Multivisceral and extended resections during pancreatoduodenectomy increase morbidity and mortality

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Background. *Improvements in outcomes after pancreatoduodenectomy (PD) have permitted more complex resections. Complete extirpation at PD may require multivisceral resection (MVR-PD); however, descriptions of morbidity of MVR-PD are limited to small, single-institution series.*
Methods. *The National Surgical Quality Improvement Project database (2005–2011) was used to compare 30-day postoperative morbidity of PD with MVR-PD. Concurrent resection of colon, small bowel, stomach, kidney, or adrenal gland defined MVR-PD.*
Results. *Of 9,927 PDs, MVR-PD was performed in 273 patients (3%). MVR included colon (58%), small bowel (30%), and gastric (12%) resections. Preoperative comorbidities were similar between groups. Pancreatic, duodenal, or periampullary cancer was present in 75% of patients. Mortality (8.8% vs 2.9%) and major morbidity (56.8% vs 30.8%) were much greater for MVR-PD versus PD alone (*$P < .001$*). MVR-PD patients also experienced greater rates of wound, pulmonary, cardiac, thromboembolic, renal, and septic complications. On multivariable regression, MVR was an independent predictor of death (odds ratio [OR], 3.4;* $P < .001$*), overall morbidity (OR, 3.01;* $P < .001$*), major morbidity (OR, 3.21;* $P < .001$*), and minor morbidity (OR, 1.65;* $P = .03$*). Among patients undergoing PD+MVR, colectomy was an independent predictor of increased overall morbidity (OR, 1.96;* $P = .03$*) and major morbidity (OR, 1.90;* $P = .02$*).*
Conclusion. *Margin-negative resection may require MVRs at the time of PD. MVR at is associated with 3-fold mortality and substantial morbidity after adjusting for comorbidities. Colectomy independently predicted major morbidity. At PD, the morbidity of MVR should be approached with caution when attempting margin-negative resection. (Surgery 2014;155:567-74.)*

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Once, pancreatoduodenectomy (PD) was considered a to be an operation with prohibitive morbidity and mortality. Advances in operative techniques and perioperative care have improved patient outcomes. High-volume centers have demonstrated the ability to further augment results.[1-4] These improvements have encouraged surgeons to extend PD to include resection of other organs when necessary. Margin-negative resection remains the standard of care to obtain optimal long-term survival. The morbidity associated with multivisceral resection (MVR) during PD remains a topic of controversy.

Existing knowledge comes from single-institution series. One study compared 101 PD+MVR with 202 matched standard PDs and noted greater operative morbidity (37.6% vs 25.3%) after PD+MVR.[5] A comparison of 19 MVRs with 86 PDs failed to find added morbidity with MVR at PD, despite greater operative times and intensive care stays.[6] These studies present conflicting conclusions and limit a surgeons'

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ability for intraoperative decision making and preoperative patient counseling.

Our study examines the morbidity of additional organ resection during PD. We utilized the prospective National Surgical Quality Improvement Project (NSQIP) data to overcome single-institution and retrospective series biases. These results should provide better information regarding the risks of MVR during PD.

MATERIALS AND METHODS

Data source and inclusion criteria. Our observational study used the NSQIP data from 2005 through 2011. The NSQIP database is a surgical outcomes research tool of the American College of Surgeons (ACS). By reviewing randomly selected surgical patients, the ACS-NSQIP collects preoperative comorbidities, intraoperative variables, and 30-day postoperative outcomes. One of the limitations of the ACS-NSQIP is that only 30-day are reported; no long-term outcomes >30 days postoperatively are available in the ACS-NSQIP. Specially trained nurses record the data, which are audited semi-annually. The database is de-identified, and therefore this study was exempt from the institutional review board process. The ACS-NSQIP and the hospitals participating in the ACS-NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

All patients who underwent PD were identified by the Current Procedural Terminology (CPT) codes 48150-48154. All NSQIP variables that included procedure codes were examined, including primary, concurrent, and other procedure fields. We excluded cases that were emergent or where disseminated cancer was found to create a population similar to those undergoing elective, operative resection with curative intent. PD is itself a MVR; however, the CPT code for a PD includes resection of proximal small bowel. Separate codes for classic and pylorus-preserving PD help to define an inherent partial gastrectomy. In essence, PD should not have additional codes for small bowel or gastric resection, unless they were not a standard part of the procedure. The MVR (MVR-PD) group was defined as those patients who underwent PD and simultaneous resection of colon, small bowel, adrenal, stomach, or kidney. This group was compared with PD alone cases. Patients undergoing "partial hepatectomy," "excisional liver biopsy," or other liver biopsies (CPT 47100 or 47120) o were placed in the PD group.

Postoperative diagnosis was included for description of the population. Duodenal malignancies were those with an ICD-9 of 152.*. Malignancies of the ampulla of Vater and extrahepatic biliary tree (ICD-9 of 156.*) were grouped as "Periampullary malignancies." The pancreatic cancer group was defined as those with invasive adenocarcinoma or carcinoma in situ (ICD-9 157* or 230*).

The primary analysis assumes that coding of partial gastrectomy or small bowel resection refers to additional organ resection rather than what is included and coded in a standard PD. Nevertheless, to assess the impact of potential miscoding of standard gastric or small bowel resections as separate/additional procedures, we performed a sensitivity analysis comparing a more restrictive group of PD+MVR with the control group. In this, only patients who underwent nephrectomies, colectomies, or adrenalectomies were classified PD+MVR, whereas all others were considered PD.

Data and outcomes. We examined demographic data, postoperative diagnosis, and the following comorbidities as potential confounders: (1) Diabetes, (2) cardiac disease (hypertension, angina, previous myocardial infarction, cardiac angioplasty or bypass surgery), (3) active pulmonary disease [pneumonia and severe chronic obstructive pulmonary disease], (4) chemo- or radiotherapy within 30 days of operation, and (5) weight loss. Intraoperative need for a vascular repair or perioperative transfusions was also analyzed.

The primary outcome was mortality. The secondary outcome was any morbidity. We defined major morbidity as re-intubation, prolonged intubation (>48 hours), pneumonia, cardiac arrest, myocardial infarction, renal failure requiring dialysis, deep or organ space infections, pulmonary embolus, bleeding, sepsis, shock, stroke, or coma. We defined minor morbidity as urinary tract or superficial wound infections, deep vein thrombosis, or creatinine increased >2 mg/dL above baseline without the need for dialysis.[7]

Statistical analysis. Mean and median values were used to describe continuous data. Discrete variables were displayed as frequencies. For bivariable analyses, 2-tailed *t*-tests and Mann–Whitney *U* tests were used to compare continuous data, whereas Fisher's exact or Chi-squared tests were used for categorical variables. For our multivariable regression, we derived separate logistic regression models for the effect of MVR on mortality, overall, major, and minor morbidity. A priori, age and American Society of Anesthesiologists (ASA) class >2 were included as covariables owing to the known association with morbidity and mortality. Additional covariables were chosen using

stepwise selection to include variables with a $P < .1$. The Hosmer–Lemeshow test was used to ensure goodness of fit.

As an alternate means of adjusting for baseline differences between groups, we performed a propensity score (PS) matched analysis. The PS model for mortality and overall, major, and minor morbidity was estimated using a logistic regression model with MVR-PD as the dependent variable and with age, sex, chemotherapy, steroid use, weight loss, history of chronic obstructive pulmonary disease, red cell transfusion, ASA class, and previous percutaneous coronary stent as covariates. Each patient in the MVR-PD group was matched to 3 patients with the closest PS but with a range of no more than ±0.02 from the index value of the case.

The primary metric for the PS analysis was the average effect of treatment on the treated (ATT). This is the difference in outcome between the MVR-PD case and the matched controls. To deal with the uncertainty induced by both the selection process and the data, bootstrapping was used to compute 95% confidence intervals. Reported inferences for the ATT are based on 500 bootstrap replicates. All statistical analyses were performed using STATA (version 12.1, StataCorp LLP, College Station, TX) and the psmatch2 routines.[8]

RESULTS

Population characteristics. Of 10,305 eligible PDs, 97 (1%) emergency cases, 247 (2.4%) patients with disseminated cancer, and 34 (0.5%) cases where the extent of resection was ambiguous were excluded. The final study sample consisted of 9,927 cases where 9,654 (97%) were PD alone and 273 (3%) were MVR-PD as defined. Overall, the population was 51% male with a median age of 65 years. The groups were well-matched in preoperative characteristics. Pancreatic cancer was the leading postoperative diagnosis in 56% of cases, similar for both groups (Table I). Benign pancreatic disease was slightly more common in the PD alone group (25%) than the MVR-PD group (19%). In the MVR-PD group, duodenal malignancies were more common (12% vs 4%; $P < .0001$), whereas periampullary malignancies were less common (4% vs 11; $P < .0001$).

Although nearly 30% of patients had no comorbidities, only 10% of patients had ≥3 comorbidities. Medical comorbidities were well-matched between PD and MVR-PD groups; ASA class was ≥3 in 70% of cases. More patients who underwent MVR-PD had an ASA class of ≥3 (78% vs 69%; $P = .002$). In the MVR-PD group, the most common concurrent resections were colon (58%) and small bowel (30%). MVR usually meant only one additional organ (90.5%). As expected, the MVR-PD group had greater operative times and greater durations of hospitalization ($P < .001$).

Outcomes. The primary outcome, mortality, occurred in 3% of patients. Mortality was greater for the MVR-PD cases on bivariable analysis (8.8% vs 2.9%; $P < .001$; Table II). In this population, age, preoperative cardiopulmonary disease, chemo- or radiotherapy, steroid use, ASA class, and perioperative transfusion of ≥2 units of red blood cells were predictive of mortality on stepwise logistic regression. The final diagnosis was not predictive of mortality. Even after adjusting for these possible confounders as well as the overall greater ASA class in the MVR group on multivariable analysis, MVR was associated with an odds ratio (OR) of 3.40 for mortality when compared with PD alone ($P < .001$; Table III).

Patients in the MVR-PD group experienced greater rates of overall morbidity compared with those in the PD group (65.2% vs 39.8%; $P < .001$). Rates of both major (56.8% vs 30.8%) and minor (24.9% vs 16.7%) morbidity were greater in the MVR-PD group (each $P < .001$; Table II). Cardiac, pulmonary, thromboembolic, and wound morbidity were all statistically greater and nearly twice as common after MVR-PD. The MVR-PD groups also experienced more renal failure, sepsis, shock, and bleeding events ($P < .001$).

On multivariable regression, the odds of overall major and minor morbidity were greater for the MVR-PD group (Table III). MVR-PD was associated with an OR of 3.21 for major morbidity ($P < .001$) and 1.65 for minor morbidity ($P = .03$). In addition to previously mentioned factors, colon resection and preoperative weight loss of >10% were independent predictors of overall and major morbidity and were controlled for in the regression model (Table IV). Colon resection was associated with an OR 1.90 (95% confidence interval [CI], 1.1–3.2) for major morbidity ($P = .02$). Weight loss and colon resection were not independently associated with minor morbidity ($P > .1$).

Among groups matched for PS, MVR-PD patients had a mortality rate of 7.7% compared with 3.5% of PD patients. The ATT was statistically significant, 4.2% ($P = .015$; 95% CI, 0.0081–0.75). In the PS-matched analysis, morbidity of MVR-PD was 62.7% compared with 39.2% for PD patients giving an ATT of 23.5% ($P < .0001$; 95% CI, 0.16–0.31). Major morbidities were also greater for MVR-PD compared with PD with an ATT of 24.4% ($P < .0001$; 95% CI, 0.17–0.32).

Table I. Description of study sample

Characteristic	*Pancreatoduodenectomy*	*Multivisceral resection*	P *value*
n (%)	9,654 (97)	273 (3)	
Age, median (y)	65	63	.01
>65	5,064 (62)	124 (42)	.02
Male	4,934 (51)	161 (59)	.03
Smoking	2,086 (22)	69 (25)	.35
Independent function	6,144 (64)	151 (55)	.004
Diagnosis			
Pancreatic cancer	5,373 (56)	155 (57)	.7
Benign pancreatic disease	2,431 (25)	53 (19)	.3
Duodenal cancer	421 (4)	32 (12)	<.001
Periampulary cancer	1,087 (11)	12 (4)	<.001
Comorbidities			
Radiotherapy	270 (3)	6 (2)	.7
Chemotherapy	197 (2)	7 (3)	.7
COPD	415 (4)	15 (5)	.3
Preventive coronary stent	594 (6)	21 (8)	.5
Hypertension	5,152 (53)	138 (51)	.4
Diabetes	1,943 (20)	63 (23)	.2
Weight loss >10%	1,780 (18)	57 (21)	.3
ASA class ≥3	6,693 (69)	213 (78)	.002
Operative procedures			
Jejunal tube	172 (2)	7 (3)	.3
Vascular repair	339 (4)	14 (5)	.2
Hepatectomy		7 (3)	
Colectomy		157 (58)	
Small bowel resection		83 (30)	
Nephrectomy		13 (5)	
Adrenalectomy		12 (4)	
Gastrectomy		34 (12)	
Operative time	355	426	<.0001

ASA, American Society of Anesthesiology; *COPD*, chronic obstructive pulmonary disease.

In our sensitivity analysis, 101 patients who were classified originally as PD+MVR were reclassified as PD. The PD+MVR group was 172 patients (1.7%) who underwent resection of colon, kidney, or adrenal at the time of PD. The standard PD group was 9,755 patients (98.%). The groups were similar at baseline with the same differences as in the primary analysis. When comparing PD+MVR cases with standard PD, the sensitivity analysis showed an even greater difference in mortality (10.5% vs 2.9%) and major morbidity (62.8% vs 31%). There were no changes in the findings.

DISCUSSION

A nihilistic attitude toward PD was pervasive throughout the 1960s and 1970s in many institutions. Improvements in technique, perioperative care, and interventional radiology ushered in an era where PD can be performed with less mortality and a more acceptable albeit still substantial morbidity.[9,10] From near abandonment, perhaps the pendulum regarding PD has swung too far the other way. Excellent perioperative outcomes have allowed for expansion of indications to include premalignant disease. Indeed, in our study, 25% of cases carried a postoperative diagnosis of benign disease. Increasingly complex resections are common, employing venous or arterial reconstruction without ostensible major worsening of morbidity or oncologic survival reported.[11-14] In the modern era, PD has matured, and complex resections are well accepted.

In this study of 9,961 PDs performed across the United States, nearly 3% of these PDs included resection of other viscera. We must presume that the operating surgeons deemed the benefit of additional resection greater than the risk of more complex operations. The most likely explanation for MVR is that additional organ resection was necessary to achieve R0 margins during oncologic surgery, although bystander organ injury owing to adhesions and the complexity of the pancreatic resection is possible. Similarly, it must be inferred that these surgeons felt that the additional

Table II. Outcomes

Outcome	*Pancreatoduodenectomy*	*Multivisceral resection*	P *value*
n (%)	9,654 (97)	273 (3)	
Death	276 (2.9)	24 (8.8)	<.001
Any morbidity	3,841 (39.8)	178 (65.2)	<.001
Major morbidity	2,974 (30.8)	155 (56.8)	<.001
Minor morbidity	1,616 (16.7)	68 (24.9)	<.001
Superficial SI	951 (9.9)	44 (16.1)	.001
Deep SI	211 (2.2)	7 (2.6)	.7
Organ-space infection	1,007 (10.4)	58 (21.2)	<.001
Pneumonia	485 (5)	24 (8.8)	.005
Reintubation	487 (5)	29 (10.6)	<.001
Prolonged intubation	514 (5.3)	37 (13.6)	<.001
Pulmonary embolism	93 (1)	4 (1.5)	.4
Deep venous thrombosis	205 (2.1)	13 (4.8)	.003
Thromboembolism	275 (2.8)	16 (5.9)	.004
Cardiac arrest	120 (1.2)	11 (4)	<.001
Myocardial infarction	55 (0.6)	5 (1.8)	.008
Bleeding	929 (9.6)	61 (22.3)	<.001
Sepsis	1,040 (10.8)	59 (21.6)	<.001
Shock	412 (4.3)	28 (10.3)	<.001
Duration of stay, median days	10	13	<.0001

SI, Surgical-site infection.

resection did not add prohibitive morbidity to the case. Has the pendulum swung too far? We performed this study to ascertain whether additional organ resection during PD can be performed safely or if it worsens outcomes in a large population of patients from a diverse group of medical institutions participating in the ACS-NSQIP.

The mortality rate of 2.9% in our control group was similar to other studies from large series and other national databases with mortality <6%.[1,15,16] This finding lends external validity and allows some generalization of our results. In contrast with several small, single-institution studies, our study reveals an increased rate (8.8%) and 3.4 times greater odds of mortality in patients undergoing MVR+PD. This increased morbidity and mortality was present despite adjusting for potential confounders (such as cardiopulmonary comorbidities) and differences between groups (such as the greater ASA class in the MVR group) using multivariable regression. Should this substantially increased risk of mortality preclude potentially curative resection? Comparing these data with other major resections for malignancy, elective MVR+PD carries a mortality risk greater than lung resection (4.2%) or cystectomy (3.7%), but less than esophagectomy (8.9%).[2] The mortality of MVR+PD is similar to the mortality of standard PD at medium volume hospitals (5–19 pancreatic resections annually with the reported mortality of 7%) and the mortality in low-volume hospitals (12–16%).[3,17] Because NSQIP data lack identifiers, we could not assess volume–outcome relationships. The need for MVR at PD should not preclude resection, especially for a known malignancy.

Overall morbidity was 65.2% in the MVR group. Although this morbidity was much greater than the 39.8% after PD alone, similar complication rates of 30–60% have been reported previously at major institutions and high volume centers.[4,18] The additional morbidity observed in the MVR group may be owing to either (1) the additional resection and complexity of surgery or (2) the more invasive disease that required concurrent resection of another organ. The associated increase in both operative time and need for transfusion cannot be ignored, because both these variables have been shown to increase the risk of pulmonary and infectious complications.[19-21]

The added morbidity, although expected and common, consists primarily of major complications. Deep-space surgical site infections, sepsis, bleeding requiring transfusion, pneumonia, and prolonged ventilator dependence were the most common morbidities. These complications decrease patient quality of life substantially and constitute a monetary burden on the health care system.[22-24] The leading complication was organ-space surgical infection or intra-abdominal abscess. The incidence of organ-space surgical infection, 10.4%

Table III. Adjusted odds of morbidity with multivisceral resection

Outcome	*Adjusted odds ratio*	*95% confidence interval*	P *value*
Death	3.40	2.1–5.4	<.001
Any morbidity	3.01	2.3–4.0	<.001
Major morbidity	3.21	2.5–4.2	<.001
Minor morbidity	1.65	1.2–2.2	.03

Table IV. Organ resections independently associated with morbidity

Outcome	*Adjusted odds ratio*	*95% confidence interval*	P *value*
Any morbidity			
Colon	1.96	1.1–3.6	.03
Major morbidity			
Colon	1.90	1.1–3.2	.02

among PD alone and 21.2% among MVR, correlated almost exactly with rates of sepsis, at 10.8% and 21.6%, respectively. Occurring in approximately 20% of cases, pancreatic leak could explain the observed rates of organ-space surgical infection and sepsis.[25,26]

The sensitivity analysis aimed to ensure that the PD+MVR group was in fact patients who underwent resection of additional organs beyond the scope of a standard PD. After reclassifying some patients, the sensitivity analysis yielded the same findings as the primary analysis, that is, the increased morbidity and mortality among patients undergoing PD+MVR. In fact, the disparity in outcomes were worse in the sensitivity analysis. A potential explanation of this difference may have been because some patients were misclassified in the primary analysis. Alternatively, this analysis may demonstrate that small bowel and gastric resections are less morbid resections than colectomies, nephrectomies, or adrenalectomies. This latter hypothesis is supported by the finding that colectomies were an independent predictor of major morbidity on multivariable analysis.

As first introduced in 1983 by Rosenbaum and Rubin,[27] PS matching is used to decrease the impact of selection bias in the estimation of treatment effects when studying observational data. In our study, PS matching showed results parallel to our logistic regression model. By employing a second statistical method, we demonstrated the robustness of our overall findings.

Multivisceral or extended resection at PD fits the trend toward increasingly complex resections attempted for cure. In a series of en-bloc PD and right nephrectomies for malignancy, the morbidity was 60%, similar to this analysis.[11] The long-term outcomes were remarkable given the advanced malignancies and showed a 100% survival after a median follow-up of 14 months. Our group reported previously a series of 14 patients who underwent partial colectomy en bloc with PD. Despite 8 of 14 patients (57%) having some morbidity, the median survival was 20 months and 2-year survival was 37%.[28] In another study of 303 pancreatic resections, median overall survival was equivalent for standard resections compared with MVR (23.1 vs 19.8 months; $P = .8$), but the n values for MVR-PD are small.[5] Based on single-institution reports, long-term survival after MVR-PD seems similar to PD alone. Similarly, complex resections include vascular resection and/or reconstruction. Muller et al[29] published 110 venous resections with 41.8% morbidity and 3.6% mortality. Another series of 59 venous resections and 8 combined arterial and venous resections quotes 54% morbidity but demonstrates good long-term outcomes.[30] These and other studies evince morbidity after vascular resection similar what we have demonstrated for MVR.[31] The trend in pancreatic surgery is to attempt R0 resection even utilizing radical surgery because of a demonstrable survival benefit.

There are limitations to consider. The available data do not reference the final pathologic diagnosis, margin status, or intent of the surgeon when pursuing a more complex resection. Complex MVR is a well-recognized means of complete resection at the time of PD and so we believe the assumptions are justified. Although the data are rigorously audited and collected by dedicated and trained nurses, it is possible that simple PDs were miscoded as MVR if the distal gastrectomy or small bowel resection inherent to a PD were coded incorrectly as separate procedures. Moving simple PDs out of the MVR group would only serve to increase the morbidity in the MVR group and widen and highlight the difference between groups. NSQIP includes only perioperative events, without long-term survival data, and does not provide assessment of pancreatic leak or delayed gastric emptying. A newly created HPB-specific NSQIP may be available for future analyses.[32] A major limitation of our study is the lack of any credible survival data; indeed, the ACS-NSQIP has only 30-day outcomes and no mid- to long-term survival data. In the absence of any such long-term survival data for these patients, we can only comment on the risk of MVR and not the benefit. A large, longitudinal, multicenter,

prospective trial would be needed for this assessment. Our regression analysis on which organ resections independently predicted morbidity was limited by the overall small number of MVRs and also the relatively small number of individual organ resections. By contrast, the relatively large number of colectomies permitted proper analysis of this as a predictor. Last, despite the strengths of PS matching, it cannot account for selection bias related to unmeasured confounders.

In conclusion, only complete extirpation of periampullary and pancreatic malignancies permits the possibility of cure or long-term survival for these tumors. With improvements in perioperative morbidity, more radical resections have been attempted. In other much smaller studies, long-term survival has been suggested for vascular reconstruction and visceral resection. This study presents the largest group of MVR at PD yet reported and demonstrates increased mortality, morbidity and sepsis accompanying more radical resections. The risk of incomplete resection compared with MVR must be decided for individual patients. MVR at PD carries an increased risk of adverse events and should be employed judiciously.

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