Review Article

Is robotic pancreatectomy indicated for patients with pancreatic cancer?

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Abstract: Minimally invasive pancreatic surgery (MIPS) is becoming more popular in the recent years. Robotic pancreatic surgery represents an important step, mostly for Whipple procedures, in order to reproduce the same surgical steps performed in open surgery and to facilitate the access to MIPS even by surgeons without a large experience in laparoscopic surgery. The short-term results of pancreatic robotic surgery are comparable with the one obtained by the traditional open surgery, even if the peri-operative costs, still represent a problem. Very few data are currently available regarding the long-term oncologic outcome of robotic pancreatectomy for pancreatic cancer. For this reason, more and larger studies, with a long follow-up are necessary to define the oncologic role and safety of robotic pancreatectomies.

Keywords: Robotic pancreatectomy; pancreatic cancer; minimally invasive pancreatic surgery (MIPS)

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Introduction

The technique for pancreaticoduodenectomy (PD) was first published by Dr. Allen O. Whipple in 1935 (1). Since the procedure had been initially described, up to now, the perioperative morbidity and mortality have improved dramatically by means of better patient selection and preparation, as well as perioperative care (2-5). Furthermore, the surgical technology used in theatre has marked enormous progress. The introduction of minimally invasive surgical techniques (MIST), that encompass laparoscopy and robotics, has been a cornerstone for many surgical subspecialties. Laparoscopy was first performed at Karolinska Institute by Hans-Christian Jacobeaus in 1910. In 1998, Himpens *et al.* (6) were the first to report minimally invasive cholecystectomy using the da Vinci Surgical System (Intuitive Surgical, Inc.). The worldwide abundant application of MIST has started since the 1990s and nowadays minimally invasive surgical approaches have become the standard care for a wide range of abdominal procedures. Current evidence suggests that laparoscopy is superior to open procedure for a variety of applications in terms of blood loss, postoperative pain, surgical site infection, and length of hospital stay, while being equivalent in terms of oncological outcome (7,8).

MIST has been introduced in pancreatic surgery, too, with growing amount of literature confirming benefits over open approaches and so forth growing popularity among surgeons (9-13). The implementation of MIST in pancreatic surgery, though, has occurred much slower than in other types of abdominal surgery. Some of the reasons are the complexity of the surgical procedure (particularly PD), that is technically more challenging to reproduce by MIST, and the high procedure-specific perioperative morbidity, that diminishes the benefit of lesser traumatic access. As for distal pancreatectomy, a multi-institutional case-matched cohort study reported comparable survival for pancreatic cancer with MIST and open surgery, although there were some differences in radicality and lymph-node retrieval (14). Recently, a randomized controlled trial on distal pancreatectomy has opened, which aims to compare time to functional recovery, complications, quality of life, and costs between MIST and open surgery (15,16).

Generally, what hampers the implementation of MIST in pancreatic surgery is the complexity of pancreatic surgery and the necessity to acquire a steep learning curve for the utilization of laparoscopic technique. The known limitations of laparoscopic surgery, such as the restricted operative field and the consequent limitation of movements, two-dimensional view, and the unnatural position of the surgeon during a long procedure are additional hurdles. A separate concern is the risk of brisk onset of high-volume hemorrhage that can occur during the procedure and that needs to be controlled instantly. The use of a robotic system may potentially overcome these issues. Robot-assisted surgery provides three-dimensional vision, a magnified view of the operative field, ability to access the surgical field under broad-angle and change the field if necessary, reduced operator fatigue, stabilization of movements, and an enhanced maneuverability of the tips of the instruments by wrist-like joints. The flexibility of motion allows for much more precise surgical technique that has the potential advantage to access difficult areas at difficult angles, to avoid kinking of the needles and damage of a fragile pancreas, and thus possibly creating safer anastomoses compared to laparoscopic approach. The robotic surgical approach simulates much closer an open approach, and does not require change of the anastomotic technique to adapt to the approach, which is a potential flaw with laparoscopy.

The aim of this article is to review the literature on robotic pancreatic surgery and discuss the impact of the robotic technique on outcome for pancreatic cancer.

Methods

A search in the PubMed database was performed with the following combinations of keywords: ["robotic surgery" or "robotic pancreatectomy"] and ["pancreatic cancer"], from 1990 to 2017. Relevant hits were selected and screened for comparative studies of open, laparoscopic, or robotic pancreatic procedures for patients with diagnosis of pancreatic cancer. Series of less than 10 procedures performed with robotic pancreatic surgery were excluded from the analysis. The results on outcome of robotic surgery for pancreatoduodenectomy and distal pancreatectomy were analyzed.

Results

Perioperative outcome

PD

Robotic pancreaticoduodenectomy (RPD) performed for pancreatic cancer was reported by 12 institutions (17-28). The characteristics of the included studies are depicted in *Tables 1* and *2*. All studies but one was retrospective case series. Nine of the studies compared the outcomes of robot-assisted to open and/or laparoscopic pancreatic surgery in a non-randomized fashion (17,20-25,27,28), two studies (20,22) were case-matched series. Three studies reported on more than 100 RPD (17-19). The proportion of RPDs performed for malignant disease ranged from 46.8% to 91.7%, and for pancreatic ductal adenocarcinoma (PDAC) in particular—between 19.8% and 68.2%. In the largest multi-institutional comparison study of 1,028 PDs by Zureikat *et al.*, patients undergoing RPD as compared to open pancreaticoduodenectomy (OPD) had larger tumor size and number of lymph nodes retrieved, but required longer operative time, had higher percent of positive surgical margins, and fewer had PDAC on final histology (17).

In all 7 studies comparing RPD to OPD (17,20-23,25,27), the operative time was significantly longer in the robotic group and 3 of the studies (20,22,27) showed the postoperative hospital length of stay (LOS) was significantly shorter in the robotic group. In the 2 studies comparing RPD to laparoscopic pancreaticoduodenectomy (LPD), one showed the operative time and LOS to be significantly shorter in the robotic group (24,28).

None of the studies could demonstrate any difference in postoperative complications or mortality after RPD compared to OPD or LPD.

In 2017, Ricci *et al.* (29) published a meta-analysis comparing robotic, laparoscopic and open PDs. The study analyzed 20 studies in total. The RPD seemed to show advantage in terms of number of harvested lymph nodes, lesser overall postoperative morbidity and delayed gastric emptying, and length of hospital stay. On the contrary, the LPD was often the worst approach, especially for overall and major complications, postoperative bleeding and biliary leak.

Two publications focused on the cost estimate after RPD. Baker *et al.* reported that although the operative cost of the robotic procedure was greater ($50,535 *vs.* $32,309, P<0.001), the overall hospital costs were no different than for the open procedure ($142,149 *vs.* $150,473, ns) (25). On

Table 1 Perioperative results for RPD

Author	Year	Comparison	Number of patients	Mean operative time (min)	Conversion to open rate (%)	Morbidity (%)	Mortality (%)	Mean LOS (day)
Zureikat AH *et al.* (17)	2016	RPD	211	402*	4.7	23.7	1.9	8
		OPD	817	300*	–	23.9†	2.8	8
Boone BA *et al.* (18)	2015	–	200	417†	3.3†	23.3†‡	3.3†	9†
Kauffmann EF *et al.* (19)	2016	–	116	522	3.0	17.2‡	1.7	18
Chen S *et al.* (20)	2015	RPD	60	410*	–	11.7	1.7	20*
		OPD	120	323*	–	13.3‡	2.5	25*
Buchs NC *et al.* (21)	2011	RPD	44	444*	4.5	36.4	4.5	13
		OPD	39	559*	–	48.7	2.6	14.6
Chalikonda S *et al.* (22)	2012	RPD	30	476*	10	30	4	9.8*
		OPD	30	367*	–	43	0	13.3*
Bao PQ *et al.* (23)	2014	RPD	28	431*	14.3	–	7	7.4
		OPD	28	410*	–	–	7	8.1
Liu R *et al.* (24)	2017	RPD	26	387*	0	29.6	3.7	17*
		LPD	25	442*	4	44.0	0	24*
Baker EH *et al.* (25)	2016	RPD	22	454*	13.6	13.6	0	7
		OPD	49	364*	–	20.4‡	4.1	9
Rashid OM *et al.* (26)	2015	–	21	621	9.5	28.5	0	8
Lai EC *et al.* (27)	2012	RPD	20	492*	5	50	0	13.7*
		OPD	67	265*	–	49.3	3	25.8*
Piedimonte S *et al.* (28)	2015	RPD	12	597	0	25	0	7.5
		LPD	14	593	0	25‡	7.1	8

*, P<0.05; †, results for the last 120 patients; ‡, complication rate according to Clavien-Dindo classification ≥3. RPD, robotic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; LPD, laparoscopic pancreaticoduodenectomy; LOS, length of stay.

the other hand, Shi Chen *et al.* reported the overall hospital costs are greater in robotic procedure ($19,755±$10,067 *vs.* $12,111±$6456; P<0.001) (20). The cost estimated should be interpreted with care since the price per robotic procedure is an integrate of the overall utility of the robotic equipment and the background economic environment.

Distal pancreatectomy (DP)

The results after robotic distal pancreatectomy (RDP) performed for pancreatic cancer have been reported by 7 institutions (30-36). The characteristics of the included studies are depicted in *Tables 3* and *4*. All studies directly compared the outcomes of robot-assisted surgery with those of open and/or laparoscopic pancreatic surgery in a non-randomized fashion. Five series were retrospective case series. One study included more than 50 RDP (30). The proportion of RDP performed for PDAC ranged from 11% to 56%. In the study by Daouadi *et al.* 43% of RDPs were performed for PDAC compared to 15% in LDP group. With regard to cancer-specific outcomes, they reported a statistically significant 36% increase in R0 resection rate in the robotic group, with an average of 19 lymph nodes harvested in the compared to 9 lymph nodes in the laparoscopic group (32).

Two series (31,35) reported the operative time to be significantly longer in the robotic compared to the laparoscopic group, while two studies (30,32) showed the opposite—the operative time to be shorter in RDP. All

Table 2 Pathological results of resected specimens after RPD

Author	Year	Comparison	Number of patients	Malignancy rate (%)	PDAC (%)	Tumor size	Lymph nodes harvested (N, mean)	R1 (%)
Zureikat AH *et al.* (17)	2016	RPD	211	–	33.2*	29*	27.5*	50*
		OPD	817	–	55.3*	25*	19*	31*
Boone BA *et al.* (18)	2015	–	200	83	41.0	27	26†	8.6†
Kauffmann EF *et al.* (19)	2016	–	116	58.6	19.8	–	44.6	26.1
Chen S *et al.* (20)	2015	RPD	60	63.3	31.7	29	13.6	2.2
		OPD	120	63.3‡	31.7‡	30	12.5	4.3
Buchs NC *et al.* (21)	2011	RPD	44	75	50	–	16.8*	19.1
		OPD	39	69.2	30.8	–	11*	18.5
Chalikonda S *et al.* (22)	2012	RPD	30	46	46	30	13.2	0*
		OPD	30	46‡	46‡	29	11.7	13*
Bao PQ *et al.* (23)	2014	RPD	28	67.9*	35.7	–	15	38
		OPD	28	92.9*	46.4	–	19.5	12
Liu R *et al.* (24)	2017	RPD	26	84.6	25.9	22.4	8	0
		LPD	25	92	20	19	6	0
Baker EH *et al.* (25)	2016	RPD	22	81.8	68.2	27	–	22.2
		OPD	49	81.6	61.2	31	–	36.8
Rashid OM *et al.* (26)	2015	–	21	71.5	52.4	23	16	0
Lai EC *et al.* (27)	2012	RPD	20	75	35	21	10	26.7
		OPD	67	79.1	35.8	29	10	35.9
Piedimonte S *et al.* (28)	2015	RPD	12	91.7	50	28.5	22.5	8.3
		LPD	14	85.7	62.5	34	22	18.8

*$P<0.05$; †, the results about the latest 120 patients; ‡, the matched factor for comparison. RPD, robotic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; LPD, laparoscopic pancreaticoduodenectomy; PDAC, pancreatic ductal adenocarcinoma.

Table 3 Perioperative results for robotic distal pancreatectomy

Author	Year	Comparison	Number of patients	Mean operation time	Conversion to open rate (%)	Morbidity (%)	Mortality (%)	Mean LOS (day)
Chen S *et al.* (30)	2015	RDP	69	150*	0	8.7	0	11.6
		LDP	50	200*	6	10.0†	0	14.7
Lee SY *et al.* (31)	2015	RDP	37	213*	38	43	0	5
		LDP	131	193*	31	22	0	5
		ODP	637	185*	–	25†	0.6	7
Daouadi M *et al.* (32)	2013	RDP	30	293*	0	20	0	6.1
		LDP	94	372*	16	14†	1.1	7.1
Butturini G *et al.* (33)	2015	RDP	22	265	4.5	–	–	7
		LDP	21	195	4.7	–	–	7
Ryan CE *et al.* (34)	2015	RDP	18	225	11.1	16.7	5.6	5
		LDP (SILS)	16	190	18.8	18.8	0	4
Lai EC *et al.* (35)	2015	RDP	17	221*	–	47.1	0	11.4
		LDP	18	174*	–	38.9	0	14.2
Duran H *et al.* (36)	2014	RDP	16	315	12.5	0*	0	8.9*
		LDP	18	250	27	44*	0	19.2*
		ODP	13	367	–	7.6*	7.6	20.4*

*, $P<0.05$; †, complication rate of Clavien-Dindo classification ≥3. RPD, robotic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; LPD, laparoscopic pancreaticoduodenectomy; LOS, length of (hospital) stay; SILS, single incision laparoscopic surgery.

studies except for one found the postoperative length of hospital stay to be the same as in the laparoscopic group.

Regarding postoperative morbidity and mortality, almost none of the studies could observe any difference among the RDP, LDP and the open surgery group. Only one trial, including relatively few patients, showed superiority of RDP to open or laparoscopic approach in terms of postoperative morbidity (37).

Two studies conveyed data on the costs for performing RDP. Kang *et al.* (37) reported much higher mean cost of \$8,305±\$870 for RDP and \$3,862±\$1,724 for LDP (P<0.01). Waters *et al.* (38) compared the costs for open, laparoscopic, and robotic DP, and found out that the increased cost of the robotic procedure was offset by the shorter LOS, so at the end there was no significant difference between total hospital costs among the three groups (\$10,588 for the robot-assisted surgery *vs.* \$12,900 for laparoscopic surgery *vs.* \$15,521 for open surgery, P=0.26).

In 2017, Guerrini *et al.* (39) published a meta-analysis comparing robotic and laparoscopic distal pancreatectomies, analyzing ten studies in total. RDP group had a significantly higher rate of spleen preservation, lower rate of conversion to open, a shorter hospital stay, but a higher cost than the laparoscopic DP group. There was no significant difference between the two groups in terms of the other surgical outcomes. The results suggested that RDP procedure seems to be safe and comparable when compared to laparoscopic DP.

Long-term oncologic outcomes

The true oncologic outcome of robotic pancreatic surgery is currently difficult to assess for a few reasons. First, there are only few reports in literature and few patients per series who have been followed long enough to be able to report on survival data. Furthermore, there is a selection bias for the patients undergoing robotic pancreatic surgery—usually fewer cases with oncologic diagnoses and particularly with PDAC.

Giulianotti *et al.* who published one of the largest series on robotic pancreatectomies (despite heterogeneous population) reported on the long-term survival of 10

Table 4 Pathological results of resected specimens after robotic distal pancreatectomy

Author	Year	Comparison	Number of patients	PDAC (%)	Tumor size	Lymph nodes harvested (N, mean)	R1 (%)
Chen S *et al.* (30)	2015	RDP	69	23.2	9.1	–	–
		LDP	50	22.0†	8.9	–	–
Lee SY *et al.* (31)	2015	RDP	37	11*	–	12*	0
		LDP	131	15*	–	10.4*	0
		ODP	637	39*	–	15.4*	12
Daouadi M *et al.* (32)	2013	RDP	30	43*	31	19*	0*
		LDP	94	15*	34	9*	36*
Butturini G *et al.* (33)	2015	RDP	22	13.6	25.5	11.5	–
		LDP	21	9.5	35	15	–
Ryan CE *et al.* (34)	2015	RDP	18	22.2	35	10	–
		LDP (SILS)	16	25	35	6	–
Lai EC *et al.* (35)	2015	RDP	17	17.6	–	–	–
		LDP	18	11.1	–	–	–
Duran H *et al.* (36)	2014	RDP	16	56	27.8	12.5	0
		LDP	18	44	41.3	5	0
		ODP	13	46	53.3	13.2	0

*, P<0.05; †, Malignant disease rate. RPD, robotic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; LPD, laparoscopic pancreaticoduodenectomy; SILS, single incision laparoscopic surgery.

patients who had robotic procedures for pancreatic cancer—median overall survival (OS) of 15 months (7–29 months) (40). Zhan *et al.* reported on the survival outcomes on 72 patients with pancreatic cancer followed for 1–45 months (mean, 15.6±5.8 months), and out of them 19 received adjuvant chemotherapy (41). The disease-free survival (DFS) was 3–18 months (median, 9.6 months) and the median OS—19.6 months. Only a few studies about the long follow-up time make it difficult to assess the oncological outcomes of robot-assisted pancreatic surgery.

Vascular resections

The reports on vascular resections for pancreatic cancer using robotic technology come from very small series reported by four institutions. Giulianotti *et al.* described five cases of robotic extended pancreatectomy with vascular resection for locally advanced pancreatic cancer—two extended distal pancreatectomies with celiac axis resection (DP-CAR) and three pancreatectomies with portal vein resection, all intended as curative (42). The mean time of portal vein clamping was 22 minutes, with no further complications with regard to the vascular procedure reported. Ocuin *et al.* reported the results of 11 robotic DP-CARs compared to 19 open procedures (43). Robotic DP-CAR was associated with decreased operation time, reduced estimated blood loss, and lower rates of blood transfusion while having similar preoperative/tumor characteristics in the two groups. There were no differences in terms of postoperative/oncological outcomes between the groups. Although these series are small, the results demonstrate the safety and feasibility of the robotic approach even in challenging cases.

Palliative robotic procedures for pancreatic cancer

Robotic surgery may even be beneficial in the case of locally advanced pancreatic cancer where palliative and/or digestive bypass are indicated to alleviate symptoms. Besides the reduced postoperative pain and LOS, one of the most important advantages of MIST is the enhanced recovery which provides the chance of timely initiation of palliative chemotherapy (44,45). Laparoscopic hepaticojejunostomy has been reported, but the reports are still limited as advanced skills are necessary for laparoscopic suturing. Robotic surgery overcomes these limitations, adding on precise movements to manipulate and suture tissue within a limited space. Yet, the reports on its feasibility are scarce (44,45).

Conclusions

Minimally invasive robot-assisted surgical approach has growing popularity particularly in surgical areas where the access by laparoscopy or open technique is difficult, such as the pelvis. Robotic properties like instrument flexibility, stabilized three-dimensional view, and the possibility to work at a much larger surgical field and thus improving the precision and care to deal with the tissues, resembles much more an open approach than laparoscopy and that has drawn the attention of the pancreatic surgeons, too.

The results on robotic pancreatic resections, though, still come from few studies and few centers that in most cases have a low-volume of pancreatic surgery (46). Due to the considerable patient heterogeneity in the studies and focus usually on the feasibility of the procedure, with relatively short follow-up, it is difficult to draw firm conclusions related to the oncologic safety of the robotic pancreatectomies. On the short run, it seems that perioperative morbidity, procedure-related mortality and at least short-term oncologic outcomes (resection margins, lymph node yield) with robotic technique is equivalent to open surgery, which is an important message. Compared to open or laparoscopic approaches, the operating time using the robotic approach has so far been reported to be longer, while the hospital stay—shorter. Enhanced patient recovery might increase the chances for induction of adjuvant chemotherapy. However, considering the specific problems related to pancreatic surgery and mostly to Whipple procedures (i.e., pancreatic-anastomoses-related complications), it seems extremely difficult to understand how IPS can reduce the hospital stay in a significant way. Regarding cost-effectiveness, the results are contradicting, but in case of appropriate management the overall hospital costs with the robotic procedure do not need to exceed the costs with the open approach. Thus, in specialized centers with relevant surgical expertise, robotic pancreatic surgery might be safe and feasible and a relevant alternative to open approach. However, it seems quite difficult to understand why a vascular resection should be done robotically, increasing significantly the cross-clamping time, compared to open procedures (47). Further data is still needed to evaluate the long-term oncological outcomes of robotic pancreatic surgery. The precision of the robotic procedure and the possibility for dexterous reconstruction and dissection around the big vessels, could be an effective way to make minimally invasive pancreatic surgery (MIPS) more accessible even by the surgeons without a strong background in laparoscopy (48). Even if the scientific community needs to be open to innovation and changes, MIPS should be used if advantages can be proven for the patients and not as a marketing instrument (49). Today it is clear that robotic pancreatectomy can be performed safely, however, the real oncologic value should be demonstrated by larger studies with a long follow-up. It is expected that pancreas cancer will be the 2nd cause of cancer related death in the year 2030 (50). More than new surgical techniques, the scientific community should be focused on more efficient multimodal treatment and new drugs that, together with surgical resection, can guarantee a better long-term outcome.

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