Best Practice & Research Clinical Endocrinology & Metabolism 33 (2019) 101294

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

6

# Pre- and intraoperative diagnostic requirements, benefits and risks of minimally invasive and robotic surgery for neuroendocrine tumors of the pancreas

Dr Joseph Gharios, surgeon [a], Dr Elisabeth Hain, surgeon [a],
Dr Anthony Dohan, radiologist [b, c],
Pr Fréderic Prat, endoscopist [b, d],
Pr Benoit Terris, pathologist [b, e],
Pr Jérôme Bertherat, endocrinologist [b, f],
Pr Romain Coriat, oncologist [b, d],
Pr Bertrand Dousset, surgeon [a, b],
Pr Sébastien Gaujoux, surgeon [a, b, *]

[a] *Department of Digestive, Hepato-biliary and Endocrine Surgery, Referral Center for Rare Adrenal Diseases, Cochin Hospital, APHP, Paris, France*
[b] *Faculté de Médecine Paris Descartes, Université Paris Descartes, Sorbonne Paris Cité, France*
[c] *Department of Radiology, Cochin Hospital, APHP, Paris, France*
[d] *Department of Gastroenterology, Cochin Hospital, APHP, Paris, France*
[e] *Department of Pathology, Cochin Hospital, APHP, Paris, France*
[f] *Department of Endocrinology, Cochin Hospital, Referral Center for Rare Adrenal Diseases, Cochin Hospital, APHP, Paris, France*

A R T I C L E I N F O

*Article history:*
Available online 10 July 2019

*Keywords:*
neuroendocrine tumors
surgery
laparoscopy
staging

Pancreatic neuroendocrine tumours (PanNET) are rare tumours, accounting for 1%–2% of all pancreatic neoplasms. These tumors are classified as functioning neuroendocrine tumours (F-PanNETs) or non-functioning (NF-PanNETs) depends on whether the tumour is associated with clinical hormonal hypersecretion syndrome or not. In the last decades, diagnosis of PanNETs has increased significantly due to the widespread of cross-sectional imaging. Whenever possible, surgery is the cornerstone of PanNETs management and the only curative option for these patients. Indeed,

* Corresponding author. Department of Digestive, Hepato-biliary and Endocrine Surgery, Referral Center for Rare Adrenal Diseases, Cochin Hospital, APHP, Paris, France.
*E-mail address:* sebastien.gaujoux@aphp.fr (S. Gaujoux).

https://doi.org/10.1016/j.beem.2019.101294

*Abbreviation:*
PanNET
pancreatic neuroendocrine tumors
NF-PanNETs
non-functional pancreatic neuroendocrine tumors
EN
enucleation
PD
pancreaticoduodenectomy
DP
distal pancreatectomy
PSP
pancreas-sparing pancreatectomies

after R0 resection, the 5-year overall survival rate is around 90–100% for low grade lesions but significantly drops after incomplete resections. Compared to standard resections, pancreatic sparing surgery, *i.e.* enucleation and central pancreatectomy, significantly decreased the risk of pancreatic insufficiency. It should be performed in patients with good general condition and normal pancreatic function to limit the operative risk and enhance the benefit of surgery. Nowadays, due to many known advantages of minimally invasive surgery, there is an ongoing trend towards laparoscopic and robotic pancreatic surgery. The aim of this study is to describe the pre- and intraoperative diagnostic requirements for the management of PanNETs and the benefits and risks of minimally invasive surgery including laparoscopic and robotic approach in view of the recent literature.



## Introduction

Well-differentiated pancreatic neuroendocrine tumours (PNET) are rare tumours, accounting for only 1%–2% of pancreatic neoplasms [1–3]. PNET are carrying an overall good prognosis, despite a heterogeneous biological behavior. In the last decades, due to the widespread use of advanced imaging techniques, diagnosis of pancreatic neuroendocrine tumours (PanNETs) has increased fourfold to sevenfold [4,5] and is now well documented [6,7]. Most of newly diagnosed pancreatic neuroendocrine tumours are currently classified as non-functional (NF-PanNETs) [8], and they are more and more frequently diagnosed as incidentaloma, representing up to 82% of all resected non-functioning PNET [9]. Whenever possible, resection remains the cornerstone of PanNETs management and the only curative option for these patients. While all patients presenting with functional PanNETs should be evaluated for surgery, there is still an ongoing debate between surgical resection and observation of small asymptomatic, NF-PanNETs (*i.e.* below 2 cm in size) [10] (Fig. 1).

Nowadays, due to many advantages of minimally invasive surgery such as cosmetic results, reduction of intraoperative blood loss, pain, length of hospital stays and time for recovery, there is an ongoing trend towards laparoscopic and robotic pancreatic surgery. Nevertheless, this technical enthusiasm should not alter the quality of pre- and intraoperative diagnostic requirements, and the benefits and risks of minimally invasive approach need to be carefully weighted in view of the available literature and surgical expertise.

The aim of this review is to first describe pre- and intraoperative diagnostic requirements for the management of pancreatic neuroendocrine tumours and benefits and risks of minimally invasive surgery including laparoscopic and robotic approach in view of the recent literature.

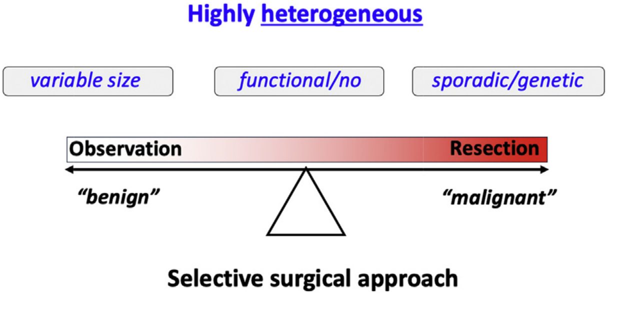


**Fig. 1.** PanNET are highly heterogeneous tumours.

## Pre- and intraoperative diagnostic requirements for pancreatic neuroendocrine tumors - a surgical perspective

### *Clinical assessment*

The classification of pancreatic neuroendocrine tumors as functioning (F-PanNETs) or non-functioning (NF-PanNETs) depends on whether the tumour is associated with clinical hormonal hypersecretion syndrome or not [11], despite systematic immunochemical examination of most PanNETS showing expression of numerous hormones [12]. Consequently, a detailed patient interview is needed before all surgery in order to detect symptoms in relation with tumour oversecretion (Table 1) and correct their clinical and/or biological consequences before surgery. It is also important to look for specific familial or personal past medical history that could suggest a genetic syndrome such as Multiple endocrine neoplasia type 1 (MEN1), or more rarely Von Hippel-Lindau disease or Neurofibromatosis 1 (NF1). NF-PanNETs are more and more frequently discovered as incidentaloma, on cross-section imaging. When they present with symptoms like vague abdominal pain, tenderness, abdominal mass, this is important to stress since this might be associated with a worst prognosis, even in small tumors, and might influence surgical indication [13–15].

### *Biological assessment*

Beside specific biochemical evaluation of F-PanNETs, biological assessment of PanNETs might be useful for diagnosis, monitoring response to treatment, or surveillance of recurrences. Preoperative biological evaluation should mainly focus on chromogranin A (CgA), however CgA levels should be interpreted cautiously in patients with decreased renal function, treated with proton pump inhibitors or somatostatin analogs. Systematic assessment of neuron specific enolase (NSE), pancreastatin, pancreatic polypeptide (PP) proinsulin, insulin, C-peptide, fasting levels of, gastrin, vasoactive intestinal peptide (VIP), glucagon, and somatostatin is not recommended. Otherwise, when F-PanNETS is suspected, corresponding hormones should be specifically evaluated [11].

### *Radiological assessment*

Radiological assessment is, of course, key in the surgical management of PanNETs. CT-Scan is largely used, usually showing hyperdense tumours (Fig. 2A) on arterial phase. This typical pattern can be missing especially in large and/or G2/G3 tumours. CT-Scan also helps to assess local and distant invasion. Magnetic resonance imaging (MRI), with the advantage of no irradiation, provides additional information such as for the diagnosis of small liver metastasis with diffusion weighted sequences [16], or the distance between main pancreatic duct and the tumour which is essential if enucleation is planned.

### *Endoscopic assessment*

Endoscopic ultrasound (EUS) is an invasive and operator-dependent procedure, but one of the key modalities of pancreas evaluation. If a pathological proof is not necessarily required before surgical

**Table 1**
Characteristic symptoms of most frequent F-PanNETS.

| Tumor | Symptoms |
|---|---|
| Insulinoma | Whipple's triad: *documentation of low blood sugar, presence of symptoms, and reversal of these symptoms when the blood glucose level is restored to normal*… and many others. |
| Gastrinoma *Zollinger-Ellison syndrome* | Gastric acid hypersecretion, severe peptic ulceration |
| VIPoma *WDHA syndrome* | Watery Diarrhea, Hypokalemia, Acidosis |
| Glucagonoma | Hyperglycemia, necrolytic migratory erythema, glossitis, stomatitis |
| Somatostatinoma | Steatorrhea, Cholelithiasis, hyperglycemia |

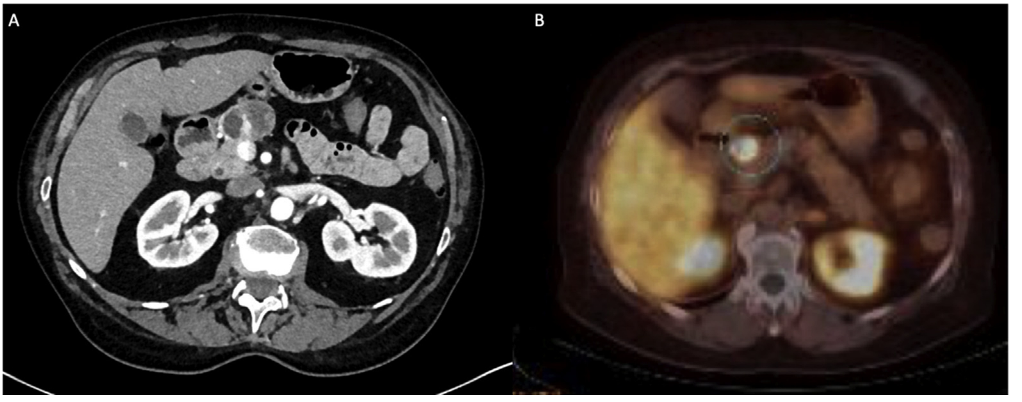


**Fig. 2.** Classical imaging of PanNET. A/Imaging a Pan NET, with a cystic presentation, with its typical hypervascular rim. B/Uptake on Gallium-68 DOTATOC PET.

treatment of PanNET, endoscopic assessment can sometimes be useful. It first allows FNA, and accurate tumour grading (Table 2). The WHO 2017 classification is currently used and should again be updated in 2019. In addition to MRI-T2 sequences, EUS accurately assess the distance between main pancreatic duct and the tumour. Contrast-Enhanced Endoscopic Ultrasonography [17] might help in the diagnostic and accurate localization of PanNET.

*Nuclear medicine assessment*

Since neuroendocrine tumors are known for overexpression of somatostatin receptors, Octreoscan somatostatin receptor scintigraphy (SRS) is highly sensitive for detecting PanNETs [18]. When available, PET imaging with Gallium-68 somatostatin receptors [16] (Fig. 2B) is even more accurate with a sensitivity and specificity of 96% and 100% respectively for PanNETs detection [19]. $^{18}$FDG-PET could be interesting, in addition to SRS imaging, for evaluating more aggressive PanNETs, *i.e.* PanNETs with Ki-67 above 10%, that carrying a high risk of metastasis [20].

*Intraoperative assessment — ultrasound and frozen section*

At least for small lesions, intraoperative ultrasound can confirm preoperative evaluation with a sensitivity >95% in detecting small pancreatic tumors (2–5 mm) [21]. Besides, several studies showed that intraoperative ultrasound could change surgical management with accurate localization of PanNETs and detecting its proximity to the pancreatic duct which can allow for simple tumors enucleation instead of standard pancreatic resection [22]. Moreover, intraoperative sonography could be helpful in

**Table 2**
WHO 2017 classification for PanNET.

| | KI-67 index | Mitotic count by 10 High power field |
|---|---|---|
| **Well differentiated NEN** | | |
| Neuroendocrine Tumor (NET) G1 | <3% | <2/10 HPF |
| Neuroendocrine Tumor (NET) G2 | 3–20% | 2-20/10 HPF |
| Neuroendocrine Tumor (NET) G3 | >20% | >20/10 HPF |
| **Poorly differentiated NEN** | | |
| Neuroendocrine carcinoma (NEC) | >20% | >20/10 HPF |
| Small cell type | | |
| Large cell type | | |
| **Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)** | | |

evaluating hepatic metastasis when suspected. Finally, intraoperative frozen section can be selectively used for diagnostic evaluation and negative margin assessment of PanNETs [23]. Fig. 3, resumes various factors which can influence PanNET surgical management.

## Determination of the best surgical procedure

Historically, standard pancreatic resection based on oncologic principles, including pancreaticoduodenectomy and distal pancreatectomy, were proposed for treatment of PanNETs. The only accepted exceptions for those surgery were: i) sporadic insulinoma, which is in most of cases benign, justifying a limited resection, and ii) PanNETs developed on MEN 1, in which surgical indications are much more difficult to standardize due to the multiplicity, variable aggressiveness, and secretion of tumors. Although recent publications from high-volume centers have shown that standard pancreatic resections are now performed with very low mortality [24,25], it is still associated with a significant postoperative early morbidity ranging from 30% to 50% [26,27]. These results are not confirmed on a nationwide level, where mortality of pancreatic surgery is about 8–10% [28,29]. Both endocrine and exocrine insufficiency after standard pancreatic resection are frequent [30–33]. Indeed, reported rate of *de novo* diabetes after pancreaticoduodenectomy (PD) and distal pancreatectomy (DP) ranges from 10% to 20% [31] and from 10% up to 40%, respectively [34,35]. This wide range of diabetes after DP can be explained by the variable length of the resected specimen. Exocrine insufficiency rate is 22%–60% after pancreaticoduodenectomy [36] and around 8% after DP [30,37]. To improve long-term postoperative outcome, pancreas-sparing surgery including central pancreatectomy, first reported by Dagradi and Serio, and popularized by Iacono [38], and enucleation has been developed. Indeed, long-term pancreatic function has become a major concern after pancreatectomy for low-grade tumours such as small Pan NET or incidentaloma as those patients are associated with a good prognostic and a long life-expectancy [39].

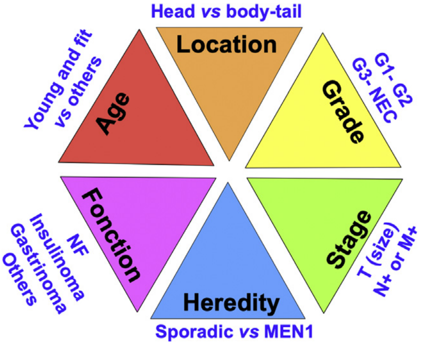


**Fig. 3.** Factors influencing PanNET surgical management.

**Table 3**
Pancreatic insufficiency after standard and parenchyma-preserving pancreatectomies: comparative studies.

| Author | | | | | | Exocrine insufficiency | | | | Endocrine insufficiency | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Year | Nb patients | CP | PD | DP | CP | PD | DP | P | CP | PD | DP | P |
| Crippa [42] | 2007 | 145 | 100 | – | 45 | 5% | – | 15% | 0,039* | 4% | – | 38% | 0,0001* |
| Falconi [32] | 2008 | 162 | 21 | 62 | 64 | 0% | 33% | 18% | 0,001**/0,009* | 3% | 18% | 14% | 0,001**/0,14* |
| Ocuin [9] | 2008 | 31 | 13 | – | 18 | 10% | – | 27% | 0,62** | 11% | – | 57% | 0,04* |
| Hirono [35] | 2009 | 52 | 24 | – | 28 | 0% | – | 0% | NS | 5% | – | 35% | 0,01* |
| Shikano [37] | 2010 | 121 | 26 | 60 | 35 | 4% | 31% | 3% | 0,009**/0,99* | 0% | 14% | 19% | 0,089**/0,032* |
| Cataldegirmen [41] | 2010 | 105 | 35 | 35 | 35 | 9% | 24% | 29% | 0,03**/0,06* | 6% | 28% | 34% | 0,02**/0,05* |
| DiNorcia [43] | 2010 | 100 | 50 | – | 50 | 10% | – | 6% | NS | 14% | – | 28% | NS |

CP=Central pancreatectomy; PD = pancreaticoduodenectomy; DP = distal pancreatectomy *p: CP versus DP **p: CP versus PD.

**Table 4**
Results of prospective randomized controlled comparing laparotomy, laparoscopy *or* robotic approach for pancreatic resection.

| Authors/Year | Procedure | Number of patients included | Design | Primary Outcome | Results |
|---|---|---|---|---|---|
| Thijs de Rooij [60]/2019 | left-sided pancreatic resection | 108 | Multicenter patient-blinded randomized controlled superiority trial | Days to functional recovery | In left-sided pancreatic tumors confined to the pancreas, MIDP reduces time to functional recovery compared with ODP |
| Poves [61]/2018 | pancreaticoduodenectomy | 66 | Prospective, randomized, parallel-group, and open-label clinical trial | Number of nights spent in the hospital postoperatively | Laparoscopic PD is associated with a shorter Length of hospital stay compared to the open approach |
| Palanivelu [62]/2017 | pancreaticoduodenectomy | 64 | Single-centre, non-stratified, balanced allocation (1:1) open-label, parallel-group RCT | Duration of postoperative hospital stay | Laparoscopy offered a shorter hospital stay than open pancreatoduodenectomy |
| Jony van Hilst [63]/2019 | pancreaticoduodenectomy | 99 | multicentre, patient-blinded, parallel-group, randomized controlled phase 2/3 trial | safety of laparoscopic pancreatoduodenectomy (phase 2)<br>time to functional recovery (phase 3) | Although not statistically significant, laparoscopic pancreatoduodenectomy was associated with more complication-related deaths than was open pancreatoduodenectomy, and there was no difference between groups in time to functional recovery. |

Pancreas-sparing pancreatectomies (PSP) reduce the risk of surgically induced pancreatic insufficiency especially compared to pancreaticoduodenectomy (PD) (Table 3 and Fig. 4). Endocrine insufficiency incidence after PSP ranges from 0% for EN up to 16% for CP [26,40]. After CP, exocrine insufficiency incidence ranges from 0 to 12% [37], that is less frequent than observed after standard resection. For example, Cataldegirmen et al. compared pancreatic insufficiency after CP to standard resection and showed an exocrine insufficiency rate of 9% for CP versus 24% for PD [41]; endocrine insufficiency was observed in 6% of CP, 28% of PD and 34% for DP, respectively (see Table 4).

However, overall postoperative morbidity of PSP is significantly higher compared to standard resection. Thus, overall morbidity is 25%–70% after CP [38,44] and 43%–47% after EN [34,45], compared to 30–50% after PD and 25–30% after DP [26]. In series comparing morbidity after PSP and standard resection, this difference was not always reported probably because of the low number of patients included [32,35,43,46,47]. The higher morbidity is mainly represented by pancreatic fistula (PF) [48], despite shorter operative time and lower blood loss [49,50]: PF rates after PSP ranges from 0 to 63% after CP [38,44] and from 27% to 50% after EN [34,45], compared to 25–30% after PD and from 15 to 25% after DP [26].

The higher rate of PF can be explained by the proximity of the main pancreatic duct from the resection margin after EN [48] and by the existence of two pancreatic stumps after CP. As reported by some high-volume centers, the increased risk of PF is not associated with a significant mortality [41,47]. Moreover, mortality after both EN [45,51,52] and CP [9,49,53] is not nil, deaths after PSP is associated with both surgical [49,53] and medical complications [9]. Overall, the better long-term pancreatic function observed after PSP regarding exocrine and endocrine insufficiency is counterbalanced by an increased early morbidity, particularly an increased risk of postoperative PF. This higher rate of early complications and, particularly the increased risk of death after PSP, should lead to a careful assessment of the benefit/risk balance of the procedure: technical aspects patient's and tumor's characteristics should be studies before surgical management [9,54]. Main surgical indications for PanNET is summarized in Fig. 5. Otherwise, lymphadenectomy in NF-PanNETs should be routinely performed when tumors are larger than 2 cm, moderately differentiated G2 or poorly differentiated G3.

### *Determination of the best surgical approach: laparotomy* vs *laparoscopy* vs *robotic approach*

Advantages of laparoscopic over open approach in surgery are nowadays well-known and include decrease in postoperative pain, a decreased blood loss, depression of immune system, a fast recovery, a short hospital stay, and certainly smaller incisions. It is also important to note that all prospective randomized controlled trials comparing laparoscopic surgery vs open approach, such as for colonic or rectal surgery, were non-inferiority trials. Although the first laparoscopic surgery was performed in 1983, the first laparoscopic pancreatoduodenectomy and laparoscopic distal pancreatectomy were described by Gagner in 1994 [55,56]. Nevertheless, adoption of minimally invasive approaches never gained widespread popularity in pancreatic surgery due to intrinsic complexity, retroperitoneal location of the organ, and challenging resections due to its proximity to major vessels. However, robotic

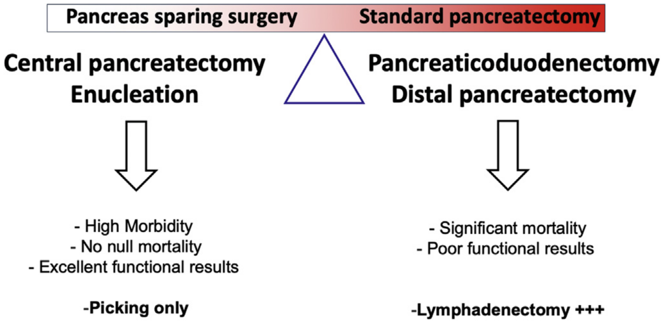


**Fig. 4.** Main characteristic of pancreas sparing surgery vs standard pancreatectomy.

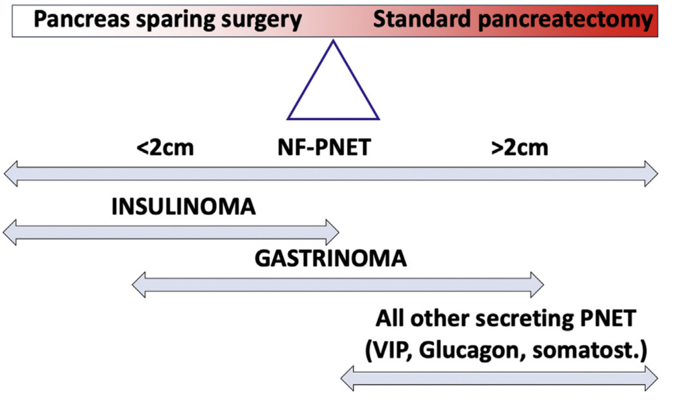


**Fig. 5.** Surgical indication for PanNET.

technology with the advantages of reduction of natural tremors, restoration of hand-eye coordination, high 3D definition vision, and the improvement in ergonomics could overcome laparoscopic limitations for pancreatic surgery, especially when reconstructions are needed, and might help to widespread the technique.

The first described robotic DP was reported in 2003 by Melvin et al. and since then, the number of patients operated robotically is increasing. Numerous retrospective studies, showed that robotic surgery resulted to be safe, feasible and at least equal to laparoscopy in pancreatic surgery. These studies are mostly single center studies with a limited number of patients [57–59]. Increased costs and longer operative time remain major limitations of robotic surgery. It also remains important to underline that open pancreatectomy remains up to now the standard of care, and that there is no general consensus regarding indications for a minimally invasive approach in pancreatic surgery. Nevertheless, few prospective randomized controlled trails, European or North American national/international cohorts [64,65], and conferences consensus are now published. Nevertheless, most of the available literature does not deal specifically with PanNET, but also include other tumours and pancreatic adenocarcinoma.

*Minimally invasive distal pancreatectomy*

For tumors located in the body or the tail of the pancreas, minimally invasive DP is more frequently performed with or without splenic vessel and spleen preservation. Nowadays, in several specialized centers, laparoscopic DP is the treatment of choice for non-invasive pancreatic tumors located in the body or the tail. This approach is technically feasible with a shorter hospital stay, faster recovery and fewer blood loss than in open approach DP. Recent studies also show equivalent results for distal pancreatectomy for pancreatic adenocarcinoma, even if these results from non-randomized studies should be taken with caution [66].

When studies were conducted to compare laparoscopic vs open pancreatic surgery, it showed that laparoscopic approach was associated with lower overall complication rate, shorter hospital stay than open approach. There were no significant differences in PF rates and overall morbidity [47,67]. It is important to note that most of these studies were retrospective comparative studies, except the LEOPARD trial [60]. This study shows that in patients with left-sided pancreatic tumors confined to the pancreas, minimally invasive DP reduces time to functional recovery compared with ODP. Although the overall rate of complications was not reduced, MIDP was associated with less delayed gastric emptying and a better quality of life without increasing costs. Even if most of included patients had PanNET, they only represent 35% of included patients. Additionally, the laparoscopic approach seems equivalent to the open approach regarding the oncologic outcome [68].

Recent studies specifically comparing outcomes between laparoscopic and open distal pancreatectomy for PanNETs tumors found that patients who underwent minimally invasive approach had significantly lower complication rates, less intra-operative blood loss and shorter hospital stay with comparable oncological outcomes than open approach. No statistically differences for PF rate were found between open and minimally invasive approach [69,70].

When splenic vessel preservation is recommended, the procedure becomes more complicated which requires higher technical expertise and is associated with longer operating time [71]. Although splenic preservation is generally encouraged when possible, in aggressive PanNETs or in the presence of hilar inflammation, it's still recommended to perform a DP with splenectomy in order to have a larger and formal lymphadenectomy, or at least resection of splenic vessel in order to have a proper lymphadenectomy [72]. In case of large tumors, with involvement of adjacent organs and/or vascular elements with tumour vein thrombus, the open approach remains the gold standard.

Recent studies also showed higher rates of spleen preservation, lower risk of excessive blood loss, and greater numbers of lymph nodes harvested in robotic surgery compared to laparoscopic for DP [73–76]. Interestingly, a meta-analysis of nine non-randomized observational studies conducted by Peng L *et. al* [77] concluded although that there was no difference in the number of lymph nodes harvested, robotic surgery was superior in terms of negative margin rate than open surgery. In those studies, patients undergoing robotic DP tend to have smaller and rarely malignant lesions due to a selection bias justifying caution in the interpretation of oncologic outcome.

When examining the learning curve of robotic DP, data showed a significant improvement in conversion rate after 20 performed procedures [78]. This procedure should only be performed in specialized centers to avoid dreadful complications.

### *Minimally invasive pancreaticoduodenectomy*

Although the first minimally invasive PD was performed by Gagner et al. in 1994 [55], this approach has never gained widespread popularity even in experienced high volume centers. It remains important to note that this procedure is not yet widely performed due to technical difficulties of the resection and digestive reconstruction [79]. Although many studies showed effectiveness and safety of laparoscopic PD when performed by sufficiently-trained surgeons, a recent prospective randomized controlled study comparing laparoscopic PD versus open PD for pancreatic or periampullary tumours (LEOPARD-2) was prematurely stopped because of an increased morbidity in the laparoscopic PD group. Difference in 90-days complication related mortality (5 [10%] of 50 patients in the laparoscopic pancreatoduodenectomy group *vs* 1 [2%] of 49 in the open pancreatoduodenectomy group).

Recently, many authors revealed technical advantages of robotic PD especially with reconstruction and anastomosis, an experience that could spread minimal invasive PD [80–82]. Zhang J et al. demonstrated that there were no statistical difference in term of PF, morbidity and mortality between robotic PD and the open approach for PD [83].

Patients with PanNETs could be good surgical candidates for minimally invasive PD since these tumors are for most of them not highly aggressive, small and present with low risk of local invasion. On the other hand, they are most of the time associated with soft pancreas and small pancreatic duct, that carries a very high risk of postoperative PF. Overall, regarding PD, the open approach should remain the standard of care, the laparoscopic approach should only be considered in experienced team, within a formal trial. In view of the recent results of Leopard-2, the laparascopic approach should be considered with extreme caution. It is possible than some technical issue, especially for the reconstruction will be solved by the robotic approach.

### *Minimally invasive central pancreatectomy*

PSP including EN and CP, has been investigated as an alternative to standard resection (PD or left/distal pancreatectomy) for pancreatic neuroendocrine neoplasm. In selected patients, with small (<2 cm) and low-grade tumors, PSP are associated with excellent overall and disease-free survival [14,84,85]. CP consists in resection of the neoplastic pancreatic tissue usually in the neck of the pancreas, followed by restoration of pancreatic continuity with pancreatojejunostomy using Roux-en-Y loop or gastrojejunostomy on the left remnant pancreas [86]. CP is based on the fact of achieving radical removal of pancreatic tumors while preserving full exocrine and endocrine pancreatic function, indications of this procedure are limited to benign or low grade malignant tumors of the neck of the pancreas [87]. In fact, PanNETs of the neck of the pancreas smaller than 3–5 cm are perfect indications for CP, and should be associated with lymphadenectomy or at least a lymph node picking for lesions above 2 cm. If CP is associated with an excellent pancreatic function, this is at the expense of a significant morbidity and a nonnihil mortality underestimated by the published literature. CP is best indicated for young and fit patients who can sustain a significant postoperative morbidity and could benefit from the excellent long-term results [88].

Currently, several centers worldwide are studying the feasibility of CP with a minimally invasive approach. Orsenigo et al. showed that laparoscopic CP for the treatment of neuroendocrine tumour of the neck of the pancreas is a feasible and safe procedure despite requiring the expertise of highly skilled laparoscopic surgeons [89]. Regarding the robotic approach, 5 consecutive CP were evaluated and compared to open central pancreatectomy by Kang et al. [90]. Authors did not observe any differences regarding overall complication rate and perioperative mortality, whereas the robotic group had lower blood loss and length of hospital stay. All publication reporting minimally invasive CP are retrospective, unicentric, and reporting very few, highly selected patients, in specialized centers. Consequently, minimally invasive CP for PNET should not be considered as a standard of care.

### *Minimally invasive enucleation*

Pancreatic EN, is indicated for small benign pancreatic tumors that generally doesn't require lymph node evaluation (e.g. small non-functioning neuroendocrine tumors and insulinomas) [91]. Although this procedure is characterized by the absence of exhaustive dissection and reconstruction, preoperative imaging and if possible an intraoperative ultrasound assessment and eventually an intraoperative frozen section examination are required to ensure that the tumor could be resected while leaving the main pancreatic duct intact [92]. In fact, to avoid direct complications, tumors should be at least 2–3 mm far from main pancreatic duct [93,94]. Data comparing pancreatic EN to standard pancreatic surgery for PanNETs didn't show any difference in overall survival or recurrence rates in selected tumours [95]. Controversially, whereas pancreatic EN seems to be less aggressive than standard pancreatic surgery due the fact of maintaining pancreatic endocrine and exocrine function, incidence of PF is superior after EN, especially for deep lesion close to the main pancreatic duct [46,96]. Due to their small sizes when diagnosed (usually smaller than 2 cm), most of insulinomas, generally benign, could be treated with pancreatic EN when the distance between the tumour and the main duct is more than 2–3 mm. In contrast, EN could be only suggested for patients with NF-PanNETs when the tumour is smaller than 2 cm with absence of locoregional and distant metastases [22,97]. In the other hand, some authors suggested a careful observational strategy for these small NF-PanNETs, as they showed in their studies that there were no statistical difference in overall survival between patients who were operated or observed [98]. During laparoscopic procedure, the use of intraoperative echography might be needed to accurately locate the lesion, since intraoperative palpation is not possible, and assess distance between the lesion and the pain pancreatic duct.

The technical feasibility of the minimally invasive technique of pancreatic EN is now clearly shown. Numerous studies showed that this approach is associated with lower intraoperative blood loss, and shorter hospital stay [52,67,96]. Data showed that for small solitary PanNETs, laparoscopic EN is technically feasible with comparable complication rates compared to open surgery [47,99]. Kuroki et al. reported a lower incidence of fistula with laparoscopic EN compared with open approach [100], even if this remain controversial. Recently, in their study comparing robotic and open EN for PanNETs, Tian et al. found comparable results in terms of complication rates with a non-significant decreased severe PF rate in the robotic group [101]. Additionally, Jin JB et al. reported a shorter operative time and less blood loss in the robotic approach while proving that the minimal invasive approach could be useful for tumors located on the right side of the pancreas without increasing the risk of complications [102]. The minimally invasive approach for PanNET EN is feasible and seems to provide equivalent results in terms of long-term outcome and postoperative morbidity, with a decreased postoperative pain and length of stay.

## Conclusion

Complete surgical resection of PNETs is the only potentially curative treatment. After R0 resection, the 5-year overall survival rate is around 90–100% for low grade lesions but significantly drops after incomplete resections. Consequently, the quality of the initial surgery should remain the cornerstone of PanNET management.

PanNET surgical management requires accurate and complete pre- and intraoperative diagnostic, in order to best tailor the surgical strategy to the clinical situation.

Compared to standard resections, pancreatic sparing surgery, i.e. enucleation and central pancreatectomy, clearly decreased the long-term risk of pancreatic insufficiency but not the early morbidity of surgery. For this reason, PSP should be only performed in patients in good general condition and normal preoperative pancreatic function to limit the operative risk and enhance the benefit of surgery.

Nowadays, minimally invasive and robotic surgery for neuroendocrine tumors of the pancreas is a suitable option, in experienced center both in minimally invasive and pancreatic surgery. Nevertheless, the benefit-risk balance of these procedures should be carefully weighted. Distal pancreatectomy and enucleation remain today, the only 2 procedures, that can be safely performed laparoscopically or robotically.

## Conflicts of interest

None of the authors have any financial or any other kind of personal conflicts of interest in relation with this study.

**Practice points**

- Whenever possible, resection remains the cornerstone of PanNETs management and the only curative option
- Preoperative clinical, biological and radiological assessment is key in surgical indication and management of PanNETs.
- Octreoscan somatostatin receptor scintigraphy (SRS) and more recently PET imaging with Gallium-68 somatostatin receptors are highly sensitive for detecting PanNETs
- $^{18}$FDG-PET is interesting for evaluating more aggressive PanNETs, i.e. usually with a Ki-67 > 10%
- Endoscopic ultrasound might help in the diagnostic and accurate localization of PanNET and accurately assess the distance between main pancreatic duct and the tumour
- Pancreas-sparing pancreatectomies (PSP) reduce the risk of surgically induced pancreatic insufficiency.
- Overall postoperative morbidity of PSP is significantly higher compared to standard resection.
- PSP should be only performed in patients in good general condition and normal preoperative pancreatic function to limit the operative risk and enhance the benefit of surgery.
- Minimally invasive and robotic surgery for neuroendocrine tumors of the pancreas is a suitable option, in experienced center.
- Distal pancreatectomy and enucleation remain today, the procedures than can be safely performed in experienced centers. The use of minimally invasive pancreaticoduodenectomy remains controversial.

**Research agenda**

- Surgeons should, as their medical counterparts, propose international prospective, randomised research on PanNETs to better understand their long-term natural history and make available high-quality tumour biobanks for research.
- The WHO 2017 classification of PanNET is currently used and should again be soon updated.
- Most of the available technical literature does not specifically deal with PanNET, but also include other tumors and pancreatic adenocarcinoma, future research should specifically target PanNET management.
- High quality prospective randomized controlled trials comparing laparotomy, laparoscopy and robotic approach for pancreatic resection are needed.

## References


[1] Milan SA, Yeo CJ. Neuroendocrine tumors of the pancreas. Curr Opin Oncol 2012;24:46–55.
[2] Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology 2008; 135:1469–92.
[3] Falconi M, Plockinger U, Kwekkeboom DJ, et al. Well-differentiated pancreatic nonfunctioning tumors/carcinoma. Neuroendocrinology 2006;84:196–211.
[4] Kuo EJ, Salem RR. Population-level analysis of pancreatic neuroendocrine tumors 2 cm or less in size. Ann Surg Oncol 2013;20:2815–21.
*[5] Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol 2017;3:1335–42.
[6] Lawrence B, Gustafsson BI, Chan A, et al. The epidemiology of gastroenteropancreatic neuroendocrine tumors. Endocrinol Metab Clin N Am 2011;40:1–18 [vii].
[7] 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;26:3063–72.
[8] Halfdanarson TR, Rabe KG, Rubin J, et al. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. Ann Oncol 2008;19:1727–33.
[9] Ocuin LM, Sarmiento JM, Staley CA, et al. Comparison of central and extended left pancreatectomy for lesions of the pancreatic neck. Ann Surg Oncol 2008;15:2096–103.
[10] Libutti SK. Evolving paradigm for managing small nonfunctional incidentally discovered pancreatic neuroendocrine tumors. J Clin Endocrinol Metab 2013;98:4670–2.
*[11] Falconi M, Eriksson B, Kaltsas G, et al. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology 2016;103:153–71.
[12] Ehehalt F, Saeger HD, Schmidt CM, et al. Neuroendocrine tumors of the pancreas. Oncologist 2009;14:456–67.
[13] Cheema A, Weber J, Strosberg JR. Incidental detection of pancreatic neuroendocrine tumors: an analysis of incidence and outcomes. Ann Surg Oncol 2012;19:2932–6.
[14] Birnbaum DJ, Gaujoux S, Cherif R, et al. Sporadic nonfunctioning pancreatic neuroendocrine tumors: prognostic significance of incidental diagnosis. Surgery 2014;155:13–21.
[15] Crippa S, Partelli S, Zamboni G, et al. Incidental diagnosis as prognostic factor in different tumor stages of nonfunctioning pancreatic endocrine tumors. Surgery 2014;155:145–53.
[16] Schmid-Tannwald C, Schmid-Tannwald CM, Morelli JN, et al. Comparison of abdominal MRI with diffusion-weighted imaging to 68Ga-DOTATATE PET/CT in detection of neuroendocrine tumors of the pancreas. Eur J Nucl Med Mol Imaging 2013;40:897–907.
[17] Saftoiu A, Dietrich CF, Vilmann P. Contrast-enhanced harmonic endoscopic ultrasound. Endoscopy 2012;44:612–7.
[18] Sundin A, Garske U, Orlefors H. Nuclear imaging of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metabol 2007;21:69–85.
[19] Garin E, Le Jeune F, Devillers A, et al. Predictive value of 18F-FDG PET and somatostatin receptor scintigraphy in patients with metastatic endocrine tumors. J Nucl Med 2009;50:858–64.
[20] Abgral R, Leboulleux S, Deandreis D, et al. Performance of (18)fluorodeoxyglucose-positron emission tomography and somatostatin receptor scintigraphy for high Ki67 (>/=10%) well-differentiated endocrine carcinoma staging. J Clin Endocrinol Metab 2011;96:665–71.
[21] Wong M, Isa SH, Zahiah M, et al. Intraoperative ultrasound with palpation is still superior to intra-arterial calcium stimulation test in localising insulinoma. World J Surg 2007;31:586–92.
[22] Gorman B, Charboneau JW, James EM, et al. Benign pancreatic insulinoma: preoperative and intraoperative sonographic localization. AJR Am J Roentgenol 1986;147:929–34.
[23] Cioc AM, Ellison EC, Proca DM, et al. Frozen section diagnosis of pancreatic lesions. Arch Pathol Lab Med 2002;126: 1169–73.
[24] McPhee JT, Hill JS, Whalen GF, et al. Perioperative mortality for pancreatectomy: a national perspective. Ann Surg 2007;246:246–53.
[25] Hackert T, Hinz U, Fritz S, et al. Enucleation in pancreatic surgery: indications, technique, and outcome compared to standard pancreatic resections. Langenbecks Arch Surg 2011 Dec;396(8):1197–203.
[26] Brown KM, Shoup M, Abodeely A, et al. Central pancreatectomy for benign pancreatic lesions. HPB (Oxford) 2006;8: 142–7.
[27] Zerbi A, Falconi M, Rindi G, et al. Clinicopathological features of pancreatic endocrine tumors: a prospective multicenter study in Italy of 297 sporadic cases. Am J Gastroenterol 2010;105:1421–9.
[28] Farges O, Bendersky N, Truant S, et al. The theory and practice of pancreatic surgery in France. Ann Surg 2017;266: 797–804.
[29] Krautz C, Nimptsch U, Weber GF, et al. Effect of hospital volume on in-hospital morbidity and mortality following pancreatic surgery in Germany. Ann Surg 2018;267:411–7.
[30] King J, Kazanjian K, Matsumoto J, et al. Distal pancreatectomy: incidence of postoperative diabetes. J Gastrointest Surg 2008;12:1548–53.
[31] Andersen HB, Baden H, Brahe NE, et al. Pancreaticoduodenectomy for periampullary adenocarcinoma. J Am Coll Surg 1994;179:545–52.
[32] Falconi M, Mantovani W, Crippa S, et al. Pancreatic insufficiency after different resections for benign tumours. Br J Surg 2008;95:85–91.
[33] Lemaire E, O'Toole D, Sauvanet A, et al. Functional and morphological changes in the pancreatic remnant following pancreaticoduodenectomy with pancreaticogastric anastomosis. Br J Surg 2000;87:434–8.
[34] Crippa S, Bassi C, Salvia R, et al. Enucleation of pancreatic neoplasms. Br J Surg 2007;94:1254–9.

[35] Hirono S, Tani M, Kawai M, et al. A central pancreatectomy for benign or low-grade malignant neoplasms. J Gastrointest Surg 2009;13:1659–65.
[36] Huang H, Dong X, Gao SL, et al. Conservative resection for benign tumors of the proximal pancreas. World J Gastroenterol 2009;15:4044–8.
[37] Shikano T, Nakao A, Kodera Y, et al. Middle pancreatectomy: safety and long-term results. Surgery 2010;147:21–9.
[38] Iacono C, Bortolasi L, Facci E, et al. The Dagradi-Serio-Iacono operation central pancreatectomy. J Gastrointest Surg 2007;11:364–76.
[39] Currie CJ, Peters JR, Tynan A, et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375:481–9.
[40] Goldstein MJ, Toman J, Chabot JA. Pancreaticogastrostomy: a novel application after central pancreatectomy. J Am Coll Surg 2004;198:871–6.
[41] Cataldegirmen G, Schneider CG, Bogoevski D, et al. Extended central pancreatic resection as an alternative for extended left or extended right resection for appropriate pancreatic neoplasms. Surgery 2010;147:331–8.
[42] Crippa S, Bassi C, Warshaw AL, et al. Middle pancreatectomy: indications, short- and long-term operative outcomes. Ann Surg 2007;246:69–76.
[43] DiNorcia J, Ahmed L, Lee MK, et al. Better preservation of endocrine function after central versus distal pancreatectomy for mid-gland lesions. Surgery 2010;148:1247–54. discussion 1254-1246.
[44] Sperti C, Beltrame V, Milanetto AC, et al. Parenchyma-sparing pancreatectomies for benign or border-line tumors of the pancreas. World J Gastrointest Oncol 2010;2:272–81.
[45] Casadei R, Ricci C, Rega D, et al. Pancreatic endocrine tumors less than 4 cm in diameter: resect or enucleate? a single-center experience. Pancreas 2010;39:825–8.
[46] Crippa S, Boninsegna L, Partelli S, et al. Parenchyma-sparing resections for pancreatic neoplasms. J Hepatobiliary Pancreat Sci 2010;17:782–7.
[47] 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;14:1536–46.
[48] Pitt SC, Pitt HA, Baker MS, et al. Small pancreatic and periampullary neuroendocrine tumors: resect or enucleate? J Gastrointest Surg 2009;13:1692–8.
[49] Sauvanet A, Partensky C, Sastre B, et al. Medial pancreatectomy: a multi-institutional retrospective study of 53 patients by the French Pancreas Club. Surgery 2002;132:836–43.
[50] Cherif R, Gaujoux S, Couvelard A, et al. Parenchyma-sparing resections for pancreatic neuroendocrine tumors. J Gastrointest Surg 2012;16:2045–55.
[51] Menegaux F, Schmitt G, Mercadier M, et al. Pancreatic insulinomas. Am J Surg 1993;165:243–8.
[52] Dedieu A, Rault A, Collet D, et al. Laparoscopic enucleation of pancreatic neoplasm. Surg Endosc 2011;25:572–6.
[53] Muller MW, Friess H, Kleeff J, et al. Middle segmental pancreatic resection: an option to treat benign pancreatic body lesions. Ann Surg 2006;244:909–18. discussion 918-920.
[54] Reber HA. Middle pancreatectomy: why I rarely do it. J Gastrointest Surg 2007;11:730–2.
[55] Gagner M, Pomp A. Laparoscopic pylorus-preserving pancreatoduodenectomy. Surg Endosc 1994;8:408–10.
[56] Gagner M, Pomp A, Herrera MF. Early experience with laparoscopic resections of islet cell tumors. Surgery 1996;120: 1051–4.
[57] Boggi U, Napoli N, Costa F, et al. Robotic-Assisted pancreatic resections. World J Surg 2016;40:2497–506.
[58] Milone L, Daskalaki D, Wang X, et al. State of the art of robotic pancreatic surgery. World J Surg 2013;37:2761–70.
[59] Zhang J, Jin J, Chen S, et al. Minimally invasive distal pancreatectomy for PNETs: laparoscopic or robotic approach? Oncotarget 2017;8:33872–83.
*[60] de Rooij T, van Hilst J, van Santvoort H, et al. Minimally invasive versus open distal pancreatectomy (LEOPARD): a multicenter patient-blinded randomized controlled trial. Ann Surg 2019;269:2–9.
[61] Poves I, Burdio F, Morato O, et al. Comparison of perioperative outcomes between laparoscopic and open approach for pancreatoduodenectomy: the PADULAP randomized controlled trial. Ann Surg 2018;268:731–9.
[62] Palanivelu C, Senthilnathan P, Sabnis SC, et al. Randomized clinical trial of laparoscopic versus open pancreatoduodenectomy for periampullary tumours. Br J Surg 2017;104:1443–50.
*[63] van Hilst J, de Rooij T, Bosscha K, et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomized controlled phase 2/3 trial. Lancet Gastroenterol Hepatol 2019;4:199–207.
*[64] Nassour I, Wang SC, Christie A, et al. Minimally invasive versus open pancreaticoduodenectomy: a propensity-matched study from a national cohort of patients. Ann Surg 2018;268:151–7.
*[65] Klompmaker S, van Hilst J, Wellner UF, et al. Outcomes after minimally-invasive versus open pancreatoduodenectomy: a pan-european propensity score matched study. Ann Surg 2018 June 1 [Epub ahead of print].
*[66] van Hilst J, de Rooij T, Klompmaker S, et al. Minimally invasive versus open distal pancreatectomy for ductal adenocarcinoma (diploma): a pan-european propensity score matched study. Ann Surg 2019;269:10–7.
[67] Drymousis P, Raptis DA, Spalding D, et al. Laparoscopic versus open pancreas resection for pancreatic neuroendocrine tumours: a systematic review and meta-analysis. HPB (Oxford) 2014;16:397–406.
[68] Fernandez-Cruz L, Blanco L, Cosa R, et al. Is laparoscopic resection adequate in patients with neuroendocrine pancreatic tumors? World J Surg 2008;32:904–17.
[69] Xourafas D, Tavakkoli A, Clancy TE, et al. Distal pancreatic resection for neuroendocrine tumors: is laparoscopic really better than open? J Gastrointest Surg 2015;19:831–40.
[70] Han SH, Han IW, Heo JS, et al. Laparoscopic versus open distal pancreatectomy for nonfunctioning pancreatic neuroendocrine tumors: a large single-center study. Surg Endosc 2018;32:443–9.
[71] Tagaya N, Kasama K, Suzuki N, et al. Laparoscopic resection of the pancreas and review of the literature. Surg Endosc 2003;17:201–6.
[72] Fernandez-Cruz L, Saenz A, Astudillo E, et al. Outcome of laparoscopic pancreatic surgery: endocrine and non-endocrine tumors. World J Surg 2002;26:1057–65.

[73] Daouadi M, Zureikat AH, Zenati MS, et al. Robot-assisted minimally invasive distal pancreatectomy is superior to the laparoscopic technique. Ann Surg 2013;257:128–32.
[74] 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;25:2004–9.
[75] Lee SY, Allen PJ, Sadot E, et al. Distal pancreatectomy: a single institution's experience in open, laparoscopic, and robotic approaches. J Am Coll Surg 2015;220:18–27.
[76] Goh BK, Chan CY, Soh HL, et al. A comparison between robotic-assisted laparoscopic distal pancreatectomy versus laparoscopic distal pancreatectomy. Int J Med Robot 2017;13.
*[77] Peng L, Lin S, Li Y, et al. Systematic review and meta-analysis of robotic versus open pancreaticoduodenectomy. Surg Endosc 2017;31:3085–97.
[78] Boone BA, Zenati M, Hogg ME, et al. Assessment of quality outcomes for robotic pancreaticoduodenectomy: identification of the learning curve. JAMA Surg 2015;150:416–22.
[79] Jacobs MJ, Kamyab A. Total laparoscopic pancreaticoduodenectomy. J Soc Laparoendosc Surg 2013;17:188–93.
[80] Asbun HJ, Stauffer JA. Laparoscopic vs open pancreaticoduodenectomy: overall outcomes and severity of complications using the Accordion Severity Grading System. J Am Coll Surg 2012;215:810–9.
[81] Kuroki T, Adachi T, Okamoto T, et al. A non-randomized comparative study of laparoscopy-assisted pancreaticoduodenectomy and open pancreaticoduodenectomy. Hepato-Gastroenterology 2012;59:570–3.
[82] Zureikat AH, Moser AJ, Boone BA, et al. 250 robotic pancreatic resections: safety and feasibility. Ann Surg 2013;258: 554–9. discussion 559-562.
[83] Zhang J, Wu WM, You L, et al. Robotic versus open pancreatectomy: a systematic review and meta-analysis. Ann Surg Oncol 2013;20:1774–80.
*[84] Cherif R, Gaujoux S, Couvelard A, et al. Parenchyma-sparing resections for pancreatic neuroendocrine tumors. J Gastrointest Surg 2012 Nov;16(11):2045–55.
[85] Cherif R, Gaujoux S, Sauvanet A. Enucleation of pancreatic lesions through laparotomy. J Vis Surg 2012 Dec;149(6): 295–9.
[86] Christein JD, Smoot RL, Farnell MB. Central pancreatectomy: a technique for the resection of pancreatic neck lesions. Arch Surg 2006;141:293–9.
[87] Iacono C, Bortolasi L, Serio G. Indications and technique of central pancreatectomy-early and late results. Langenbecks Arch Surg 2005;390:266–71.
*[88] Goudard Y, Gaujoux S, Dockmak S, et al. Reappraisal of central pancreatectomy: a 12-year single-center experience. JAMA Surg 2014 Apr;149(4):356–63.
[89] Abood GJ, Can MF, Daouadi M, et al. Robotic-assisted minimally invasive central pancreatectomy: technique and outcomes. J Gastrointest Surg 2013;17:1002–8.
[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;25:1101–6.
[91] Liang S, Hameed U, Jayaraman S. Laparoscopic pancreatectomy: indications and outcomes. World J Gastroenterol 2014;20:14246–54.
[92] Fernandez-Cruz L, Molina V, Vallejos R, et al. Outcome after laparoscopic enucleation for non-functional neuroendocrine pancreatic tumours. HPB (Oxford) 2012;14:171–6.
[93] Ore AS, Barrows CE, Solis-Velasco M, et al. Robotic enucleation of benign pancreatic tumors. J Vis Surg 2017;3:151.
[94] Heeger K, Falconi M, Partelli S, et al. Increased rate of clinically relevant pancreatic fistula after deep enucleation of small pancreatic tumors. Langenbecks Arch Surg 2014;399:315–21.
[95] Zhou Y, Zhao M, Wu L, et al. Short- and long-term outcomes after enucleation of pancreatic tumors: an evidence-based assessment. Pancreatology 2016;16:1092–8.
[96] Jilesen AP, van Eijck CH, Busch OR, et al. Postoperative outcomes of enucleation and standard resections in patients with a pancreatic neuroendocrine tumor. World J Surg 2016;40:715–28.
[97] Partelli S, Bartsch DK, Capdevila J, et al. ENETS consensus guidelines for standard of care in neuroendocrine tumours: surgery for small intestinal and pancreatic neuroendocrine tumours. Neuroendocrinology 2017;105:255–65.
[98] Sadot E, Reidy-Lagunes DL, Tang LH, et al. Observation versus resection for small asymptomatic pancreatic neuroendocrine tumors: a matched case-control study. Ann Surg Oncol 2016;23:1361–70.
[99] Hu M, Zhao G, Luo Y, et al. Laparoscopic versus open treatment for benign pancreatic insulinomas: an analysis of 89 cases. Surg Endosc 2011;25:3831–7.
[100] Kuroki T, Eguchi S. Laparoscopic parenchyma-sparing pancreatectomy. J Hepatobiliary Pancreat Sci 2014;21:323–7.
*[101] Tian F, Hong XF, Wu WM, et al. Propensity score-matched analysis of robotic versus open surgical enucleation for small pancreatic neuroendocrine tumours. Br J Surg 2016;103:1358–64.
[102] Jin JB, Qin K, Li H, et al. Robotic enucleation for benign or borderline tumours of the pancreas: a retrospective analysis and comparison from a high-volume centre in asia. World J Surg 2016;40:3009–20.