J Gastrointest Surg (2012) 16:89–103
DOI 10.1007/s11605-011-1753-x

2011 SSAT PLENARY PRESENTATION

A Root-Cause Analysis of Mortality Following Major Pancreatectomy

Charles Mahlon Vollmer Jr. · Norberto Sanchez · Stephen Gondek · John McAuliffe · Tara S. Kent · John D. Christein · Mark P. Callery · The Pancreatic Surgery Mortality Study Group

Received: 5 May 2011 / Accepted: 13 October 2011 / Published online: 8 November 2011

Abstract
Introduction Although mortality rates from pancreatectomy have decreased worldwide, death remains an infrequent but profound event at an individual practice level. Root-cause analysis is a retrospective method commonly employed to understand adverse events. We evaluate whether emerging mortality risk assessment tools sufficiently predict and account for actual clinical events that are often identified by root-cause analysis.
Methods We assembled a Pancreatic Surgery Mortality Study Group comprised of 36 pancreatic surgeons from 15 institutions in 4 countries. Mortalities after pancreatectomy (30 and 90 days) were accrued from 2000 to 2010. For root-cause analysis, each surgeon "deconstructed" the clinical events preceding a death to determine cause. We next tested whether mortality risk assessment tools (ASA, POSSUM, Charlson, SOAR, and NSQIP) could predict those patients who would die (n=218) and compared their prognostic accuracy against a cohort of resections in which no patient died (n=1,177).
Results Two hundred eighteen deaths (184 Whipple's resection, 18 distal pancreatectomies, and 16 total pancreatectomies) were identified from 11,559 pancreatectomies performed by surgeons whose experience averaged 14.5 years. Overall 30- and 90-day mortalities were 0.96% and 1.89%, respectively. Individual surgeon rates ranged from 0% to 4.7%. Only 5 patients died intraoperatively, while the other 213 succumbed at a median of 29 days. Mean patient age was 70 years old (38% were >75 years old). Malignancy was the indication in 90% of cases, mostly pancreatic cancer (57%). Median operative time was 365 min and estimated blood loss was 700 cc (range, 100–16,000 cc). Vascular repair or multivisceral resections were required for 19.7% and 15.1%, respectively. Seventy-seven percent had a variety of major complications before death. Eighty-seven percent required intensive care unit care, 55% were transfused, and 35% were reoperated upon. Fifty percent died during the index admission, while another 11% died after a readmission. Almost half (n=107) expired between 31 and 90 days. Only 11% had autopsies. Operation-related complications contributed to 40% of deaths, with pancreatic fistula being the most evident (14%). Technical errors (21%) and poor patient selection (15%) were cited by surgeons. Of deaths, 5.5% had associated cancer progression—all occurring between 31 and 90 days. Even after root-cause scrutiny, the ultimate cause of death could not be determined for a quarter of the patients—most often between 31 and 90 days. While assorted risk models predicted mortality with variable discrimination from nonmortalities, they consistently underestimated the actual mortality events we report.
Conclusion Root-cause analysis suggests that risk prediction should include, if not emphasize, operative factors related to pancreatectomy. While risk models can distinguish between mortalities and nonmortalities in a collective fashion, they vastly miscalculate the actual chance of death on an individual basis. This study reveals the contributions of both comorbidities and aggressive surgical decisions to mortality.

Presented orally at the 52nd Annual Meeting of the Society for Surgery of the Alimentary Tract (SSAT), Chicago, IL, 10 May 2011.

C. M. Vollmer Jr. (✉) · N. Sanchez · S. Gondek · T. S. Kent · M. P. Callery
Department of Surgery,
Beth Israel Deaconess Medical Center,
Harvard Medical School, Boston, MA 02215, USA
e-mail: charles.vollmer@uphs.upenn.edu

J. McAuliffe · J. D. Christein
Department of Surgery, School of Medicine,
University of Alabama at Birmingham, Birmingham, AL, USA

The Pancreatic Surgery Mortality Study Group
International, Multi-institutional Consortium, Boston, MA, USA

Keywords Mortality · Death · Outcomes · Root-cause analysis · Pancreatectomy · Whipple's resection · Risk prediction

Introduction

Mortality rates following major pancreatic resection were initially almost prohibitive—ranging from 30% to 50%.[1] Gradually, improvement was made to the point where some surgeons touted large series of consecutive patients who did not die in the perioperative period.[2,3] Still, others insisted that continuing to perform these complex procedures was not justified given that overall mortality rates remained in the range of 25% or higher.[4] Improvements in operative technique and perioperative care in the 1980s led to a substantial decrease in mortality to <5% in specialist's hands,[5–7] allowing indications for pancreatectomy to expand beyond malignancy. Subsequent advances in specialization, training, and regionalization have allowed for even safer and more effective resections such that mortality rates have steadily decreased.[8–11] While some single institutions report rates of this outcome to be between 1% and 2%,[12–14] analysis of more ubiquitous administrative data indicates that mortality can still exceed 15%—particularly for those surgeons who perform these operations infrequently.[15] It is also evident that definitions of what constitutes an operative mortality after pancreatectomy and other high-acuity surgery are neither universally established nor consistently reported.[16,17]

Root-cause analysis is a retrospective method commonly employed to understand adverse outcomes. This technique allows for a more objective review of the sequence of events which lead to any given endpoint. While often employed in medical quality assurance and safety processes,[18] there is little in the way of literature regarding its value in surgical performance. One report demonstrated how this approach improved quality measures in a single liver transplant program.[19] Another showed how root-cause analysis could discover a relationship between inadequate surgical technique and development of a procedure-specific complication.[20] This approach is potentially useful in "dissecting" the course of care and linking its effects to various postsurgical outcomes.

Recently, there has been much enthusiasm over risk prediction models in high-acuity surgery. Pancreatectomy is often performed in the setting of daunting physiologic and pathologic considerations. Various models have been developed, assessed, and validated for predicting outcomes following pancreatic resections with the aim of selecting good candidates or optimizing their preparedness for pancreatectomy. Numerous tools are available, each with strengths and weaknesses. One approach (POSSUM) relies on the patient's physiologic and operative considerations.[21,22] Another, the SOAR score, considers a patient's preoperative condition using the Charlson comorbidity scale as a foundation.[23] Still others, derived from the ACS-NSQIP database, blend elements of both.[24,25] While these may be effective at segregating outcomes at the population level, the real ability of these tools to forecast an actual, individual mortality is unknown.

Today, death following pancreatectomy remains an infrequent but profound and often misunderstood occurrence. Often, the surgeon is left wondering, "What happened?" Given that little is known about *how* people die following pancreatectomy, that this outcome is now infrequent for any given surgeon, and that administrative database analyses lack granular detail, we sought to scrutinize the course of patients who suffer this fate at a collective practice level. We also wonder whether emerging mortality risk assessment tools sufficiently predict and account for actual clinical events that are often identified by root-cause analysis. To achieve these goals, a multi-institutional, multinational consortium of pancreatic surgical specialists (Pancreatic Surgery Mortality Study Group [PSMSG]) was assembled to study the nature of mortality following major pancreatic resection.

Methods

High-volume (>11 resections/year) pancreatic surgical specialists from 14 academic, academic affiliate, or private institutions and 4 countries participated in the PSMSG. Participants were asked to provide data on all patients who suffered mortality within 90 days following pancreaticoduodenectomy, distal pancreatectomy, central pancreatectomy, total pancreatectomy, or any other form of partial pancreatectomy (including enucleation) performed between 1 January 2000 and 1 October 2010. For each participating surgeon, characteristics studied include total number of pancreatic resections performed, total number of mortalities, mortalities by procedure, institutional mortality rate, and number of years of experience with pancreatic surgery following fellowship or emergence from residency training. Mortality rates for each specific form of pancreatectomy were not obtained as data regarding the total number of pancreatectomies performed at each institution were not subdivided by procedure type.

Participating surgeons were asked to provide, on a predeveloped and standardized spreadsheet, data regarding preoperative demographics, disease process, medical comorbidities, operative details, and the course of postoperative care for all mortalities in their practice during the study period. Complications, exclusive of death (grade 5), were categorized by the Clavien scale, with major complications considered to be grades 3–4.[26]

Pancreatic fistula is indicated by the International Study Group of Pancreatic Fistula (ISGPF) classification scheme with clinically relevant fistulas (CR-POPF) being grades B and C. Detailed definitions of other complications are described elsewhere.[27] Specific data were also accrued to allow for calculation of risk by various prediction models previously applied to pancreatic resection (POSSUM, Charlson-based, and ACS-NSQIP),[22–24] as well as for other recognized surgical prediction models (ASA and MELD).[28,29] Facts surrounding the temporal nature of the death as well as intraoperative technical considerations were sought. Individual surgeons were asked to provide details regarding the circumstances surrounding the death and to indicate whether an autopsy was formally obtained. Ultimately, each surgeon was asked to "tell a story" about the course of events in a free-text process.

For root-cause analysis, the operating surgeon "deconstructed" the sequence of clinical events preceding each death to retrospectively determine cause. They were specifically asked to opine, as objectively as possible, whether they felt the death could be attributed to dubious patient selection, a technical error, poor intraoperative judgment, or mismanagement during the recovery period. They were asked if, in hindsight, the death was predictable. From all this, surgeons were asked to provide, to their best understanding, what the cause of death was. Finally, a single objective arbiter (CMV) then reviewed the temporal order of events and the descriptive story for each individual mortality and assigned and categorized the most reasonable precipitant of death.

For purposes of comparison, a cohort of resections in which no patient died was identified. This group was accrued from the fully annotated prospective databases of *all* pancreatic resections performed by four surgeons (average of 8.5 years experience) at two of the participating PSMSG institutions—Beth Israel Deaconess Medical Center (BIDMC) and the University of Alabama at Birmingham (UAB). While it was neither practical nor feasible to accrue complete data on every operation performed from each institution involved (due to variance in the sophistication of databases), this robust sample (n=1,200) represents approximately one tenth of all the resections performed by the PSMSG throughout the same period studied. Twenty-three mortalities from these practices (11% of the overall mortality tally) were excluded from consideration with this distinct comparison group for an overall n=1,177. The demographics and characteristics of this cohort are similar to those evident in the contemporary literature for pancreatic surgical specialty practice. Pancreaticoduodenectomy was performed in 64%, distal pancreatectomy in 28%, total pancreatectomy in 5%, and other pancreatic resections accounted for 3%. The mean age was 60 years and 16% were >75 years old. The full spectrum of pancreatic surgical disease was represented; 47% of operations were performed for malignancy, 18% were for cystic lesions, 20% were for pancreatitis, and 15% were for other conditions.

Quantitative data were analyzed in aggregate (all resections), by individual operations (proximal, distal, and total pancreatectomies), timing of death (>30 or <30 days post resection), and assigned cause of death (surgical vs. nonsurgical). Univariate analysis and multivariate logistic regression of factors deemed to be clinically significant were performed to determine potential predictors for mortality. We next tested whether recognized mortality risk assessment tools (ASA, MELD, POSSUM, Charlson, SOAR score, and ACS-NSQIP) could predict those patients who would die. POSSUM (morbidity) and Portsmouth-POSSUM (P-POSSUM; mortality) scores were calculated similar to the methods described by Copeland[21] and Pratt.[22] SOAR score calculations, using Charlson scores as a foundation, were performed using a web-based tool designed and validated by Hill et al.[23] Finally, an ACS-NSQIP-based risk prediction tool for pancreaticoduodenectomy, tested and validated by Greenblatt et al.,[24] was employed. While Kelly et al. have described a similar process for distal pancreatectomy,[25] a working tool for this is not yet available. Analogous ACS-NSQIP-based systems for either total or segmental pancreatectomies are also not yet developed.

Data were prospectively collected under separate institutional review board (IRB)-approved protocols for analysis of all pancreatic resections performed at BIDMC and the UAB. Data accrued for mortalities at all other involved institutions were exempt from typical IRB requirements for the study of living subjects. Instead, approvals were obtained to allow for the study of deceased individuals according to local standards and protocols at each participating institution.

Statistical analysis was performed using PASW 18.0 for Macintosh. For all univariate data, significance was determined using a Student's t test for continuous variables, Fisher's exact test for binary variables, and Pearson's chi-squared test for categorical variables. ASA scores were treated as categorical, while MELD, POSSUM, NSQIP, Charlson, and SOAR analyses were all treated as continuous variables. Univariate odds ratios were confirmed with a Mantel–Haenszel test. A multivariate logistic regression was performed on all variables deemed to be clinically significant, with only clinically significant variables shown for the preoperative and intraoperative characteristics demonstrated in Table 6.

Results

From January 2000 through October 2010, 36 attending surgeons whose experience averaged 14.5 years (range, 3–

43 years) performed 11,559 major pancreatectomies. Two hundred eighteen deaths occurred (184 pancreaticoduodenectomies, 18 distal pancreatectomies, and 16 total pancreatectomies) for an overall 90-day mortality rate of 1.89%. There were no reported deaths following central pancreatectomy, segmental pancreatectomy, or enucleation procedures. Individual surgeon's mortality rates ranged from 0% to 4.7%. One hundred eleven patients died within 30 days of the index operation (0.96% rate), representing 51% of all reported deaths, while another 107 succumbed between 31 and 90 days. One hundred forty-two patients, representing 77.2% of this mortality cohort, expired during either the index hospitalization *or* within 30 days of the operation for a rate of 1.23%. The mean time to death was 35 days postoperatively, with a median of 29 days. Five patients (2.3%) died intraoperatively (one during a reoperation) and 49.5% died during the initial hospitalization for the index operation. An additional 11% expired in the hospital during a readmission. Therefore, 39.5% expired outside of a known hospitalization.

Of the overall mortality cohort, 120 were male and 98 were female. The average age was 70 years (range, 18–93 years) and 38.1% were considered elderly (>75 years old). Malignancy was the indication in 90% of cases, with pancreatic adenocarcinoma comprising 57% (n=124), followed distantly by ampullary adenocarcinoma (n=30; 13.8%). Cystic pathology was infrequently the indication (11%). The mean body mass index (BMI) was 25.7; 59.2% presented with obstructive jaundice and 108 patients received any form of preoperative biliary decompression (42.2% endobiliary; 7.3% percutaneously). Neoadjuvant chemoradiation therapy was applied to 7.2% of the patients. Eighty-three patients were hospitalized directly prior to the operation, while a majority (62%) was admitted on the day of the operation. The mortalities were compared to a cohort of 1,177 patients who did not die following their operation. Table 1 delineates numerous differences in the frequency with which common preoperative medical comorbidities were encountered.

There were also significant differences in operative features and postoperative management approaches (Table 1). Characteristics of the operations include a median operative time of 365 min (mean, 395 min), a median estimated blood loss (EBL) of 700 mL (mean, 1,240 mL; range, 100–16,000 mL), and a median of 4,850 mL of fluids administered (mean, 5,500 mL; range, 400–36,500 mL). Epidural catheters were used infrequently (29 patients). Vascular resection was performed in 33 (15.1%), while vascular repair occurred in an additional 10 patients. Multivisceral resection was necessary 33 times. For the proximal and total resections, 48% were of the pylorus-preserving variant.

Postoperatively, 192 patients (88.1%) suffered a complication exclusive of mortality. The mean number of complications per patient was 2.2 (median, 2.0; range, 0–10). Major complications affected 77.1% of patients. Specific complication rates are displayed in Table 2 and are compared to the cohort without any mortality. Hemodynamic compromise requiring either fluid or pressor resuscitation occurred 62.4% of the time. Multisystem organ failure affected one third of the patients among the mortality group (n=73).

Management of these complications is outlined in Table 1. Total parenteral nutrition (TPN; 44%), antibiotics (68%), and percutaneous drains (28%) were more often employed in the recovery period for mortality cases. Transfusions were administered at any point in the hospitalization to 55% of the patients—intraoperatively for 73 patients (33.5%) and postoperatively for 88 patients (40.4%—not mutually exclusive). Reoperation was undertaken 35.3% of the time, and multiple reoperations were required for 6% of all patients (n=13; 17% of the reoperative group). The intensive care unit (ICU) was used, at any point in the recovery, by 86.7%; 73.9% were admitted there directly from the operating room, while 45% were subsequently transferred there for management of complications. Patients spent an average of 8.7 days in the ICU (median, 3 days; range, 0–67 days). Dispositions following the initial admission included home (29.8%), home with visiting nurse support (7.8%), and rehabilitation (9.6%). The remaining 115 patients died in the hospital.

Surgeons were asked to answer a number of questions as objectively as possible. They indicated that 25 mortalities (12%) were attributable to an intraoperative event (e.g., hemorrhage, aberrant anatomy). They also suggested that technical errors or poor intraoperative judgment contributed to 45 poor outcomes (21%). Suboptimal postoperative management choices were felt to negatively impact the course of 8%. After detailed scrutiny, the operating surgeon felt they could identify a clear-cut cause of death in just over half the cases. Only 8.3% (n=18) of the mortalities were deemed predictable in hindsight and 14.7% were reasonably associated with poor patient selection in their minds. Finally, a formal autopsy was performed in only 33 patients (11%).

Root-cause analysis allowed for broad categorizations of cause of death. Table 3 illustrates that complications attributed to the operation (26.6%), followed by pancreatic fistula, were most often causative. However, for a full quarter of the patients, the reason for demise was "unknown." This category was far more evident in patients who died between 31 and 90 days (42.1%). Of deaths, 5.5% had associated cancer progression—all occurring between 31 and 90 days. The majority of patients with liver failure as the cause of death (five out of nine) had liver cirrhosis and the other four suffered decompensation secondary to the effects of major vascular resections. Whipple resections

Table 1 Frequency of medical comorbidities, operative features, and postoperative management approaches in patients who suffered a mortality following major pancreatic resection compared to a cohort of patients who did not suffer a mortality accrued from complete experience of two PSMSG practices and representing a 10% sample of the overall resection total

Comorbidity	Mortality, n=218		Nonmortality, n=1,177		P value
	Number	Percent	Number	Percent	
Age (years)	70.01		59.76		*<0.001*
Age >75 years	83	38.1	191	16.0	*<0.001*
BMI	25.70		26.57		0.077
Male gender	120	55.1	539	45.8	*0.012*
Malignant diagnosis	196	90.0	552	46.9	*<0.001*
Coronary artery disease	62	28.4	125	10.6	*<0.001*
Congestive heart failure	20	9.2	30	2.5	*<0.001*
Pulmonary condition	24	11.0	356	30.2	<0.001
Hypertension	133	61.0	306	26.0	*<0.001*
Peripheral vascular disease	23	10.6	50	4.2	*<0.001*
Cerebral vascular disease	18	8.3	27	2.3	*<0.001*
Diabetes	65	29.8	292	24.8	0.258
Gastrointestinal condition	22	10.1	109	9.3	0.724
Renal disease	25	11.5	61	5.2	*<0.001*
Liver disease	11	5.1	42	3.6	0.312
Prior (nonpancreatic) malignancy[a]	57	26.2	284	24.1	0.202
Anemia[a]	9	4.1	64	5.4	0.007
Coagulopathy	6	2.8	18	1.5	0.253
Psychiatric illness[a]	15	6.9	100	8.5	0.001
Current alcohol use[a]	41	18.8	262	22.3	<0.001
Smoking history	85	39.0	442	37.6	0.449
Illicit drug use[a]	7	3.2	32	2.7	0.348
Preoperative obstructive jaundice[a]	129	59.2	232	19.7	*<0.001*
Prior abdominal operation[a]	100	45.9	291	24.7	0.455
Operative/management variables					
Epidural analgesia used[a]	29	13.3	354	53.6	*<0.001*
Neoadjuvant therapy applied	16	7.4	7	0.6	*<0.001*
Preoperative biliary stent[a]	108	49.5	143	21.6	*<0.001*
Nonelective admission	83	38	72	6.1	*<0.001*
EBL (median/mean, mL)	700/1,240		300/384		*<0.001*
Operative time (median/mean, min)	365/395		307/321		*<0.001*
Intraoperative fluids (median/mean, mL)[a]	4,850/5,449		4,000/4,303		*<0.001*
Transfusion (intraoperative)	73	33.5	120	10.2	*<0.001*
Vascular resection of repair	43	19.7	16	1.4	*<0.001*
Multiorgan resection performed	33	15.1	N/A	N/A	N/A
Soft gland texture	62	28.4	380	32.3	<0.001
Small pancreatic duct (≤3 mm)	58	26.6	204	17.3	0.233
Parenteral nutrition used (TPN)	96	44.0	161	13.7	*<0.001*
Antibiotics used	137	62.8	342	29.14	*<0.001*
Percutaneous drain placed	61	28.0	50	4.3	*<0.001*
Reoperation (after index case)	77	35.3	52	4.4	*<0.001*
Transfusion (at any point in hospital)	119	54.6	246	20.9	*<0.001*

Italicized values indicate significance in favor of the mortality cohort

[a] Indicates that the numerator of the nonmortality group is 661

rarely suffered pulmonary embolism and otherwise followed a similar pattern to the overall cohort. Distal resections had fewer operation-related complications, but disease progression, pulmonary embolism, and medical conditions contributed more frequently. Naturally, total pancreatectomies were never affected by pancreatic fistula, but infection was a significantly more prominent cause than with other forms of resection.

Table 2 Frequency of complications experienced by 218 patients who suffered a mortality following major pancreatic resection

Complication	Mortality, n=218		Nonmortality, n=1,177		P value
	Number	Percent	Number	Percent	
Any complication	192	88.1	646	54.9	*<0.001*
Minor complication (Clavien 1–2)	88	40.4	525	44.6	0.760
Major complications (Clavien 3–4)	168	77.1	162	13.8	*<0.001*
Hemodynamic compromise	136	62.4	138	11.7	*<0.001*
Multisystem organ failure	73	33.5	N/A	N/A	N/A
Ileus	28	12.8	59	5.0	*<0.001*
Delayed gastric emptying	33	15.1	80	6.8	*0.001*
Biloma	11	5.1	32	2.7	*0.05*
Bleeding	58	26.6	52	4.4	*<0.001*
Abscess	44	20.2	85	7.2	*<0.001*
Myocardial infarction	22	10.1	18	1.5	*<0.001*
Acute renal failure	67	30.7	33	2.8	*<0.001*
Pneumonia	47	21.6	59	5.0	*<0.001*
Respiratory distress	90	41.3	76	6.5	*<0.001*
Neurological	28	12.8	33	2.8	*<0.001*
Sepsis	78	35.8	35	3.0	*<0.001*
Wound infection	33	15.1	148	12.6	0.199
Wound dehiscence	8	3.7	21	1.8	0.065
Urinary tract infection	21	9.6	69	5.9	*0.023*
Pancreatic fistula (ISGPF)					
Any fistula	62	28.4	255	21.7	*0.022*
Grade A	14	6.4	97	8.2	0.385
Grade B	9	4.1	136	11.6	*0.001*
Grade C	39	17.9	22	1.9	*<0.001*
Clinically relevant (B+C)	48	22.0	158	13.4	*<0.001*

These are compared to a cohort of patients who did not suffer a mortality accrued from complete experience of two PSMSG practices (representing a 10% sample of the overall resection total). Italicized values indicate significance in favor of the mortality cohort

Table 3 Categorization of reasons of death after root-cause analysis for 218 patients who suffered a mortality following major pancreatic resection

Category	Overall n=218	Proximal n=184	Distal n=18	Total n=16	P value
Operation-related complication[a]	58 (26.6%)	52 (28.3%)	1 (5.5%)	5 (31.3%)	0.104
Pancreatic fistula	30 (13.8%)	28 (15.2%)	2 (11%)	0	0.224
Cardiac event[b]	19 (8.7%)	16 (8.7%)	2 (11%)	1 (6.3%)	0.882
Postoperative infection	18 (8.3%)	13 (7%)	1 (5.5%)	4 (25%)	0.04
Disease progression	12 (5.5%)	8 (4.4%)	2 (11%)	1 (6.3%)	0.539
Liver failure	9 (4.1%)	9 (5%)	0	0	0.420
Vascular event	6 (2.8%)	5 (2.7%)	1 (5.5%)	0	0.612
Medical condition	5 (2.3%)	3 (1.6%)	2 (11%)	0	0.03
Pulmonary embolism	4 (1.8%)	1 (0.5%)	2 (11%)	1 (6.3%)	0.002
Postoperative fluke event[c]	3 (1.4%)	2 (1.1%)	1 (5.5%)	0	0.265
Unknown cause	54 (24.8%)	47 (25.5%)	4 (22%)	4 (25%)	0.966

Results are subgrouped by resection type as well. P values correspond to comparison between subgroups

[a] Includes aspiration events, bleeding events, bowel obstruction, ischemic bowel, pancreatitis, anastomotic leak exclusive of pancreatic fistula, vascular injuries incurred during surgery, graft thromboses, and other effects from an intraoperative event

[b] Includes myocardial infarction (MI), pulseless electrical activity (PEA) arrest, and sudden death

[c] Includes hip fracture, heparin-induced thrombocytopenia, and intracranial bleed s/p a fall

Deaths following pancreatectomy were further characterized according to type of resection performed. Table 4 features demographics, intraoperative factors, and postoperative outcomes where there are discrepancies between the various operations. In general, total pancreatectomies mirrored proximal resections, while distal pancreatectomies differed in many ways. Distal resections were more often younger, had fewer reoperations, suffered fewer bleeding complications, utilized the ICU less frequently, had fewer transfusions, and less often required vascular resection. They more frequently had splenectomies as well as multivisceral resections and more often manifest clinically relevant fistulas. They were discharged to home more often and died less frequently in the hospital or during the index hospitalization.

Patients who expired from operative-related factors (n=58) and pancreatic fistulas (n=30) were compared to those who died of other causes, specifically looking at intraoperative characteristics and risk factors for fistula development. Operative times did not differ between the three groups (mean, 395 min). Patients who died of "surgical" complications had substantially higher mean EBL (1,992 vs. 1,000 mL), received more intraoperative fluids (6,521 vs. 5,495 mL) and interoperative transfusions (39.3% vs. 31.5%), and were subjected to vascular resections more often (37.9% vs. 14.6%). Similarly, patients who expired due to pancreatic fistula also had higher mean EBL (1,592 vs. 1,000 mL) and application of intraoperative transfusions (46.2% vs. 31.5%). Not surprisingly, softer pancreatic parenchyma and pancreatic ducts smaller than 3 mm in size were more frequently encountered (80% vs. 37% and 55% vs. 40%, respectively).

Those patients who succumbed within 30 days of the index operation were compared to those who expired between 31 and 90 days (Table 5). For deaths that occurred within 30 days, operation-related causes were most frequently seen, cardiac events were common, and almost all patients with liver decompensation succumbed in this early time frame. Conversely, in the extended phase (31–90 days), the reasons for deaths were "unknown" nearly half the time. All cases of disease progression occurred later, and neither pulmonary embolism nor postoperative fluke events were evident.

Preoperative comorbidities, management techniques, and intraoperative variables that were either felt to be clinically

Table 4 Characteristics of deaths following proximal, distal, and total pancreatectomies

Outcome	Proximal, n=184	Distal, n=18	Total, n=16
Age (mean years)	70.4	66.9	68.6
Elderly (>75 years old)	41.3%	5.6%	37.5%
Malignancy	90.8%	83.3%	87.5%
Pancreatic adenocarcinoma	54.3%	61.0%	87.5%
Preoperative jaundice	67.0%	0	37.5%
Neoadjuvant therapy administered	6.0%	5.6%	25.0%
EBL (median; mL)	675	500	2,000
Splenectomy performed	2.7%	89.0%	75%
Reoperation	35.9%	22.2%	35.3%
Clinically relevant fistula	20.1%	28.0%	0
Bleeding complication	28.8%	5.5%	25.0%
ICU use	86.0%	66.0%	86.7%
Hemodynamic compromise	62.5%	38.9%	75.0%
Multisystem organ failure	34.7%	22.2%	33.5%
Percutaneous drain placed	29.3%	27.8%	12.5%
Intraoperative transfusion	32.6%	27.8%	50.0%
Any hospital transfusion	55.4%	27.7%	50.0%
Vascular resection	19.0%	5.6%	31.3%
Multivisceral resection	6.0%	61.1%	62.5%
Death during index hospitalization	52.7%	22.2%	43.8%
Death in the hospital (at any point)	69.0%	38.9%	50%
Death within 30 days of operation	53.8%	50%	37.5%
Death between 31 and 90 days	46.2%	50%	62.5%
Death by pancreatic fistula	15.2%	11.1%	0
Discharged to home	27.7%	44.4%	31.0%
Survival (median days)	29	30	42

Table 5 Cause of death following major pancreatectomy analyzed by timing of death

Category	<30 days n=111	31–90 days n=107	P value
Operation-related complication[a]	38 (34.2%)	20 (18.7%)	0.014
Pancreatic fistula	17 (15.3%)	13 (12.1%)	0.558
Cardiac event[b]	16 (14.4%)	3 (2.8%)	0.009
Postoperative infection	10 (9.0%)	8 (7.4%)	0.807
Disease progression	0	12 (11.2%)	<0.001
Liver failure	8 (7.2%)	1 (0.9%)	0.036
Vascular event	3 (2.7%)	3 (2.8%)	1.00
Medical condition	3 (2.7%)	2 (1.9%)	1.0
Pulmonary embolism	4 (3.6%)	0	0.122
Postoperative fluke event[c]	3 (2.7%)	0	0.247
Unknown cause	9 (8.1%)	45 (42.1%)	<0.001

[a] Includes aspiration events, bleeding events, bowel obstruction, ischemic bowel, pancreatitis, anastomotic leak exclusive of pancreatic fistula, vascular injuries incurred during surgery, graft thromboses, and other effects from an intraoperative event

[b] Includes MI, PEA arrest, and sudden death

[c] Includes hip fracture, heparin-induced thrombocytopenia, and intracranial bleed s/p a fall

significant or were significant by univariate analysis (Table 1) were subjected to a multivariate analysis (MVA) to determine what factors are associated with higher chance of mortality. Table 6 shows those variables which are statistically significant, broken down by preoperative and intraoperative influences. Some clarification is necessary: (1) The odds ratio for malignancy is extreme and probably overestimated due to the overwhelming preponderance of that variable in the mortality group (90%); (2) Having a pulmonary condition is significant, but in a protective manner against mortality (OR is <1); (3) A similar situation exists for the use of an epidural catheter, i.e., NOT using an epidural is associated with mortality; (4) Smoking history was not significant on original univariate analysis, but rises to significance in the multivariate model; (5) EBL is not significant on the MVA given its covariance with intraoperative transfusion—which is strongly significant; (6) In contrast to the univariate analysis, the effects of operative time on morbidity reverse in the MVA where *shorter* operations are more lethal.

Table 7 compares various risk assessment scores of the mortalities to a cohort of patients who did not die following their operation. While assorted risk models predicted mortality with variable discrimination from nonmortalities, they consistently underestimated the actual mortality events we report, as the overwhelming majority of deaths were NOT accurately forecast. For the vast majority of patients, ASA scoring offered little discrimination between patients who would expire and survive, but it demonstrates that operating on class 4 patients is more lethal (odds ratio, 3.95). Analysis with POSSUM predicted the highest mortality rate for the true mortalities (21.7%), but this was not significantly different from the nonmortality cohort. Conversely, it more accurately discriminated the occurrence of morbidities between the cohorts. The impact of operative performance on determining outcome is distinguished by POSSUM. While the physiologic component of the scoring system was similar, there was a real difference in the operative score for the mortalities, indicating more difficult technical circumstances. Observed to expected (O/E) ratios were calculated using POSSUM and demonstrate inferior performance in the mortality cohort. The MELD, ACS-NSQIP, Charlson, and SOAR models all predicted mortality would occur more often in the mortality group, albeit at

Table 6 Multivariate logistic regression of factors significantly associated with mortality within 90 days of major pancreatic resection

	P value	Odds ratio	Confidence interval
Preoperative comorbidities			
Malignant diagnosis	<0.001	782.19	180.39–3,391.56
Pulmonary condition	<0.001	0.001	0.000–0.004
Smoking history	<0.001	5.93	2.50–14.10
Cerebral vascular disease	0.002	9.18	2.19–38.45
Congestive heart failure	0.002	7.43	2.13–25.93
Age >75 years	0.008	3.40	1.37–8.41
Neoadjuvant therapy applied	0.035	30.53	1.28–728.10
Operative factors			
Vascular resection	<0.001	7.23	2.64–20.00
Intraoperative blood transfusion	<0.001	6.55	3.09–13.887
Epidural catheter	<0.001	0.28	0.142–0.567
Small pancreatic duct (<3 mm)	0.002	3.050	1.49–6.25
Operative time	0.034	0.41	0.184–0.905

Separate analyses were conducted for preoperative and intraoperative variables. Univariate significance for each factor can be found in Table 1. Estimated blood loss, intraoperative fluids, and a soft gland did not rise to significance in the operative factor analysis

Table 7 Comparison of mortality risk prediction tools applied to major pancreatectomies

Risk prediction tool (all mean values)	Mortality, n=218	No mortality, n=1,177	P value	Odds ratio (95% CI)	P value
ASA score	2.56	2.66	0.231		
Countable items	(n=101)	(n=923)			
ASA=1, n (%)	7 (6.9)	8 (0.9)	<0.001		
ASA=2	40 (39.6)	324 (35.1)			
ASA=3	44 (43.6)	566 (61.3)			
ASA=4	10 (9.9)	25 (2.7)			
ASA>3	54/101 (53.5)	591/923 (64.0)	0.040	0.645 (0.427–0.976)	0.048
ASA=4	10/101 (9.9)	25/923 (2.7%)	0.001	3.947 (1.838–8.477)	<0.001
MELD score	11.30	9.60	<0.001		
POSSUM					
Physiologic score	20.27	19.53	0.110		
Operative score	18.19	15.24	<0.001		
P-POSSUM (mortality)	21.7%	17.6%	0.579		
POSSUM score (morbidity)	64.4%	49.4%	<0.001		
O/E ratio	1.37 1.55[a]	1.11			
NSQIP (Whipple resections only)					
Predicted morbidity	28.98%	25.46%	<0.001		
Predicted mortality	6.07%	2.08%	<0.001		
Charlson					
Raw score	12.62	8.43	<0.001		
Group score, n (%)					
Low risk	38 (17.4)	652 (55.4)	<0.001		
Intermediate risk	161 (73.9)	520 (44.2)			
High risk	19 (8.7)	5 (0.4)			
High risk vs. all others	19/218 (8.7)	5/1,177 (0.40)		22.38 (8.262–60.624)	<0.001
High/intermediate risk vs. low risk	180/218 (82.6%)	652/1,177 (44.6)		5.88 (4.065–8.47)	<0.001
SOAR score					
Predicted mortality	5.09%	2.95%	<0.001		
Institutional-adjusted mortality	2.39%	0.86%	<0.001		

Cases of mortality were compared to a cohort of cases where there was no death (sampled from two institutions in the study)

[a] If mortality is considered a complication, then the observed complication rate in the mortality cohort is 100% and the O/E ratio increases

fairly low rates. Institutional-adjusted predicted mortality in the latter scheme was lower, reflecting the influence of the relatively low mortality rates of the surgeons participating in the PSMSG (all <5%).

Discussion

Today, death following major pancreatectomy is fortunately an infrequent event in the hands of pancreatic surgical specialists, yet it still occurs at rates as high as 16% when performed by low-volume surgeons.[15] Regardless, its occurrence is a profound, frequently unexpected event for the patient, their family, and the surgeon—who is often at a loss to explain how it occurred. While administrative datasets have been used to provide a global picture of this postoperative metric, they lack granular detail of many of the perioperative factors which may contribute to death. They also suffer from selective study cohorts or random sampling processes. Often, demographic, institutional, or systems considerations are analyzed in this manner, but the contribution of surgical decision making and performance is left unaccounted. Root-cause analysis is a technique employed regularly by safety and quality officers in the medical field. Its purpose is to retrospectively "deconstruct" the sequence of events leading to an adverse outcome, often using an objective arbiter. The aim is to identify points of impact where improvement of the quality of care can be rendered. To better understand the problem of mortality after pancreatic resection, we used this approach to scrutinize deaths collected from an international consortium of pancreatic surgical practices in the contemporary era.

Various definitions are used in the literature to describe mortality rates in high-acuity surgery ranging from "in-hospital," to "30-day," to "30-day or in-hospital," and even "up to 90-day." In this series, death occurred infrequently but rates differed based on these various definitions. Deaths occurred within 30 days of the index operation under 1% of the time. Using 30-day mortality *or* during the index hospitalization as a standard, this rose to 1.23%, and 90-day mortality climbed further to 1.89%—double that of 30-day mortality. As time accrues postoperatively, reasons for death which are not attributable to the operation itself, such as malignant disease progression, become evident. As opposed to the seminal experiences with these major operations, death on the operating table is now exceedingly rare (usually the result of hemorrhage). Instead, the mean time to death was over a month, indicating improved capabilities for short-term survival in intensive care settings for patients who suffer major complications. Surprisingly, a third of patients expired outside of a known hospitalization, indicating that they were initially well and ultimately deteriorated. More alarming, despite root-cause analysis, a full quarter of the overall mortalities were unexplainable. Detailing this by period of death, there were few in the <30-day period which were enigmatic (n=9, 4% of the overall series), but 42% of the deaths between 31 and 90 days were unsolved. This undoubtedly is an effect of lack of follow-up and could be a reflection on regionalization where patients are treated at centers distant from the original community.

Major complications, exclusive of death, were the rule (77%). Across the board, almost every relevant post-pancreatectomy complication occurred more frequently in the mortality group (Table 2). Without root-cause analysis, it is difficult to tell if these complications are causative or derivative. This analysis revealed pancreatic fistulae to be the second most common cause of death. Fistulas were more likely clinically relevant and of the lethal grade C variety by ISGPF classification. These aggressive fistulas may suggest disintegration of the pancreaticoenterostomy from poor construction, suboptimal local organ factors, or tenuous physiologic influences. In fact, deaths attributed to pancreatic fistulas were more often in the setting of soft glands and small ducts (80% and 55%, respectively) and high blood loss—all recognized risks for fistula development.[30] When surgical performance is judged by an O/E ratio using the POSSUM system, subpar values were obtained (1.37; 1.55 if mortality is included as a complication) compared to a nonmortality cohort (1.11). Surgeons were aggressive in managing these complications by reoperating over a third of the time. Intensive care resources were also liberally required. Due to the heterogeneity of the institutions and countries involved in the PSMSG, costs were not evaluated in this study. However, it could be surmised from the heavy resource utilization demonstrated herein (reoperations, protracted ICU use, transfusions, etc.) that costs are extensive—particularly disappointing since the resource investment fails to prevent a terminal event.

The nature of deaths in this series varied based upon the type of major resection performed. Importantly, no deaths were reported for parenchymal-sparing procedures such as segmental or central resections or enucleations. In many ways, the profile of proximal and total pancreatectomies was similar, but distal pancreatectomies differed in a number of respects. Collectively, they were younger and had more straightforward intraoperative characteristics including less blood loss, fewer transfusions, and fewer vascular resections. This translated into fewer "operation-related" deaths. Instead, pulmonary embolism and malignant disease progression were more common. Few died during the initial hospitalization; many were discharged to home and subsequently died outside of the hospital setting.

With the physiologic makeup of the patients in the mortality group demonstrating significant differences when compared to the nonmortality cohort, the question of patient selection is raised. Surgeons themselves indicated that only a fraction (8%) of these poor outcomes could be predicted in hindsight. Furthermore, they felt that only 15% were poorly selected. Table 1 shows numerous differences in the frequency of comorbid conditions in the mortality group. This translates into the POSSUM physiologic scores, Charlson raw scores, and SOAR group scores, which are considerably high and are greater than those of the nonmortality cohort. In this series, malignancy was the overwhelming diagnosis in the mortality cohort. It may be that surgeons' and patients' decisions to proceed with an operation in the setting of these risks are significantly influenced by the fact that cure from these diseases cannot be afforded without complete surgical resection.

It has been demonstrated that, for pancreatic resection, escalating physiologic risk worsens postoperative morbidity, increases resource utilization, and escalates costs. Yet, improved operative performance attenuates this effect.[31] This study now corroborates that perspective in terms of mortality following major pancreatectomy. The most frequent cause of death, as judged by root-cause analysis, was operative-related complications. This includes hemorrhage, anastomotic leaks, vascular injuries, graft thromboses, ischemic bowel, aspiration, pancreatitis, and bowel obstruction—all events put in motion by the process of laparotomy. Numerous operative variables are worse in the mortality cohort, including blood loss, operative time, fluid administration, and intraoperative transfusions. Additionally, vascular resections/repairs were more frequently required and multivisceral resections occurred frequently. The POSSUM operative score, which is largely driven by blood loss in elective settings, was significantly higher in this cohort. Importantly, for patients whose cause of death was either an operative-related complication or pancreatic fistula, blood loss was very high. The significance of this is emphasized in the MVA where intraoperative transfusions were highly significant. These are a surrogate of excessive blood loss in this series. The average blood loss of a patient receiving a transfusion was ~1 L more than those who did not receive intra-operative transfusion (388 vs. 1,298 mL; $P<0.001$). Local anatomic factors may also be in play. Neoadjuvant therapy was also a significant predictor—quite possibly reflecting more advanced or "borderline" tumors. Finally, the surgeon is faced with managing soft glands and small pancreatic ducts. Intraoperative decisions on how to best reconstruct pancreatic–enteric continuity may impact the development of a fistula and possibly whether a patient succumbs to this complication or not.

It has been proposed that risk-predictive scoring systems may improve patient selection. It is evident that no single system analyzed in this study is superior; each is derived by a different premise. While ASA showed no discrimination between mortalities and nonmortalities across the total population, it was useful in emphasizing a sizably increased risk in operation on precarious (class 4) patients. MELD has not yet been tested or validated for pancreatectomy, yet it did significantly discriminate between the two cohorts. As bilirubin and the international normalized ratio are two crucial components of the MELD score, it is likely that the high rate of obstructive jaundice from malignancy in the mortality cohort was influential in this observation. The POSSUM score has previously been validated as an accurate predictor of morbidity in pancreatic surgery[22] and this was confirmed in this study as well. However, its cousin, the Portsmouth-POSSUM, does not allow for accurate prediction of mortality. Its advantage, however, is that it allows for understanding of operative performance through its separate operative score component. Our findings indicate that there is a significant increase in this score in the mortality cohort, suggesting that the conditions of the operation are more unfavorable. This is largely driven by two factors in elective operations—the extent of malignancy and increased blood loss. NSQIP analysis of Whipple's resections did show value, but it is derived from preoperative factors and does not consider the impact of the operation itself. Finally, Charlson raw scores and group score analysis of underlying comorbidities demonstrated significant discrimination of patient acuity. This was also supported by the SOAR score integrated risk predictor which takes into account the procedure performed and other influences. What is well demonstrated from this data is the "dampening" effect of the institutional-adjusted rates, suggesting that mortality outcomes can be positively influenced by surgical and institutional expertise. The nature of the focal 10% sample cohort used for comparison in this study precludes proper statistical analysis of the discriminatory strengths and weaknesses of these systems.

The profile of a death in this series is of an elderly male with obstructive jaundice from cancer who has significant medical comorbidities (cardiopulmonary, vascular, or renal). While malignancy was an almost universal indication, pancreatic adenocarcinoma in particular was frequently the diagnosis. Extensive elements of surgical care were frequently employed in these patients, including neoadjuvant chemo-radiation therapy, vascular resections, and multiorgan resections. Specifically, blood loss and fluid administration were more significant in the mortality cohort, and transfusions, both intraoperatively (33%) and postoperatively (55%), were also alarmingly high. The cases were over an hour longer. Neoadjuvant therapy was strongly associated with death by MVA. This could indicate that these patients are more vulnerable physiologically in the wake of that therapy, but more likely it is a surrogate for more extensive disease burden which could equate to a more difficult technical operation. A particular point needs to be made about the total pancreatectomy mortalities in this series. Malignancy was the indication in 88%, with a median blood loss of 2 L and 31% vascular resection and 63% multivisceral resection rates. Furthermore, over 50% of the pancreatectomies who died from liver failure were known cirrhotics. The findings of this study suggest that there are costs associated with pushing boundaries in our assault on cancer, where poor choices are particularly magnified in patients with dubious baseline physiology or significant comorbidity.

The nature of this investigation using the root-cause technique allowed the original operating surgeon to reflect, perhaps more objectively at a distant point in time, on possible reasons for the death. Often, in the original period directly following the death, objectivity is clouded by feelings of dismay, confusion, and grief. The event may be more reasonably assessed when viewed from a distance and perhaps through the prism of further accrued experience in pancreatic surgery. Upon review, surgeons in this series admitted that their own technical performance, poor decisions, or management judgments may have contributed to about 30% of these deaths. They also acknowledged that intraoperative events, like major hemorrhage, possibly contributed to the patient's eventual demise. It is alarming that so few autopsies were performed (11%). More liberal use of this inquiry may shed more light upon the cause of death. This is best requested and obtained by the attending physician who has the strongest relationship with the patient and family.

There are three significant limitations to this study. First, this represents data accrued from the practices of pancreatic surgical specialists who are each high-volume providers at recognized tertiary care centers of excellence. Furthermore, the individual and institutional mortality rates are low (<5%). Therefore, generalizations to the full spectrum of surgeons who perform major pancreatectomy may be limited. These data may not accurately reflect generalized norms in patient selection or surgical practice. Second, the cohort used for comparison was limited in that it was not practical to accrue such exhaustive data for all 11,559 patients operated upon by the PSMSG surgeons. Instead, two practices with fully annotated databases, involving four surgeons and a tenth of the cases and mortalities, were scrutinized. There is certainly opportunity for bias given particular approaches employed by these surgeons and their institutional support systems. The inclusion of two different institutions should provide an element of variety—even if all institutions cannot contribute. However, the demographics and global outcomes of this cohort are congruent with literature benchmarks for pancreatic resection.[14] Finally, data interpretation by the original surgeons is, to a degree, hampered by inadequate means of patient follow-up and possible subjective bias. The vast majority of the patients with an "unknown" cause of death occurred in the delayed time frame (31–90 days). The surgeons' own interpretations were most commonly that of complete ignorance about the circumstances of death, as the patients expired remote from their direct care.

Conclusion

Pancreatectomy is often performed in the setting of daunting physiologic and pathologic considerations. This series discloses mortality following pancreatectomy to be an infrequent occurrence in the care of specialists. The profile is of an older patient with cancer and notable comorbidities. Root-cause analysis allows for identification of precipitants of death and reveals that 40% of mortalities in this series were attributed to the effects of the surgical intervention, including the construction of the pancreaticoenteric anastomosis. While preoperative prediction systems are useful in aggregate analysis of outcomes, they remain ineffective in prospectively predicting the course of any given patient's operation and recovery. Instead, this study emphasizes the importance of optimal operative performance. This is crucial given the already high baseline acuity of these patients—prominently illustrated in this analysis.

Acknowledgements The authors would like to acknowledge the hard work of the following people who accrued data for this project: Carolyn Phillips (Washington University of St. Louis), Karen Parks, BS (University of Alabama School of Medicine), and Minna Lee, MD (Columbia University School of Medicine). Finally, we acknowledge the useful collaboration of Dr. David Greenblatt, Dr. Kaytlin Kelly, Dr. Sharon Weber, and Mr. Todd Hanson from the University of Wisconsin regarding the use of the ACS-NSQIP risk prediction tool they developed. Finally, we appreciate the contribution of Dr. Jennifer Tseng (University of Massachusetts) for her insight into surgical risk scoring systems and pancreatic surgical mortality.

Appendix A. Members of the Pancreatic Surgery Mortality Study Group

David Adams, MD (Medical University of South Carolina, Charleston, SC, USA)

John Allendorf, MD (Columbia University, New York, NY, USA)

Claudio Bassi, MD (University of Verona, Verona, Italy)

Oliver Bathe, MD (University of Calgary, Calgary, Canada)

Stephen Behrman, MD (University of Tennessee, Memphis, TN, USA)

Giovanni Butturini, MD (University of Verona, Verona, Italy)

Mark P. Callery, MD (Beth Israel Deaconess Medical Center, Boston, MA, USA)

John Cameron, MD (Johns Hopkins University, Baltimore, MD, USA)

Carlos Chan, MD (Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico)

Michael Choti, MD (Johns Hopkins University, Baltimore, MD, USA)

John D. Christein, MD (University of Alabama at Birmingham, Birmingham, AL, USA)

Aram Demirjian, MD (Johns Hopkins University, Baltimore, MD, USA)

Elijah Dixon, MD (University of Calgary, Calgary, Canada)

Fred Eckhauser, MD (Johns Hopkins University, Baltimore, MD, USA)

Barish Edil, MD (Johns Hopkins University, Baltimore, MD, USA)

Massimo Falconi, MD (University of Verona, Verona, Italy)

William Hawkins, MD (Washington University of St. Louis, St. Louis, MO, USA)

John Hoffman, MD (Fox Chase Cancer Center, Philadelphia, PA, USA)

Thomas J. Howard, MD (Indiana University, Indianapolis, IN, USA)

Robert Jury, MD (Beaumont Hospital, Royal Oak, MI, USA)

Eugene Kennedy, MD (Thomas Jefferson University, Philadelphia, PA, USA)

Tara S. Kent, MD (Beth Israel Deaconess Medical Center, Boston, MA, USA)

Harish Lavu, MD (Thomas Jefferson University, Philadelphia, PA)

David Linehan, MD (Washington University of St. Louis, St. Louis, MO, USA)

Martin Makary, MD (Johns Hopkins University, Baltimore, MD, USA)

Giovanni Marchegiani, MD (University of Verona, Verona, Italy)

Katherine Morgan, MD (Medical University of South Carolina, Charleston, SC, USA)

Salvatore Paiella, MD (University of Verona, Verona, Italy)

Timothy Pawlik, MD (Johns Hopkins University, Baltimore, MD, USA)

Paolo Pederzolli, MD (University of Verona, Verona, Italy)

Taylor Riall, MD (University of Texas—Galveston, Galveston, TX, USA)

Roberto Salvia, MD (University of Verona, Verona, Italy)

Richard Schulick, MD (Johns Hopkins University, Baltimore, MD, USA)

Beth Schrope, MD (Columbia University, New York, NY, USA)

Steven Strasberg, MD (Washington University of St. Louis, St. Louis, MO, USA)

Francis Sutherland, MD (University of Calgary, Calgary, Canada)

Charles M. Vollmer, MD (Beth Israel Deaconess Medical Center, Boston, MA, USA)

Christopher Wolfgang (Johns Hopkins University, Baltimore, MD, USA)

Charles Yeo, MD (Thomas Jefferson University, Philadelphia, PA, USA)

References

1. Hunt VC, Budd JW. Transduodenal resection of the ampulla of Vater for carcinoma of the distal end of the common duct with restoration of continuity of the common and pancreatic ducts with the duodenum. *SG&O* 1935; 61:651–661.
2. Howard JM. Pancreatico-duodenectomy: forty-one consecutive Whipple resections without an operative mortality. Ann Surg. 1968 Oct;168(4):629–40.
3. Cameron JL, Pitt HA, Yeo CJ, Lillemoe KD, Kaufman HS, Coleman J.One hundred and forty-five consecutive pancreatico-duodenectomies without mortality.*Ann Surg.* 1993 May;217 (5):430–5.
4. Crile G Jr. The advantages of bypass operations over radical pancreaticoduodenectomy in the treatment of pancreatic cancer. *SG&O* 1970; 130:1049–1053.
5. Crist DW, Sitzman JV, Cameron JL. Improved hospital morbidity, mortality, and survival after the Whipple procedure. *Ann Surg* 1987; 206:358–365.
6. Trede M, Schwall G, Saeger H. Survival after pancreaticoduodenectomy. *Ann Surg* 1990; 211:447–458.
7. Cameron JL, Crist DW, Sitzmann JV, et al. Factors influencing survival following pancreaticoduodenectomy for pancreatic cancer. *Am J Surg* 1991; 161:120–125.
8. McPhee JT, Hill JS, Whalen GF, Zayaruzny M, Litwin DE, Sullivan ME, Anderson FA, Tseng JF. Perioperative mortality for pancreatectomy: a national perspective. *Ann Surg.* 2007 Aug;246 (2):246–53.
9. Eppsteiner RW, Csikesz NG, McPhee JT, Tseng JF, Shah SA. Surgeon volume impacts hospital mortality for pancreatic resection. *Ann Surg.* 2009 Apr;249(4):635–40.
10. Hill JS, McPhee JT, Whalen GF, Sullivan ME, Warshaw AL, Tseng JF. In-hospital mortality after pancreatic resection for chronic pancreatitis: population-based estimates from the nationwide inpatient sample. *J Am Coll Surg.* 2009 Oct;209 (4):468–76. Epub 2009 Aug 20.
11. Murphy MM, Knaus WJ 2nd, Ng SC, Hill JS, McPhee JT, Shah SA, Tseng JF. Total pancreatectomy: a national study. *HPB* (Oxford). 2009 Sep;11(6):476–82.
12. Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, Sauter PK, Coleman J, Hruban RH, Lillemoe KD. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg.* 2000 Nov–Dec;4 (6):567–79.
13. Fernández-del Castillo C, Rattner DW, Warshaw AL. Standards for pancreatic resection in the 1990s. *Arch Surg.* 1995 Mar;130 (3):295–9; discussion 299–300.
14. Vollmer, C.M., Jr., Pratt, W., Vanounou, T., et al., Quality assessment in high-acuity surgery: volume and mortality are not enough. *Arch Surg,* 2007. 142(4): p. 371–80.
15. Birkmeyer JD, SiewersAE, Finlayson EVA, et al. Hospital volume and surgical mortiality in the United States. *N Engl J Med* 2002; 346:1128–1137.
16. Carroll JE, Smith JK, Simons JP, Murphy MM, Ng SC, Shah SA, Zhou Z, Tseng JF. Redefining mortality after pancreatic cancer resection. *J Gastrointest Surg.* 2010 Nov;14(11):1701–8. Epub 2010 Sep 16.
17. Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S, Abdalla EK, Curley SA, Capussotti L, Clary BM, Vauthey JN. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. *J Am Coll Surg.* 2007 May;204 (5):854–62.
18. Peleg O, Givot N, Halamish-Shani T, Taicher S. Wrong tooth extraction: root cause analysis. *Quintessence Int* 2010;41 (10):869–72.
19. Perkins JD, Levy AE, Duncan JB, Carithers RL. Using root cause analysis to improve survival in a liver transplant program. J Surg Res 2005;129(1):6–16.
20. Ahmed AR, Miskovic D, Vijayaseelan T, O'Malley W, Hanna GB. Root cause analysis of internal hernia and Roux limb compression after laparoscopic Roux-en-Y gastric bypass using observational clinical human reliability assessment. *Surg Obes Relat Dis* 2011 Jan 14. doi:10.1016/j.soard.2010.12.009.
21. Copeland GP, Jones D, and Walters M. POSSUM: a scoring system for surgical audit. *Br J Surg* 1991; 78:356–360.
22. Pratt, W., Joseph, S., Callery, M.P., et al., POSSUM accurately predicts morbidity for pancreatic resection. *Surgery,* 2008. 143(1): p. 8–19.
23. Hill JS, Zhou Z, Simons JP, Ng SC, McDade TP, Whalen GF, Tseng JF. A simple risk score to predict in-hospital mortality after pancreatic resection for cancer. *Ann Surg Oncol.* 2010 Jul;17 (7):1802–7.
24. Greenblatt DY, Kelly KJ, Rajamanickam V, Wan Y, Hanson T, Rettammel R, Winslow ER, Cho CS, Weber SM. Preoperative Factors Predict Perioperative Morbidity and Mortality After Pancreaticoduodenectomy. *Ann Surg Oncol.* 2011 Aug;18 (8):2126–35. Feb 20. doi:10.1245/s10434-011-1594-6.
25. Kelly KJ, Greenblatt DY, Wan Y, Rettammel RJ, Winslow E, Cho CS, Weber SM. Risk stratification for distal pancreatectomy utilizing ACS-NSQIP: preoperative factors predict morbidity and mortality. *J Gastrointest Surg.* 2011 Feb;15(2):250–9.

26. Dindo D, Demartines N, and Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240:205–213.
27. Pratt W, Maithel SK, Vanounou T, Huang Z, Callery MP, Vollmer CM. Clinical and economic validation of the International Study Group of Pancreatic Fistula (ISGPF) Classification Scheme. *Annals of Surgery* 2007 Mar.; 245(3):443–451.
28. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, and Kim WR. A Model to Predict Survival in Patients With End-Stage Liver Disease *Hepatology* 2001; 33:464–470.
29. New Classification of Physical Status. Anestesiology 1963;24:111
30. Pratt WB, Callery MP, and Vollmer CM. Risk prediction for Development of Pancreatic fistula Using the ISGPF Classification Scheme. *World J Surg* 2008; 32:419–428.
31. Pratt, W., Callery, M.P., and Vollmer, C.M., Jr., Optimal surgical performance attenuates physiologic risk in high-acuity operations. *J Am Coll Surg*, 2008. 207(5): p. 717–30.

Discussant

Dr. Jennifer F. Tseng (Boston, MA): I applaud you for the monumental effort to get at the causes of our most dreaded event after pancreatectomy. I have two questions and a comment. First, you used self-reported data, which is subject to recall and selection bias. How did you control for this? Second, those that lived and died were drawn from different populations and thus are not directly comparable. Did or could you perform this analysis in a true population, and were the results the same? Finally, I would like to clarify the use of risk scores such as our SOAR score (which you refer to as Charlson-based in your manuscript draft) and ACS-NSQIP. Risk calculators are designed to identify individuals in a preoperative or prospective fashion that fall into higher-risk groups. Note that the highest-risk group in our SOAR score—customized at a high-volume center with 2% perioperative mortality—would have an average mortality on the order of 5%, compared to 0.5% in the lowest group. These scores are not designed to post hoc confirm known mortality, but to identify patients at greater risk. A better test of a score would be: how often did these known mortalities fall into the highest risk? Those identified high-risk patients might have benefited from an individualized strategy preoperative, decreasing their risk for perioperative death.

Closing Discussant

Dr. Charles M. Vollmer, Jr.: Thank you, Jennifer, for your discerning review. No doubt the method we employed is subject to the biases you point out. The mechanism for data acquisition simply could not accommodate a fully objective approach. I believe these are honorable, trustworthy surgeons who agreed to participate in this sometimes uncomfortable "soul-searching" process for the ultimate benefit of their, and others', patients. One element of balance was the fact that I served as a final objective arbiter in determining the root cause of death for each patient after scrutinizing the facts presented.

For your second question, I'd like to clarify that the comparison group of 1,177 patients is *not* drawn from an entirely different population. This did not represent some sort of obtuse historical control cohort. I am sorry if I gave you that impression. Rather, it was the full experience during that time frame of 2 of the 15 institutions involved that had complete annotation of data. This represents roughly a 10% sample (albeit not completely random) of both the overall cases (11,500), deaths (23 out of 218), and surgeons involved (4 out of 36). As you can imagine, it was practically unfeasible to accrue the depth of necessary data from so many index cases spread across databases of various sophistication. However, given that deaths were so infrequent in any given practice, the surgeons *were* able to concentrate on the data for these rare events in a manageable fashion. You are certainly correct in that the "best" process would be a complete head-to-head comparison of the mortalities to all cases performed, or at least a "better" process would be a truly random sample of the index cases. We feel that the comparison group we used was the best option we had to discern the characteristics between mortalities and nonmortalities. Finally, we are comfortable that the demographics and outcomes from the comparison group we used are comparable to current benchmarks in the literature for pancreatic resection surgery.

In response to your important final remark … I continue to struggle conceptually with the fact that these prediction scores are forecasting the chance of death to be only in the single digits for what is in fact a "pure" cohort. What I mean is, each of these patients actually experienced the outcome of death. You are entirely correct—we show data in a post hoc fashion as these systems have been applied to broad populations. These scores are not necessarily intended as audit tools (with possibly the exception of POSSUM), but rather for pre-event decision making. So, to your point that perhaps we will maximize their value through relying on risk stratification, we do have some data to share. For instance, for all comers, ASA did not show a significant difference between the mortality and nonmortality cohorts. However, if you drill down to the ASA IV class, there is indeed a fourfold increased risk for death (odds ratio, 3.95). Similarly, we segregated the Charlson score by risk groups. Mortalities were far more likely to be in either the high-risk (8.7% vs. 0.4%) or intermediate-risk (73.9% vs. 44.2%) strata. Furthermore, the odds ratio for death among the patients deemed high risk was 22.38. So, using these prediction tools, we can conclude that, by and large, the patients in the mortality cohort were of higher preoperative risk. You make reference to applying an individualized preoperative strategy for such patients. Perhaps, given the findings of this study, one such strategy (that of declining an operation) might be given more serious consideration in patients with dubious constitution.