–46.
79. Giulianotti PC, Addeo P, Buchs NC, et al. Robotic extended pancreatectomy with vascular resection for locally advanced pancreatic tumors. *Pancreas* 2011;40(8):1264–70.
80. Giulianotti PC, Sbrana F, Bianco FM, et al. Robot-assisted laparoscopic pancreatic surgery: single-surgeon experience. *Surg Endosc* 2010;24(7):1646–57.
81. Zureikat AH, Nguyen KT, Bartlett DL, et al. Robotic-assisted major pancreatic resection and reconstruction. *Arch Surg Chicago, IL*. 1960 2011;146(3):256–61.
82. Zeh HJ, Zureikat AH, Secrest A, et al. Outcomes after robot-assisted pancreaticoduodenectomy for periampullary lesions. *Ann Surg Oncol* 2012;19(3):864–70.
83. Nguyen KT, Zureikat AH, Chalikhonda S, et al. Technical aspects of robotic-assisted pancreaticoduodenectomy (RAPD). *J Gastrointest Surg* 2011;15(5):870–5.
84. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005;138(1):8–13.
85. Daouadi M, Zureikat AH, Zenati MS, et al. Robot-assisted minimally invasive distal pancreatectomy is superior to the laparoscopic technique. *Ann Surg* 2013;257(1):128–32.
86. Kim DH, Kang CM, Lee WJ, et al. The first experience of robot assisted spleen-preserving laparoscopic distal pancreatectomy in Korea. *Yonsei Med J* 2011;52(3):539–42.
87. Kang CM, Kim DH, Lee WJ, et al. Conventional laparoscopic and robot-assisted spleen-preserving pancreatectomy: does da Vinci have clinical advantages? *Surg Endosc* 2011;25(6):2004–9.
88. Waters JA, Canal DF, Wiebke EA, et al. Robotic distal pancreatectomy: cost effective? *Surgery* 2010;148(4):814–23.
89. Giulianotti PC, Sbrana F, Bianco FM, et al. Robot-assisted laparoscopic middle pancreatectomy. *J Laparoendosc Adv Surg Tech A* 2010;20(2):135–9.
90. Kang CM, Kim DH, Lee WJ, et al. Initial experiences using robot-assisted central pancreatectomy with pancreaticogastrostomy: a potential way to advanced laparoscopic pancreatectomy. *Surg Endosc* 2011;25(4):1101–6.

91. Ekeblad S, Skogseid B, Dunder K, et al. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. *Clin Cancer Res* 2008;14(23):7798–803.
92. Phan GQ, Yeo CJ, Hruban RH, et al. Surgical experience with pancreatic and peripancreatic neuroendocrine tumors: review of 125 patients. *J Gastrointest Surg* 1998;2(5):473–82.
93. Liang H, Wang P, Wang X-N, et al. Management of nonfunctioning islet cell tumors. *World J Gastroenterol* 2004;10(12):1806–9.
94. Chu QD, Hill HC, Douglass HO, et al. Predictive factors associated with long-term survival in patients with neuroendocrine tumors of the pancreas. *Ann Surg Oncol* 2002;9(9):855–62.