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EVIDENCE-BASED CURRENT SURGICAL PRACTICE

Development of Minimally Invasive Pancreatic Surgery: an Evidence-Based Systematic Review of Laparoscopic Versus Robotic Approaches

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Abstract

Introduction Laparoscopic and robotic surgery of the pancreas has only recently emerged as viable treatment options for benign and malignant disease. This review seeks to evaluate the current body of evidence on these approaches to pancreaticoduodenectomy and distal pancreatectomy.

Methods A systematic review of large published series was performed utilizing the PubMed search engine.

Results Based on these reports, both the laparoscopic and robotic techniques for these complex procedures appear to be safe and effective, if performed by high volume experienced pancreatic surgeons. The advantages of each approach are highlighted, emphasizing the data available on the learning curve and potential dissemination.

Conclusions Both minimally invasive approaches to pancreatic resection are safe and feasible.

Introduction

The advent of minimally invasive abdominal surgery is generally credited to Kurt Semm, a German gynecologic surgeon who performed the first laparoscopic appendectomy in 1980.[1] Stimulated by the theories proposed by Semm, Erich Muhe performed the first laparoscopic cholecystectomy in 1985 using endoscopic instruments including a clip applier and shears to ligate the cystic duct.[2] By the late 1980s, Phillipe Mouret and Francois Dubois had introduced techniques for laparoscopic cholecystectomy and helped this movement cross the Atlantic where J. Barry McKernan and William B. Saye performed the first of these procedures in the USA.[3] The worldwide movement had gained momentum and laparoscopic cholecystectomy would soon become the gold standard.

The first report of laparoscopic pancreatic surgery originated in Canada in 1994 when Gagner and Pomp described a pylorus-preserving pancreaticoduodenectomy (PD) for chronic pancreatitis (Whipple procedure).[4] This technique was also applied to periampullary tumors but was met with resistance due to concerns about high morbidity and oncologic efficacy. Alfred Cuschieri, another European pioneer, described the first laparoscopic distal pancreatectomy (DP) that same year.[5] Like his Canadian colleagues, Cuschieri was also pessimistic about the potential applications of these new platforms.

Robotic surgery spawned from the laparoscopic movement with the added benefits of three-dimensional high-definition viewing and movement with 7 degrees of freedom akin to the human wrist. Melvin and colleagues reported the first robotic pancreatectomy in 2003, performing a DP with splenectomy for a pancreatic neuroendocrine tumor.[6] Giulianotti subsequently described the first robot-assisted PD in which the

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hepaticojejunostomy and gastrojejunostomy were hand sewn utilizing the robot.[7] While significant laparoscopic portions were included in these earlier robotic series, further refinement of the techniques has led to the development of a totally robotic approach to both of these procedures.

While the theoretical benefits of a minimally invasive approach to pancreatic surgery are clear, there is no consensus among the surgical community regarding the applications of these techniques. This report is an up-to-date systematic review of laparoscopic and robotic pancreatectomy focusing on the safety, oncologic efficacy, and learning curve of both approaches Additionally we provide experience and personal insight into the evolution of robotic surgery and the lessons learned from applying this approach to the majority of pancreatic resections at the University of Pittsburgh.

Methods

The review was conducted using the framework provided by the PRISMA statement for reporting systematic reviews.[8] The predetermined benchmark for study inclusion was a sample size of 50 or more patients who underwent laparoscopic or robotic PD or DP. For series comparing laparoscopic and robotic approaches this threshold was lowered to a sample size of 40 patients. This criteria intended to select out high-volume centers with relatively mature experiences. A search was conducted utilizing the U.S. National Library of Medicine's search engine PubMed (ncbi.nlm.nih.gov/PubMed/). Key foundational search terms included "pancreaticoduodenectomy", "distal pancreatectomy", and "left pancreatectomy". These were combined with "laparoscopic", "robotic", "robot-assisted," and "minimally invasive" to generate the query. The query generated a total of 1309 related articles. Screening of the article abstracts pared the content down to 37 original articles. Prior systematic reviews or meta-analyses were reviewed but not statistically evaluated. The data points collected included operative time, rate of conversion to open surgery, estimated blood loss, hospital length of stay, morbidity, and mortality. Summary statistics were tabulated and decimal points were rounded to the nearest integer.

Results

Pancreaticoduodenectomy

Laparoscopic

Five series met the criteria for inclusion (Table 1).[9–13] The authors of these manuscripts each had other smaller series published, but only the largest experience from each institution was considered. While subtle differences were identified in the placement of ports and the order in which the procedure was performed, the techniques were fundamentally similar. This included predominant use of intracorporeal suturing for each of the three anastomoses. The series by Gumbs, et al. was included as the procedures were performed laparoscopically, albeit with the aid of a robotic camera holder.[11] Mean operative time and conversion rates were widely variable between studies while morbidity and mortality rates were fairly consistent. Kendrick and Palanivelu both identified acceptable oncologic outcomes in their series, dispelling one of the common myths regarding minimally invasive PD.[12,13] A recent comparative study of laparoscopic PD with the open technique was performed using the National Cancer Data Base (NCDB).[14] This also demonstrated equivalent oncologic outcomes despite a significant increase in 30-day mortality. Notably, the increased mortality was *only* identified in centers performing <10 laparoscopic PDs annually.

Robotic

There is significant heterogeneity among the published robotic PD series since the technique and proportion of the case performed robotically is often variable. Two series met our inclusion criteria based on sample size (Table 2).[15,16] Giulianotti published his single surgeon experience spanning a practice that included cases in both Italy and the USA.[15] The data presented require careful review as the initial length of stay data appears concerning with a mean length of stay of 22 days. However, significant variation in healthcare delivery between the two countries can explain many of the disproportionate outcomes. Our group published the largest experience to date with 200 consecutive robotic PDs.[16] While operating room time was 8 h for the entire cohort, progress along the learning curve during this time-frame led to a significant decrease to 6.5 h for the last 40 cases in the series. All other pertinent postoperative outcomes were similar to historic OPD controls, implying that the approach was safe and feasible even in its early stages.

Laparoscopic vs. Robotic

There are no head-to-head series comparing laparoscopic and robotic PD. A recent systematic review of laparoscopic PD, however, did attempt to make some observations; patients who underwent laparoscopic PD had shorter operative time, reduced blood loss, and lower rate of pancreatic fistula compared to robotic PD.[17] Other comparisons have lumped laparoscopic and robotic PD as a single entity and compared it to open PD. Correa-Gallego and colleagues for example, demonstrated reduced blood loss and length of stay, higher lymph node yield and R0 resection rates among minimally invasive PD cases.[18] While selection bias may have played a role in those beneficial oncologic outcomes (greater tumor size in the MI group), the results are encouraging. These results were confirmed in another meta-analysis of the same topic.[19] On the other hand, two other recent publications have questioned

Table 1 Laparoscopic Pancreaticoduodenectomy Series

Case series	*n*	OR time	Conversion (%)	EBL	LOS	Morbidity (%)	Mortality (%)
Asbun, 2012[9]	53	541	15	195	8	25	6
Kim, 2013[10]	100	487	5	*	15	25	1
Gumbs, 2013[11]	72	436	19	400	9	33	1
Kendrick/Croome, 2014[12]	108	379	6	492	**	***	2
Palanivelu, 2015[13]	130	310	1	110	8	30	2
Total	463	410 min	8	294 mL	9 days	29	2

*Transfusion rate = 31 %, **Median = 6 days, ***Only ≥ IIIB reported = 6 %

the efficacy of minimally invasive PD using data acquired from the NCDB.[20,21] These studies point to increased 30-day mortality with minimally invasive PD without benefit in receipt or time to initiation of systemic chemotherapy. It is important to note that approximately half the centers in the study reported only a single minimally invasive PD. This is addressed further in the discussion below.

Learning Curve for MI Pancreatoduodenectomy

The learning curve is perhaps the most important aspect of minimally invasive PD. Kendrick and Kim discuss the improvement over time with use of laparoscopic PD, though their described learning curve of 10 cases is no doubt a product of cumulative experience with other complex hepatobiliary and foregut procedures by these surgeons.[10,12] We define a learning curve of 80 cases for operative time (581 to 417 min), 40 cases for fistula rate (27 to 14 %), and 20 cases for EBL and conversion (600 to 250 ml, and 35 to 3 %, respectively) over the first 200 robotic PDs.[16] This learning curve may seem long, but is a true reflection of the time and effort needed to safely implement this platform in the absence of any prior experience, guidance or training. As new surgeons have been integrated into our program, it is becoming apparent that the actual learning for new adopters is much shorter, since the operative steps are now refined, and the training and mentorship available expedites the time to master the platform.

Distal Pancreatectomy

Laparoscopic

Laparoscopic DP (LDP) has become relatively commonplace among pancreatic surgeons. It first gained popularity for use in benign disease as concerns were levied over the oncologic efficacy of the laparoscopic approach in malignant cases. A number of large series however have been published over the past decade, demonstrating the safety and efficacy of LPD in the setting of pancreatic ductal adenocarcinoma. These series are highlighted in Tables 3, 4 and 5.[11,22–36] While conversion rates were highly variable based on institution, operative time, length of stay, morbidity, and low mortality rates were consistent. This appears to be a safe approach in the hands of experienced surgeons and is considered by most to be the gold standard in benign disease. Recent interest has been expressed for a large, randomized trial comparing LDP with open surgery in the setting of malignancy.[36]

Robotic

Robotic DP has not been as widely adopted since many doubt its advantages over LDP. To date, only two large non-

Table 2 Robotic pancreaticoduodenectomy series

Case series	*n*	OR time	Conversion (%)	EBL	LOS	Morbidity (%)	Mortality (%)
Giulianotti, 2010[14]	60	421	11	394	13*	–	2
Boone (UPMC) 2015[15]	200	483	7	250	9	26	3
Total	260	469 min	8	283 mL	10 days	26	3

*US patients

Table 3 Laparoscopic distal pancreatectomy series

Case series	Institution	*n*	OR time	Conversion (%)	EBL	LOS	Morbidity (%)	Mortality (%)
Mabrut, 2005[22]	Multicenter	96	199	10	–	7	33	0
Fernandez-Cruz, 2007[23]	Barcelona	82	–	7	–	7	22	0
Kooby, 2008[24]	Multicenter	159	232	13	371	6	40	0
Rosok, 2010[25]	Oslo	117	186	5	168	5	17	2
Vijan, 2010[26]	Mayo-Rochester	104	214	4	171	5	34	3
DiNorcia, 2010[27]	Columbia	95	191	25	150	5	28	0
Song, 2011[28]	Seoul	359	195	–	–	8	12	0
Kneuertz, 2012[29]	Emory	132	156	6	197	6	43	1
Stauffer, 2012[30]	Mayo-Jacksonville	82	188	7	70	4	13	0
Adam, 2013[31]	Bordeaux	140	205	11	310	10	34	0
Gayet/Gumbs, 2013[11]	Paris	67	203	15	100	6	21	2
Braga, 2015[32]	Milan	100	239	23	464	–	9	0
deRooij, 2015[33]	Multicenter	64	213	33	275	8	16	3
Sharpe, 2015[34]	NCDB	144	–	–	–	7	–	0
Sahakyan, 2015[35]	Multicenter	196	220	3	250	8	32	0
Sulpice, 2015[36]	French database	347	–	–	–	15	33	1
Total		2284	203 min	9	243 mL	8 days	26	1

comparative series have been published to date.[37,38] The University of Pittsburgh published a report of its first 100 cases utilizing robotic DP, with evidence of outcome optimization after 40 cases.[38] Importantly, this report demonstrated a low conversion rate of 2 % even in the presence of a significant number of PDA cases (30 %). Although outcomes of RPD and LPD may seem similar, RPD may be associated with a lower conversion rate, particularly for PDA. An Italian series of 55 patients demonstrated no conversions to laparotomy, very low serious morbidity, and no perioperative mortality.[37] The learning curve in the Italian report was similar to the Pittsburgh experience.

Laparoscopic vs. Robotic

Higher comfort levels for laparoscopic and robotic DP compared with PD has allowed for greater comparative study between these two minimally invasive techniques. Six series met our criteria for inclusion with a total of 349 laparoscopic DPs and 195 robotic DPs.[39–44] Analysis of these data demonstrate similar operative time, length of stay, morbidity, and mortality. However, the robotic approach has been demonstrated to have lower conversion rates to laparotomy and reduced blood loss. While not a primary focus of this review, some series have also reported better rates of splenic preservation with robotic DP.[40,43] In the author's experience, robotic DP has also led to improved negative margin rate and lymph node yield when compared with laparoscopic DP.[41] In a large database study, minimally invasive pancreatectomy compared well with open surgery in regards to oncologic outcomes with shorter associated hospital stays.[45]

Other Applications

The growing experience with minimally invasive pancreatic surgery has led to a variety of additional reports of applying laparoscopic or robotic approaches to less common procedures. The use of intraoperative ultrasound has been applied to identify small pancreatic neuroendocrine tumors amenable to laparoscopic or robotic enucleation.[46] Other reported procedures for malignant disease include central pancreatectomy and distal pancreatectomy with en bloc celiac axis resection (modified Appleby procedure) while pancreatic cystogastrostomy with

Table 4 Robotic distal pancreatectomy series

Case series	*n*	OR time	Conversion (%)	EBL	LOS	Morbidity (%)	Mortality (%)
Shakir (UPMC) 2015[38]	100	246	2	150	6	14	0
Boggi, 2015[37]	55	278	0	*	13	4	0
Total	155	266 min	1	150 mL	8 days	10	0

*Transfusion rate = 8 %

Table 5 Laparoscopic vs. robotic distal pancreatectomy series

Case series	Case no.		OR time*		Conversion (%)		EBL**		LOS***		Morbidity (%)		Mortality (%)	
	Lap	Robot	Lap	Robot	Lap	Robot	Lap	Robot	Lap	Robot	Lap	Robot	Lap	Robot
Waters, 2010[39]	28	17	224	298	11	12	667	279	6	4	33	18	0	0
Kang, 2011[40]	25	20	258	349	–	–	420	320	7	7	16	10	0	0
Daouadi, 2013[41]	94	30	372	293	16	0	150	150	7	6	14	20	1	0
Butturini, 2015[42]	21	22	195	265	5	5	–	–	7	7	5	14	0	0
Chen, 2015[43]	50	69	200	150	3	0	290	100	15	12	10	9	0	0
Lee, 2015[44]	131	37	193	213	31	38	262	193	5	5	22	43	0	0
Total	349	195	249	230	19	10	281	172	7	8	17	18	<1	0

*in min, **in mL, ***in days

necrosectomy, and the Frey procedure have been performed for benign disease.[47–49]

Discussion

Minimally invasive surgery has become the standard in many common surgical procedures such as cholecystectomy, appendectomy, anti-reflux operations, and obesity surgery, among others. The utilization of minimally invasive techniques among pancreatic surgeons has been significantly slower. The underlying reasons for this slow uptake are the complexity of the procedures, minimal comparative data with the gold-standard open techniques, concerns about oncologic efficacy, and lack of access to appropriate training. Despite early skeptical reports from pioneering surgeons, the minimally invasive pancreatic surgery is gaining momentum. There are essentially four key elements to continue this momentum: safety (perioperative outcomes), oncologic efficacy, cost, and reproducibility.

Both laparoscopic and robotic approaches to PD and DP have been established as safe. Despite a lack of randomized trials to date, many of the aforementioned case series were matched with equivalent populations undergoing open operations. For PD, operative times for laparoscopic and robotic approaches have both been found to be longer than for the open approach. However, this increased operative time has not been associated with any increase in perioperative morbidity or mortality among large single institution series or meta-analyses. In the study by Adam et al, the NCDB was used to identify a statistically significant increase in perioperative mortality for minimally invasive PD.[20] The limitations of this study, however, are noteworthy. Most strikingly, half of the centers included contributed only one minimally invasive case on average. Furthermore, the study was completed using data from 2010–2011, due to the lag time in availability of the database. As robotic PD was in its relative infancy, the outcomes may be substantially different in 2015 and beyond. As expertise matures, a closer look at morbidity, mortality and other important endpoints such as *completion* of adjuvant chemotherapy—rather than time to its receipt—will deserve further attention.[21]

During the development of MI pancreatectomy, the primary concerns regarding its use were related to oncologic efficacy. Lack of tactile sensation and haptic feedback in robotic surgery, has been cited as a factor that may contribute to higher rates of margin positivity. Initial reports also suggested that MI approaches were inadequate for lymphadenectomy in PD and DP.[4,5] However, contemporary series have alleviated these concerns. To the contrary, Kendrick and colleagues found that for laparoscopic PD there were fewer delays to initiation of systemic chemotherapy, and a longer progression-free survival interval, albeit with similar OS.[12] A French database series noted improved survival for laparoscopic vs. open DP.[36] Selection bias must be considered, as those performing MI pancreatectomy are likely to be high volume surgeons, with favorable outcomes compared to lower volume surgeons using the open approach. Despite this limitation, minimally invasive PD and DP appear to be at least as efficacious as the open approach in the setting of malignancy.

Opponents of robotic surgery routinely cite cost as a prohibitive factor to its applicability, since data from other surgical specialties indicates that robotic surgery is more costly than both laparoscopic and open surgery.[50] The initial investment in the robotic console is approximately $1.2 million; with an additional $100,000–150,000 per year in maintenance costs owing to finite use instrumentation. Despite these additional costs, robotic surgery can be demonstrated to be profitable to hospital systems.[51] When compared with open surgery, an improvement in length of stay seen with robotic pancreatectomy may negate the cost differential as was seen in the University of Indiana DP experience.[39] This was also reaffirmed in a large Nationwide Inpatient Sample (NIS) comparison of laparoscopic and open PD that reported a reduction in LOS for the laparoscopic group resulting in significantly lower hospital charges.[52] Furthermore, as the utilization of robotic surgery becomes more widespread, market forces may drive down instrument prices if adequate demand is present and new competitors enter the market.

Perhaps the greatest hurdle toward widespread adoption of minimally invasive pancreatectomy is its safe dissemination. Proponents of the laparoscopic approach suggest that due to the fact that laparoscopic training is already inherently embedded into the current surgical training paradigm, that this should be the preferred minimally invasive approach to the pancreas.[12] However, the technical ability to perform laparoscopic PD safely and efficiently has only been demonstrated by a handful of surgeons worldwide despite nearly a decade of lead-time bias over the robotic approach. Although robotic surgery has not been formally integrated into the training of residents and fellows, it is arguably easier to disseminate. The stereotactic vision and wristed instruments, features akin to open surgery, allow rapid acquisition of skills and mastery of the platform. Additionally, robotic simulators are advanced, user-friendly, and offer increasing levels of training complexity. The presence of a dual console allows the trainee to perform increasing portions of a complex case, while receiving continuous feedback by the attending surgeon at the second console. Importantly, the attending has the ability to rapidly "take over" the proceedings of the case, should the trainee face problematic bleeding during dissection. At the University of Pittsburgh, increasing trainee familiarity with the robotic platform is established using both simulators and bio tissue models that mimic various phases of PD reconstruction. Although the presence of an experienced bedside assistant is required, fellows matriculating through the robotic pancreatic program are able to complete various pancreatic operations without compromising patient safety and operative efficiency.

Limitations to the aforementioned studies must be emphasized. Most of the minimally invasive PD and DP series originate from high volume pancreatic surgery centers, and such outcomes may not be reproducible at low volume centers. Data from the NCDB study quoted above clearly highlights the increased mortality associated with low volume minimally invasive pancreatic surgeons.[20] Additionally, morbidity was not standardly reported throughout these series making comparisons across them difficult. Finally, although all the series reviewed above had >50 cases, most of these reports reflect surgeons still working through their learning curves.

In conclusion, minimally invasive PD and DP can be performed safely with equivalent, outcomes to the standard open techniques by experienced high volume pancreatic surgeons. Both laparoscopic and robotic approaches seem to have comparable outcomes, although the robotic approach may be associated with fewer conversions and easier dissemination. Further investment in standardized training programs with well-defined benchmarks is needed to aid in the advancement and widespread adoption of these complex techniques.

Learning Objectives

- To identify the clinical outcomes in large series of laparoscopic pancreatectomy.
- To identify the clinical outcomes in large series of robotic pancreatectomy.
- To understand the learning curves for laparoscopic and robotic pancreaticoduodenectomy.
- To understand the benefits and limitations of laparoscopic and robotic approaches to pancreatectomy.

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Questions & Answers

1)When performed at high volume centers, by experienced high volume pancreatic surgeons on select case, minimally invasive pancreaticoduodenectomy is associated with similar morbidity compared to the open approach

a.True
b.False

2)An advantage of minimally invasive pancreaticoduodenectomy over the open approach is:

a.Lower mortality rate
b.Shorter operative time
c.Lower operative blood loss
d.Lower morbidity rate

3)A potential advantage of robotic distal pancreatectomy over the laparoscopic approach includes:

a.Reduced operative time
b.Reduced length of stay
c.Lower morbidity rate
d.Higher splenic preservation and lower conversion rate

4)The learning curve for robotic distal pancreatectomy is reported to be around:

a.10 cases
b.20 cases
c.40 cases
d.60 cases

5)If performed by experienced high volume pancreatic surgeons, the oncologic efficacy of minimally invasive pancreatectomy is inferior to the open approach:

a.True
b.False

6)Mortality rate is higher for robotic distal pancreatectomy when compared with laparoscopic distal pancreatectomy:

a.True
b.False

7)Future comparative effectiveness studies of minimally invasive versus open pancreatectomy should take into consideration the following factors:

a.Surgeon experience
b.Surgeon volume
c.The effect of the learning curve on outcomes
d.Case selection
e.All of the above