Review Article

Surgical resection of pancreatic neuroendocrine neoplasm by minimally invasive surgery—the robotic approach?

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Abstract: Over the past decade, there has been increasing adoption of minimally invasive pancreatic surgery world-wide and this has naturally expanded to the management of pancreatic neuroendocrine neoplasms (PNENs). More recently, robotic pancreatic surgery (RPS) was introduced to overcome the limitations during laparoscopic pancreatic surgery (LPS). Due to the relative rarity of PNEN and the novelty of minimally invasive pancreatic surgery in particular RPS today, the evidence for robotic surgery in PNENs remains extremely limited. Presently, the available evidence is limited to a few low level retrospective case-control studies. These studies suggest that RPS may be associated with a higher splenic preservation rates and lower open conversion rates compared to conventional laparoscopic surgery. Ideally a prospective randomized trial should be performed but this would be extremely challenging due to the rarity of PNEN, making it almost impossible to conduct a sufficiently powered trial.

Keywords: Robotic pancreatectomy; laparoscopic pancreatectomy; pancreatic neuroendocrine neoplasm (PNEN)

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Introduction

Pancreatic neuroendocrine neoplasms (PNENs) are rare entities with an estimated incidence of 4–5 cases per million population in the United States, and constitutes 1–2% of all pancreatic neoplasms (1). A widely heterogenous group of tumours, PNENs may be broadly classified into functioning and non-functioning tumours depending on their clinical presentation. Patients with functioning tumours usually present with a syndrome of over-production of related hormones, while patients with non-functioning tumours usually present with mass effect or symptoms of metastatic disease. Increasingly, more non-functioning PNENs are being detected incidentally due to improvement in imaging techniques.

Although widely recognized to be indolent tumours with long survival outcomes, there may be significant variation in their outcomes due to biological variability. Several studies have been conducted to delineate the prognostic factors influencing long term survival in patients, and factors including tumour size, presence of metastases, lymph node status, positive margins and tumour characteristics have been demonstrated to be prognostic (1,2). At present, surgical resection remains the only potentially curative treatment for PNEN and is the treatment of choice for localized tumours greater than 2 cm. Complete surgical resection is also recommended in the presence of local invasion or metastatic disease if technically feasible (3). It has been well-demonstrated that surgical resection is associated with improved survival rates for PNEN (1,4).

The advent of laparoscopy and advances in surgical techniques has led to an increasing uptake of minimally

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invasive techniques in pancreatic surgery and this has naturally expanded to the management of PNENs (5). It has been reported that in comparison to the open approach, laparoscopic pancreatic surgery (LPS) provides the added benefits of smaller incisions and better cosmetic results, decreased post-operative pain, decreased estimated blood loss, shorter length of hospital stay and recovery time, while maintaining an equivalent morbidity and overall mortality rate (5-12). However, it is important to emphasize that no randomized controlled trial has been performed to date comparing LPS with conventional open surgery, and the evidence supporting the use of LPS is presently limited to retrospective case control studies (5-12).

Despite its potential clinical advantages, the main obstacle to the widespread adoption of LPS is that it is technically demanding with a steep learning curve. This is attributed to the retroperitoneal location of the organ, its proximity to major vasculature and high propensity for complications such as pancreatic fistula. Laparoscopic surgery is associated with several inherent limitations, including loss of haptic feedback, dexterity and natural hand-eye coordination. Attempting to perform surgery on a three-dimensional subject while observing a two-dimensional screen is counter-intuitive and it compromises hand-eye coordination (fulcrum effect). Furthermore, laparoscopic instruments have a limited range of motion, diminished dexterity and may augment physiological tremor.

Robotic surgery was introduced to overcome the limitations of laparoscopic surgery. Since the first robotic distal pancreatectomy (RDP) reported in 2003 (13), several case series have been published proving the feasibility of the technique (14-18). More recently, Calin *et al.* reported on the first case of robotic multi-visceral resection for liver metastases from PNENs with favourable outcomes (19). Presently, the only robotic assisted surgical platform is the Da Vinci system by intuitive surgical, which offers the advantages of three-dimensional view that off-sets the loss of hand-eye coordination in laparoscopic surgery, seven degrees of freedom that replicates human's movement, elimination of physiological tremor and ergonomic comfort.

Today, most of the available evidence for robotic pancreatic surgery (RPS) pertains to RDP. Three meta-analyses have been published in recent years comparing the outcomes of RDP with its laparoscopic counterpart (20-22). These studies demonstrated that RDP is a feasible alternative to laparoscopic distal pancreatectomy (LDP) with regards to short term outcomes in terms of complications rates, mortality rate and oncological outcomes. Some of these studies suggest several advantages of the robotic platform including its superior spleen preservation and splenic vessel ability, lower conversion rates to open surgery, and superior lymph node harvest rates (20-22).

The evidence for robotic pancreatoduodenectomy (RPD) is much more limited, although its adoption has occurred at quicker rate than for laparoscopic pancreatoduodenectomy (LPD). This could be attributed to the improved dexterity and visualisation in robotic surgery that is advantageous to performing complex manoeuvres such as precise suturing required during PD, hence levelling the steep learning curve in LPD. Several studies have demonstrated that RPD is a feasible option, although its superiority to the other approaches remains unproven (23).

Zeh *et al.* reported on a series of 51 RPD, out of which 9 were performed on PNENs (24). The team found that RPD could be performed to achieve comparable outcomes to open PD, but acknowledged some of the limitations of current robotic platforms. These include the size and positioning of the robotic arms which often led to collisions between arms, and surgeons could not utilize gravity to retract abdominal viscera as in laparoscopic surgery. Furthermore, the lack of tactile feedback was not addressed with robotic surgery.

Given the rarity of PNENs and the technical difficulty associated with LPS, there is a lack of robust evidence on the efficacy of MIS in managing PNENs. Although several meta-analyses and systematic reviews have concluded that RPS is a safe and feasible option, most of these studies were not specific in analysing the underlying pathology (20-22). This review aims to summarize the available evidence in describing the feasibility of minimally invasive surgery used in the context of PNENs.

Outcomes of minimally invasive surgery for PNEN

In general, benign PNENs with a low risk of regional lymph node involvement such as insulinomas and small (<2–3 cm) non-functioning PNEN may be treated via parenchyma-sparing or organ sparing surgery such as enucleation, central pancreatectomy or spleen-preserving DP without the need for a formal regional lymphadenectomy (25-27). Larger tumors or those with an increased incidence of malignancy such as gastrinomas have a significant risk of regional lymph node involvement and should undergo formal pancreatic resections such as PD and DP (25-27).

Cienfuegos *et al.* (28) presented a decision-making algorithm in their recent study for deciding the type of

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surgical technique to be undertaken for the laparoscopic management of PNENs. Tumours more than 3 mm from the pancreatic duct and less than 2 cm in size were enucleated, and those that did not fulfil these criteria require formal resection. The group performed 1 enucleation, 8 central pancreatectomies (CP), 1 resection of the uncinate process, and 26 distal pancreatomies, and reported favourable results. Fifty percent of their patients developed complications which were mostly mild (Clavein Dindo I/II), 36.1 developed peri-pancreatic fluid collections that were mostly asymptomatic, and 11% developed new-onset pancreatogenic diabetes mellitus in the long term.

Although several studies have been performed comparing minimally invasive pancreatic surgery with the open approach, most of these studies were not specific to any underlying pathology (5,7,8). Only two meta-analyses have been found to be specific to PNEN (29,30). Data obtained from studies non-specific to PNENs must be interpreted with a caveat, as characteristics inherent to PNENs should be taken into account when determining the surgical approach. For example, 60–70% of gastrinomas are frequently found to be metastasized at presentation, and are hence not suitable for laparoscopic approach. In addition, disease processes that result in fibrotic pancreatic parenchyma (such as pancreatic adenocarcinoma) are less likely to result in post-operative pancreatic fistula (POPF), which is a frequent complication of pancreatic surgeries.

A meta-analysis performed by Drymousis *et al.* reviewed 11 observational studies specific to PNEN (6) and found that in comparison to the open approach, LPS was associated with less complications and shorter length of stay while maintaining comparative outcomes in terms of operative time, pancreatic fistula rate and operative mortality. The oncological outcome of laparoscopic surgery was not evaluated in the meta-analyses.

Tamburrino *et al.* (30) conducted another meta-analysis in 2017, and similarly found that laparoscopic surgery had significantly lower complication rates, less blood loss and shorter length of stay. Interestingly, the study showed that open pancreatic surgery was associated with longer operative time, although this result showed significant heterogeneity. (I^2=53%, P=0.04) The study further found that laparoscopic surgery had lower odds of recurrence, although this did not achieve statistical significance (OR =0.46, I^2=36%, P=0.15).

However, a common limitation to the two meta-analyses is that sub-group analyses according to type of procedure were not performed and selection bias likely accounted for many of the advantages of LPS over open surgery. For example, the perceived superiority of LPS may be because more complex procedures such as pancreatoduodenectomies (PDs) are commonly performed via the open approach. PDs are commonly associated with higher surgical morbidity, and the minimally invasive approach is often limited to a few institutions. Hence despite these results, it is too early to definitively conclude that laparoscopic surgery is superior to the open approach.

Enucleation

Enucleation is frequently performed for small benign PNENs as it avoids loss of parenchyma and more invasive surgery such as DP and Whipple (26). This reduces the rate of long term complications such as exocrine or endocrine insufficiency (31). Enucleation is generally recommended for well-circumscribed lesions smaller than 3 cm, with non-invasive features, located peripherally and away from the main pancreatic duct (26,27). Intra-operative ultrasound is usually utilized to assist in delineating the location of the tumour and its relation to critical surrounding vasculature and the main pancreatic duct before enucleation is carried out.

Enucleation is often associated with higher POPF rates compared to other pancreatic surgeries (32), which could be in part due to the difficulty in suturing the pancreatic parenchyma together after enucleation (27). Haugvik *et al.* (33) found that the overall rate of pancreatic fistula in their study of 72 patients who underwent laparoscopic enucleation was 50%, which was much higher than that for LDP (13.7%). However, it has been demonstrated that the POPF that develops after enucleation are usually less severe than those after traditional resections. Inchauste *et al.* (34) compared the rate of clinically significant POPF in a group of 122 who underwent enucleations and pancreatic resections, and found that the difference was not significant (27.4% *vs.* 20%, P=0.4).

Fernandez-Cruz *et al.* (35) performed a retrospective review of 49 patients with non-functioning neuroendocrine tumours (NF-PNEN) who underwent laparoscopic enucleation and concluded that it was a safe and feasible option for NF-PNEN smaller than 3 cm. It was found that post-operative complications were significantly higher in the laparoscopic enucleation group compared to the LDP group, (42.8% *vs.* 22%, P<0.001) which were mainly POPFs. However, operative time and blood loss was significantly lower in the enucleation group, and all fistulas following enucleation were successfully managed conservatively. In addition, the study found that

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laparoscopic enucleation provided the additional benefits of reduced parietal damage to the abdomen, although further lymph node sampling was required after the procedure to ensure oncological safety as it was hard to differentiate between benign and malignant tumours during the time of laparoscopy.

Several studies have found that laparoscopic enucleation is limited in lesions located in the pancreatic head or neck, due to longer operative times, higher complication rates and estimated blood loss (36,37). Interestingly, Sahakyan *et al.* (38) found that left-sided laparoscopic enucleation had a tendency towards higher rates of complications compared to right-sided laparoscopic enucleation in, although not to clinical significance. Further comparisons found that left-sided laparoscopic enucleation was associated with a higher risk of post-operative morbidity and readmission rates than LDP, while right-sided laparoscopic enucleation was a reasonable alternative to PD. It was recommended that enucleations should be performed for head of pancreas lesions if feasible to avoid major procedures like the PD, although DP may be favoured over enucleation for other lesions.

Dedieu *et al.* (39) reported on their series of 23 laparoscopic enucleations in 2011, and described a conversion rate of 8.7%. The mean duration of surgery in the study was 124 min, with a mortality and morbidity rate of 4% and 17% respectively. The pancreatic fistula rate was 13%, and mean hospital stay was 9 days. The group found that in comparison to previous studies of open enucleations in the literature, their findings showed that laparoscopic enucleation had the additional benefits of shorter operative time, lower morbidity and POPF rate, as well as shorter hospital stays.

A recent study by Tian *et al.* (40) conducted a propensity score-matched analysis comparing robotic and open enucleation of PNENs (n=120, 60 per group). The team described a conversion rate of 5%, and found that although the two groups were comparable in terms of complication rates and POPF; robotic surgery had a tendency towards less severe fistula and complications. In addition, robotic surgery offered technical advantages in terms of three-dimensional visualisation and improved dexterity, which enabled better vascular control and pancreatic mobilisation, translating to improved operative time and estimated blood loss levels (117 *vs.* 150 min, P=0.071; 32.5 *vs.* 80 mL, P=0.008). Another study conducted by Jin *et al.* (41) reported on their experience with 56 cases of enucleation, in which majority of them were for PNENs. Twenty-five patients underwent the open approach and 31 patients underwent a robotic approach. The group similarly found that the robotic group had a shorter operative time and less blood loss. More importantly, the study found that robotic enucleation could be applied on for tumours located on the right side of the pancreas without increasing the incidence of clinical PF or other complications.

Central pancreatectomy

CPs are in general an uncommon procedure, and is even more rarely performed via minimally invasive techniques. As with enucleation, despite the high propensity for pancreatic fistula, CP preserves maximal exocrine and endocrine functions compared to other traditional resections (31). As for PD, two types of anastomosis may be performed with CP—either the pancreaticojejunostomy or pancreaticogastrostomy. Evidence for minimally invasive CPs are limited to case reports and small case series, which are not specific to PNENs. Despite this, it has been shown that CP is a safe and feasible procedure for benign and borderline neoplasms (42). In comparison to the open approach, laparoscopic CPs have been found to be associated with lower estimated blood loss, faster recovery and better quality of life (43,44). Kang *et al.* (45) reported on the largest series of 5 robotic CP in 2011, and compared it to 10 open CP performed at their institution. The study found that in robotic CP, tumours were significantly larger, operative time significantly longer and blood loss significantly less. Due to the rarity of this procedure, no study specific to PNEN has been reported to date.

Distal pancreatectomy with and without splenectomy

DP has been proposed as the ideal resection for minimally invasive techniques as it does not require any anastomosis or other complex reconstruction of the alimentary tract. It may be performed with or without spleen preserving techniques. *En bloc* splenectomy is usually performed together with pancreatectomy as it is technically easier and shortens operating time due to the close relationship between the splenic vessels and the pancreas. However, recent studies have recommended spleen preservation as it reduces the risk of post splenectomy infection and thrombocytosis, haematologic abnormalities, and overall morbidity (28). Presently, most pancreatic surgeons agree that the spleen should be preserved whenever possible for benign and borderline malignant neoplasms.

Two techniques have been described for the spleen preserving procedure—the Warshaw and Kimura technique.

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The Warshaw technique involves resection of the splenic artery and vein, leaving only the short gastric vessels for perfusion of the spleen, while the Kimura technique spares the splenic vessels. Splenic vessel preservation procedures are more technically demanding, as it requires meticulously separating the splenic vessels from the pancreatic parenchyma and ligation of numerous branches of the splenic vessels supplying the pancreas. Hence, operating time tends to be longer. However, the Warshaw technique has reportedly been associated with a higher incidence of splenic infarction and left-sided portal hypertension with gastric varices (46,47).

The main factors that determine the type of procedure performed are location of the tumour within the pancreatic body or tail, the distance from the splenic hilum and relation to splenic vessels. Malignant tumours usually require more radical approaches involving the removal of splenic vessels to allow adequate lymphadenectomy and sufficient oncological clearance. Uncontrolled bleeding from vessels at the upper border of the pancreas may also call for ligation of splenic vessels. Previous inflammation that resulted in splenic hilar fibrosis or malignant tumours adjacent to the splenic hilar may necessitate en-bloc pancreato-splenectomy.

Several studies have shown that LDP is a safe and feasible alternative to the open approach in PNENs, and laparoscopic approach to DP is increasingly considered as the standard procedure for benign and borderline neoplasms. Recent studies comparing laparoscopic and open DP have found that LDP was superior to the open approach in terms of blood loss, time to first oral intake and length of hospital stay, while maintaining similar operative morbidity and safety profile (5,6,11). However, most available evidences today are in the form of retrospective case-control studies or meta-analyses of these highly heterogenous case-control studies which are not specific to any single underlying pathology.

Xourafas *et al.* (48) conducted a study on 171 PNEN patients comparing the outcomes between laparoscopic and open DP, and found that patients who underwent LDP had significantly lower complication rates (70% *vs.* 53%, P=0.028), less intra-operative blood loss and shorter hospital stays (5 *vs.* 7 days, P=0.008). The two groups were also found to have comparable oncological outcomes in terms of negative margins of resection specimen, recurrence rate and 5-year survival outcomes. An analysis of costs found that the total direct costs between the two approaches did not differ significantly. More recently, Han *et al.* (49) performed a similar study on 95 patients with NF-PNENs, and similarly found that overall complication rates (P=0.379) and oncological outcomes did not differ significantly, although LDP patients had a significantly shorter hospital stay compared to ODP patients. The real advantage of LDP over ODP on the rates of POPF remains an open debate, as there is significant inconsistency regarding the definition of POPF and the differences between clinical grading of POPF across different institutions are not always evaluated (48). Nevertheless, LDP has been shown to be a safe and feasible alternative to ODP.

With regards to the robotic platform, an important clinical advantage that it potentially provides is the superior spleen-preservation rate (14,15,17,18,47,50,51). It is hypothesized that the improved dexterity of the robotic system facilitates suturing in tight spaces and more accurate control of the splenic tributaries, allowing for more accurate dissection of splenic vessels from the pancreatic parenchyma. This improves the rate of spleen and splenic vessel preservation in DP, which is beneficial to patients as it avoids complications such as splenic infarction and post-splenectomy infection. Zhang *et al.* (52) compared outcomes in 74 patients with PNENs who underwent minimally invasive DP (n=43 in RDP group; n=31 in LDP group). There was a significantly higher rate of splenic conservation in patients who underwent RDP compared to the LDP group (78.1% *vs.* 48.45%; P=0.006), and the Kimura technique was more frequently utilized in the RDP group (72.1% *vs.* 16.1%; P<0.001).

Other possible advantages of the robotic platform include a lower conversion rate to open surgery compared to laparoscopic surgery, although this has not been validated in the PNEN sub-group of patients. Zhang *et al.* found that both groups (LDP and RDP) of patients in their study did not require open conversion (52), A meta-analysis conducted by Zhou *et al.* including all types of pancreatic pathology found that this difference did not achieve statistical significance, although there was a moderate level of heterogeneity among the studies that limited the generalisability of the results (OR =0.69, P=0.44, I^2=50%) (22). Confounders to the finding may include different stages of learning curve and different surgeons' experience with minimally invasive surgery. Conversion to the open procedure is undesirable, as it increases operating time, intra-operative blood loss and need for blood transfusion, complication rates and length of hospital stay (53,54). Common indications for conversion include elevated body mass index, malignancy, intra-operative bleeding, and

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proximity to vascular structure, difficulty in pancreatic dissection and surgeon's experience (17,53,54). Robotic assistance potentially provides technical advantages such as motion scaling and stabilization as well as reduced operator fatigue, which facilitates haemostasis and control of the vascular structures surrounding the pancreas.

Most concerns with minimally invasive surgery lie with its oncological safety, and commonly include parameters such as mortality and recurrence rates, resection margins as well as lymph node harvest rates. Mortality and recurrence rates require long term follow up in PNENs due to their indolent nature. Interestingly, R1 resection of PNENs have been shown to not be associated with a worse survival compared to R0 rejections (55). Furthermore, controversy remains with regards to the significance of lymph node metastasis as a prognostic factor. Some studies have shown that lymph node metastases is associated with poorer prognosis for PNENs and correlated with pathological grading (56,57), while others have failed to demonstrate an association (1). Nevertheless, regardless of the role of lymphadenectomy in prognosis, adequate lymph nodes retrieval should still be achieved for accurate staging. Zhang *et al.* (52) found that there was no difference in terms of resection margins in their group of patients with PNENs, as both groups achieved negative margins in all patients. The study did not evaluate for lymph nodes harvest rates. Drawing conclusions from other studies not specific to PNENs, most studies have found that RPD has a higher number of harvested lymph nodes compared to LDP (16,51) although Zhou *et al.* (22) demonstrated that there was no statistical difference between the two approaches with regards to the number of lymph nodes harvested (OR =1.94, P=0.22, I^2=91%). Similarly, the meta-analysis (22) found that surgical resections completed via the robotic approach were more likely to have negative surgical margins, although this did not achieve statistical significance (OR =6.55, P=0.10, I^2=0%).

Pancreatoduodenectomy

Tumours located in the pancreatic head require formal resection via PD, and the minimally invasive approach is often limited to a few selected surgeons due to the highly complex manipulations required during resection and anastomoses thereafter (58,59). Garner *et al.* (60) reported on the first experience with LPD in 1994, but the steep learning curve resulted in a much slower adoption rate in comparison to LDP. Only a few centres reported their experience with LPD in small case series, and these included a wide spectrum of diagnosis that was not specific to PNENs only. Most of these studies found that LPD had similar mortality and morbidity rates as compared to the open approach (61). Several other case series also found that LPD had comparable oncological outcomes to open PD, in terms of R0 resection and lymph node retrieval rates (62,63). This was at the expense of higher operating costs and longer operative times. Given the technical complexity of the procedure and the lack of perceived advantages over the open approach, the laparoscopic approach to PD has been tempered thus far.

In comparison to DPs and enucleations, PDs are less frequently performed for PNENs. No reports have been found with regards to the use of RPDs in PNENs specifically, and conclusions regarding its efficacy may only be drawn from evidence in other pathologies. Even then, there remain limited comparative studies advocating for the routine use of RPD over the laparoscopic approach. A recent study conducted based on a national database (23) (RPD =193; LDP =235) found that RPD was superior to LPD in terms of conversion rate, (11.4% *vs.* 26.0%, P<0.001) although demonstrating similar outcomes in terms of complication rate and 30-day mortality rate. There was no significant difference observed between the two approaches in terms of operative time.

There is emerging evidence that RPD may be superior to open PD in terms of oncological efficiency. A meta-analysis conducted in 2017 pooled together results from nine non-randomized observational studies (64), and found that robotic surgery was superior to the open approach in terms of negative margins rate, (OR =0.40, P=0.006, I^2=0%) although there was no significant difference in the number of lymph nodes harvested. (WMD =2.05, P=0.092, I^2=58.1%). Similarly, a multi-institutional study conducted by Zureikat *et al.* (65) found that the robotic approach was comparable to the open approach in terms of resection margins and accurate operative tumour staging. Although the study found that RPD was associated with a higher positive margin rate, multi-variate analysis did not find operative approach to be independently associated with positive margin rate or tumour under-staging (defined as lymph nodes harvest rate of less than 12). However, further studies are required to substantiate this finding in terms of long term survival outcomes, which is of paramount importance in PNENs given that their nature as indolent tumours.

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General limitations of robotic surgery

In general, operative times have often been reported to be longer for robotic surgery than laparoscopic or open surgery. Zhou *et al.* found that RDP requires on average 45.9 minutes more operative time than its laparoscopic counterpart, although there was a high level of heterogeneity included in the studies ($P<0.05$, $I^2=86\%$) (22). On the other hand, Zhang *et al.* demonstrated in their study that there was no difference between the two groups in operative time (139.3 *vs.* 133.3 min, P=0.625). The reportedly longer operative time may be attributed to several factors. A meta-analysis conducted on robotic PD found that operative time for robotic PD was longer than that for open PD, although this did not achieve statistical significance (64) (WMD =114.87, P=0.131, $I^2=97.2\%$). Firstly, an additional 30 minutes was required to dock and undock the robot. Actual time spent on the operating console was much shorter than the reported operative time. Secondly, instrument change in robotic surgery is often more time consuming compared to laparoscopic surgery. Thirdly, operative time is often dependent on surgeon's skill, and surgeons at different stages of the learning curve possess different skills. In general, to date most studies reporting on RPS represent the initial experience of surgeons beginning to embark or RPS.

An analysis of 100 consecutive cases at a high-volume centre estimated that the learning curve of RDP is optimized at around 40 cases (66). Boone *et al.* estimated the learning curve for robotic PD to be at around 80 cases (67). Considering the relative rarity of pancreatic resections to other surgical procedures, this is a long learning curve to overcome especially in smaller volume centres. However, as surgical techniques are standardized with time and surgeons get increasingly familiar with the robotic platform; this learning curve may possibly be overcome in the future.

Undoubtedly, the use of robotic systems increases direct operative costs, due to the use of disposable devices and longer operative times (15,50). The cost-benefit ratio of robotic surgery has not been well studied, although Waters *et al.* suggested that the amortized cost of the robotic system is estimated to add an extra $1,300 per case (14). Such high costs are prohibitive to its widespread adoption as the procedure of choice, despite offering technical advantages. Yet, this may be justified by the reduction in indirect costs. Reduction in length of post-operative hospital stay and lower morbidity in the robotic group may reduce the cost of hospital stay, compensating for the higher operating cost. Interestingly, Waters *et al.* reported that overall costs associated with hospital stay is largely similar between the robotic and laparoscopic approach in their group of patients, and the total cost of RDP was actually lower than both the open and LDP (14). Furthermore, it is important to add that it is inevitable that costs of robotic system will decrease with increasing availability and the emergence of competing products.

Multiple endocrine neoplasia type 1 (MEN-1)

MEN-1 related PNENs are more likely to be multifocal, develop at a young age and have a malignant potential. As such, patients with MEN-1 are typically young patients and frequently require multiple resections. The indications for surgery in MEN-1 include functioning PNENs and non-functioning tumours greater than 2 cm in size. Minimally invasive surgery and parenchyma preserving procedures may have a greater role to play in these patients as they minimize morbidity, and splenic preservation may decrease post-operative sepsis.

POPF is a major morbidity in pancreatic resections, especially MEN-1 patients. Inchauste *et al.* (34) found that 89% (25 out of 29) of their MEN-1 patients developed POPF, which was significantly higher than the rate of POPF in sporadic PNENs (P<0.05). This could be attributed to the abnormal pancreatic parenchyma secondary to the underlying genetic defect (34). Nell *et al.* (68) hypothesized that minimally invasive pancreatic surgery may play a role in reducing the rates of POPF, although Lopez *et al.* (69) found that the rate of POPF in the group who underwent minimally invasive surgery did not differ significantly from that in the open surgery group (67% *vs.* 62%, P=0.74).

Lopez *et al.* (69) conducted a comparative study between minimally invasive and open surgery in 33 patients with MEN-1. Majority of the minimally invasive procedures were conducted laparoscopically (n=8) and 4 were conducted with the assistance of the robotic system, although separate analyses was not performed. The study demonstrated that minimally invasive surgery had a shorter operative time (200 *vs.* 260 min, P=0.036), less intra-operative blood loss (120 *vs.* 280 mL, P<0.001), and shorter hospital stay (11 *vs.* 15.5 days, P=0.034). Morbidity rates did not differ significantly between the two groups.

Nell *et al.* (68) compared robotic surgery with the laparoscopic approach in a group of 21 patients with MEN-1 and PNENs. Two enucleations were performed robotically and 7 laparoscopically, while 5 DPs were performed

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Table 1 Summary of selected studies comparing robotic pancreatic surgery with other approaches for PNENs

Study	Number of patients	Type of procedure	Conversion rate (%)	Operating time (min)	Blood loss (mL)	Length of stay (days)	Complication rates (%)	Spleen preservation rate (%)	R0 resection rate (%)	Lymph node harvest rate (%)	Mortality rate (%)	Pancreatic fistula (%)
Zhang *et al.* 2017 (52)	74 (43 RDP *vs.* 31 LDP)	RDP *vs.* LDP	0 *vs.* 0	139.3 *vs.* 133.3 (P=0.625)	*50 vs. 200 (P<0.001)*	12.8 *vs.* 14.4 (P=0.327)	25.0 *vs.* 41.9 (P=0.138)	*78.1 vs. 48.4 (P=0.006)*	100 *vs.* 100	NR	0 *vs.* 0	25.6 *vs.* 38.7 (P=0.229)
Tian *et al.* 2016 (40)	120 (60 RPE, 60 OPE)	RPE *vs.* OPE	5	*117 vs. 150 (P<0.001)*	*32.5 vs. 80 (P=0.008)*	12.0 *vs.* 13.5 (P=0.071)	3 *vs.* 19 (P=0.272) (grade III/IV complications only)	NA	NR	NA	NR	10 *vs.* 17 (P=0.283)
Nell *et al.* 2016 (68)	21 (2 RPE, 5 LPE, 5 RDP, 9 LDP)	Robotic surgery *vs.* laparoscopic surgery	0 *vs.* 43 (P=0.06)	185 *vs.* 268 (P=0.28)	50 *vs.* 100 (P=0.54)	7 *vs.* 7 (P=0.20)	43 *vs.* 50 (P=1.00) (grade III/IV complications only)	0 *vs.* 36 (P=0.12)	86 *vs.* 43 (P=0.10)	NR	0 *vs.* 0	57 *vs.* 86 (P=0.37)

Data in italic signify statistical significance (P<0.05). RDP, robotic distal pancreatectomy; LDP, laparoscopic distal pancreatectomy.

robotically and 9 laparoscopically. It was found that the robotic approach resulted in less splenectomies than the laparoscopic approach (0% *vs.* 36%, P=0.12). In addition, the robotic approach was superior in terms of conversion rate to open surgery (0% *vs.* 43%, P=0.06), which occurred due to inadequate tumour localisation or bleeding. The group found that the lack of digital palpation in minimally invasive surgery to be the main cause of failed procedures in the study. The multi-focal nature of MEN-1 tumours made it exceptionally difficult for tumour localisation without digital palpation. However, the improved dexterity of the robotic system was found to be beneficial in assisting with haemostatic control which reduced open conversion rates in the robotic group.

Conclusions

The evidence for robotic surgery in PNENs remains limited today. This is due to the relative rarity of the tumour and novelty of the procedure. The evidences available today are currently limited to retrospective studies, which have many inherent limitations. *Table 1* summarizes several of the major comparative studies reporting on robotic surgery for PNEN. Non-randomized studies may result in selection bias, and confounding factors may account for the observed differences between robotic surgery and laparoscopic or open surgery. For example, surgeons may be more likely to choose patients who require spleen preservation for robotic surgery (70), hence accounting for its higher spleen preservation rate. Furthermore, the lower conversion rate observed in robotic surgery may be secondary to the fact that surgeons performing robotic resections are often those with substantial experience in both the open and laparoscopic approach, and hence are more experienced in handling the technical difficulties of the procedure (71,72).

A prospective randomized trial would be extremely challenging to perform due to the rarity of PNEN, making it almost impossible to conduct a sufficiently powered trial. Current evidence suggests that robotic pancreatic resections are a safe and feasible option, and that RDP confer potential advantages in terms of better spleen preservation rates and lower conversion rates. For robotic PD, it remains controversial with regards to its true superiority over the other approaches due to the limited experience with this approach especially for PNEN today. Cost effectiveness of RPS needs to be investigated as well to truly address the practical problems of introducing a RPS programme. As experience with robotic surgery accumulates and problems

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with learning curves and insufficiently powered studies are overcome, the emerging evidence would be better poised to address the question.

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Footnote

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