Review Article

# Surgical resection of neuroendocrine tumors of the pancreas (pNETs) by minimally invasive surgery: the laparoscopic approach

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**Abstract:** Neuroendocrine tumors of the pancreas (pNETs) are a rare group of neoplasms that originate from the endocrine portion of the pancreas. Tumors that either secrete or do not secrete compounds, resulting in symptoms, can be classified as functioning and non-functioning pNETs, respectively. The prevalence of such tumors has recently increased due to the use of more sensitive imaging techniques, such as multidetector computed tomography, magnetic resonance imaging and endoscopic ultrasound. The biological behavior of pNETs varies widely from indolent, well-differentiated tumors to those that are far more aggressive. The most effective and radical treatment for pNETs is surgical resection. Over the last decade, minimally invasive surgery has been increasingly used in pancreatectomy, with laparoscopic pancreatic surgery (LPS) emerging as an alternative to open pancreatic surgery (OPS) in patients with pNETs. Non-comparative studies have shown that LPS is safe and effective. In well-selected groups of patients with pancreatic lesions, LPS was found to results in good perioperative outcomes, including reduced intraoperative blood loss, postoperative pain, time to recovery, and length of hospital stay. Despite the encouraging results of studies from highly specialized centers with extensive experience, no randomized trials to date have conclusively validated these findings. Indications for minimally invasive LPS for patients with pNETs remain unclear. This review presents the current state of LPS for pNETs.

**Keywords:** Neuroendocrine tumor of the pancreas (pNETs); laparoscopic pancreatic surgery (LPS); minimally invasive surgery

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## Introduction

Neuroendocrine tumors of the pancreas (pNETs) are a rare group of neoplasms that originate from the endocrine portion of the pancreas. These tumors, which newly affect 2–3 per 100,000 individuals per year, constitute only about 1% to 2% of all pancreatic neoplasms (1,2). Tumors that do and do not secret compounds, resulting in symptoms, can be classified as functioning and non-functioning pNETs, respectively (3). Complete surgical resection plays an important role in the curative treatment of patients with pNETs.

Improvements in science and technology have led to increases in the use of minimally invasive surgical methods, such laparoscopic surgery, for pancreatic diseases. Minimally invasive pancreatic surgery was introduced in the early 1990s, with laparoscopic pylorus-preserving pancreaticoduodenectomy (LPPPD) (4) and pancreatic left

resection (5) first reported in 1994, and laparoscopic distal pancreatectomy (LDP) (6), laparoscopic surgery for islet cell tumor (7) first described in 1996. Minimally invasive surgery may be a promising treatment for pNETs, with the laparoscopic approach providing better outcomes than open surgery (8-10), likely because pNETs are often small in size and behave less aggressively.

Robotic surgical systems have overcome the limitations of laparoscopic technology by providing an isometric 3D or 4D view and a high level of flexibility for manipulation. The first robotic distal pancreatectomy was reported in 2002 (11), and the first robotic pancreaticoduodenectomy in 2003 (12). The clinical benefits of robotic surgical systems are unclear because many expert surgeons perform advanced LPS safely without a robotic system, and surgery with the robotic system costs much more than the conventional laparoscopic approach (13).

We evaluated LPS for patients with pNETs, in addition to reviewing and discussing various minimally invasive surgical techniques, including their benefits and limitations.

## Types of pNETs

### *Insulinoma*

Insulinomas are the most common functional pNETs as well as the most common cause of hypoglycemia related to endogenous hyperinsulinemia. Most insulinomas are sporadic, and the majority of these most sporadic insulinomas are solitary and benign. Sporadic insulinomas are therefore frequently managed by parenchyma-sparing procedures, such as enucleation and central pancreatectomy. Conversely, because multiple endocrine neoplasia type 1 is frequently multifocal distal pancreatectomy, with or without enucleation of masses in the head of the pancreas, is the standard of care in patients with these neoplasms (14).

### *Gastrinoma*

Most functional pNETs are either gastrinomas or insulinomas. Most patients with gastrinoma present with peptic ulcer disease, particularly multiple ulcers and ulcers that are resistant to medical treatment. About 60% to 90% of gastrinomas are malignant, regardless of size, and lymph node metastasis is frequent (15). Thus, pancreatectomy with lymph node dissection has been recommended for patients with gastrinoma.

### *Glucagonoma*

Glucagonomas, the alpha-cell counterparts of insulinomas, are rare tumors of the pancreas. Unlike insulinomas, most glucagonomas are 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 (16).

### *Vasoactive intestinal peptideomas*

Vasoactive intestinal peptideomas are exceedingly rare tumors, with an estimated incidence of only 1 in 10 million per year (17). Approximately 70% of patients present with malignant tumors, as shown by hepatic, distant, and/or lymph node metastases (18). Most tumors are at least 3 cm in diameter, with a mean diameter of about 5 cm at initial presentation. Most tumors are found primarily in the body and tail of the pancreas, but other tumors have been observed 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.

### *Somatostatinoma*

pNETs secreting somatostatin are rare, with an incidence of only 1 in 40 million people per year (2). Most tumors are located in the head of the pancreas, but lesions may be observed in 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.

### *Non-functional pNETs*

Progress of in diagnostic imaging has resulted in an increase in the discovery of small pNETs, with these tumors currently accounting for 60–90% of all pNETs (19). The Japan NeuroEndocrine Tumor Society has recommended enucleation for tumors <1 cm, enucleation or pancreatectomy for tumors 1–2 cm, and pancreatectomy with lymph node dissection for tumors >2 cm (20). In comparison, the National Comprehensive Cancer Network guidelines has recommended enucleation or pancreatectomy with lymph node dissection for tumors <2 cm and pancreatectomy with lymph node dissection for tumors >2 cm (21).

Intraoperative ultrasonography (IOUS) is also very important in determining surgical procedures. Current treatment guidelines strongly recommend enucleation of sporadic solitary pNETs with a diameter <2 cm on IOUS, and if structural integrity of the pancreatic duct can be maintained (22).

## Determination of operative techniques

Many treatments other than surgery have been reported effective in selected patients. These methods include medical treatment with somatostatin analogues (23) and everolimus (24), peptide receptor therapy (25), and ablative treatments for liver metastases (26). However, surgical resection is the only curative treatment for patients with pNETs. Surgery may also alleviate symptoms resulting from hormone production by functioning tumors or from a mass of nonfunctioning tumors. The planned surgical procedure is mainly dependent on preoperative localization, but it may be altered by intraoperative IOUS findings. Methods include traditional resection and/or parenchyma-sparing resection, depending on indications.

## With or without lymph node dissection

Lymph node metastases of pNETs are indicative of poor prognosis (27-29), and correlate positively with pathological grade with 15–20%, 30–40%, >50% classified as G1, G2, and G3, respectively (30). However, those studies did not clearly show that omitting lymphadenectomy could increase the rate of local recurrence, a requirement for recommending lymph node dissection in patient with pNETs. Regional lymph node metastasis of pNETs have been reported to have oncologic effects (31,32). A retrospective study of patients with non-functional G1 pNETs who underwent limited pancreatectomy or distal pancreatosplenectomy found that lymph node metastasis had no adverse impact on oncologic outcomes, suggesting no need for routine local lymph nodes resection (33). Indeed, most well differentiated insulinomas and non-functional pNETs located in the distal pancreas are quite small and seldom accompanied by lymph node metastasis, with no radiographic evidence of lymph node involvement (34).

## Surgical options in LPS and their advantages and disadvantages for pNETs

The success rates of minimally invasive techniques to treat pNETs have been found to vary. Several recent systematic reviews showed that the minimally invasive approach was associated with lower intraoperative blood loss, great splenic preservation, and a shorter hospital stay (9,35). Minimally invasive pancreatic resection is currently considered the treatment of choice for small sporadic pNETs, especially for those located in the pancreatic body and tail.

Many highly specialized centers have accrued experience in the use of advanced laparoscopic techniques for pancreatic surgery (36-39). On a practical level, pancreatic surgery is technically vexing for professionals. The pancreas is in a retroperitoneal position, is in close proximity to major vessels and has a very fragile consistency, making it extremely vulnerable to manipulations. Despite being complex, laparoscopic pancreaticoduodenectomy (LPD) remains technically feasible in specialized institutions, with results comparable to those of open pancreaticoduodenectomy (OPD) (40,41). Most cases reported in the literature involve laparoscopic enucleation of solitary lesions in the body or tail of the pancreas and LDP with or without spleen preservation (36,38). LPS is regarded as a safe approach for pNETs (9), and should be included in the surgical armamentarium for these patients.

### *Laparoscopic enucleation for pNETs*

Solitary pNETs are particularly amenable to laparoscopic enucleation because of their small size and benign behavior. Tumor location and its relationship to the pancreatic duct and peripancreatic vessels are routinely evaluated by IOUS allowing the margin of resection to be determined before enucleation. The most important surgical complication is pancreatic fistula (7.2% in all types of laparoscopic procedures), which can result in serious consequences, including poor quality of life, extended hospital stays, intra-abdominal bleeding, and infection (42). Current treatment guidelines strongly recommend enucleation in patients with pNETs <2 cm on IOUS, but only if the structural integrity of the pancreatic duct can be maintained (22). A 2–3-mm distance from the pancreatic duct on IOUS is also recommended (43-45). Larger tumors, up to 3 cm in diameter, have been associated with an increased risk for malignancy and increased rates of postoperative complications following enucleation. Although there is no current consensus on an optimal (10,37,46), a review of the literature found that laparoscopic enucleation in selected patients is technically feasible procedure, with complication rates comparable to those of open surgery (36,37).

### *Surgical technique for laparoscopic enucleation of pNETs at the head of the pancreas*

Once the laparoscopic ports have been placed, the pancreas is exposed by opening the gastrocolic ligament, thereby gaining access to the lesser sac. Subsequent IOUS can accurately localize the tumor, rule out the presence of additional lesions, and determine the exact location of the tumor and its relationship to the pancreatic duct and major vessels. Special care is taken during dissection to avoid injury to the pancreatic duct and mesenteric and splenic vessels during the dissection. However, advanced laparoscopic techniques are required to isolate the splenic artery and vein from the pancreatic parenchyma, thereby safely preserving the splenic vessels (47,48).

### *Surgical technique for laparoscopic enucleation of pNETs at the body and/or tail of the pancreas*

Laparoscopic ports are placed and IOUS is performed to localize the tumor and assess its relationship to surrounding structures. The spleen is mobilized superiorly and laterally, while the splenic flexure is taken down inferiorly. If the tumor is located anteriorly, an opening is created in the anterior visceral peritoneum of the pancreas, followed by careful dissection between the tumor and the normal pancreatic parenchyma until the mass is successfully enucleated. If the tumor is located in the posterior aspect of the pancreatic body or tail, the inferior margin of the pancreas is dissected and the pancreas is mobilized and lifted up, allowing exposure of the posterior pancreatic surface. 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.

### *LDP for pNETs*

The process of LDP, without reconstruction of alimentary tract is relatively straightforward and can be easily performed within a short time, indicating that LDP is beneficial and can be safely used to treat pNETs located in the body or tail of the pancreas (9,14,49).

Preservation of the spleen during distal pancreatectomy is considered beneficial in patients with benign tumors or low-grade malignant tumors. Spleen-preserving distal pancreatectomy can involve either the removal (50) or preservation (51) of the splenic vessels, with the latter avoiding the secondary infection and postoperative spleen infarction frequently observed with the former. LDP is superior technically to open distal pancreatectomy, with the former showing enhanced feasibility and safety and higher rates of preservation of the spleen and the splenic vessels.

Previous meta-analyses on LDP have analyzed studies, irrespective of the underlying pancreatic pathology (52-54). LDP was found to result in reductions in intraoperative blood loss and length of hospital stay, as well as lower risks of overall postoperative complications and wound infection, without a substantial increase in operation time and no differences in rates of pancreatic fistula, reoperation and mortality (49). Oncologic outcomes were similar in patients who underwent LDP or pNETs, with LDP associated with a reduced rate of postoperative complications without compromising survival (55).

### *LPD for pNETs*

LPD and LPPPD remain technically difficult surgical procedures, with high mortality and morbidity rates. Problems encountered with LPD for resection of pancreatic head lesions include a long operation time, technical difficulties performing the dissection arising from the proximity of large vessels, complex reconstruction procedures, and perceived inappropriateness of this intervention for patients with highly advanced malignant disease. Few studies have compared long-term oncologic outcomes and mortality rates in patients with pNETs who underwent LPD/LPPPD and OPD.

It remains unclear whether the minimally invasive approach can be considered a standard in performing LPD and if the outcomes of LPD are the same or over as those of OPD (56,57). Despite the absence of randomized control trials, compared intraoperative outcomes, postoperative complications, postoperative recovery and oncological safety of OPD and LPD.

## Discussion

pNETs are uncommon tumors (1), their natural history has not yet been completely understood owing to their often indolent course, which can delay diagnosis and treatment. In addition, pNETs exhibit a spectrum of biological behaviors, ranging from benign to highly malignant (58). This heterogeneity has made it difficult to both devise clinically effective stratification systems as well as determine the extent of resection needed for cure.

 

Over the last decade, use of a laparoscopic approach in pancreatic surgery has increased markedly, such almost all previously open procedures can be performed by minimally invasive methods. In general, these methods should be restricted to high volume centers, which have experience in the full range of open operative procedures in pancreatic surgery. Low-risk patients and those with small sized pNETs in the body and tail of the pancreas are especially suitable for minimally invasive surgery, with the laparoscopic approach resulting in better outcomes than open surgery (9,10). 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. LDP may be superior to the open approach in patients with benign disease, resulting in reduced blood loss, shorter hospital stays, and equivalent rates of complications (35).

A review of 11 studies, involving 906 patients with pNETs, of 22% and 78% of whom underwent LPS and OPS, respectively found that LPS was associated with a significantly lower overall complication rate (38% *vs.* 46%, P<0.001), a 67-mL reduction in blood loss (P<0.001) and a 5-day reduction in hospital stay (P<0.001) (9). There were no differences between the LPS and OPS groups in rates of postoperative pancreatic fistula [29% (51/178) *vs.* 37% (146/396), P=0.590], and mortality; and no difference in operation time, which was 4 min lower in the OPS group (P=0.740). LPS is a safe approach for pNETs and should be in the surgical armamentarium for patients.

The most common surgical complication of laparoscopic enucleation is pancreatic fistula. Laparoscopic techniques have been reported successful in the management of sporadic pNETs, especially in the body or tail of the pancreas (36,38,39). Rates of pancreatic fistula after laparoscopic enucleation for various pathologies have been reported to vary from 13% to 56% and may depend on the location of the lesion and its pathology (59-61). Concerns persist in the management of solitary lesions located in the head of the pancreas due to complications after enucleation, as up to 64% of patients may develop a fistula (52,61). Nevertheless, laparoscopic enucleation in selected patients is a technically feasible procedure with complication rates comparable to those open enucleation (36,37).

In a study of 171 patients with pNETs, of whom 73 (42.7%) and 98 (57.3%) underwent LDP and ODP, respectively, LDP was associated with a lower rate of postoperative complications (30% *vs.* 47%, P=0.028), and a significantly shorter median hospital stay [5 days (range, 3–18 days) *vs.* 7 days (range, 4–39 days), P=0.008] (55). There were no differences in rates of postoperative pancreatic fistula (22% *vs.* 33%, P=0.168) and operation time (352 *vs.* 409 min, P=0.065). Long-term oncologic were similar for LDP and ODP, indicating that LDP reduced overall morbidity, as shown by rates of postoperative complications, without compromising survival.

Comparisons of LPS and OPS have shown that similar operation times and complication and mortality rates. LPS, however, has been associated with reductions in blood loss and length of hospital stay, as well as superior oncologic outcomes. Although the demographic characteristics of the LPS and OPS groups in many of these studies were similar, selection bias favoring LPS continues to be a problem. Many studies excluded patients with vascular involvement and those at higher surgical risk.

Minimally invasive procedures are a safe modality for the surgical treatment of pNETs. Multiple studies have shown that overall complication rates in patients with benign, small tumors were lower with minimally invasive than with open surgery. Although laparoscopy requires advanced surgical skills in patients with malignant pNETs, minimally invasive procedures were not associated with a compromise in oncologic resection, while providing benefits that included reduced postoperative pain, shorter hospital stay and shorter postoperative recovery period.

## Conclusions

Further prospective, multicenter, randomized control trials are required to analyze these minimally invasive surgical techniques in the treatment of pNETs and their comparison with traditional OPS. Extended experience with hepatopancreaticobiliary surgery and advanced laparoscopic skills are crucial requirements.

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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