Minimally-Invasive vs Open Pancreaticoduodenectomy: Systematic Review and Meta-Analysis

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Laparoscopic approaches are routinely used for a variety of procedures in general surgery and various surgical specialties including surgical oncology. Since publication of the first series of laparoscopic cholecystectomy in the late 1980s, the field of minimally invasive surgery (MIS) has expanded dramatically and is now regarded as an established specialty. Many oncologic procedures have proved not only feasible and safe, but oncologically equivalent to traditional open procedures regarding both immediate operative variables of interest (margins, lymph node retrieval, and morbidity) and long-term outcomes.1-10

Pancreaticoduodenectomy (PD) poses a particular challenge. During this procedure, there is extensive retroperitoneal dissection around anatomically complex and hazardous structures, and a prolonged reconstruction that includes 3 technically demanding anastomoses. Given this complex gastrointestinal reconstruction, it has been generally thought that the minimally invasive approach would not significantly decrease recovery time (hospital stay), yet it would significantly increase operative time. Even though minimally invasive PD was reported as early as 1994,11 laparoscopic surgeons have been reluctant to routinely perform it. Since this first description now almost 20 years ago, a large number of single-institution series of minimally invasive (including laparoscopic-assisted, totally laparoscopic, and more recently robotic) PD performed for a variety of indications have been reported.12-27

Based on safety data derived from those retrospective reports, these procedures are now offered to selected patients at a limited number of institutions. However, there is currently no level 1 evidence that compares outcomes between MIS and the traditional open approach. We present a systematic review of the literature and a comparative effectiveness analysis of minimally invasive vs open PD. Using meta-analytic techniques, we set out to evaluate the surgical and oncologic outcomes of patients undergoing either procedure as reported in the published literature.

METHODS

This study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.28 We queried medical databases in search for manuscripts comparing operative, postoperative, and oncologic outcomes of minimally invasive and open PD. An experienced information scientist (IS) designed the search strategy, which was refined and revised by a surgeon (CC).

Literature search

Comprehensive literature searches were performed of the PubMed, EMBASE, and Cochrane Library databases for the years 1994 through January 2013. No language restriction was imposed. Three categories of terms were “ANDED” together: pancreaticoduodenectomy terms, laparoscopy/robot-assisted/minimally invasive terms, and outcomes terms. For PubMed, a search using Medical Subject Headings (MeSH) terms was run, as well as a textword search. For EMBASE, a search using Emtree (EMBASE vocabulary) terms was run, as was a textword search. For Cochrane, a search using MeSH terms was run, as well as a textword search. All retrieved records were added to an EndNote (Version X6 — Thomson Reuters) library. The last search was performed on January 15, 2013. A total of 703 references were retrieved, and after removal of duplicates, 527 references remained.
Study selection
Minimally invasive PD was defined as completely laparoscopic or robotic resection of the head of the pancreas and duodenum, followed by completely intracorporeal reconstruction of the pancreatic, biliary, and intestinal continuity. Hybrid procedures, in which part of the dissection or reconstruction was extracorporeal or through a “mini-laparotomy” were not considered for this study.

Studies were included only if they were original series comparing minimally invasive and open PD that reported at least 1 of the outcomes variables of interest. We included only published studies dating back to 1994 (first report of minimally invasive PD) regardless of language.

Studies were excluded from our analysis if they did not report at least 1 of the outcomes of interest, included minimally invasive or open PDs but not both, or did not perform a comparison between the 2 techniques; reported hybrid procedures; reported on fewer than 8 cases; if they were technical “how-to” reports, or if they were animal or unpublished studies for which complete data for pooling were not available.

Two authors (CC and HD) evaluated all titles to identify relevant articles. Abstracts of these were re-evaluated to identify those meeting inclusion criteria, and full texts of these articles were obtained for data extraction. Disagreement was solved by a third author (SF).

Data extraction
Two authors independently extracted the data of interest from the manuscripts. Results were compared and consensus was reached. The outcomes of interest for our study were: operative/pathology variables (operative time, estimated blood loss, R0 resection, lymph node harvest, and tumor size), postoperative outcomes (overall complications, pancreatic fistula rate [and grade ≥3], delayed gastric emptying, postpancreatectomy hemorrhage, wound infection, length of hospital stay, and reoperation rate). Operative outcomes largely determine the ultimate oncologic outcomes of these patients (in the setting of malignancy); the postoperative outcomes evaluated represent the major drivers of morbidity after pancreaticoduodenectomy. Because our search was not limited to a specific indication for this operation, long-term oncologic outcomes were not included in our analysis. The reference sections of the selected studies were searched for additional relevant papers. Corresponding authors were not contacted.

Statistical analysis
The meta-analysis was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement. Whenever missing from a study, mean and standard deviation were estimated from the data available, if possible, as previously described. Studies were combined using a random-effects model and estimates were expressed as weighted mean differences (WMD) for continuous data and odds ratios (OR) for event-related outcomes. In addition, 95% confidence intervals (CI) were calculated. I² values were preferred for quantification of statistical inconsistency, defined as the percentage of variation between studies due to heterogeneity. Analyses were performed with Comprehensive MetaAnalysis Version 2.0 (Biostat Solutions Inc).

Assessment of methodologic quality of our meta-analytic techniques
The previously validated Overview Quality Assessment Questionnaire (OQAQ) was used to assess the methodologic rigor of our study. This questionnaire includes a self-reported subset of questions regarding items that should be fulfilled to ensure quality: 1. Was the search comprehensive? 2. Was selection bias avoided? 3. Was validity assessed appropriately? and 4. Were the methods used to combine results from studies appropriate?

RESULTS
The predefined inclusion criteria were met by 6 studies that included 542 patients (169 MIS and 373 open) and these were pooled in the meta-analysis. A PRISMA flow diagram depicting the selection process is shown in Figure 1. General study characteristics are detailed in Table 1. There were no randomized controlled trials identified. All the studies found were retrospective reviews of variable quality that compared consecutive cases of minimally invasive PD with either consecutive or matched open procedures performed during the same time period. All indications were included; however, the majority of cases were performed for malignancy. All studies focused on operative and perioperative outcomes, there were no reports of long-term oncologic results, and there were no multicenter studies.

Meta-analysis
Results of the meta-analysis are summarized in Table 2. Forest plots of those comparisons that showed a significant
difference are shown in Figures 2 to 7. Minimally invasive surgery was associated with a reduction in intraoperative blood loss (WMD 1,460 mL, 95% CI 726 to 2,194 mL, \( p < 0.001, I^2 = 95\% \)), although longer operative times were observed (WMD 131 minutes, 95% CI 43 to 218 minutes, \( p = 0.003, I^2 = 96\% \)). In addition, in the MIS group, retrieval of lymph nodes was significantly higher by 3 nodes (95% CI 0.3 to 6.0 nodes, \( p = 0.03, I^2 = 61\% \)) and the likelihood of an R1 resection in patients with malignancy was lower (OR 0.4, 95% CI 0.2 to 0.9).

Table 1. General Study Characteristics

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Study design</th>
<th>Total n</th>
<th>Indication, n</th>
<th>Approach, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Benign</td>
<td>MIS</td>
</tr>
<tr>
<td>Asbun(^{32})</td>
<td>2012</td>
<td>Retrospective</td>
<td>268</td>
<td>53</td>
<td>215</td>
</tr>
<tr>
<td>Buchs(^{33})</td>
<td>2011</td>
<td>Retrospective</td>
<td>83</td>
<td>44</td>
<td>39</td>
</tr>
<tr>
<td>Chalikonda(^{34})</td>
<td>2012</td>
<td>Retrospective</td>
<td>60</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Lai(^{35})</td>
<td>2012</td>
<td>Retrospective</td>
<td>87</td>
<td>20</td>
<td>67</td>
</tr>
<tr>
<td>Zhou(^{36})</td>
<td>2011</td>
<td>Retrospective</td>
<td>16</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Zureikat(^{37})</td>
<td>2011</td>
<td>Retrospective</td>
<td>28</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

MIS, minimally invasive surgery.
CI 0.2 to 0.8, \( p = 0.007, \, I^2 = 0\% \)). Of note, tumor size was significantly larger in the open group (WMD 0.6 cm, 95% CI 0.1 to 1.1 cm, \( p = 0.02, \, I^2 = 51\% \)). Thirty-five of 169 patients (21%) in the MIS group and 63 of 373 (17%) in the open group developed a pancreatic fistula; for clinically relevant pancreatic fistula, the proportions were 13 of 169 (8%) and 26 of 373 (7%), respectively; \( p = 0.9 \) (Table 2 and Fig. 8). Overall morbidity, reoperations, and other specific complications (delayed gastric emptying, postpancreatectomy hemorrhage, and wound

<table>
<thead>
<tr>
<th>Variable</th>
<th>Studies included</th>
<th>Patients*</th>
<th>OR/WMD 95% CI p Value ( I^2, % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time, min</td>
<td>6</td>
<td>169/373</td>
<td>131 43–218 ( p = 0.003 ) 96 ( I^2 )</td>
</tr>
<tr>
<td>Blood loss, mL</td>
<td>6</td>
<td>169/373</td>
<td>((-)) 1.460 ((-)) 2.194–((-) 726 &lt;0.001 ( I^2 )</td>
</tr>
<tr>
<td>Harvested lymph nodes</td>
<td>5</td>
<td>161/365</td>
<td>((-)) 3.2 ((-)) 6.0–((-) 0.3 ( 0.03 ) 61 ( I^2 )</td>
</tr>
<tr>
<td>R1/R2 resection</td>
<td>6</td>
<td>121/253</td>
<td>0.4 0.20–0.80 ( p = 0.007 ) 0 ( I^2 )</td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td>4</td>
<td>117/326</td>
<td>0.6 0.1–1.1 ( p = 0.02 ) 51 ( I^2 )</td>
</tr>
<tr>
<td>Overall complications</td>
<td>6</td>
<td>169/373</td>
<td>0.67 0.39–1.16 ( p = 0.15 ) 39 ( I^2 )</td>
</tr>
<tr>
<td>PF Overall</td>
<td>6</td>
<td>169/373</td>
<td>1.11 0.68–1.83 ( p = 0.67 ) 0 ( I^2 )</td>
</tr>
<tr>
<td>PF Clinically relevant</td>
<td>6</td>
<td>169/373</td>
<td>0.97 0.48–1.99 ( p = 0.94 ) 0 ( I^2 )</td>
</tr>
<tr>
<td>DGE</td>
<td>4</td>
<td>147/351</td>
<td>0.75 0.35–1.63 ( p = 0.48 ) 0 ( I^2 )</td>
</tr>
<tr>
<td>PPH</td>
<td>4</td>
<td>147/351</td>
<td>1.55 0.70–3.42 ( p = 0.28 ) 0 ( I^2 )</td>
</tr>
<tr>
<td>Wound infection</td>
<td>4</td>
<td>147/351</td>
<td>0.49 0.23–1.1 ( p = 0.077 ) 0 ( I^2 )</td>
</tr>
<tr>
<td>Reoperation</td>
<td>5</td>
<td>155/359</td>
<td>0.54 0.25–1.18 ( p = 0.12 ) 0 ( I^2 )</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>5</td>
<td>139/343</td>
<td>((-)) 3.7 ((-)) 6.8–((-) 0.5 ( 0.02 ) 78 ( I^2 )</td>
</tr>
</tbody>
</table>

*Total number of patients evaluated in each category.

\( ^{1} \)Significant statistical difference.

\( ^{2} \)Calculated over the number of patients with a malignancy.

DGE, delayed gastric emptying; MIS, minimally invasive surgery; OR, odds ratio; PF, pancreatic fistula; PPH, post-pancreatectomy hemorrhage; WMD, weighted mean difference.

**Figure 2.** Pooled estimate of operative time for minimally invasive surgery (MIS) vs open pancreaticoduodenectomy. All studies except for Buch’s show a statistically significant longer operative time for MIS procedures.
infection) were also comparable (Table 2). Hospital stay was significantly reduced in the MIS group by 3.7 days (95% CI 0.5 to 6.8 days, $p = 0.02$, $I^2 = 78\%$).

A total of 17 patients in the MIS group (10%) required conversion to an open procedure. The majority of these (13 of 17) were due to bleeding or the inability to obtain adequate vascular control laparoscopically; there was 1 perioperative death reported that was directly related to surgical hemorrhage. Only 2 of the studies included patients undergoing conversion in the MIS arm in an intention-to-treat analysis.

**Assessment of methodologic quality and bias**

All the studies identified were case series. Because there have been no randomized controlled trials of MIS vs open PD, the Cochrane Collaboration’s tool for assessing

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Difference in means and 95% CI</th>
</tr>
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<tbody>
<tr>
<td><strong>Difference</strong></td>
<td><strong>Lower limit</strong></td>
<td><strong>Upper limit</strong></td>
</tr>
<tr>
<td>MIS - Open</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buchs</td>
<td>44</td>
<td>39</td>
</tr>
<tr>
<td>Zhou</td>
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<td>Zureikat</td>
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<tr>
<td>Asbun</td>
<td>53</td>
<td>215</td>
</tr>
<tr>
<td>Chalikonda</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Lai</td>
<td>20</td>
<td>67</td>
</tr>
<tr>
<td>169</td>
<td>373</td>
<td>-1460.2</td>
</tr>
</tbody>
</table>

**Figure 3.** Pooled estimate of estimated operative blood loss for minimally invasive surgery (MIS) vs open pancreaticoduodenectomy.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Difference in means and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Difference</strong></td>
<td><strong>Lower limit</strong></td>
<td><strong>Upper limit</strong></td>
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<tr>
<td>MIS - Open</td>
<td></td>
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<tr>
<td>Buchs</td>
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<tr>
<td>Chalikonda</td>
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<tr>
<td>Lai</td>
<td>20</td>
<td>67</td>
</tr>
<tr>
<td>161</td>
<td>365</td>
<td>-3.2</td>
</tr>
</tbody>
</table>

**Figure 4.** Pooled estimate of number of harvested lymph nodes during minimally invasive surgery (MIS) vs open pancreaticoduodenectomy.
risk of bias was not applied. The studies included in our meta-analysis represent the experience of single referral centers and in most cases, a single surgeon’s experience. Furthermore, they correspond to the initial experience with this complex minimally invasive technique and do not account for the learning curve to perform these procedures. In most cases, the selection criteria for patients to undergo MIS were not reported.

DISCUSSION
Continuous improvement and technical advances (in equipment as well as training) have made possible the application of minimally invasive techniques to a wide variety of surgical procedures, including complex oncologic operations. Properly conducted randomized trials have shown noninferiority of MIS compared with open approaches, as long as oncologic principles are preserved. The identified benefits of minimally invasive oncologic resection have been a smaller incision and shorter recovery time. However, to date there have been no identified benefits associated with these less invasive procedures with regard to oncologic outcomes.

In surgical oncology, minimally invasive approaches do not (and should not) significantly modify the operative techniques or the steps defining the operation itself; the only significant difference linked to MIS lies in the way these goals are achieved. The expectation that a different incision would significantly improve the outcomes of an otherwise identical operation is therefore not realistic. Although early wound complications (infections, dehiscence, etc) are a major source of distress for general surgical patients, the 2 major drivers of morbidity after PD are failure of the pancreatic anastomosis leading to pancreatic fistulae and delayed gastric emptying. Both of these complications are unrelated to the abdominal incision. On the other hand, late wound complications (eg, incisional hernias) have been identified as a source of delayed morbidity after pancreatic resection; however, the morbidity associated with an incisional hernia must be interpreted in the context of pancreatic malignancy.

Minimally invasive surgery techniques have shown to be associated with lower wound infection rates in different kinds of abdominal operations, and this is one of its main advantages. Four of the studies included in our meta-analysis report specifically on wound infection rates. We found a nonsignificant trend toward fewer wound infections in patients who underwent minimally invasive PD (OR 0.49, 95% CI 0.23 to 1.1, p = 0.077, \( I^2 = 0\% \)). Theoretically, decreased wound complication rates (and decreased morbidity in general)
have the potential to allow eligible patients to initiate postoperative chemotherapy in a timely manner, and therefore possibly contribute to an improved oncologic outcome. However, these theoretical advantages are unproven, and the studies included in our pooled analysis did not address this issue specifically because the indications for resection (and the need for adjuvant therapy) were variable and the long-term oncologic outcomes were not reported. Furthermore, despite a trend toward improved wound infection rates, there was no difference...
Figure 8. (A) Pooled estimate of incidence of postoperative pancreatic fistula and (B) clinically-relevant postoperative pancreatic fistula for minimally invasive surgery (MIS) vs open pancreaticoduodenectomy.
in overall complications (Table 2). These important (and yet unanswered) questions underscore the need for adequately designed trials that evaluate the MIS approach in patients with prespecified inclusion and matching criteria.

The findings in this study indicate that minimally invasive PD is a feasible procedure in highly selected patients who are cared for in select centers. These data suggest that minimally invasive PD may be associated with a decreased hospital stay, and possibly higher lymph node retrieval. The findings of lower operative blood loss and higher rate of R0 resection must be viewed in the setting of highly selected patients with significantly smaller tumors. The likelihood of bias is significant, and not until randomized data are available, or retrospective data that demonstrate clear outcome equivalence or improvement, can this approach be considered standard.

Operative blood loss was shown in the pooled analysis to be lower in MIS cases. This is often attributed to the magnified view of small vessels that laparoscopy allows for, particularly during dissection of the plane between the uncinate process and the superior mesenteric vessels. It is important to underscore though, that all the studies in this meta-analysis systematically excluded patients with known vascular involvement for consideration of the MIS approach, and those with unexpected vascular involvement were converted to an open approach. Lack of adequate matching in this regard makes comparison of operative blood loss inherently flawed and at a high risk for confounding. Furthermore, not all studies performed an intention-to-treat analysis and included patients who required conversion from MIS to an open approach in the open arm for the analysis. This introduces considerable bias because these patients have expected higher blood loss and longer operating times. Dissection of the porto-mesenteric axis is an intrinsically challenging and hazardous part of PD, and failure to expeditiously control these vessels may lead to massive bleeding and exsanguination. Therefore, it is of the utmost importance that surgeons embarking on this operation are capable of controlling hemorrhage laparoscopically and that the resources are readily available for conversion to a laparotomy.

The median postoperative length of stay of patients undergoing minimally invasive PD was 11 days (interquartile range: 8 to 14 days); it was 14 days (interquartile range: 12 to 24 days) for open cases. Most current series from referral centers report median stays of 7 or 8 days after open PD, and the considerably longer postoperative stays may have been related to local preferences and different health care systems.42-44 Furthermore, the shorter recovery period in these patients did not seem to translate into (or be explained by) lower postoperative morbidity. The current median length of stay at our institution after open PD is 8 days,45 which is 3 days shorter than that in the MIS groups reported by the studies included in our meta-analysis.

Although long-term oncologic outcomes are not addressed in these early studies, R0 status and lymph node retrieval are used as indicators of the oncologic adequacy of MIS techniques. Lymph node staging is a very relevant prognostic factor for pancreatic cancer patients. However, different pathologic processing techniques of the surgical specimen have been shown to yield significantly different lymph node counts.46 Without an indication of how the specimens were processed in these studies, it’s hard to draw strong conclusions in this regard. Moreover, the higher R0 resection rate seen should be interpreted with caution. Our pooled analysis also showed that patients in the MIS group had smaller tumors, which must be considered a confounder that may account for the higher R0 resection rates.

To date there are no published randomized controlled trials comparing minimally invasive (either robotic or plain laparoscopic) PD, nor are there, to our knowledge, any registered trials ongoing. Enthusiasm has been primarily guided by a small number of surgeons at large volume centers. There is no doubt that minimally invasive techniques have earned a significant role in the treatment of abdominal malignancies and there is no reason to believe that the indications will not continue to expand into PD as instrumentation and training continue to evolve.47 However, it is at this time of equipoise that a well-designed prospective study of minimally invasive PD could be accomplished at select centers. The value of quality clinical trial research will become even more important in the upcoming era of cost containment, when our interventions are likely to be subject to much tighter scrutiny by regulatory agencies.48

Our study has several limitations. First, there are no randomized controlled trials, and no prospective studies of high quality that provide unbiased data for our analysis. This is, however, not only a limitation of our study, but an important indication that the widespread application of these techniques is yet to be achieved. The first laparoscopic PD was reported almost 20 years ago, and the lack of penetrance of this approach into the vast majority of institutions should be given consideration. Additionally, there is high variability between the studies we analyzed, which is addressed (albeit incompletely) by the random-effects model we used for our meta-analysis. Furthermore, given the paucity of data, we grouped together the outcomes of pure laparoscopic and robotic-assisted cases, which may be intrinsically different between themselves. Another major limitation
lies in the possibility of publication bias, in which centers and individual surgeons who have had positive outcomes with MIS major pancreatic resection are more likely to publish their findings. These limitations notwithstanding, we believe that our study fulfills the Overview Quality Assessment Questionnaire evaluation and provides important information regarding the very limited available data on the outcomes of minimally invasive PD.

CONCLUSIONS

Minimally invasive PD is currently a feasible operation in select patients being treated at select centers. Although the findings of this meta-analysis suggest there might be improved outcomes associated with minimally invasive PD in comparison with the open approach, the lack of randomized trials or high-quality, nonrandomized prospective studies comparing both techniques does not allow for firm conclusions to be drawn, so minimally invasive PD cannot be considered superior or standard at this time. Randomized controlled trials or prospective cohort studies, which avoid selection and experimenter bias and control for confounding factors are necessary to adequately evaluate this question before routine application can be recommended.

Author Contributions

Study conception and design: Correa-Gallego, Dinkelspiel, Sulimanoff, Fisher, Viñuela
Acquisition of data: Correa-Gallego, Dinkelspiel, Sulimanoff, Viñuela
Analysis and interpretation of data: Correa-Gallego, Dinkelspiel, Fisher, Viñuela, Kingham, Fong, DeMatteo, D’Angelica, Jarnagin, Allen
Drafting of manuscript: Correa-Gallego, Dinkelspiel, Sulimanoff, Fisher, Viñuela
Critical revision: Correa-Gallego, Dinkelspiel, Sulimanoff, Fisher, Viñuela, Kingham, Fong, DeMatteo, D’Angelica, Jarnagin, Allen

REFERENCES