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TOPIC HIGHLIGHT

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Laparoscopic resection of pancreatic adenocarcinoma: Dream or reality?

Blaire Anderson, Shahzeer Karmali

Blaire Anderson, Shahzeer Karmali, Department of Surgery, University of Alberta, Edmonton, Alberta T6G 2B7, Canada
Shahzeer Karmali, Center for the Advancement of Minimally Invasive Surgery, Royal Alexandra Hospital, Edmonton, Alberta T5H 3V9, Canada
Author contributions: Anderson B reviewed the literature and wrote the paper; Karmali S supervised the review.
Correspondence to: Shahzeer Karmali, BSc, MD, MPH, Assistant Professor, Surgical Director, Weight Wise Bariatric Surgery, Minimally Invasive Gastrointestinal and Bariatric Surgery, Center for the Advancement of Minimally Invasive Surgery, Royal Alexandra Hospital, Room 405 Community Services Center, 10240 Kingsway, Edmonton, Alberta T5H 3V9, Canada. shahzeer@ualberta.ca
Telephone: +1-780-7356650 Fax: +1-780-7356652
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Abstract

Laparoscopic pancreatic surgery is in its infancy despite initial procedures reported two decades ago. Both laparoscopic distal pancreatectomy (LDP) and laparoscopic pancreaticoduodenectomy (LPD) can be performed competently; however when minimally invasive surgical (MIS) approaches are implemented the indication is often benign or low-grade malignant pathologies. Nonetheless, LDP and LPD afford improved perioperative outcomes, similar to those observed when MIS is utilized for other purposes. This includes decreased blood loss, shorter length of hospital stay, reduced post-operative pain, and expedited time to functional recovery. What then is its role for resection of pancreatic adenocarcinoma? The biology of this aggressive cancer and the inherent challenge of pancreatic surgery have slowed MIS progress in this field. In general, the overall quality of evidence is low with a lack of randomized control trials, a preponderance of uncontrolled series, short follow-up intervals, and small sample sizes in the studies available. Available evidence compiles heterogeneous pathologic diagnoses and is limited by case-by-case follow-up, which makes extrapolation of results difficult. Nonetheless, short-term surrogate markers of oncologic success, such as margin status and lymph node harvest, are comparable to open procedures. Unfortunately disease recurrence and long-term survival data are lacking. In this review we explore the evidence available regarding laparoscopic resection of pancreatic adenocarcinoma, a promising approach for future widespread application.

Key words: Laparoscopic surgery; Pancreatic cancer; Laparoscopic distal pancreatectomy; Laparoscopic pancreaticoduodenectomy; Adenocarcinoma

Core tip: Laparoscopic pancreatic surgery is in its infancy despite initial procedures reported two decades ago. Both laparoscopic distal pancreatectomy and laparoscopic pancreaticoduodenectomy can be performed competently with improved perioperative outcomes, similar to those observed when minimally invasive surgical (MIS) is utilized for other purposes. However, when MIS approaches are implemented the indication is often benign or low-grade malignant pathologies. In this review we explore the evidence available regarding laparoscopic resection of pancreatic adenocarcinoma, a promising approach for future widespread application.

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INTRODUCTION

In 2013 an estimated 45220 new cases of pancreatic

cancer will be diagnosed in the United States resulting in approximately 28460 deaths[1]. Pancreatic adenocarcinoma is one of the most aggressive malignant tumors. Overall, prognosis is dismal with recent 5-year survival estimates merely 6%[1]. Oncologic surgical resection is the only potentially curative treatment[2,3]. Unfortunately only 15%-20% of patients have resectable disease at presentation[4]. This is secondary to rapid local spread, invasion of critical surrounding structures, and early distant metastases. Surgical options are as follows; pancreatic body and tail tumors can be resected by subtotal or distal pancreatectomy (DP), while pancreatic head tumors are amendable to pancreaticoduodenectomy (PD).

LAPAROSCOPIC PANCREATIC SURGERY

Laparoscopic pancreatic surgery has been slow to evolve, primarily reserved for staging and palliation[5-9] despite the performance of initial minimally invasive surgical (MIS) pancreatic procedures two decades ago[10-12]. This delay can likely be attributed to multiple factors, including the retroperitoneal location of the pancreas, anatomic complexity of surrounding structures, friable nature of the gland, and propensity for post-operative complications. To date laparoscopic procedures currently executed include: (1) diagnostic laparoscopy with or without biopsy; (2) palliative interventions including gastro- and hepaticojejunostomy; (3) DP with or without splenectomy; (4) PD; (5) tumor enucleation; and (6) central pancreatectomy. Feasibility is well established[13-16]; however by no means are MIS techniques mainstream and when utilized reserved for benign and low-grade malignant tumors.

LAPAROSCOPIC SURGERY FOR PANCREATIC ADENOCARCINOMA

The results of the Clinical Outcomes of Surgical Therapy trial have promoted the implementation of MIS techniques in the treatment of colon cancer with equivalent recurrence and overall survival rates[17]. As well, further studies have demonstrated oncologic outcomes in MIS resection of other abdominal malignancies to be equivalent to open techniques[18-22]. MIS approaches offer the added benefits of decreased blood loss, shorter length of hospital stay, reduced post-operative pain, and expedited time to functional recovery. These improved perioperative outcomes are of paramount importance in regards to pancreatic adenocarcinoma, where improved recovery can mean earlier instigation of adjuvant treatment. Skepticism persists surrounding oncologically sound surgical resection, crucial in any malignancy. Additionally, due to tumor biology and aggressiveness of disease process pancreatic resections for adenocarcinoma are not commonly performed making it difficult to overcome the associated learning curve. Long-term survival data is scarce leaving evidence reliant on short-term surrogate markers including margin status and lymph node retrieval. In general, lack of quality data has hindered MIS progress for pancreatic malignancies.

LAPAROSCOPIC DISTAL PANCREATECTOMY

Laparoscopic approaches to DP improve visualization of the retroperitoneal pancreas and minimize incisional trauma. This procedure is amendable to MIS techniques, as it requires limited dissection and no anastamoses. However, pancreatic stump management and the prevention of fistulae prove trying. Variations exist in the utilizations of hand-access approaches, which provide the benefit of improved tactile feedback, and splenic preservation, which has been reported to reduce postoperative and overall infectious complications[23]. Overall, cosmesis, reduced blood loss, shorter length of hospital stay, less post-operative pain, and expedited time to functional recovery results from laparoscopic distal pancreatectomy (LDP)[14,24-33]. Additionally, in a Canadian study, Fox *et al*[34] demonstrated equal surgical costs, decreased length of stay, and decreased overall costs ($10842 *vs* $13656 for LDP and ODP respectively). Long-term oncologic outcomes have yet to be reported; however R0 resection and lymph node harvest are comparable to open resections (Table 1)[35-47].

Pancreatic fistulae

In several large case control series morbidity has proven to be comparable to open approaches (Tables 1 and 2). The potentially devastating nature of complications associated with pancreatic fistula has led to great debate regarding the optimal management of the pancreatic stump[48]. Techniques currently utilized include staple closure with or without staple line reinforcement, electrocautery, ultrasound coagulation, radiofrequency, omental patch, fibrin glue, enteric anastamosis, octreotide administration, or a combination[49-55]. There has yet to be a consensus on the best method for stump management, even in the literature for open procedures[55]. Kooby *et al*[45] reported fistula rates to be similar between LDP and ODP (26% *vs* 32%, $P = 0.28$). In this study linear stapler was utilized for pancreatic transaction. Topical sealants and perioperative octreotide were added at the discretion of the treating surgeon. With MIS approaches providing comparable results in terms of pancreatic fistula rates, this should not deter laparoscopic advancement.

Splenic preservation

MIS approaches lead to greater splenic preservation[26,45,56]; however, in the case of malignancy, proximity of tumor to splenic vasculature often makes preservation difficult while achieving oncologic resection. The Warshaw technique, in which splenic vessels are resected *en bloc*, leaves the spleen to survive on the short gastric and left gastroepiploic vessels; providing an alternative more oncologically appropriate approach[57]. Complications associated with this method include gastric variceal hemorrhage and splenic infarction. Ferrone *et al*[58] in a retrospective

Table 1 Published comparisons of laparoscopic distal pancreatectomy and open distal pancreatectomy with at least five cases of adenocarcinoma

Study	Cases		Malignant pathology		Mean node harvest		R0 margins		Mean blood loss (mL)		Mean length of stay (d)		Pancreatic fistula rate		Mortality		Overall morbidity	
	LDP	ODP	LDP	ODP	LDP	ODP	LDP	ODP	LDP	ODP	LDP	ODP	LDP	ODP	LDP	ODP	LDP	ODP
Rehman *et al*[35]	8	14	100%	100%	16[1]	14[1]	88%	86%	306	650	8	12	25%	21%	0%	0%	NR	NR
Mehta *et al*[36]	30	30	23%	23	8	14	NR	NR	294	726	9	13	17%	13%	0%	3%	50%	43%
Limongelli *et al*[37]	16	29	36%	45%	NR	NR	94%	93%	160	365	6	9	18%	20%	0%	3%	25%	41%
Abu Hilal *et al*[38]	35	16	19%	11%	NR	NR	75%	67%	200	394	7	11	29%	44%	0%	6%	40%	69%
DiNorcia *et al*[39]	71	168	13%	39%	6	8	97%	87%	150	900	5	6	11%	14%	0%	1%	28%	44%
Vijan *et al*[40]	100	100	23%	23%	NR	NR	0%	0	171	519	6	9	17%	17%	3%	1%	34%	29%
Kooby *et al*[41]	23	189	100%	100%	14	12	73%	74%	422	790	7	11	NR	NR	0%	1%	NR	NR
Jayaraman *et al*[42]	107	236	17%	47%	6	7	97%	96%	175	300	5	6	15%	13%	0%	1%	26%	33%
Baker *et al*[43]	27	85	29%	30%	5	9	NR	NR	219	612	4	8	22%	14%	0%	2%	37%	35%
Finan *et al*[44]	44	98	25%	42%	NR	NR	0%	0%	157	719	6	9	50%	46%	0%	5%	NR	NR
Kooby *et al*[45]	142	200	36%	49%	NR	NR	92%	93%	357	588	6	9	11%	18%	0%	1%	40%	57%
Eom *et al*[46]	31	62	10%	7%	NR	NR	NR	NR	NR	NR	12	14	10%	7%	0%	0%	36%	24%
Velanovich[47]	15	15	20%	32%	NR	NR	NR	NR	NR	NR	5	8	13%	13%	0%	0%	20%	27%

[1]Median. NR: Not reported; LDP: Laparoscopic distal pancreatectomy; ODP: Open distal pancreatectomy.

Table 2 Definitions of post-operative pancreatic fistulae

Study	Definition of post-operative pancreatic fistula
Rehman *et al*[35]	ISGPF definition
Mehta *et al*[36]	ISGPF (grade B and C)
Limongelli *et al*[37]	ISGPF definition
Abu Hilal *et al*[38]	ISGPF definition
DiNorcia *et al*[39]	ISGPF definition
Vijan *et al*[40]	ISGPF definition
Kooby *et al*[41]	NR
Jayaraman *et al*[42]	ISGPF definition
Baker *et al*[43]	ISGPF definition
Finan *et al*[44]	ISGPF definition
Kooby *et al*[45]	ISGPF definition
Eom *et al*[46]	Drainage > 30 mL with amylase > 600 U/dL
Velanovich[47]	Amylase-rich fluid after POD 3

ISGPF: International Study Group on Pancreatic Fistula; NR: Not reported; POD: Post-operative day.

review of 721 patients who underwent open distal pancreatectomy, 158 of who had a Warshaw spleen preserving distal pancreatectomy, reported evidence of perigastric varices in 25% of patients on follow-up computed tomography scan. Perhaps a paraphysiologic finding, as no clinically relevant adverse events were observed at up to 21 years follow-up. Re-operation, splenectomy, for splenic infarction was required in only 3 cases. From this, it was postulated that splenic preservation using the Warshaw technique should be considered in patients undergoing distal pancreatectomy for nonmalignant pathologies. Only 6% of this study population had pancreatic adenocarcinoma leaving reservations in the extrapolation of results to this subgroup. Similar findings have been published in laparoscopic series[25,59-63]. Jean-Philippe Adam *et al*[64] reviewed a cohort of 154 patients who underwent LDP with splenic preservation. Again, the indication for operation was benign or low-grade malignant tumors. Overall morbidity, pancreatic fistula, and reoperation were similar regardless of technique. Splenic preservation was less successful with the Warshaw technique compared with splenic vessel preservation, 84.7% *vs* 96.4% respectively ($P = 0.03$). Nine patients in the Warshaw group presented to hospital with symptomatic post-operative splenic infarction, necessitating splenectomy in four. Greater splenic preservation without compromised oncologic resection is favorable and achievable with laparoscopic approaches.

Oncologic outcomes

Potential for cure in this disease process is approached with R0 resection, therefore margin status is of paramount importance[65]. Another short-term surrogate measure of oncologic outcome is lymph node harvest. Venkat's[24] recent systematic review and meta-analysis reported no significant difference between R0 resection in LDP, 95.5%, and ODP, 91.2% ($P = 0.27$). Meta-analysis was not completed for lymph node harvest due to inadequately reported data. A retrospective cohort study by Jayaraman *et al*[42] compared 343 patients. The laparoscopic group had fewer cancer cases (17% *vs* 47%, $P < 0.0001$); however oncologic outcomes including R0 negative margins (97% *vs* 96%, $P = 0.76$) and lymph node harvest (6 *vs* 7, $P = 0.53$) were equivalent. Subsequently, Kooby *et al*[41] in a multicenter analysis of LDP (11%) *vs* ODP (89%) for adenocarcinoma, which included 212 patients, published similar results for R0 resection (27% *vs* 26% positive margins, $P = 0.98$) and lymph node harvest (12.5 ± 8.5 *vs* 13.8 ± 8.4 nodes, $P = 0.47$). DiNorcia *et al*[39] retrospective cohort study of 360 patients reported lymph node yield (6 LDP *vs* 8 ODP, $P = 0.29$); however more successful R0 resection in the LDP group with 2.8% positive margins compared to 13% in the ODP group ($P = 0.01$). Song *et al*[62] presented results of a 359 patients case series, 6.7% with adenocarcinoma. They achieved a 91% R0 resection and mean lymph node harvest of 10.3 ± 8.6 with overall survival rates of 85.2% at up to 2 years follow-up. Contrarily, Baker *et al*[43] in a retrospective cohort study of 112 patients reported a "less robust lymphadenectomy" with 5 compared to

Table 3 Published series on laparoscopic and robotic pancreaticoduodenectomy with at least five cases of adenocarcinoma (variables reported for entire series, not just malignant cases)

Study	Cases	Malignant pathology	Mean node harvest (range)	R0 margin	Mean blood loss (mL)	Mean length of stay (d)	Pancreatic fistula rate	Mortality	Overall morbidity	Mean operative time (min)
[2]Bao *et al*[77]	28	4 AC 10 PDAC	15 (8-32)[1]	63%	100[1]	7[1]	21%	7%	NR	431[1]
Kim *et al*[78]	100	4 AMP 7 PDAC	13 (7-34)	100%	NR	14	6%	1%	25%	487
Asbun *et al*[76]	53	8 AMP 22 PDAC	23 (SD 10)	95%	195	8	17%	6%	22%	608
[2]Chalikonda *et al*[79]	30	14 adeno-carcinoma	13 (1-37)	100%	486	10	7%	3%	30%	476
[2]Lai *et al*[80]	20	5 AC 7 PC	10 (SD 60)	73%	247	14	35%	0%	50%	492
[2]Zeh *et al*[81]	50	9 AMP 14 PDAC	17 (5-37)	89%	350[1]	10	20%	2%	30%[3]	568[1]
Suzuki *et al*[72]	6	4 AMP 1 PDAC	18 (16-27)	100%	471[1]	23[1]	33%	0%	33%	581[1]
Ammori *et al*[15]	7	2 AMP 5 PDAC	20.8 (11-32)	NR	350	11	14%	0%	29%	628
[2]Giulianotti *et al*[82]	60	15 AMP 27 PDAC	18 (5-45)	92%	394	22	31%	14%	31%	421
Kendrick *et al*[83]	62	8 AMP 31 PDAC	15 (6-31)	89%	240	7	18%	2%	42%	368[1]
Cho *et al*[66]	15	1 AMP 4 PDAC	19 (NR)	100%	445	16	13%	0%	27%	338
Palanivelu *et al*[84]	75	29 AMP 33 PDAC	14 (8-22)	97%	74	8	7%	1%	27%	357
Pugliese *et al*[67]	19	4 AMP 6 PDAC	12 (4-22)	100%	180	18	23%	0%	37%	461
Dulucq *et al*[75]	25	4 AMP 11 PDAC	18 (NR)	100%	107	16	5%	5%	32%	287
Staudacher *et al*[69]	7	1 PDAC	26 (16-47)	100%	325	12	0%	0%	0%	416
Gagner *et al*[85]	10	3 AMP 4 PDAC	7 (3-14)	100%	NR	22	17%	0%	50%	510

[1]Median; [2]Robotic hybrid; [3]Clavien Ⅲ/Ⅳ. AC: Ampullary cancer; PDAC: Pancreatic ductal adenocarcinoma; AMP: Ampullary adenocarcinoma/ampullary dysplastic adenoma; NR: Not reported; PC: Pancreatic cancer.

9 nodes harvested with the open approach (P = 0.04). Again, in this cohort study adenocarcinoma was more commonly found on final pathology in the open group (21% *vs* 4%). Perhaps this difference partially explains the observed results. Unfortunately, margin status was not reported.

LAPAROSCOPIC PANCREATICODUODENECTOMY

Approaching PD laparoscopically is more complex owing to the intricacy of dissection and reconstruction as well as the necessity of multiple critical anastomoses. None-the-less feasibility has been demonstrated[66-70]. The use of a mini-laparotomy and hand-port for creation of the anastomoses is helpful[67,71-75]. MIS approaches are promising, with lower rates of delayed gastric emptying and wound infection when compared to historic open PD controls[16]. Asbun and Stauffer[76] unmatched comparative trial of patients undergoing laparoscopic pancreaticoduodenectomy (LPD) (n = 53) and OPD (n = 215) demonstrated advantages for LPD in terms of blood loss (103 mL *vs* 195 mL, P < 0.001), transfusion requirement (4.7 units *vs* 0.6 units, P < 0.001), length of intensive care unit stay (3 d *vs* 1 d, P < 0.001), and total hospital stay (12 d *vs* 8 d, P < 0.001). Again, long-term oncologic outcomes have yet to be reported[76]; however R0 resection and lymph node harvest seem sufficient (Table 3)[15,67,69,72,75-85]. It is clear that higher levels of evidence including controlled trials are needed to elucidate clear conclusions.

Resource allocation

In the absence of definitive clinical improvements, feasibility with no poorer results may not justify LPD in light of prolonged operative times, with initial case reports taking upwards of 750 min to completion[10,86]. The learning curve can be overcome in high volume centers, with average operative times decreased to less than 400 min, similar to open PDs (Table 3). Kendrick and Cusati[83], in one of the largest single series available, describe their initial duration of LPD to be 7.7 h, which improved to 5.3 h after approximately 50 cases. Time is money. Mesleh *et al*[87] in an American cost-analysis study comparing open and LPD at a single institution proclaimed that LDP was associated with equivalent overall costs compared with open PD. In their study, operating time and supply costs were higher for LPD; however post-operative admission was more

cost-effective. Neither operative time nor cost should be detrimental to further application of novel MIS approaches in pancreatic surgery.

Oncologic outcomes

PD is mainly utilized for malignant rather than benign disease therefore oncologic safety must be demonstrated prior to widespread application. Gumbs *et al*[16] published a large review that incorporated 27 published papers for a total of 285 cases, of which 32% were adenocarcinoma. Cumulatively, the mean number of lymph nodes harvested ranged from 7 to 36 with a weighted average of 15 nodes. Of the reported margins (174) only 0.4% were positive. Perioperative morbidity and mortality rates were similar compared to open PDs. The study of Kendrick and Cusati[83], described earlier, which included 65 patients who underwent total LPD, 48% for pancreatic adenocarcinoma and 12% for ampullary adenocarcinoma, published outcomes comparable to the open approach. Their study demonstrated an 89% R0 resection with an average of 15 lymph nodes harvested (range 6-31). Recently, 2-year survival rates of 43% and 36% were reported for LDP and OPD respectively[88]. Dulucq *et al*[75] performed a prospective case series of 25 patients, 44% with pancreatic adenocarcinoma and 12% with ampullary adenocarcinoma. They demonstrated a 100% R0 resection with an average lymph node retrieval of 18 ± 5. Gumbs and Gayete[89] found similar results in their experience with the posterior approach, laparoscopic duodenopancreatectomy, retrieving an average of 16 lymph nodes. Unfortunately, resection margins were not reported. Results are encouraging.

A WORD ON ROBOTICS

Robotic-assisted procedures are of interest in pancreatic resection as theoretically they add increased maneuverability, provide precise tissue manipulation, and improve visualization in three dimensions. Disadvantages include loss of tactile feedback, equipment setup and maintenance issues, increased operative times, and associated learning curve. Several studies have presented promising results for robotically assisted DP, with operative morbidity and mortality comparable to other techniques[90-95]. Similarly, supportive evidence exists for combined laparoscopic-robotic and purely robotic PD procedures[95-102]. Additionally, cost does not appear to be as much of a factor as was initially perceived. An American study by Waters *et al*[91] confirmed cost effectiveness for robotic DP. The total cost of robotic DP was $10588, compared to $16059 and $12986 for ODP and LDP respectively. Boggi *et al*[97] reported costs of robotic PD to be an additional 6193 Euros compared to OPD. Yet in its infancy, enthusiasm should not be dampened for robotic pancreatic surgery, as preliminary results are praiseworthy.

CONCLUSION

Current evidence suggests that laparoscopic pancreatic surgery is feasible and provides benefits over open surgery including decreased blood loss, shorter length of stay, reduced post-operative pain, and expedited time to functional recovery. However, the implementation of MIS approaches to pancreatic adenocarcinoma is limited compared to open approaches. The technical complexity and lack of resectable cases necessary to overcome steep learning curves partly explains the limited utilization by surgeons. Concerns regarding oncologic outcomes may also be implicated. Data on long-term outcomes of tumor recurrence and patient survival are not well defined and ultimately, the success of oncologic operations depends on cancer related long-term survival. Currently laparoscopic pancreatic surgery remains a reasonable surgical option for benign disease and low-grade malignant tumors when performed by expert surgeons in high volume specialty centers. In the future, perhaps after oncologic safety has been well demonstrated, MIS techniques can be recommended for pancreatic adenocarcinoma, as early results are promising.

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