A Randomized Prospective Multicenter Trial of Pancreaticoduodenectomy With and Without Routine Intraperitoneal Drainage

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Objective: To test by randomized prospective multicenter trial the hypothesis that pancreaticoduodenectomy (PD) without the use of intraperitoneal drainage does not increase the frequency or severity of complications.

Background: Some surgeons have abandoned the use of drains placed during pancreas resection.

Methods: We randomized 137 patients to PD with (n = 68, drain group) and without (n = 69, no-drain group) the use of intraperitoneal drainage and compared the safety of this approach and spectrum of complications between the 2 groups.

Results: There were no differences between drain and no-drain cohorts in demographics, comorbidities, pathology, pancreatic duct size, pancreas texture, baseline quality of life, or operative technique. PD without intraperitoneal drainage was associated with an increase in the number of complications per patient [1 (0-2) vs 2 (1-4), $P = 0.029$]; an increase in the number of patients who had at least 1 ≥grade 2 complication [35 (52%) vs 47 (68%), $P = 0.047$]; and a higher average complication severity [2 (0-2) vs 2 (1-3), $P = 0.027$]. PD without intraperitoneal drainage was associated with a higher incidence of gastroparesis, intra-abdominal fluid collection, intra-abdominal abscess (10% vs 25%, $P = 0.027$), severe (≥grade 2) diarrhea, need for a postoperative percutaneous drain, and a prolonged length of stay. The Data Safety Monitoring Board stopped the study early because of an increase in mortality from 3% to 12% in the patients undergoing PD without intraperitoneal drainage.

Conclusions: This study provides level 1 data, suggesting that elimination of intraperitoneal drainage in all cases of PD increases the frequency and severity of complications.

Keywords: drain, multicenter, pancreaticoduodenectomy, randomized, Whipple

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Advances in operative technique and perioperative management have reduced the mortality for pancreaticoduodenectomy (PD) to 3%. However, the morbidity of the procedure remains high and pancreatic fistula continues to be a common complication.[1] An unrecognized, and untreated, pancreatic fistula can lead to increased morbidity and mortality after PD. Routine placement of intraperitoneal drains after PD has traditionally been considered mandatory. The rationale behind placement of these drains is to evacuate blood, bile, pancreatic juice, or chyle that may accumulate after surgery and to serve as an early warning sign of anastomotic leak and associated hemorrhage. Pancreatic fistula is thought to contribute to the most morbid complications of the operation such as erosion of retroperitoneal vessels and hemorrhage, intra-abdominal abscess, sepsis, multisystem organ failure, and death.

Although the use of drains has proven to be unnecessary or even deleterious in other operations such as splenectomy, hepatectomy, gastrectomy, and colorectal resection, many surgeons fear that abandoning routine intraperitoneal drainage after PD may not be safe.[2] However, the majority of patients do not develop a postoperative pancreatic fistula; furthermore, the experience with drains in other operations suggests that drains may do more harm than good. Common concerns, which may be unfounded, are that drains can serve as portal of entry for bacteria; this may change a benign postoperative fluid collection into an abscess. Concerns also exist that drains may cause trauma from suction and can potentially erode into anastomoses and cause a fistula. Because most patients do not develop a pancreatic fistula, routine intraperitoneal drainage may subject many patients to the potential drain-related morbidities with potentially no benefit. With significant improvements in abdominal imaging and image-guided drain placement, a growing number of pancreatic surgeons have abandoned the routine use of drains arguing that a drain can be placed postoperatively in the minority of patients who require drainage.

The safety of this approach has been suggested recently in retrospective cohort studies and 1 single-institution randomized controlled trial.[3–9] The objective of this multicenter randomized

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prospective trial was to test the hypothesis that PD without the use of routine intraperitoneal drainage does not increase the frequency or severity of complications.

METHODS

Pancreatic surgeons from 9 academic high-volume (~50 PD/yr) pancreas surgery centers in the United States were recruited to contribute patients to this multicenter randomized prospective clinical trial. Patients were randomized to PD with and without the use of routine intraperitoneal drainage. Patients were followed for 90 days and the safety of this approach and spectrum of complications were compared. The trial was originally designed to include patients undergoing PD or distal pancreatectomy. However, the study was stopped because of excess mortality in the patients undergoing PD without drains. Herein, we report the results from patients undergoing PD. Accrual of patients undergoing distal pancreatectomy is currently ongoing and the results with that portion of the study will be reported separately in the future.

It was mandatory that each surgeon offered participation in the study to all patients undergoing PD within their practice during the study period. All patients were enrolled unless they refused the randomization process or refused to comply with follow-up. All patients undergoing PD by participating surgeons during the study period were registered by the study and eligibility criteria were assessed. If a patient was not enrolled, a valid reason was recorded. Comorbid conditions or the indication for resection were not allowed to influence enrollment. Randomization was performed using a computerized randomization system at the coordinating center (Baylor College of Medicine) and occurred before surgery. To ensure an equal distribution among treatment groups of patients with a soft or hard pancreas, randomization was substratified for anticipated diagnosis (Fig. 1).

The trial was registered at clinicaltrials.gov (NCT01441492). A uniform protocol was submitted to and approved by the institutional review boards and other required regulatory organizations at each subsite, and amendments to the protocol could be initiated only by the coordinating center. The coordinating center trained the research personnel at each subsite before initiating enrollment at that site. All complications of any significant nature were reported immediately by the subsite PI directly to the coordinating center. Operative notes, anesthesia records, hospital notes, discharge summaries, and all other documents were reviewed as supporting documents to validate the information being reported by each subsite. All supporting data were collected from each subsite using a secure, Web-based electronic data capture system. Electronic case report forms (eCRFs) were designed to maximize accurate data collection with "pop-up boxes" to define complications and grading systems. The coordinating center followed quality assurance procedures to ensure the timely and accurate prospective completion of all eCRFs. Subsites forwarded source documents from the medical record to support all data entered. Every source document was reviewed by trained analysts and a surgeon at the coordinating center to confirm that all complications were recorded and graded accurately.

At the time of enrollment, demographics and comorbid conditions were recorded, and subjects filled out a previously validated pancreas-specific quality-of-life questionnaire (FACT-PA),[10] which was repeated 30 days after surgery. Intraoperative data were collected from the operative note and anesthesia record. For subjects assigned to the intraoperative drain group, the specific size, brand, and number of closed-suction drains were at the discretion of the surgeon. The concentration of amylase in a sample of drain fluid was measured and recorded on postoperative day (POD) 3 and at any additional POD desired by the treating surgeon. In the case of multiple drains, the highest concentration of amylase was used. The date the drains were removed was recorded. Drains were left in place until either the amylase concentration was $<3\times$ the upper limit of normal serum amylase concentration in the study subsite hospital laboratory and/or the output was 20 mL/d or less for 2 consecutive days.

Particular attention was focused on the use of postoperative imaging, abdominal paracentesis, and percutaneous drainage. If paracentesis was performed or a percutaneous abdominal drain was placed, the fluid was sent for amylase concentration, Gram stain, and culture. Complications were recorded from the discharge summary, hospital daily progress notes and laboratory reports, and outpatient progress notes. Outpatient follow-up visits were required at 30 and 60 days after surgery. All complications occurring within 60 days of surgery were recorded and graded. Subjects were followed for mortality for 90 days because recent reports suggest shorter periods of follow-up result in underreporting.[11] Complications were graded (grades 1–5) in severity using the Common Terminology Criteria for Adverse Events (v4.0), which is a widely accepted standardized classification of adverse events produced by the National Cancer Institute for use in clinical trials.[12]

In addition to the Common Terminology Criteria for Adverse Events grading, postoperative pancreatic fistula was also defined and graded using the 3-tiered definition proposed by the International Study Group on Pancreatic Fistula.[13] Delayed gastric emptying was also defined and graded using the schema proposed by the International Study Group of Pancreatic Surgery.[14] Common Terminology Criteria for Adverse Events grades were used to calculate the average complication severity score for each patient (sum of all complication grades experienced by the patient divided by the number of complications experienced by the patient). Length of hospital stay was calculated from the day of surgery through and including the day of discharge. Readmission was defined as an admission to any hospital for 24 hours or more for any reason within 60 days after surgery. Readmission was not considered as an independent additional complication but was used to grade the severity of the complication that was the reason for readmission.

STATISTICS

Based on preliminary data, the study was originally designed to detect a 10% difference in the grade II or greater complication rate between the drain and no-drain groups for the patients undergoing PD and distal pancreatectomy. A total of 752 evaluable patients were needed for the 2 study groups ($n = 376$ per group) in order to achieve 80% power to detect a 10% increase or decrease in the complication rate with a significance level of 0.05. The primary endpoint for this study, the 60-day grade II or greater complication rate, was compared using the χ^2 test. Other secondary outcomes were similarly compared between the 2 groups for categorical variables using the χ^2 test or Fisher exact test as appropriate. For continuous variables, the *t* test or Wilcoxon rank sum test was used. *P* values less than 0.05 were considered statistically significant. All the *P* values were not adjusted for multiple comparisons because except for the comparison for the primary endpoint, all the other comparisons were secondary or exploratory, and we obtained only less than one-fifth of the patients needed for the comparisons because the trial was stopped early.

RESULTS

At the time the study was stopped, 357 patients had been screened and 282 were enrolled from September 15, 2011 to December 6, 2012 (Fig. 1). The most common reason for screen failure was that the patient refused to be randomized. Nine patients had to be withdrawn from the study because the scheduled surgery date after the study was stopped by the Data Safety Monitoring Board. Five patients withdrew their consent before surgery. Three patients had undergone imaging after enrollment, demonstrating metastatic

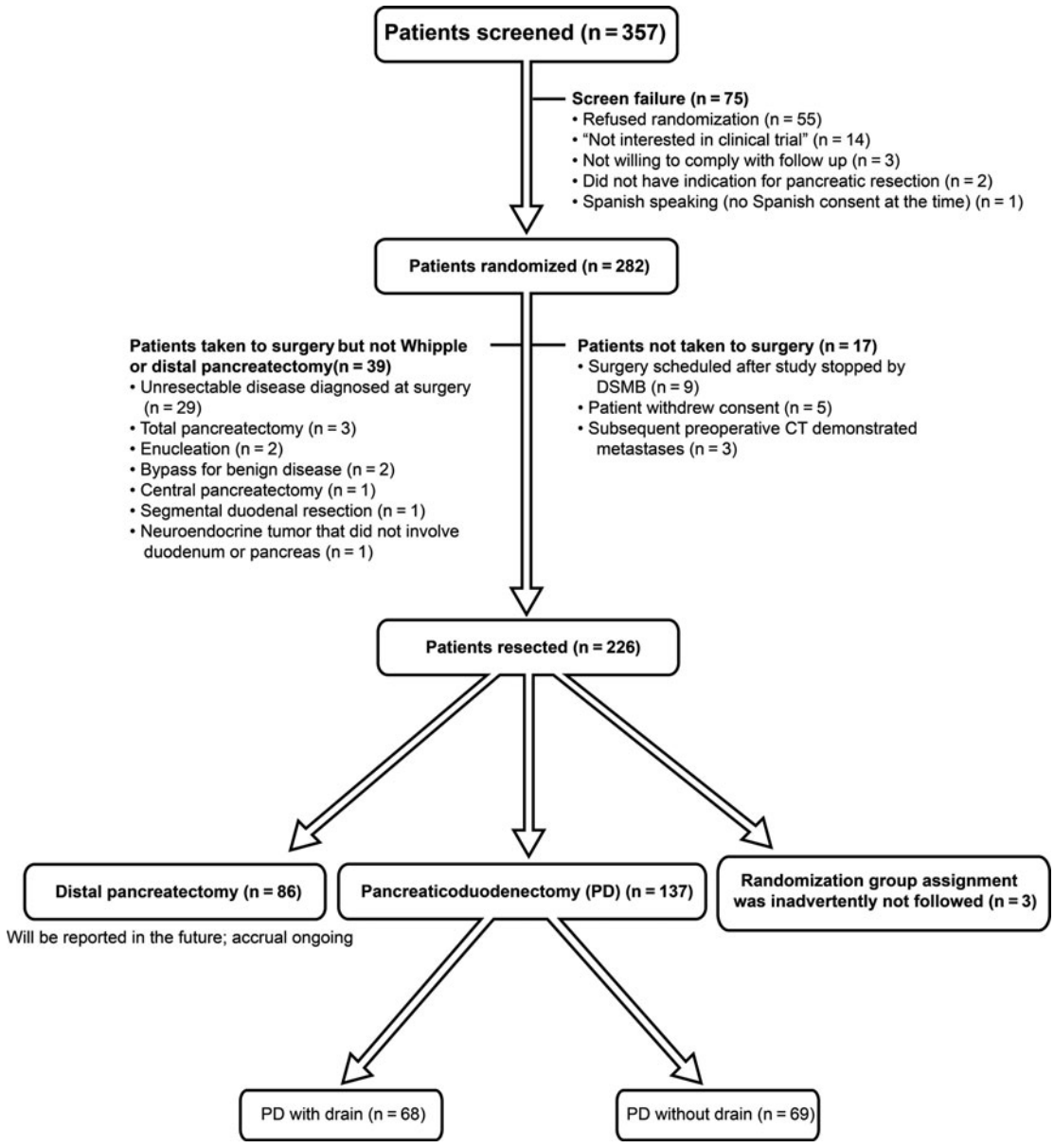

FIGURE 1. Flow chart of participants in the study. DSMB indicates Data Safety Monitoring Board.

disease. Eighty-six patients underwent distal pancreatectomy and are not included in this analysis because that portion of the study is ongoing. Thirty-nine patients who were randomized and scheduled for PD were not evaluable because they were found to have unresectable disease at the time of exploration, or had an enucleation, or a total pancreatectomy rather than a PD. These patients were excluded from the study and were not followed. There were 3 cases for which the randomization group assignment was inadvertently not followed: 1 patient in the drain group did not have a drain placed and 2 patients in the no-drain group had a drain placed. Each of the 3 surgeons for these cases verified that the protocol deviation was not intentional. With these patients excluded from the analysis (which did not alter the results), there were 137 evaluable patients—68 in the drain group and 69 in the no-drain group. No patients were lost to follow up. The eCRFs had 114 data fields per patient for a total of 15,618 for the study. Data capture was very complete with 15,606 data fields (99.9%) successfully acquired.

There were no significant differences between the 2 cohorts in demographics or comorbidities (Table 1). In addition, there was no significant difference between the 2 cohorts in the indications for surgery, pancreatic duct size, pancreas texture, and operative technique, including the use of a laparoscopic approach, anastomotic technique, vascular resections, additional procedures, operative time, blood loss, or transfusion requirements (Table 2). Among the patients in the group that had drains placed at the time of resection, two-thirds had 2 drains and one-third had 1 drain (Table 2). The drains were removed typically by POD 7. There was no difference between the 2 groups in the utilization of postoperative computed tomography or

TABLE 1. Demographics and comorbid conditions of the participants in the study

N (%) or Mean (SD)	All (137)	Drain (68)	No Drain (69)	*P*
Sex				
Male	75 (56)	37 (54)	38 (55)	0.938
Age, mean (SD)	63.2 (12.2)	62.1 (11.7)	64.3 (12.6)	0.289*
Coronary artery disease	28 (20)	12 (18)	16 (23)	0.421
Hypertension	79 (59)	35 (51)	44 (64)	0.145
Chronic obstructive pulmonary disease	7 (5)	3 (4)	4 (6)	1*
Diabetes mellitus	41 (30)	17 (25)	24 (35)	0.211
Renal insufficiency	7 (5)	4 (6)	3 (4)	0.718*
Chronic pancreatitis	15 (11)	7 (10)	8 (12)	0.808
Peripheral vascular disease	3 (2)	1 (1)	2 (3)	1*
Tobacco use				
Current	27 (20)	13 (19)	14 (20)	0.736
Ever	52 (40)	24 (35)	28 (41)	
Never	58 (42)	31 (46)	27 (39)	
Body mass index (kg/m^2)	27.7 (6.9)	27.8 (7.7)	27.6 (6.1)	0.869†
Albumin (mg/dL)	3.7 (0.6)	3.8 (0.5)	3.6 (0.7)	0.061†
Hemoglobin (g/dL)	12.6 (1.5)	12.7 (1.6)	12.4 (1.4)	0.304†
Creatinine (mg/dL)	0.9 (0.5)	0.95 (0.63)	0.89 (0.34)	0.502†
Neoadjuvant chemotherapy	14 (10)	8 (12)	6 (9)	0.553
Radiation (yes)	7 (5)	5 (7.4)	2 (2.9)	0.274*
ASA				
1	2 (1)	2 (3)	0 (0)	0.265*
2	19 (14)	12 (18)	7 (10)	
3	101 (74)	48 (71)	53 (77)	
4	15 (11)	6 (9)	9 (13)	

*Fisher exact test.

†*T* test; others: χ^2 test.

ASA indicates American Society of Anesthesiologists; 1, a normal healthy patient; 2, a patient with mild systemic disease; 3, a patient with severe systemic disease; 4, a patient with severe systemic disease that is a constant threat to life.

other abdominal imaging procedures, the need for readmission, or reoperation (Table 2).

PD without routine intraperitoneal drainage was associated with a higher morbidity (Table 3). There was an increase in the number of complications per patient, an increase in the number of patients who had at least 1 grade 2 or more complication, and a higher mean complication severity score. PD without routine intraperitoneal drainage was associated with a higher incidence of gastroparesis, intra-abdominal fluid collection, intra-abdominal abscess, severe (≥grade 2) diarrhea, need for a postoperative percutaneous drain, and a prolonged length of stay. There was no difference between drain and no-drain groups in quality of life when assessed at baseline and at 30 days after surgery (see Supplemental Digital Content Table 1, available at http://links.lww.com/SLA/A521).

The study was stopped early by the Data Safety Monitoring Board because of excess mortality in the patients undergoing PD without routine intraperitoneal drainage. After 90 days of follow-up, there were 8 deaths (12%) in the no-drain group and only 2 deaths (3%) in the drain group ($P = 0.097$) (Table 4). Among the 10 patients who died, 90% were male, 80% had a soft pancreatic texture, 60% had a pancreatic duct of 3 mm or less, and 80% developed a pancreatic fistula. Two patients (20%) had a combined biliary and pancreatic fistula and 70% developed an intra-abdominal abscess. Five deaths (50%) were associated with intra-abdominal hemorrhage (see Supplemental Digital Content Table 2, available at http://links.lww.com/SLA/A522).

Percutaneous drains were placed in 3 (30%) of the patients who died. Seventy percent of the patients who died were returned to the operating room on average at POD 11 (range: 1–24). One patient who died had a percutaneous drain but was not returned to the operating room. (See Supplemental Digital Content 1, available at http://links.lww.com/SLA/A520, which describes the postoperative course of the 10 patients who died.)

Two deaths, 1 in the drain group and 1 in the no-drain group, were related to recurrent cancer. One patient in the no-drain group had a laparoscopic PD, did not have a documented pancreatic leak, and was discharged on POD 10. However, the patient returned on POD 24 in shock and died from postoperative hemorrhage from the hepatic artery. The remainder of the deaths, 70%, occurred in the setting of a pancreatic fistula associated with sepsis, multisystem organ failure, and/or hemorrhage (Table 4 and Supplemental Digital Content Table 2, available at http://links.lww.com/SLA/A522).

DISCUSSION

This is the first randomized prospective multicenter trial to evaluate the outcome of PD without routine intraperitoneal drainage. Experienced pancreatic surgeons from 9 high-volume (≥50 PD/yr) academic pancreas centers in the United States enrolled 137 patients who were randomly assigned to either receive (n = 68, drain group) or not receive (n = 69, no-drain group) intraperitoneal drains at the time of the resection. The balance between the groups in all factors thought to potentially affect outcome afforded by the randomized prospective design of this trial supports the conclusion that the difference in outcomes is caused by omitting the abdominal drain at the time of resection. Elimination of intraperitoneal drains at the time of PD was associated with increased morbidity and mortality.

Intraperitoneal drainage after PD has been the common practice for pancreatic surgeons, which is understandable given the frequency of pancreatic fistula and its associated complications. Jeekel[9] was the first to question this practice in the literature more than 2 decades ago with a case series of 22 patients who underwent PD without drainage with acceptable results. In recent years, the practice

TABLE 2. Operative data and subsequent interventions in the participants in the study

N (%) or Mean (SD)	All (137)	Drain (68)	No Drain (69)	*P*
Laparoscopic Whipple	11 (8)	5 (7)	6 (9)	0.773
Vascular resection	24 (18)	9 (13)	15 (22)	0.191
Additional procedure	21 (15)	10 (15)	11 (16)	0.841
Anastomotic technique	—	—	—	—
End-to-side, duct-to-mucosa	93 (68)	45 (66)	48 (70)	0.805
End-to-side, intussuscepted	23 (17)	13 (19)	10 (14)	—
End-to-end, intussuscepted	16 (12)	7 (10)	9 (13)	
Pancreaticogastrostomy	5 (4)	3 (4)	2 (3)	
Stented (internal) anastomosis	48 (35)	26 (38)	22 (32)	0.436
Soft pancreatic texture	69 (50)	34 (50)	35 (51)	0.932
Pancreatic duct size (mm)	3.9 (2)	3.9 (1.9)	4 (2)	0.895*
Operating time (min)	416 (154)	425 (151)	407 (157)	0.497*
Estimated blood loss (mL)	451 (347)	460 (352)	443 (344)	0.781*
RBC transfusion	10 (7)	4 (6)	6 (9)	0.745
Pathology	—	—	—	—
Pancreatic adenocarcinoma	67 (49)	34 (50)	33 (49)	0.871
Ampullary adenocarcinoma	17 (12)	7 (10)	10 (14)	
Neuroendocrine carcinoma	11 (8)	4 (6)	7 (10)	—
Pancreatitis	11 (8)	6 (9)	5 (7)	—
Cystic lesion	8 (6)	4 (6)	4 (6)	—
Other	23(17)	13(19)	10(14)	
Number of drains placed	—	—	—	—
1	N/A	23 (34)	N/A	N/A
2	N/A	45 (66)	N/A	N/A
POD last drain removed	N/A	7 (5-13)	N/A	N/A
Length of stay (days), median (interquartile range)	7 (6-11)	7 (6-9)	8 (7-14)	0.016†
Postoperative imaging (CT/MRI/US)	50 (37)	20 (29)	30 (44)	0.087
Postoperative percutaneous drain	22 (16)	6 (9)	16 (23)	0.022
POD percutaneous drain placed, median (interquartile range)	25 (13-46)	43 (15-81)	23 (13-39)	0.516†
Hospital readmission	28 (20)	16 (24)	12 (17)	0.373
Reoperation	8 (6)	2 (3)	6 (9)	0.274*

*T test.

†Wilcoxon rank sum test; others: χ^2 test.

CT indicates computed tomography; MRI, magnetic resonance imaging; POD, postoperative day; RBC, red blood cell; US, ultrasound.

of routine intraperitoneal drainage after PD has been further scrutinized.

Enthusiasm for pancreatectomy without routine intraperitoneal drainage has been promoted in part by several publications from the Memorial Sloan-Kettering group.[3,7,8] In 1998, Heslin et al[8] published a retrospective review of 89 patients, 51 undergoing PD with drains and 38 without drains. There was no difference in the rate of major complications between the 2 groups. The only previous randomized prospective trial was a single-center study published by Conlon et al[7] from the same institution in 2001. This study included patients undergoing PD (n = 139) and distal pancreatectomy (n = 40), with 88 randomized to drainage and 91 randomized to pancreatic resection without drainage. There was no significant difference in the mortality rate or the number or type of complications experienced by the 2 groups. In addition, drainage at the time of resection did not reduce the need for subsequent percutaneous drainage or reoperation. The authors concluded that routine drainage after pancreatic resection should no longer be considered mandatory.

A follow-up study from the same group published in 2013 showed that this concept was not universally accepted even in their own institution, with drains still being placed in half of pancreatic resections.[3] However, this single-center retrospective study of 1122 patients concluded that operative drains were associated with increased grade 3 or more complications, pancreatic fistula, readmission, and a longer hospital stay, and elimination of drains did not affect mortality. The authors concluded that routine prophylactic drainage after pancreatic resection can be safely abandoned.

Other groups, including participants in this study, have previously reported retrospective studies supporting the concept that pancreatic resection without drains is safe. Fisher reported on 2 consecutive cohorts of patients who underwent pancreatic resection with (n = 179) and without (n = 47) intraperitoneal drainage.[6] Elimination of routine intraperitoneal drainage did not increase the frequency or severity of serious complications. However, when all grades of complications were considered, the number of patients who experienced any complication (65% vs 47%, $P = 0.020$) and the median complication severity grade (1 vs 0, $P = 0.027$) were increased in the group that had drains placed at the time of surgery. Eliminating intraoperative drains was associated with decreased delayed gastric emptying (24% vs 9%, $P = 0.020$) and a trend toward decreased wound infection (12% vs 2%, $P = 0.054$). The readmission rate (9% vs 17%, $P = 0.007$) and the number of patients requiring postoperative percutaneous drains (2% vs 11%, $P = 0.001$) were higher in patients who did not have operatively placed drains,

TABLE 3. Morbidity 30 and 60 days after pancreaticoduodenectomy

	30 d			60 d		
N (%) or Median (Interquartile Range)	**Drain (68)**	**No Drain (69)**	***P***	**Drain (68)**	**No Drain (69)**	***P***
Any complication	50 (74)	52 (75)	0.8057	50 (74)	55 (80)	0.393
Any ≥ grade 2 complication (primary endpoint)	32 (47)	44 (64)	0.049	35 (52)	47 (68)	0.047
Any ≥grade 3 complication	19 (28)	28 (41)	0.119	21 (31)	28 (41)	0.236
Median number of complications per patient (any grade)	1 (0-2)	2 (1-3)	0.123	1 (0-2)	2 (1-4)	0.029*
Mean complication grade (all subjects)	1 (0-2)	2 (1-3)	0.059	2 (0-2)	2 (1-3)	0.027†
Mean complication grade (subjects with ≥ 1 Comp.)	2 (1-2)	2 (2-3)	0.007	2 (1-3)	2 (2-3)	0.017†
Complications with a significant difference						
Gastroparesis	16 (24)	26 (38)	0.075	16 (24)	29 (42)	0.021
Intra-abdominal abscess	7 (10)	17 (25)	0.027*	8 (12)	18 (26)	0.033
Diarrhea (grade 1 excluded)	2 (3)	9 (13)	0.030	2 (3)	12 (17)	0.005
Abdominal fluid collection	1 (2)	8 (12)	0.033*	1 (2)	8 (12)	0.033*
Complications without a significant difference						
Fistulas						
Pancreatic fistula	21 (31)	14 (20)	0.155	21 (31)	14 (20)	0.155
Pancreatic fistula (grade A excluded)	7 (10)	14 (20)	0.104	8 (12)	14 (20)	0.174
Biliary fistula	3 (4)	1 (1)	0.366*	3 (4)	2 (3)	0.681*
Enteric fistula	—	1 (2)	1*	—	1(2)	1*
Chyle fistula	1 (2)		0.496*	1 (2)	—	0.495*
Infection and wound healing						
Pneumonia	3 (4)	6 (9)	0.493*	3 (4)	7 (10)	0.325*
Wound infection	6 (9)	10 (15)	0.302	7 (10)	10 (15)	0.456
Wound seroma	3 (4)	5 (7)	0.718*	3 (4)	6 (9)	0.493*
Wound dehiscence	2 (3)	4 (6)	0.681*	2 (3)	5 (7)	0.441*
Urinary tract infection	3 (4)	3 (4)	1*	4 (6)	5 (7)	1*
Bacteremia/sepsis	2 (3)	4 (6)	0.681*	4 (6)	5 (7)	1*
Cardiovascular complications						
Central venous catheter infection	2 (3)	1 (2)	0.620*	2 (3)	1 (2)	0.620*
Intra-abdominal hemorrhage	4 (6)	4 (6)	1*	4 (6)	6 (9)	0.745*
Gastrointestinal hemorrhage	2 (3)	6 (9)	0.274*	2 (3)	7 (10)	0.165*
Thromboembolic event	4 (6)	1 (2)	0.208*	5 (7)	1 (2)	0.115*
Arrhythmia	9 (13)	6 (9)	0.395	9 (13)	6 (9)	0.395
Myocardial infarction	1 (2)	—	0.496*	1 (2)	1 (2)	1*
Organ failure						
Acute respiratory distress syndrome/respiratory failure	2 (3)	4 (6)	0.681*	2 (3)	6 (9)	0.274*
Hepatic failure	—	1 (2)	1*	1 (2)	1 (2)	1*
Renal failure/insufficiency	1 (2)	7 (10)	0.062*	3 (4)	9 (13)	0.074
Neurologic complications						
Transient ischemic attack	1 (2)	—	0.496*	1 (2)	—	0.497*
Cerebral infarct/hemorrhage (stroke)	1 (2)	—	0.496*	1 (2)	—	0.497*
Altered mental status	1 (2)	5 (7)	0.208*	1 (2)	7 (10)	0.062*
Miscellaneous complications						
Urinary retention	5 (7)	3 (4)	0.493*	5 (7)	4 (6)	0.745*
Diarrhea (all grades)	9 (13)	13 (19)	0.372	10 (15)	19 (28)	0.066
Other	5 (7)	5 (7)	1*	5 (7)	9 (13)	0.272

*Fisher exact test.
†Wilcoxon rank sum test; others: χ^2 test.

but there was no difference in the reoperation rate (4% vs 0%, $P = 0.210$). The authors concluded that abandoning the practice of routine intraperitoneal drainage after pancreatic resection may not increase the incidence or severity of severe postoperative complications.

A recent larger retrospective study by Mehta et al[4] also supported PD without drainage. A series of 709 consecutive PDs, 251 without drainage, was reviewed. There was no increase in 30-day mortality (2% vs 2.5%) and patients with drains experienced higher rates of morbidity (68.1% vs 54.1%, $P < 0.01$), particularly pancreatic fistula. The authors concluded that the data supported elimination of routine primary operative drainage at the time of PD.

It seems that the results of this study are in contrast to most of the recent literature on this subject. However, careful consideration of the available data is required. In a recent meta-analysis of the available literature, van der Wilt et al[5] determined that it was premature to conclude that omitting drainage after pancreatic resection leads to a decrease in the risk for complications. This study, which is

TABLE 4. Mortality 30, 60, and 90 days after pancreaticoduodenectomy

N (%)	**All (137)**	**Drain (68)**	**No Drain (69)**	***P***
30-d mortality	4 (3)	0 (0)	4 (6)	0.120
60-d mortality	7 (5)	1 (1)	6 (9)	0.115
90-d mortality	10 (7)	2 (3)	8 (12)	0.097

Fisher exact test for all.

the only multicenter randomized prospective trial involving multiple high-volume pancreas centers, also strongly supports the conclusion that primary operative drainage at the time of PD should not be abandoned. Of all the available literature, this study is the least likely to be influenced by bias. The randomization process is critical in avoiding selection bias. In retrospective studies, patients may be selected for PD without drains on the basis of a perceived or real decreased risk for pancreatic fistula or other complications. In this study, all patients, regardless of anticipated pancreatic texture, duct size, or comorbidities were randomly assigned to the treatment groups. The comparability of the 2 groups is as close to identical as possible. Differences in rare outcomes, such as mortality, are difficult to detect in retrospective cohort studies and require a large sample size. Retrospective and single-institution studies can also be confounded by the evolution of a surgeon's technique and an institutional learning curve over time. The design of this trial with multiple expert surgeons at multiple high-volume pancreas centers eliminated these confounding factors.

Another strength of this study is the completeness and length of follow-up. It is interesting to note that 6 of the deaths (60%) occurred more than 30 days after surgery and 3 of the deaths (30%) occurred more than 60 days after surgery. Clearly, previous studies that reported only 30- or 60-day mortality figures may not be capturing the true mortality after PD. If this study followed the patients only for mortality to 30 or even 60 days, the 4-fold increase in mortality would not have been apparent. Although the mortality rate of 3% is in the expected range, a mortality rate of 12% was unacceptable and led the Data Safety Monitoring Board to conclude that it was not ethical to continue the study.

Careful analysis of the deaths in this study showed that among the 8 patients with no drain, 6 died of sepsis/multisystem organ failure in the setting of a pancreatic fistula. These patients were aggressively managed when they first had evidence of a complication in the postoperative period. However, absence of an operatively placed drain may have resulted in a period of time in which a fistula was occurring and the fluid remained undrained. One patient died of postoperative hemorrhage 24 days after an apparently uncomplicated laparoscopic PD. One patient died of early cancer recurrence 59 days after surgery. Even if the latter 2 patients were excluded, the excess mortality in the group without drains would remain very worrisome.

Many studies have evaluated pancreatic resection with and without intraperitoneal drainage in patients undergoing distal pancreatectomy and PD.[3,5–8,15] This combined approach may not be valid as PD is associated with a more severe morbidity and mortality than distal pancreatectomy. In the recent report by Correa-Gallego,[3] exclusion of patients undergoing distal pancreatectomy and focusing the analysis on just the subset of 739 patients undergoing PD showed that mortality was significantly increased [3 (1%) vs 11 (3%), $P = 0.02$] when routine drainage was eliminated in the patients undergoing PD. We found that the 90-day mortality rate was increased in the no-drain group for the patients undergoing PD although it was only marginally significant ($P = 0.097$, Table 4), which is consistent with the report by Correa-Gallego et al.[3]

This study suggests that abandoning the practice of routine intraperitoneal drainage in all patients is not safe. Some surgeons have taken a compromise position by placing drains at the time of resection but removing them in the early postoperative period on the basis of drain amylase concentration. In this study, drains were removed when the amylase concentration was low and/or the volume of output was low and this was typically about POD 7, the time of discharge from the hospital. The University of Verona group has proposed that a concentration of amylase in fluid from intraperitoneal drains of greater than 5000 U/L on the first POD can be used to predict patients who were at risk for developing a clinically significant pancreatic fistula and allow early drain removal in those at low risk.[16] The results of a randomized prospective trial suggest that in patients at low risk of pancreatic fistula, intra-abdominal drains can be safely removed on POD 3 after pancreatic resection. These data suggest that a prolonged period of drain insertion may be associated with a higher rate of postoperative complications. However, this is perhaps true only in the subset of patients at low risk of pancreatic fistula. This approach is predicated on the assumption that drain amylase concentration can accurately predict which patients are at risk for fistula. Other studies have concluded that the early dynamic postoperative changes in drain volume and amylase concentration are not clearly correlated, with the later development of a clinically significant postoperative pancreatic fistula making this approach problematic.[17,18]

Other tools to predict the subsequent development of a pancreatic fistula are currently being evaluated. A 10-point fistula risk score based on intraoperative blood loss, duct size of less than 5 mm, soft pancreatic parenchyma, and certain pathologies were recently reported and may be highly predictive of which patients are at low risk for pancreatic fistula.[19] Further studies are needed to determine whether intraperitoneal drainage can be safely eliminated in selected patients using predictive factors.

CONCLUSIONS

Based on the previous literature, we hypothesized that abandoning the practice of routine intraperitoneal drainage after pancreatic resection would not increase the incidence or severity of postoperative morbidity or mortality. This randomized prospective multicenter trial provides level 1 data, suggesting that elimination of intraperitoneal drainage in all cases of PD increases the severity and frequency of complications and contributed to a 4-fold increase in mortality from 3% to 12%. Furthermore, there is evidence that elimination of intraperitoneal drainage may directly increase mortality. The authors caution against abandoning the use of intraperitoneal drainage in all cases where PD is performed.

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The following criteria define each of the author's contributions to the study and manuscript:

1. *Contributed to design of the study*
2. *Contributed to acquisition of data*
3. *Contributed to analysis and interpretation of data*
4. *Participated in drafting of the paper*
5. *Participated in revising the paper critically for important intellectual content*
6. *Gave final approval of the version to be published*

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