Assessment of Complications After Pancreatic Surgery

A Novel Grading System Applied to 633 Patients Undergoing Pancreaticoduodenectomy

Michelle L. DeOliveira, MD,† Jordan M. Winter, MD,† Markus Schafer, MD,* Steven C. Cunningham, MD,† John L. Cameron, MD, FACS, FRCS (Eng) (Hon), FRCSI (Hon),† Charles J. Yeo, MD, FACS,† and Pierre-Alain Clavien, MD, PhD, FACS, FRCS**

Objective: To define a simple and reproducible classification of complications following pancreaticoduodenectomy (PD) based on a therapy-oriented severity grading system.

Background: While mortality is rare after PD, morbidity rates remain high. The lack of standardization in evaluating morbidity after PD has severely hampered meaningful comparisons over time and among centers. We adapted a novel classification of complication to stratify morbidity by severity after PD, to test whether the incidence of pancreatic fistula has changed over time, and to identify risk factors in a single North American center.

Methods: The classification was applied to a consecutive series of 633 patients undergoing PD between February 2003 and August 2005. Another series of 141 patients treated between 1987 and 1990 was also analyzed to identify changes in the incidence and severity of fistula. Univariate and multivariate analyses were performed to link respective complications with preoperative and intraoperative parameters, length of hospital stay, and long-term survival.

Results: A total of 263 (41.5%) patients did not develop any complication, while 370 (58.5%) had at least one complication; 62 (10.0%) patients had only grade I complications (no need for specific intervention), 192 patients (30.0%) had grade II (need for drug therapy such as antibiotics), 85 patients (13.5%) had grade III (need for invasive therapy), and 19 patients (3.0%) had grade IV complications (organ dysfunction with ICU stay). Grade V (death) occurred in 12 patients (2.0%). A total of 57 patients (9.0%) developed pancreatic fistula, of which 33 (58.0%) were classified as grade II, 17 (30.0%) as grade III, 5 (9.0%) as grade IV, and 2 (3.5%) as grade V. Delayed gastric emptying was documented in 80 patients (12.7%); half of them were scored as grade II and the other half as grade III. A significant decrease in the incidence of fistula was observed between the 2 periods analyzed (14.0% vs. 9.0%, $P < 0.001$), mostly due to a decrease in grade II fistula. Cardiovascular disease was a risk factor for overall morbidity and complication severity, while texture of the gland and cardiovascular disease were risk factors for pancreatic fistula.

Conclusion: This study demonstrates the applicability and utility of a new classification in grading complications following pancreatic surgery. This novel approach may provide a standardized, objective, and reproducible assessment of pancreas surgery enabling meaningful comparison among centers and over time.

(*Ann Surg* 2006;244: 931–939)

Mortality associated with pancreaticoduodenectomy (PD) has decreased dramatically to less than 5% over the past 2 decades in high-volume centers,[1–6] but persistent high morbidity rates have remained an important concern for patients, healthcare providers, and payers. While mortality is an objective and easily quantifiable outcome parameter, morbidity is only poorly defined, and this shortcoming has severely hampered conclusive comparisons among centers and within the same institution over time.[7–9] Similarly, the identification of risk factors related to specific complications has been difficult.

Recognizing this deficiency, there has been several recent attempts to define specific complications related to PD such as pancreatic fistula, either by individual groups[10–14] or through consensus statements from a few experts.[15] Although important, these definitions have focused only on one specific complication (pancreatic fistula), and typically lack a severity grading system. For example, when a pancreatic fistula is defined as the persistent drainage of amylase-rich fluid during the postoperative course or as radiologic evidence of pancreatic anastomotic disruption, no distinction is made between the minimal criteria and more severe manifestation leading to reoperation or even death. An attempt was recently made by a group of experts in pancreas surgery to grade pancreatic fistula by severity,[15] but the grading system is complex, includes multiple subjective criteria, and is not applicable to

From the *Swiss HPB (Hepato-Pancreato-Biliary) Center, Department of Visceral & Transplantation Surgery, Zurich University Hospital, Zurich, Switzerland; and †Department of Surgery, Johns Hopkins Medical Institutions, Baltimore, MD. The current address of Dr. Yeo is Department of Surgery, Jefferson Medical College, Philadelphia, PA.

Dr. DeOliveira is the recipient of a 2005 UNESCO-L'Oréal fellowship award for Women in Science.

Reprints: Pierre-Alain Clavien, MD, PhD, Department of Visceral and Transplantation Surgery, Zurich University Hospital, Rämistrasse 100, CH-8091 Zürich, Switzerland. E-mail: clavien@chir.unizh.ch.

ISSN: 0003-4932/06/24406-0931
DOI: 10.1097/01.sla.0000246856.03918.9a

other types of complications. Therefore, there is persistent need for the availability of a reproducible, simple, and widely acceptable system to grade all complications following PD.

A previously reported grading system[7–9] was recently revisited and validated in a large cohort of patients undergoing general surgery. An international survey confirmed the simplicity and reproducibility of the new grading system.[16] This classification was recently adopted by the International Transplantation Society[17] to prospectively monitor the outcome of living liver donors. A key feature facilitating the use of the grading system is that it mostly relies on the therapies used to correct negative events. This is crucial to minimize down grading of complications as even nursing notes can be used to secure appropriate grading in retrospective analyses. Another attractive aspect of the new classification is that it considers the patient perspective through a strong emphasis on long lasting disability. Such a grading system can be adapted to any complication as long as the minimal criteria to define each specific complication are well described and widely accepted.

We adapted this novel classification of complications by severity[16] to a large cohort of patients, who underwent a PD at Johns Hopkins Hospital, a high-volume center with the availability of a comprehensive database. We used the well-established Johns Hopkins definitions for pancreatic fistula and delayed gastric emptying (DGE),[18,19] and stratified them according to severity criteria. Of importance, the John Hopkins definition of pancreatic fistula is consistent with a recent consensus statements.[15]

The primary aims of the study were to evaluate the feasibility of grading each recorded complication in the database according to the novel classification system, to present specific complications by severity, and to identify risk factors. A secondary aim was to test the novel classification system in comparing the incidence and severity of one type of complication, pancreatic fistula, with a previous series of patients in the same institution. Finally, an attempt was made to evaluate the impact of complications on long-term survival.

MATERIALS AND METHODS

Classification of Surgical Complications

We approached negative outcomes and the grading of postoperative complications as described in previous studies.[7–9] Briefly, a negative outcome is considered to be any undesirable result, and we submitted that there are 3 types of negative results, namely, sequelae (which are inherent to a procedure), failures of therapy, and complications.[7] Sequelae are negative but unavoidable consequences of a specific surgical procedure, eg, scar after surgery or the development of diabetes after total pancreatectomy. Failures of therapy are instances in which the goal of treatment was not attained, eg, an R1 resection or tumor recurrence after surgery. Complications are considered to be any other deviation from the normal postoperative course.

A novel classification of complications by severity, recently published by our group,[16] was applied to postoperative complications after PD (Table 1). This system mostly relies on the therapy used to correct a specific complication.

TABLE 1. Classification of Surgical Complication[16] Adopted for Pancreatic Surgery

Grade	Definition
I	Any deviation from the normal postoperative course without pharmacologic treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacologic treatment with drugs other than ones allowed for grade I complications. Blood transfusion and total parenteral nutrition* are also included.
III	Requiring surgical, endoscopic, or radiologic intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication (including CNS complications)† requiring IC/ICU management
IVa	Single-organ dysfunction (including dialysis)
IVb	Multiorgan dysfunction
V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of the discharge, the suffix "d" (for disability) is added to the respective grade of complication (including resection of the pancreatic remnant). This label indicates the need for a follow-up to fully evaluate the complication.

*Note regarding DGE: The insertion of a central line for TPN or nasojejunal tube by endoscopy is a grade IIIa. However, if a central line is still in place or a feeding tube has been inserted at the time of surgery, then a TPN or enteral nutrition is a grade II complication.

†Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks.

CNS indicates central nervous system; IC, intermediate care; ICU, intensive care unit.

A special emphasis is given to life-threatening complications and permanently disabling complications. Whereas grade I and grade II complications include only minor deteriorations from the normal postoperative course that can be treated with drugs, blood transfusion, physiotherapy, and nutritional supply, grade III complications require interventional treatment. Grade IV complications are life-threatening complications with ICU management. Grade V means death of the patient.

Once the minimal criteria for each type of complication are defined (see below), each complication can be ranked according to the same grading system. In the current study, the overall complication rate was reported as the number of patients with at least one complication. For the analysis of complication severity, only the highest ranked complication was taken into account, while each complication was considered for the search of risk factors. Of note, perioperative mortality (grade V) was defined as death within 30 days of surgery or during the hospitalization following surgery.

Definition of Pancreatic Fistula and Delayed Gastric Emptying (DGE)

Both pancreatic fistula and DGE have been defined at Johns Hopkins Hospital for a long time,[1,18,19] and were recently endorsed in a recent consensus statement.[15] There-

fore, these definitions, as available in the database, were used for further analysis and appropriate grading. Pancreatic fistula was defined as the persistent drainage of ≥50 mL amylase-rich fluid (more than 3-fold elevation above upper limit of normal in serum amylase) on or after postoperative day 10, or pancreatic anastomotic disruption demonstrated radiologically. Drains near the pancreatic-enteric anastomosis were placed intraoperatively and removed between postoperative days 4 and 8 in the absence of a pancreatic fistula. However, a minimum follow-up of 30 days or to hospital discharge was considered in this analysis.

DGE was defined as either 1) nasogastric tube decompression for ≥10 days and one of the following criteria: a) emesis after nasogastric tube removal, b) postoperative use of prokinetic agents after postoperative day 10, c) reinsertion of a nasogastric tube, or d) failure to progress with diet; or 2) nasogastric tube decompression for <10 days and 2 of the 4 criteria.

Patients

A consecutive series of 633 patients undergoing PD at the Johns Hopkins Hospital from February 2003 until August 2005 was used as the target patient group. There were 340 male (54.0%) and 293 female (46.0%) patients with a median age of 65 years (range, 46–80 years). Whereas 466 patients (74.0%) had malignant disease, the remaining 167 patients (26.0%) had a variety of benign pancreatic diseases (only 36 patients, 6% of all cases and 21% of all benign cases, presented with chronic pancreatitis). Pylorus-preserving PD (n = 538) was the preferred surgical technique compared with classic PD (n = 95). Patients undergoing other types of pancreatic resections were not included. Technical details of the performed PD have been published elsewhere.[1,18] Briefly, a pancreaticojejunostomy was routinely performed using an end-to-side pancreaticojejunostomy with a double-layer suture line. Patient's characteristics, surgical technique, and postoperative diagnoses are presented in Table 2.

To test whether the incidence and severity of fistula have changed over time, we analyzed another group of 141 patients, who underwent PD between 1987 and 1990 (Table 2). There were 80 (57.0%) male and 61 (43.0%) female patients with a median age of 61 years.

TABLE 2. Patient Characteristics

	Period	
Demographics	**2003–2005 (n = 633)**	**1987–1989 (n = 141)**
Age (yr) [median, range (10th–90th percentiles)]	65 (46–80)	61 (36–74)
Gender [no. (%)]		
Male	340 (54)	80 (57)
Female	293 (46)	61 (43)
Pathologic diagnostic [no. (%)]		
Benign disease	167 (26)	38 (27)
Malignant disease	466 (74)	103 (73)
Surgical technique [no. (%)]		
PPPD	538 (85)	118 (84)
Classic PD (distal gastrectomy)	95 (15)	23 (16)

PPPD indicates pylorus-preserving pancreaticoduodenectomy; PD, pancreaticoduodenectomy.

The classification of complications was retrospectively applied to each patient, and each complication was graded from the information available in the database. The missing data were obtained by carefully reviewing medical charts. The data collection and the interinstitutional data analysis (Johns Hopkins Hospital and Zurich University Hospital) were approved by the Johns Hopkins Institutional Review Board.

Statistical Analysis

Groups were compared using χ^2 test, Fisher exact test, and the Mann-Whitney *U* test, where applicable. Correlation between factors was calculated by Spearman rank correlations. Risk factors for surgical complications and for fistulae were analyzed by a logistic regression. Survival rates were calculated according to Kaplan Meier method, and differences in survival curves were tested by the log-rank test. A *P* value of less than 0.05 was considered statistically significant. All analyses were performed with Statistical Package for the Social Sciences (SPSS, version 13.0, Chicago, IL).

RESULTS

What Is the Incidence of Complications After PD Using the Novel Classification System?

Each complication recorded in the database was easily captured and converted into the novel classification system. The overall postoperative complication rate following PD in this series of 663 patients was 58.5%; ie, at least one complication was detected in 370 patients. Thirty-seven (10.0%) of these 370 patients required additional information that was not available in the database including antibiotic, blood transfusion, and total parenteral nutrition. The remaining 263 patients (41.5%) had an uneventful postoperative course without any detectable complication.

As shown in Table 3, grade I complications occurred in 62 patients (10.0%), grade II in 192 patients (30.0%), grade IIIa in 66 patients (10.5%), and grade IIIb in 19 patients (3.0%). Grade IVa and IVb complications were found in 16 patients (2.5%) and 3 patients (0.5%), respectively. The grade V complication rate (mortality) was 2.0% (12 patients). Cause of death included sepsis with multiorgan failure in 6 patients (2 of them related to a pancreatic fistula), myocardial infarction and ventricular arrhythmia in 3, thromboembolism in 2, and mesenteric ischemia in 1 patient.

What Is the Incidence of Complications by Diagnosis and Severity?

The respective incidence of complications by diagnosis is shown in Table 3. The most common complications were of infectious nature (17.0%), followed by DGE (12.7%), pancreatic fistula (9.0%), and cardiopulmonary complications (5.0%). The most severe complications (grade III or greater) were again infection (7.5%, 47 of 633) followed by DGE (6.5%, 40 of 633), and pancreatic fistula (4.0%, 24 of 633).

TABLE 3. Overall Complication and Most Common Complications by Severity

			Complications					
Grade	n	%	Infection	DGE	Pancreatic Fistula	Cardiopulmonary	Bile Leak	Neurologic
I	62	10.0	22	0	0	0	1	1
II	192	30.0	37	40	33	17	0	1
IIIa	66	10.5	23	34	15	2	8	0
IIIb	19	3.0	10	3	2	2	2	0
IVa	16	2.5	8	1	5	4	3	2
IVb	3	0.5	0	1	0	2	0	0
V	12	2.0	6	1	2	5	1	0
Total (% of 633 patients)	370	58.5	106 (17.0%)	80 (12.7%)	57 (9.0%)	31 (5.0%)	15 (2.5%)	4 (0.6%)

DGE indicates delayed gastric emptying.

While infection was the most common source of severe morbidity, most infectious complications scored as grade I and II. The most common sites of mild infections included the surgical wound and urinary tract. Grade III infections were mostly represented by intra-abdominal abscesses (n = 14). DGE was recorded in 80 patients (12.7%) and occurred as grade II complications in half of these patients (n = 40). Most severe cases of DGE (n = 34) were grade IIIa, ie, required intervention without general anesthesia. Only 6 complications required more invasive procedures.

Fifty-seven patients (9%) developed a pancreatic fistula during the postoperative course. Of these patients, 33 (5.2%) had a fistula classified as grade II, 15 (2.4%) as grade IIIa, 2 (0.5%) as grade IIIb, and 5 (0.8%) as grade IVa. Two patients with severe pancreatic fistulae had a lethal outcome (grade V). The mortality rate related to pancreatic fistulae was 3.4%.

How Do Severity of Complications, Pancreatic Fistula and DGE Impact on the Length of Hospital Stay?

Here we tested the impact of complications on the duration of the hospitalization. Patients had a minimum follow up of 30 days or until hospital discharge. The severity of complications, as well as the occurrence of pancreatic fistulae, DGE, and infection revealed a highly significant impact on the length of the hospital stay ($P < 0.001$, Spearman rank correlation). Whereas the median hospital stay in patients without a complication was 6 days, range 5 to 9 days (10th and 90th percentiles), the length of stay for patients with a pancreatic fistula was 19 days, range 10 to 40 days (10th and 90th percentiles), DGE 14 days, range 8 to 26 days (10th and 90th percentiles), and infection 20 days, range 6 to 44 days (10th and 90th percentiles) were significantly prolonged ($P < 0.001$ for each). The length of hospital stay also correlated with complication severity ($P < 0.001$). For example, the length of hospital stay in patients with grade I complications was 7 days, with grade II 10 days, with grade IIIa 15 days, grade IIIb 11 days, grade IVa 17 days, and grade IVb 39 days. Median length of hospital stay in patients who suffered from a lethal complication (grade V) was 17 days, range 1 to 45 days (10th and 90th percentiles).

Did the Incidence of Fistula Change Over Time?

To test whether the incidence and severity of pancreatic fistulae have changed over time, we analyzed a cohort of patients who underwent PD between 1987 and 1990 (Table 2). The patient characteristics were comparable in terms of age, gender, diagnosis, and surgical technique, ie, a majority of pylorus-preserving pancreaticoduodenectomy (PPPD) was performed during both periods.

The pancreatic fistula rate was statistically significantly lower in the recent cohort compared with patients operated in the late 1980s (9.0% vs. 14.0%, $P < 0.001$) (Table 4). Most of the patients were scored as grade II in both groups, and the difference in the incidence of fistula was mostly due to increased grade II complication in the earlier period. The respective distribution of severity did not reach statistical significance.

What Are the Risk Factors for Specific Types of Complications?

An attempt was made to identify preoperative and intraoperative risk factors associated with overall complications and complication severity. Risk factors evaluated in the univariate and multivariate analyses included age, gender, pancreatitis, diabetes mellitus, a history of cardiovascular

TABLE 4. Incidence of Pancreatic Fistula

	Fistula			
	1987–1990		2003–2005	
Complication Grade	n = 141	(% of 141 patients)	n = 633	(% of 633 patients)
II	14	10.0	33	5.2
IIIa	4	3.0	15	2.4
IIIb	1	0.5	2	0.5
IVa			5	0.8
IVb	1	0.5		
V			2	0.3
Total	20	14.0	57	9.0*

*$P < 0.001$.

diseases, pancreatic gland texture (hard vs. soft), use of a preoperative biliary stent, PPPD versus classic PD, malignancy, operative time, estimated blood loss, and intraoperative blood transfusion. For malignant tumors, we also included surgical margin (positive vs. negative) and tumor stage (stage 0, I, II, III, IV). Cardiovascular disease was the only significant risk factor by multivariate logistic regression for overall complications ($P = 0.048$, OR, 1.45; 95.0% CI, 1.05–2.0), and by Spearman correlation test for complication severity (Mann-Whitney U test, $P = 0.008$). Of note, age did not significantly impact on the overall complication rate or any type of complications by severity (Spearman rank correlation, $P > 0.1$).

We tested similar risk factors for the development of a pancreatic fistula. Only cardiovascular disease ($P = 0.046$, OR, 3.05; 95% CI, 1.0–9.0) and texture of the pancreatic gland (soft pancreas) ($P = 0.005$, OR, 9.02; 95% CI, 1.91–42.66) were statistically significant parameters in the multivariate logistic regression analysis.

No risk factor could be identified in the multivariate analysis regarding the incidence and severity of DGE and infection.

May Complications Impact on Long-term Survival in Patients With Malignant Disease?

We also tested whether a type or severity of complication impacted long-term survival in patients with a malignant disease. While no statistically significant association was identified, a trend was noted correlating the severity of pancreatic fistula with long-term survival. Patients with severity grade II and III fistulae had a median survival time of 577 days, (SD, 95; 95% CI, 391–763 days), as compared with a median survival time of 302 days (SD, 41; 95% CI, 222–382 days) in patients with grade IV fistula (log rank, $P = 0.06$).

DISCUSSION

While pancreatic surgery is currently associated with low mortality rates in high-volume centers, morbidity has remained high.[1–3,5,20,21] No consensus exists on how to report and quantify morbidity after pancreatic surgery.[22] Here, we applied a novel classification of complications to a recent cohort of patients undergoing PD in a high volume center with the aims to describe each type of complication by diagnosis and severity, to compare one type of complication (pancreatic fistula) over time and identify risk factors for specific complications.

The lack of consensus on a definition of negative outcomes or a stratified grading system of complications after surgery continues to hamper proper evaluation of the surgeon's work and may affect the rate of progress in the surgical field.[16,22] In 1992, we proposed to differentiate 3 types of negative outcome, namely, sequelae, referring to an "after effect," ie, expected changes after surgery such as a scar or diabetes mellitus after total pancreatectomy; failure to cure covering negative events such as cancer recurrence after surgery; and finally, complications.[7] The term "complication" includes all other negative events. A grading system was designed to classify deviations from the normal postoperative course, based on the therapy used to treat a complication. While this grading system was subsequently used by us[8,9,23] and others[17,24–26] to assess the results of a variety of procedures, we recently revisited the classification by adding new grades with the aim to better cover life-threatening complications, such as those requiring intermediate care or ICU management. These complications are associated with a high mortality, stress for the patients, and substantial resource consumption. We also included complications involving the central nervous system (eg, stroke) in the same category (grade IV), since these patients must be treated in an ICU setting.[16] Another significant update to the grading system was the elimination of length of stay as a criterion. The duration of hospitalization varies greatly among centers and is often influenced by local historical practice. The novel classification system was tested in a cohort of 6336 patients, who underwent a variety of procedures. The acceptance and reproducibility of the classification system were demonstrated by an international survey completed by surgeons at various levels of training.[16] This classification system was also recently adopted in consensus conference (Vancouver Forum, November 15–16, 2005) organized by the International Transplantation Society[17] to prospectively monitor the outcome of living liver donors.

Pancreas surgery has been the subject of much scrutiny worldwide, with accumulating evidence assuming that high-volume centers provide better results.[1,3,6,27] This assumption is based only on the perioperative mortality rate. Although mortality can easily be assessed as an objective outcome parameter, it represents only one aspect of quality and overall outcome. Moreover, mortality has become a rare event in many centers, and its correlation with overall morbidity or specific complications, eg, pancreatic fistula and DGE, is poor. Therefore, mortality currently represents a weak surrogate of the quality of surgery. While constructive attempts were made to define and grade pancreatic fistula after PD,[12,15] the literature lacks a simple and reproducible grading system based on severity that is applicable to all types of complications.[22] Only such an approach may enable a thorough assessment of outcome following pancreas surgery.

To test whether the classification system could easily be applied to the evaluation of complications following PD, we used the criteria to analyze postoperative complications recorded in the PD database from the Johns Hopkins Hospital, which includes most postoperative events after pancreas surgery. This study demonstrates the 4-fold potential of the classification system for pancreas surgery. First, each recorded complication was easily converted into a complication grade. Additional information was required in just 37 patients (10%) to completely execute the conversion. Missing information included antibiotic use, postoperative blood transfusion requirements, and use of total parenteral nutrition. Second, the grading system provided an effective format to analyze the incidence and severity of different complications, and their impact on overall morbidity. Third, the classification system facilitated comparisons of patients treated during different decades. Finally, risk factors for morbidity, as well as for specific complications, could be identified.

The development of a pancreatic fistula after PD continues to receive a great deal of attention from pancreatic surgeons. At least 26 different definitions have been used to assess pancreatic fistulae, leakage, and peripancreatic fluid collections heralding fistula formation.[12] The lack of a universally used classification system may account for the wide range of reported pancreatic fistula-rates (from 5% to 40%),[10–13,20,28,29] so that conclusive comparisons among centers are almost impossible. An attempt was recently made by experts in pancreas surgery to establish a uniform and widely accepted definition of a postoperative pancreatic fistula,[15] which somewhat overlaps earlier definitions from the Johns Hopkins group.[18] However, the proposed definition and grading yielded 3 significant shortcomings. First, the panel accepted multiple different definitions for minimal criteria. For example minimal output may range from 10 mL to 50 mL. Second, the parameters used for the grading system (A, B, and C) are heavily dependent on subjective impressions made by the treating surgeons and are imprecise (eg, clinical condition is classified as either grade A (well), grade B (often well), or grade C (ill appearing/bad); the need for specific treatment is classified as grade A (no), grade B (yes/no), or grade C (yes). Third, the proposed system is limited to pancreatic fistula, whereas other postoperative complications cannot be assessed and compared in terms of severity. These limitations are in sharp contrast to our novel classification and grading system, which allows a consistent evaluation of different types of complications.

Using this new system, we demonstrated that pancreatic fistulae occurred in only 9% of patients after PD. About two thirds of the pancreatic fistula were grade II (ie, they did not require invasive therapies). Perioperative mortality resulted in just 3% of the patients with pancreatic fistula. Pancreatic fistula development ranks third among the different complications evaluated in terms of frequency and severity, and we may conclude that pancreatic fistula no longer represents the major and most worrisome complication after PD. The classification also enabled to compare the incidence and severity of pancreatic fistula over time. The observed fistula rate decreased significantly compared with a series of patients treated in the late 1980s, mostly due to a decrease in grade II fistula, while the incidence of more severe forms of fistula has remained unchanged. This observation is novel as other reports have suggested similar incidence of fistula over the past 2 decades.[10]

There is evidence from the current literature that DGE is responsible for almost 50% of the morbidity following PD,[1,6,30–32] whereby several surgical details, such as preservation of the pylorus and extent of lymph node removal, have no convincing impact on the incidence of DGE.[33] Furthermore, the underlying disease (chronic pancreatitis vs. pancreatic cancer) does not alter the rate of DGE after PD.[33] In the current series, 13% of patients developed a DGE, which is at the lowest limit of the reported ranges.[33] Of note, half of DGE complications were severe (grade III), leading to a substantial consumption of medical resources. This pattern may differ from the perception of many surgeons on the impact of DGE after PD.

The importance of risk factors for perioperative morbidity after pancreas surgery is not well established in the literature. Knowledge about risk factors is paramount to compare outcome among risk-adjusted populations. Our multivariate analysis did not show any correlation between the age of patients and any types or severity of complications after PD. This finding is consistent with recent reports that surgery should not be denied solely on the basis of age.[28,34,35] A history of cardiovascular disease was the only statistically significant risk factor for the frequency and severity of complications according to multivariate analysis. Soft texture of the pancreatic tissue significantly impacted the incidence of a pancreatic fistula after PD. Both of these findings are consistent with prior studies.[10,36]

CONCLUSION

We have presented a new classification of complications to evaluate the results of PD. The use of the classification system facilitated analyses of both the incidence and severity of specific complications. For instance, the analysis effectively demonstrated that pancreatic fistula is associated with a relatively low morbidity compared with the other frequent complications after PD. The classification system was easily applied to a pancreatic surgery database, demonstrating the tools broad applicability. Widespread implementation of the grading tool could benefit the surgical literature and ultimately patient care by standardizing outcome reporting. More precise discussions of perioperative morbidity are necessary to better understand technical innovations and novel neoadjuvant therapies. Furthermore, the label "center of excellence" should reflect objective assessments of morbidity, in addition to mortality.

ACKNOWLEDGMENTS

The authors thank Paul Harpes, PhD, from the Department of Biostatistics, University of Zurich for his assistance in the statistical analysis.

REFERENCES

1. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg*. 1997;226:248–257.
2. Bentrem DJ, Yeh JJ, Brennan MF, et al. Predictors of intensive care unit admission and related outcome for patients after pancreaticoduodenectomy. *J Gastrointest Surg*. 2005;9:1307–1312.
3. Fong Y, Gonen M, Rubin D, et al. Long-term survival is superior after resection for cancer in high-volume centers. *Ann Surg*. 2005;242:540–544.
4. Ho V, Heslin MJ. Effect of hospital volume and experience on in-hospital mortality for pancreaticoduodenectomy. *Ann Surg*. 2003;237:509–514.
5. Sosa JA, Bowman HM, Gordon TA, et al. Importance of hospital volume in the overall management of pancreatic cancer. *Ann Surg*. 1998;228:429–438.
6. Gouma DJ, van Geenen RC, van Gulik TM, et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. *Ann Surg*. 2000;232:786–795.
7. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. *Surgery*. 1992;111:518–526.
8. Clavien PA, Camargo CA Jr, Croxford R, et al. Definition and classification of negative outcomes in solid organ transplantation: application in liver transplantation. *Ann Surg*. 1994;220:109–120.
9. Clavien PA, Sanabria JR, Mentha G, et al. Recent results of elective

open cholecystectomy in a North American and a European center: comparison of complications and risk factors. *Ann Surg*. 1992;216:618–626.
10. Lin JW, Cameron JL, Yeo CJ, et al. Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. *J Gastrointest Surg*. 2004;8:951–959.
11. Buchler MW, Friess H, Wagner M, et al. Pancreatic fistula after pancreatic head resection. *Br J Surg*. 2000;87:883–889.
12. Bassi C, Butturini G, Molinari E, et al. Pancreatic fistula rate after pancreatic resection: the importance of definitions. *Dig Surg*. 2004;21:54–59.
13. de Castro SM, Busch OR, van Gulik TM, et al. Incidence and management of pancreatic leakage after pancreatoduodenectomy. *Br J Surg*. 2005;92:1117–1123.
14. Sato N, Yamaguchi K, Chijiiwa K, et al. Risk analysis of pancreatic fistula after pancreatic head resection. *Arch Surg*. 1998;133:1094–1098.
15. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery*. 2005;138:8–13.
16. Dindo D, Demartines N, 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.
17. Barr ML, Belghiti J, Villamil FG, et al. A Report of the Vancouver forum on the care of the liver organ donor: lung, liver, pancreas and intestine. Data and Medical Guidelines. *Transplantation*. 2006;81:1373–1385.
18. Yeo CJ, Cameron JL, Maher MM, et al. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. *Ann Surg*. 1995;222:580–588.
19. Yeo CJ, Barry MK, Sauter PK, et al. Erythromycin accelerates gastric emptying after pancreaticoduodenectomy: a prospective, randomized, placebo-controlled trial. *Ann Surg*. 1993;218:229–237.
20. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas—616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg*. 2000;4:567–579.
21. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med*. 2002;346:1128–1137.
22. Martin RC 2nd, Brennan MF, Jaques DP. Quality of complication reporting in the surgical literature. *Ann Surg*. 2002;235:803–813.
23. Sanabria JR, Clavien PA, Cywes R, et al. Laparoscopic versus open cholecystectomy: a matched study. *Can J Surg*. 1993;36:330–336.
24. Feldman L, Barkun J, Barkun A, et al. Measuring postoperative complications in general surgery patients using an outcomes-based strategy: comparison with complications presented at morbidity and mortality rounds. *Surgery*. 1997;122:711–719.
25. Targarona EM, Espert JJ, Bombuy E, et al. Complications of laparoscopic splenectomy. *Arch Surg*. 2000;135:1137–1140.
26. Ghobrial RM, Saab S, Lassman C, et al. Donor and recipient outcomes in right lobe adult living donor liver transplantation. *Liver Transpl*. 2002;8:901–909.
27. Birkmeyer JD, Finlayson SR, Tosteson AN, et al. Effect of hospital volume on in-hospital mortality with pancreaticoduodenectomy. *Surgery*. 1999;125:250–256.
28. Balcom JH, Rattner DW, Warshaw AL, et al. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. *Arch Surg*. 2001;136:391–398.
29. Bassi C, Falconi M, Salvia R, et al. Management of complications after pancreaticoduodenectomy in a high volume centre: results on 150 consecutive patients. *Dig Surg*. 2001;18:453–457.
30. Riediger H, Makowiec F, Schareck WD, et al. Delayed gastric emptying after pylorus-preserving pancreatoduodenectomy is strongly related to other postoperative complications. *J Gastrointest Surg*. 2003;7:758–765.
31. Shan YS, Tsai ML, Chiu NT, et al. Reconsideration of delayed gastric emptying in pancreaticoduodenectomy. *World J Surg*. 2005;29:873–879.
32. Muller MW, Friess H, Beger HG, et al. Gastric emptying following pylorus-preserving Whipple and duodenum-preserving pancreatic head resection in patients with chronic pancreatitis. *Am J Surg*. 1997;173:257–263.
33. Schafer M, Mullhaupt B, Clavien PA. Evidence-based pancreatic head resection for pancreatic cancer and chronic pancreatitis. *Ann Surg*. 2002;236:137–148.
34. Bottger TC, Engelmann R, Junginger T. Is age a risk factor for major pancreatic surgery? An analysis of 300 resections. *Hepatogastroenterology*. 1999;46:2589–2598.
35. Petrowsky H, Clavien PA. Should we deny surgery for malignant hepato-pancreatico-biliary tumors to elderly patients? *World J Surg*. 2005;29:1093–1100.
36. Yang YM, Tian XD, Zhuang Y, et al. Risk factors of pancreatic leakage after pancreaticoduodenectomy. *World J Gastroenterol*. 2005;11:2456–2461.

Discussions

MR. CHRIS RUSSELL: Mr. Chairman, Mr. President, thank you very much indeed for inviting me to discuss this paper, which has been so charmingly given by our Brazilian colleague, and, of course, it describes work on 2 continents: in the John Hopkins, Baltimore and the results of the analysis here in Zurich. We are obviously, as surgeons, now becoming very much involved with data analysis and prediction risk score. This is becoming so important because our work is being looked at extremely carefully; in the United States, full data have to be published, and indeed in Scotland the operative mortality of all surgeons is now published. So it is very important that we compare like with like, and really my great concern about this score is that you are dependent for the scoring very much on the way you analyze your complications. I looked at my own data, which are very similar in numbers to those presented and the one thing that we've done over the years is to change the way that we've managed complications. We now have a reoperation rate that is much less than 1% whereas previously it was 4% to 5%, merely because radiologic intervention for fistulae, abscesses, and infection has replaced operative intervention. Indeed, the management of our complications has changed such that it would make this scoring difficult to apply.

The second issue is that you mentioned cardiovascular effects, and I did not see where this was marked in your actual scoring system, but undoubtedly the prediction of a poor outcome is related much more to the general fitness of the patient than to many of the operative techniques. If patients develop a complication and they have serious comorbidities, there is a much greater chance of severe complications. What I would like to know is how you are going to validate this grading system to see that it applies to multiple experiences. How are you going to develop this score really to be a prospective score that enables us very much more to assess outcome related to the risk of the patient? Thank you very much.

DR. MICHELLE DEOLIVEIRA: Mr. Russell, thank you very much for your comments and questions. Your main point is whether and how this classification has been validated. You also wonder how cardiovascular disorders were included in

the classification. Regarding validation of this novel approach, I must refer to the publication from Prof. Clavien's group published in 2004 in this Journal [reference 16 in the manuscript]. The novel grading system was tested through an international survey including 144 surgeons, who were asked to rank a variety of complications through case presentations. The results showed an about 90% correct ranking of the complications regardless of the origin or experience of the surgeons. Additionally, the survey disclosed that most surgeons found the classification easy to apply and logical. The classification was also applied to a database available at the University Hospital of Zurich to include more than 6000 patients who underwent a wide range of general surgical procedures. A good correlation was documented between the severity of surgery or length of the hospital stay and the grades of complications. In the current study, we tested the novel classification to identify complications following pancreaticoduodenectomy. Regarding cardiovascular disorders, I would like to highlight that this was evaluated as a potential risk factor of developing postoperative complications. In the grading system, cardiovascular complications were ranked as any other types of complications, ie, based on the therapy applied. For the record, I would like to highlight that currently the Johns Hopkins group is recording their complications on the basis of this new classification.

Dr. Pierre Clavien: I would like to address the point from Chris Russell that this classification may be difficult to apply because it mostly relies on the therapy used to treat a complication. Thus, this approach may be limited by differences in treating postoperative complications among surgeons, centers, and of course over time. This is an important point, which was mostly addressed in our first attempt to grade postoperative complications, which was reported more than 10 years ago while I was a fellow at the University of Toronto, Canada [references 7–9 in the manuscript]. We had to choose the perspective through which the severity of a complication should be graded. We felt that a strong weight should be given to the suffering of the patient and associated risks that a complication may add to the expected normal course. Another point was to minimize bias in reporting a negative postoperative event. By using the treatment applied, we could minimize the bias of "down rating" a complication, as it is based on an objective and readily available information, often best documented in the nursing notes. The fact that a similar postoperative event may be graded at a lower level over times or between centers due to the use of a less aggressive therapy is, in my opinion, an advantage. The classification can catch up improvement in the risk associated to the complication and respect the patient perspective.

Dr. Markus Büchler: I enjoyed your paper, and I think it is very important in the future that we have good classification systems that we can apply worldwide for our complications. So, Pierre, congratulations. My question is that this kind of classification system only becomes acceptable if it is applied in different departments, because then, if you use your system in different departments' databases, you can see whether it is reliable. My specific question is whether you have used the Johns Hopkins database only or, if you also have your own database in Zürich, why didn't you use this one?

Dr. Pierre Clavien: Markus, thanks for your comment and question. I fully agree that such a classification will become useful only when it is widely accepted and used. Our aim is in no way to impose a grading system, but rather to stimulate discussion on how to look at our results, and hopefully to reach a consensus in reporting our negative outcomes. I would submit that the European Surgical Association may represent an excellent platform to initiate such discussion. This classification was recently adopted in a consensus conference organized in Vancouver by the International Transplantation Society to monitor prospectively the morbidity associated with living donor liver donation. In Zurich, we used this classification to grade all postoperative complications, and the data are routinely presented in our weekly morbidity/mortality conference. As Dr. DeOliveira mentioned, the grading system is now included in the pancreatic surgery database at Johns Hopkins. The focus of the current study was to test the new classification in a recent and large series of patients from a single center. Anecdotally, this idea came from a discussion that occurred last year in Stockholm, when Dr. Cameron joined our association as an honorary member. Dr. DeOliveira was a fellow at Johns Hopkins at that time, and as she was joining my group, it was only logical to propose to her the challenge of working on this project.

Dr. Hans Jeekel: Of course, it is fantastic to study more than 600 patients in 2 years, and that's a good reason to do it in Hopkins. I have a question about the parameters that you used. I missed a few, that is, obesity, smoking, transfusions. I don't know whether you used them too, and I'd like to ask about dignity. How do you evaluate dignity, which is one of your parameters? Regarding the pancreatic fistula, you only measure pancreatic fistula if there is a drainage of more than 50 mL after 10 days, so there is a drain somehow after 10 days. Why? What about the other ones that you don't notice. You also say that there are degrees of pancreatic fistulas over time. Well in the 1980s, you measured a higher percentage but was the same parameter used, such as the drainage after 10 days. Then regarding pancreatic fistula, you say that there is an association with long-term survival. How could you explain that? The association with long-term survival and pancreatic fistula is not what you say in your abstract. Does it have to do with the tissue, the soft or stronger tissue of the pancreas? Does it relate then maybe to cancer, that you have

stronger pancreatic tissue, more fibrotic tissue in cancer patients by which you have more or less fistula. I couldn't find the reason really for this association.

Dr. Michelle DeOliveira: Professor Jeekel, many thanks for your questions and comments. Regarding the evaluation of risk factors, we could only use the parameters available in the database. While this database is quite unique in many aspects, there was insufficient information to look at obesity or a history of smoking. The requirement for blood transfusion was low, and was not found to correlate with outcome. Similarly, age, blood transfusion, operating time, and the stage of the tumor were not found to predict postoperative complications. Regarding pancreatic fistula, there are at least 26 different definitions, and the participants of a consensus statement recently published by Prof Bassi [reference 12 in the manuscript] could not agree on one single definition. The definition used at Johns Hopkins has been consistent over time, which enabled us to perform a conclusive comparison between 2 periods. The definition includes the presence of an output of 30 to 50 mL after postoperative day 10. How can we assess this if patients are discharged already at postoperative day 7? The American healthcare system has focused on early discharge for many years, and at Johns Hopkins patients who do not develop complications must leave the hospital within 1 week of surgery. However, each patient comes to the outpatient facilities for follow-up. Therefore, the presence of a fistula could be well documented even after discharge. Of course, "subclinical" manifestation of a fistula not fulfilling the minimum criteria of the definition may remain undetected. Regarding your last question, I showed that the type or severity of complications occurring within 30 days of surgery in patients with a malignant disease does not correlate with long-term survival. These data are somewhat different from the one presented in the abstract of the meeting, as we obtained additional data in the interim.

Dr. Laureano Ferandez Cruz: I enjoyed your presentation very much and I think it is a very important paper, and I think we should all recognize that so far we have not had such a grading system of severity and diagnosis. That's the reason why I think we should have such a grading system to know how to manage our patients and determine the outcome of our management of complications in pancreatic surgery. My question to you is about the risk factors. You have specifically addressed 2 main risk factors in your study: cardiovascular and the pancreas texture. What about the other risk factors, which we know play an important role in complications in pancreatic surgery? These include the different tumor diagnoses, as was mentioned by Hans Jeekel, the age of the patients, and the BMI. Are all these risk factors in your study significant or not, and applicable in this grading system, so that we may know the outcome of our management of the complications. Would you comment on that?

Dr. Michelle DeOliveira: Thank you, Professor Fernández Cruz, for your support and questions. I have presented the risk factors that were statistically significant. We did analyze all potential risk factors available in the database, including dignity, type and differentiation of each tumor by univariate and, when significant, by multivariate analysis, but only the presence of cardiovascular disease was significant for overall complications, and cardiovascular disease and a soft gland texture for pancreatic fistula. I would like again to thank the association for the honor of the floor.