Editorial

Exploring the feasibility and effectiveness of robotic-assisted pancreaticoduodenectomy with modified Blumgart pancreaticojejunostomy: a look beyond the technology

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Pancreaticoduodenectomy (PD) is universally recognized as the only chance for cure for patients affected by periampullary cancers, as well as for premalignant cystic pancreatic neoplasms, and neuroendocrine tumors of the pancreatic head.

However, despite substantial advances in the surgical and oncologic treatment of these tumors have been reported over the last 50 years, the 5-year survival rate for patients who had R0 resection (≥1 mm free margin) is still only 35% (1).

The low resectability rate of less than 20% is attributable to the fact that nearly 50% of patients present with diffuse metastatic disease at diagnosis and the remaining 30% have borderline resectable or locally unresectable cancers involving the superior mesenteric vein, the portal vein, the superior mesenteric artery, or the celiac axis (2).

From a technical point of view, PD is one of the most complex gastrointestinal surgical operations, as it combines the challenge of an extensive visceral organ dissection in direct contact with major vascular structures, and the complexity related to the restoration of the digestive tract continuity with three anastomoses involving the stomach, the pancreatic stump, and the hepatic duct.

Despite advances in preoperative imaging and surgical technologies, better preoperative patient selection and perioperative care, overall morbidity following PD is reported with an incidence of 30–40% even in high-volume centers (3).

Although the first laparoscopic PD (LPD) was reported in 1994 by Gagner and Pomp, full acceptance for LPD has been probably slowed by several factors attributable either to the inherent technical limitations of laparoscopy and the scarcity of constraining results showing improved outcomes (4). Indeed LPD shows several technical limitations, such as the restricted range of instrument motions inside the abdominal cavity, poor surgeon ergonomics, and long learning curve, making it difficult either the dissection required to achieve oncologic radicality, and the performance of pancreatic and biliary anastomoses, particularly when a small Wirsung duct is encountered (5). For all these reasons, LPD is still considered a challenging operation and is currently performed at few selected centers, outside of which the results from published studies may not be generalizable.

The da Vinci Robotic Surgical System is gaining momentum in pancreatic surgery as its potential role in overcoming limitations of laparoscopy is enticing. The undoubted advantages of robotic surgery are the high ergonomics, high definition 3D visualization of the surgical field, and the increased range of motion allowed by the EndoWrist instruments.

In PD, the advantages of robotic articulated instruments are particularly relevant, as they make it feasible to perform secure biliary and pancreatic anastomoses. It also appears

that the management of the retroportal lamina and dissection of the uncinate process, as well as lymph node dissection of major vasculatures might be improved in robotic pancreaticoduodenectomy (RPD).

However, robotic surgery also shows some disadvantages. For example, it is difficult to change the patient position or adapt the camera port after docking the robot. Furthermore, the time interval to allow instrument changes is longer in RPD than in open pancreaticoduodenectomy (OPD) or LPD, thus reducing the ability for a prompt response to intraoperative difficulties encountered, especially potential occurrence of bleeding during the dissection of the superior mesenteric vein from the uncinate process.

To overcome these limitations, various approaches of hand-assisted, hybrid laparoscopic and robotic PD have been described, each of them showing potential advantages and limitations (6).

Although several non-randomized studies and subsequent meta-analyses comparing RPD and OPD recently demonstrated that the two operative technique could be equivalent in safety outcomes and short-term oncologic efficacy, the definitive answer to the question as to whether robotic assistance can give a contribution to reducing the historically high rate of postoperative morbidity following PD is slow to come (*Table S1*).

Publications on this topic included in most cases heterogeneous types of research, with substantial variation in their design (single cohort or retrospective comparative studies, case series, and case reports), clinical endpoints considered (overall morbidity, mortality, postoperative fistula rate, oncologic radicality, survival rate) and patient selection criteria.

Moreover, possible limitations of the studies published to date exploring the value of robotics in PD are related to their non-randomized design, which carries the risk of selection bias. Indeed, researchers cannot exclude that RPD was preferred for highly selected patients expected to have better chances of successful minimally invasive treatment and favorable outcomes, due to a lower tumor stage, or better preoperative performance status.

Furthermore, the robotic cohorts from most of the studies published to date represented the initial experience of pioneering institutions, which could introduce bias against the outcomes of RPD.

This, together with the lack of results on long-term oncological outcomes, cost-effectiveness, and learning curve analysis do not allow for firm conclusions to be drawn, and ultimately makes it difficult to evaluate whether RPD is superior to either OPD and LPD.

Wang published an interesting article in this context, comparing clinical outcomes of RPD and OPD with modified Blumgart pancreaticojejunostomy (7).

The author analyzed both feasibility and effectiveness of RPD in terms of surgical risks, complications, and oncologic outcomes, giving substantial strengths to a field of research characterized until now by small, retrospective, and non-randomized cohort studies with poor quality.

The primary endpoint of this study was the incidence of clinically relevant postoperative pancreatic fistula (CR-POPF).

The importance of a focused analysis comparing CR-POPF outcomes between RPD and OPD has been recently remarked by McMillan. POPF is the main contributor to the increased incidence of major complications and mortality following PD, and this complication is strongly associated with the duration of hospital stay, rates of readmission, and mortality (8). Since most of the morbidity of PD originates from POPF, any improvement in the postoperative course of this complex operation cannot occur unless a decrease in both incidence and severity of POPF is achieved.

Equivalency in terms of CR-POPF occurrence and mortality between RPD and OPD, as reported by Wang, confirms the aspects of safety of the robotic technique.

The incidence of CR-POPF was 8% in the RPD group and 12.6% in the OPD. This outcome showed no statistical difference between the two groups, either for the overall rate of incidence and after risk stratification basing on the Callery clinical score.

Furthermore, since radical R0 tumor resection and the number of lymph nodes harvested are universally considered as the most powerful independent predictors of long-term cancer-free survival following PD, a rational view of the current role of RPD in the treatment of periampullary cancers implies the achievement of an R0 resection along with removal of an adequate number of lymph nodes, all done with a low postoperative complication rate.

Wang not only reported on the feasibility of RPD, which has already been demonstrated, but his study also showed the oncologic correctness of the robotic approach.

The results by Wang showed that no statistically significant difference in surgical radicality between the two groups was found, including R0 curative resection (96.6% *vs.* 94.3%, P=0.363), R1 microscopic residual cancer (0% *vs.* 2.3%), and R2 gross residual cancer (3.4% *vs.* 3.4%), all aspects that confirmed the reliability of RPD from an

oncologic point of view. Furthermore, superiority in the number of harvested lymph nodes might demonstrate that RPD does improve the surgeon ability to clear as much lympho-neural tissue as required.

These results are in line with those reported by Kornaropoulos, who showed that the mean number of lymph nodes removed was comparable between patients underwent RPD and OPD. Furthermore, Boggi from the Pisa group found that the minimally invasive approach tends to have less positive margins (R1 ratio 12.5% and 45% in the RPD and OPD groups, respectively) (9,10).

Still, regarding safety, it is worth commenting on the low rate of postpancreatectomy hemorrhage in the RPD group reported by Wang (2.3%). Hemorrhage from ruptured visceral pseudoaneurysms is a life-threatening complication occurring in approximately 5% of OPD (11).

Undoubtedly, performing a selective ligation of arterial vessels with the assistance of the robotic system may result easier than in laparoscopy, thus confirming the safety of RPD.

As the therapeutic approach to periampullary cancers is multidisciplinary, one of the most relevant outcomes of minimally invasive PD is the lower rate of patients who have a 90-day delay in receiving adjuvant chemotherapy compared with patients undergoing OPD, as reported by Croome (12).

Although the study by Wang showed no significant difference between the two study groups in terms of length of hospitalization, the low overall complication rate and better outcomes in terms of postoperative pain after minimally invasive surgery might play a role in significantly reducing the length of hospital stay, and promoting the early initiation of the adjuvant chemotherapy after PD.

The same study by Croome showed that the inability to initiate and complete a full cycle of adjuvant chemotherapy will ultimately result in survival differences, with a longer progression-free survival noted in the minimally invasive PD group.

In RPD, reported longer operative times would be a trade-off for less blood loss and more harvested lymph nodes. However, reported longer operative time may be partially due to the docking and set-up time, and can be shortened over time by increasing experience in robotic surgery.

The largest propensity score matched-analyses published to date analyzing the outcomes of the two techniques concluded that RPD was not inferior to OPD in terms of CR-POPF and other major postoperative endpoints, including severe complications, hospital stay, and 90-day mortality. However, this study was limited by the fact that 48 surgeons performed OPD in 16 different surgical centers, whereas RPD cases were all from a single institution, leading to a high risk of bias because of the variations in surgical techniques and postoperative management by many surgeons (8).

The strength of the study by Wang lies in the very fact that a single technique for pancreatic anastomosis was applied either for RPD and OPD by the same surgical team.

This distinct feature, not only provides a more accurate representation of the pancreatic anastomosis as performed locally, limiting potential bias from the use of outside controls often heterogeneous for surgical technique and perioperative management, but also leads to a minimized risk of selection bias, theoretically leaving the type of surgical approach (RPD or OPD) as the only potential variable for the development of surgical complications.

Leslie Blumgart from the Memorial Sloan Kettering has conceived a highly reproducible pancreaticojejunal anastomosis which involves both duct-to-mucosa stitches and three or more full-thickness pancreatic "U" stitches in a mattress suture fashion. This intuitive method of positioning the pancreatic parenchymal stitches has several compelling mechanical advantages over standard techniques as it uses the jejunal mucosa as a pledget to minimize shearing forces of the stitches.

Since the first description, numerous retrospective studies reported a very low incidence of CR-POPF after pancreaticojejunostomy with the Blumgart mattress sutures, ranging between 2.5% and 20.5%. However, the single randomized controlled trial published to date investigating the effectiveness and safety of the modified Blumgart technique compared with the Kakita method did not show any advantage in terms of decreased clinically relevant POPF rate (10.3% *vs.* 6.8%) (13).

Kleespies compared a standard Cattell-Warren pancreaticojejunostomy with a Blumgart anastomosis technique, showing a decreased POPF rate from 13% to 4% (P=0.03) and overall complications from 31% to 15% (P=0.01) in favor of the Blumgart anastomosis (14).

Currently, the PANasta phase III multi-center trial is running, with the aim to compare the effectiveness of the Blumgart pancreaticojejunal anastomosis versus the standard Cattell-Warren anastomosis for patients undergoing an elective PD in terms of rates of POPF, and results are to be expected by 2020 (15).

Undoubtedly, the Da Vinci robotic platform is expensive,

with an initial capital cost of 2–3 million dollars, annual maintenance costs well over 100,000 dollars, and the costs of added disposables which may be as high as 5,000 dollars per case. Giving that, an important question surrounding the use of robotics in surgery is whether or not the benefits will offset the significantly increased costs, and whether the non-inferiority of RPD compared to OPD in terms of morbidity and oncologic outcomes is enough to justify the routine use of RPD in daily surgical practice.

Series from high-volume institutions have reported that patients were offered RPD if they had favorable tumor characteristics, such as the absence of vascular invasion, borderline resectable disease, or neoadjuvant chemotherapy or radiation (16).

When looking at the current literature, vascular resection can offer patients with superior mesenteric vein and/or portal vein involvement the chance for cure, with similar postoperative morbidity and mortality rates compared to patients with traditionally resectable disease. Infiltration of the superior mesenteric-portal vein in a locally advanced but otherwise resectable tumor is no longer considered a contraindication if the vascular resection could result in a curative resection (R0, clear resection margins) (17).

It is worth to mention that vein resection was not considered as an absolute contraindication to RPD in the study by Wang, although no data were reported neither on the number of patients underwent vascular resection in each group nor on the outcomes related to these operations.

Evidence is cumulating that the indications for the robotic approach are expected to expand in the next future, with those cases requiring vein resection and reconstruction not far to be elected as ideal conditions to be treated robotically. Indeed, the magnified visualization together with an increased degree of freedom can enable the surgeon to perform complex vessel reconstruction, thus widening the indications of minimally invasive surgery to locally advanced pancreatic tumors.

In conclusion, the study by Wang demonstrated that RPD is safe and feasible. However, owing to the current absence of level 1 evidence, more data from well-designed multicenter trials are needed to further address the real value of RPD, not only with regard to safety and feasibility profiles, but also in terms of overall oncologic advantages for patients with periampullary cancers.

In the meantime, we would argue that neither approach, open or robotic, is technically superior to the other, and performing a radical PD with a low rate of complications is probably only dependent on the clinical and technical ability of the surgeon, regardless of the technology used.

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Footnote

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Supplementary

Table S1 Overview on published meta-analyses investigating the value of minimally invasive pancreaticoduodenectomy compared with open pancreaticoduodenectomy

1st author	Year	Comparison	No. of patients	Positive margin	Harvested lymph nodes	Operative time	EBL	Overall complications	POPF	CR-POPF	DGE	Reoperation	Wound infection	Length of hospital stay	Mortality
Chen K	2017	MIPD (LPD/RPD) *vs.* OPD	MIPD: 1,064; OPD: 2,338	MIPD superior (RR: 1.06; 95% CI: 1.00, 1.12; P=0.04)	Equivalent (WMD: 1.13; 95% CI: −0.32, 2.59; P=0.13)	OPD superior (WMD: 99.28; 95% CI: 45.96, 152.82; P=0.003)	MIPD superior (WMD: −0.54; 95% CI: −0.88, −0.20; P<0.001)	Equivalent (RR: 0.89; 95% CI: 0.78, 1.02; P=0.10)	Equivalent (RR: 0.91; 95% CI: 0.78, 1.07; P=0.25)	Equivalent (RR: 1.04; 95% CI: 0.86, 1.27; P=0.68)	Not calculated	Equivalent (RR: 1.02; 95% CI: 0.70, 1.49; P=0.92)	Not calculated	MIPD superior (WMD: −3.49; 95% CI: −4.83, −2.15; P<0.00001)	Equivalent (RR: 0.81; 95% CI: 0.51, 1.30; P=0.39)
Pedziwiatr M	2017	MIPD (LPD/RPD) *vs.* OPD	MIPD: 705; OPD: 1,481	Equivalent (RR: 0.92; 95% CI: 0.51, 1.64; P=0.77)	Equivalent (WMD: 1.61; 95% CI: −1.15, 4.38; P=0.25)	OPD superior (WMD: 64.09; 95% CI: 23.97, 104.21; P=0.002)	MIPD superior (WMD: −151.28; 95% CI: −265.40, −115.89; P<0.00001)	Equivalent (RR: 0.84; 95% CI: 0.68, 1.04; P=0.12)	Equivalent (RR: 1.04; 95% CI: 0.77, 1.41; P=0.78)	Not calculated	MIPD superior (RR: 0.77; 95% CI: 0.59, 0.99; P=0.04)	Not calculated	Not calculated	MIPD superior (WMD: −1.88; 95% CI: −3.62, 0.14; P=0.03)	Not calculated
De Rooij T	2016	MIPD (LPD/RPD) *vs.* OPD	MIPD: 710; OPD: 1,123	MIPD superior (OR: 0.70; 95% CI: 0.50, 0.99; P=0.04)	Equivalent (WMD: −0.26; 95% CI: −1.95, 1.43; P=0.75)	OPD superior (WMD: 73.53; 95% CI: 29.03, 118.03; P=0.003)	MIPD superior (WMD: −384.72; 95% CI: −615.7, -153.7; P=0.001)	Not calculated	Not calculated	Equivalent (OR: 0.97; 95% CI: 0.75, 1.25; P=0.80)	MIPD superior (OR: 0.62; 95% CI: 0.46, 0.82; P=0.0009)	Not calculated	Not calculated	MIPD superior (WMD: −3.14; 95% CI: −4.71, −1.56; P<0.0001)	Equivalent (OR: 1.1; 95% CI: 0.57, 1.90; P=0.85)
Peng L	2016	RPD *vs.* OPD	RPD: 245; OPD: 435	RPD superior (OR: 0.40; 95% CI: 0.20, 0.77; P=0.006)	Equivalent (WMD: 2.05; 95% CI: −0.95, 5.05; P=0.18)	Equivalent (WMD: 114.87; 95% CI: −34.19, 263.92; P=0.131)	Not calculated	RPD superior (OR: 0.65; 95% CI: 0.47, 0.91; P=0.01)	Equivalent (OR: 0.27; 95% CI: 0.49, 1.22; P=0.27)	Equivalent (OR: 0.70; 95% CI: 0.37, 1.34; P=0.28)	Equivalent (OR: 0.52; 95% CI: 0.26, 1.04; P=0.06)	Equivalent (OR: 0.58; 95% CI: 0.30, 1.13; P=0.11)	RPD superior (OR: 0.18; 95% CI: 0.06, 0.53; P=0.002)	RPD superior (WMD: −6.00; 95% CI: −9.80, −2.21; P=0.002)	Equivalent (OR: 1.04; 95% CI: 0.44, 2.45; P=0.93)
Shin SH	2016	RPD *vs.* OPD	RPD: 160; OPD: 294	Equivalent (OR: 1.53; 95% CI: 0.82, 2.85; P=0.592)	RPD superior (WMD: −0.61; 95% CI: −3.53, 2.30; P=0.027)	OPD superior (WMD: 98.58; 95% CI: 37.82, 159.34; P<0.001)	RPD superior (WMD: −205.70; 95% CI: −367.58, −43.82; P=0.022)	Equivalent (OR: 0.68; 95% CI: 0.44, 1.05; P=0.417)	Equivalent (OR: 0.75; 95% CI: 0.44, 1.29; P=0.114)	Equivalent (OR: 0.59; 95% CI: 0.29, 1.21; P=0.593)	Equivalent (OR: 0.53; 95% CI: 0.28, 1.02; P=0.863)	Not calculated	Not calculated	RPD superior (WMD: −4.09; 95% CI: −6.88, −1.31; P=0.027)	Not calculated
Shin SH	2016	LPD *vs.* OPD	LPD: 450; OPD: 718	Equivalent (OR: 1.27; 95% CI: 0.88, 1.83; P=0.573)	LPD superior (WMD: −0.26; 95% CI: −1.86, 2.38; P=0.001)	OPD superior (WMD: 116.85; 95% CI: 54.53, 179.17; P=0.000)	LPD Superior (WMD: −240.34; 95% CI: −579.29, 98.60; P=0.000)	Equivalent (OR: 0.83; 95% CI: 0.60, 1.16; P=0.100)	Equivalent (OR: 0.99; 95% CI: 0.69, 1.44; P=0.126)	Equivalent (OR: 1.08; 95% CI: 0.71, 1.63; P=0.852)	Equivalent (OR: 0.69; 95% CI: 0.45, 1.05; P=0.453)	Not calculated	Not calculated	Equivalent (WMD: −3.68; 95% CI: −4.65, −2.71; P=0.332)	Not calculated
Correa-Gallego C	2014	MIPD (LPD/RPD) *vs.* OPD	MIPD: 169; OPD: 373	MIPD superior (OR: 0.4; 95% CI: 0.2, 0.8; P=0.007)	MIPD superior (WMD: −0.32; 95% CI: −6.0, −0.3; P=0.03)	OPD superior (WMD: 131; 95% CI: 43, 218; P=0.003)	MIPD superior (WMD: 1.460; 95% CI: 726, 2.194; P<0.001)	Equivalent (OR: 0.67; 95% CI: 0.39, 1.16; P=0.15)	Equivalent (OR: 1.11; 95% CI: 0.68, 1.83; P=0.67)	Equivalent (OR: 0.97; 95% CI: 0.48, 1.99; P=0.94)	Equivalent (OR: 0.75; 95% CI: 0.35, 1.63; P=0.48)	Equivalent (OR: 0.97; 95% CI: 0.25, 1.18; P=0.94)	Equivalent (OR: 0.49; 95% CI: 0.23, 1.1; P=0.077)	MIPD superior (WMD: −3.7; 95% CI: −6.8, −0.5; P=0.02)	Not calculated
Nigri G	2014	MIPD (LPD/RPD) *vs.* OPD	MIPD: 204; OPD: 419	Not calculated	Equivalent (SMD: 0.383; 95% CI: 0.160, 0.605; P=0.05)	OPD superior (SMD: 1.503; 95% CI: 0.0625, 2169; P<0.0001)	MIPD superior (SMD: −0.935; 95% CI: −1.252, 0.618; P<0.001)	Equivalent (OR: 0.675; 95% CI: 0.473, 0.964; P=0.3480)	Equivalent (OR: 1.042; 95% CI: 0.668, 1.784; P=0.8064)	Not calculated	Equivalent (OR: 0.828; 95% CI: 0.410, 1.671; P=0.6669)	Equivalent (OR: 0.521; 95% CI: 0.241, 1.130; P=0.5286)	Equivalent (OR: 0.494; 95% CI: 0.226, 1.080; P=0.7181)	MIPD superior (SMD: −0.392; 95% CI: −0.758, −0.0258; P=0.0497)	Equivalent (OR: 0.753; 95% CI: 0.318, 1.784; P=0.9933)
Qin H	2014	MIPD (LPD/RPD) *vs.* OPD	MIPD: 327; OPD: 542	Equivalent (OR: 0.57; 95% CI: 0.31, 1.04; P=0.07)	Equivalent (WMD: 1.15; 95% CI: −2.02, 4.32; P=0.48)	OPD superior (WMD: 105; 95% CI: −519.22, −204.63; P<0.001)	MIPD superior (WMD: −361.93; 95% CI: 49.73, 160.26; P<0.001)	Equivalent (OR: 0.73; 95% CI: 0.53, 1.00; P=0.05)	Equivalent (OR: 0.96; 95% CI: 0.65, 1.44; P=0.86)	Not calculated	Equivalent (OR: 0.99; 95% CI: 0.62, 1.56; P=0.96)	Equivalent (OR: 0.63; 95% CI: 0.34, 1.19; P=0.16)	MIPD superior (OR: 0.41; 95% CI: 0.22, 0.78; P=0.007)	MIPD superior (WMD: −2.64; 95% CI: −4.23, −1.05; P=0.001)	Equivalent (OR: 0.82; 95% CI: 0.37 1.85; P=0.16)
Lei P	2014	MIPD (LPD/RPD) *vs.* OPD	MIPD: 209; OPD: 429	MIPD superior (OR: 0.49; 95% CI: 0.26, 0.92; P=0.03)	Equivalent (WMD: 2.29; 95% CI: −0.55, 5.13; P=0.11)	OPD superior (WMD: 101.66; 95% CI: 27.77, 175.55; P=0.007)	MIPD superior (WMD: −406.16; 95% CI: −700.05, −112.28; P=0.007)	Equivalent (OR: 0.88; 95% CI: 0.48, 1.61; P=0.67)	Equivalent (OR: 1.12; 95% CI: 0.73, 1.73; P=0.61)	Not calculated	Equivalent (OR: 0.94; 95% CI: 0.51, 1.71; P=0.59)	Equivalent (OR: 0.56; 95% CI: 0.26, 1.20; P=0.14)	MIPD superior (OR: 0.48; 95% CI: 0.24, 0.96; P=0.04)	MIPD superior (WMD: −4.14; 95% CI: −7.66, −0.63; P=0.02)	Equivalent (OR: 0.89; 95% CI: 0.38, 2.07; P=0.78)
Zhang J	2013	RPD *vs.* OPD	RPD: 137; OPD: 203	RPD superior (RD: −0.12; 95% CI: −0.20, −0.03; P=0.006)	Not calculated	Not calculated	Not calculated	RPD superior (RD: −0.12; 95% CI: −0.22, −0.01; P=0.03)	Equivalent (RR: 0.61; 95% CI: 0.33, 1.14; P=0.12)	Not calculated	Not calculated	Not calculated	Not calculated	Not calculated	Equivalent (RD: 0.02; 95% CI: −0.03, 0.06; P=0.45)

MIPD, minimally invasive pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; LPD, laparoscopic pancreaticoduodenectomy; RPD, robotic pancreaticoduodenectomy; EBL, estimated blood loss; POPF, postoperative pancreatic fistula; CR-POPF, clinically relevant postoperative pancreatic fistula; DGE, delayed gastric emptying.