Early Drain Removal—The Middle Ground Between the Drain Versus No Drain Debate in Patients Undergoing Pancreaticoduodenectomy

A Prospective Validation Study

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Objective: To perform an unbiased assessment of first postoperative day (POD 1) drain amylase level and pancreatic fistula (PF) after pancreatico-duodenectomy (PD).

Background: Recent evidence demonstrated that drain abandonment in PD is unsafe. Early drain amylase levels have been proposed as predictors of PF after PD, allowing for selection of patients for early drain removal.

Methods: Daily drain amylase levels were correlated with the development of PF in 2 independent cohorts of patients undergoing PD: training cohort (n = 126; year 2008) and validation cohort (n = 369; years 2009–2012).

Results: POD 1 drain amylase level had the highest predictive ability (concordance index: 0.911) for PF in the training cohort. An amylase level of 612 U/L or higher showed the best accuracy (86%), sensitivity (93%), and specificity (79%). Thus, a cutoff value of 600 U/L was utilized. In the validation cohort, 229 (62.1%) patients had a POD 1 drain amylase level of lower than 600 U/L, and PF developed in only 2 (0.9%) cases; whereas in patients with POD 1 drain amylase level of 600 U/L or higher (n = 140) the PF rate was 31.4% (odds ratio [OR] = 52, P < 0.0001). On multivariate analysis, POD 1 drain amylase level of lower than 600 U/L (OR = 0.0192, P < 0.0001) was a stronger predictor of the absence of PF than pancreatic gland texture (OR = 0.193, P = 0.002) and duct diameter (OR = 0.861, P = 0.835).

Conclusions: After PD, the risk of PF is less than 1% if POD 1 drain amylase level is lower than 600 U/L. We propose that in this group, which comprise more than 60% of patients, drains should be removed on POD 1.

Keywords: drain amylase, early drain removal, intraperitoneal drain, pancreatic fistula, pancreaticoduodenectomy

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P ancreatic fistula (PF) remains the Achilles heel of pancreatic surgery, with the pancreaticojejunostomy representing the most fragile anastomosis in pancreaticoduodenectomy (PD).^{1–5} An uncontrolled PF from pancreaticojejunostomy failure can be catastrophic, resulting in delayed gastric emptying, intra-abdominal abscess formation, or hemorrhage from major vessel erosion⁶ and may increase threefold the in-hospital mortality.⁵ Given the frequency and severity of this complication as well as its economic impact,^{5,7} most surgeons today place intraperitoneal drains in the vicinity of the pancreati-

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cojejunostomy and hepaticojejunostomy during PD with the aim of controlling anastomotic leakage should any of the anastomoses fail.

The practice of placing routine drains after pancreatic surgery and in particular after PD is, however, not universal. Driven by concerns that drains may serve as a 2-way channel that can introduce bacteria into otherwise sterile collections or the possibility that the force generated by the negative suction can erode into the anastomosis, in itself causing a PF, some surgeons have abandoned drain placement after PD.8 They also argue that in the minority of patients who develop PF, postoperative percutaneous drainage can be performed with minimal morbidity.^{9,10} The Memorial Sloan Kettering group has provided retrospective as well as prospective level I evidence that the outcomes of patients undergoing PD without intraperitoneal drainage is superior across the board when compared to those with drainage.^{11–13} This debate prompted a recent multicenter randomized trial of drain versus no drain in patients undergoing PD. The trial, however, had to be terminated early as a result of increased morbidity and need for postoperative percutaneous drainage, as well as a fourfold increase in mortality in the no-drain group.¹⁴

Early drain removal represents a middle ground between the 2 practices. To date, randomized controlled trials and prospective studies of early drain removal after pancreatic surgery have provided compelling evidence that drain removal as early as postoperative day (POD) 3 to 4 results in fewer complications when compared to late drain removal (POD > 5).¹⁵ Recently, there has been a peak in interest in utilizing drain amylase levels as a predictor of PF to guide timing of drain removal, demonstrating excellent sensitivity and negative predictive value.¹⁶⁻²³ However, most of the studies were either retrospective, underpowered, had low applicability (small proportion of patients with the preset drain amylase threshold level), or lacked consistent drain management strategies (type, location, and number of drains placed) to allow for a homogenous analysis.

In this study, we performed an unbiased, prospective assessment of drain amylase levels as a predictor of PF development in the setting of routine drainage. To our knowledge, it is the largest study assessing drain amylase levels in predicting PF in consecutive patients. We hypothesize that amylase levels measured in operatively placed drains correlate with anastomotic failure and aimed to identify a threshold value that accurately predicts the development of a clinically relevant fistula and therefore could guide drain management.

METHODS

This study was approved by Massachusetts General Hospital's institutional review board (study protocol no. 2013P000800) and was a HIPAA compliant. We prospectively measured daily postoperative drain amylase levels and correlated them with the development of PF in 2 independent cohorts of patients undergoing PD: a training cohort and a validation cohort. A drain amylase threshold value was identified in the training cohort during the year 2008 (n = 126),

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which was later validated prospectively in another cohort of patients undergoing PD during 2009–2012 (validation cohort, n = 369).

PD was performed utilizing standard techniques as previously described.²⁴ Two closed-suction drains are placed in the right upper quadrant anterior and posterior to the pancreaticojejunostomy and hepaticojejunostomy and brought out through separate sites in the right side of the abdomen. Drain output and amylase levels were prospectively measured daily til drain removal or patient discharge. POD 1 drain amylase levels recorded in this study represent the higher level of the 2 Jackson Pratt drains. The majority of surgeons routinely utilize an external pancreatic duct stent (90.4% of study cohort), which is removed at 3 weeks during outpatient follow-up. Octreotide was not administered to any of these patients. The patient's post-operative course follows a critical pathway that has been previously described by our group.⁵

Definitions

The age-adjusted Charlson comorbidity index was used to classify the comorbidity burden of the studied population.^{25,26} Vessel resection was defined as the need for a resection or reconstruction of the superior mesenteric artery, superior mesenteric vein, portal vein, or hepatic artery. The Clavien-Dindo Classification system was utilized to grade postoperative complications after PD.^{27,28} Postoperative PF was defined according to the International Study Group on Pancreatic Fistula (ISGPF) definition, which is a drain output of any measurable amount on or after POD 3 that has amylase levels threefold higher than that of serum amylase levels. The severity of PFs was also graded according to the ISGPF classification.²⁹ Likewise, postoperative delayed gastric emptying was defined as the inability to return to a normal postoperative diet by first postoperative week, prolonged nasogastric suction more than 4 days, or reinsertion of nasogastric tube past POD 3 as described by the International Study Group on Pancreatic Surgery.³⁰

Statistical Analysis

Statistical analyses were performed using Intercooled Stata software, version 12.0 (StataCorp LP, College Station, TX). Categorical variables were analyzed using the χ^2 test or logistic regression. Continuous variables were reported as median with interquartile ranges and compared using the Student t test for data with normal distribution, and Mann-Whitney test for data that were not. The multivariate analysis was performed with a proc logistic model with a C statistic of greater than 0.6 with satisfactory convergence status. The drain amylase value's predictability of PF was performed with the receiver operating characteristic (ROC) analysis and the associated Harrel's C index as represented by the area under the curve. Values ranged from 0 to 1, with 0.5 representing no predictive ability in this study and appear as a diagonal line across the graph. Values greater than 0.5 represent good predictability, appearing as a curvilinear plot on the graph. All statistics were two tailed, and statistical significance was accepted at the P < 0.05 level.

RESULTS

The training cohort consisted of 126 patients who underwent PD between January 2008 and December 2008. POD 1 drain amylase level was the strongest predictor of PF [area under curve (AUC) 0.911, Fig. 1], with levels of 612 U/L or higher demonstrating the best accuracy (86%), sensitivity (93%), and specificity (79%). From that data, a POD 1 drain amylase level of 600 U/L was prospectively correlated with the incidence of PF in the validation cohort, which comprised 369 patients who underwent PD between January 2009 and December 2012. In the validation cohort, 229 (62.1%) patients had a POD 1 drain amylase level of less than 600 U/L, and PF developed in only 2 (0.9%) cases, whereas in patients with POD 1 drain amylase

level of 600 U/L or higher (n = 140) the PF rate was 31.4% (OR = 52, P < 0.0001). There were no ISGPF Grade C PFs in the low drain amylase group. The ROC curve for POD 1 drain amylase level as a predictor of postoperative PF was reproducible in the validation cohort, with an AUC of 0.855 (Fig. 2).

High Versus Low Drain Amylase Analysis

Patients were then dichotomized to POD 1 drain amylase level of lower than 600 U/L (low drain amylase group, n = 229) and POD 1 drain amylase level of 600 U/L or higher (high drain amylase group, n = 140) groups. The body mass index in the high drain amylase group was higher (27.4 kg/m² vs 25.7 kg/m², P = 0.0001), and the age-adjusted Charlson index lower (4 vs 5, P = 0.001) when compared to the low drain amylase group. Pancreatic adenocarcinoma was more common in the low drain amylase group, whereas intraductal papillary mucinous neoplasm was more common in the high drain amylase group (Table 1).

When analyzing intraoperative variables, the duration of surgery was longer in the low drain amylase group (344 ± 108 minutes vs 308 ± 102 minutes, P = 0.006). The pancreaticoenteric

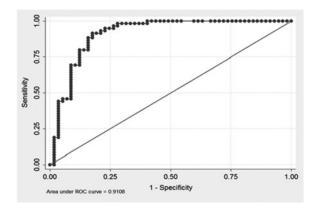


FIGURE 1. ROC curve of POD 1 drain amylase level as a predictor of PF in the training cohort of patients undergoing PD (n = 126), with an AUC of 0.911. Values along the diagonal straight line reflect no predictive ability.

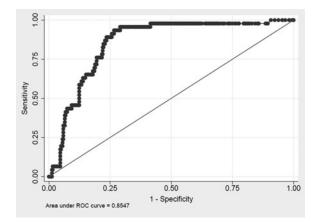


FIGURE 2. ROC curve of POD 1 drain amylase level as a predictor of PF in the validation cohort of patients undergoing PD (n = 369), with an AUC of 0.855. Values along the diagonal straight line reflect no predictive ability.

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anastomosis was predominantly a duct-to-mucosa pancreaticojejunostomy (96.9% of total cohort). As expected, there were a higher proportion of patients with hard pancreatic gland (75.5% vs 24.6%, P < 0.001) and larger pancreatic duct diameter (3.5 ± 2.5 cm vs 2.5 ± 1.7 cm, P < 0.001) in the low drain amylase group. The need for vessel resection was higher in the low drain amylase group (13.3%vs 5.0%, P = 0.01), with a resultant higher estimated operative blood loss (600 ± 689 cc, P = 0.002) and increased need for blood transfusion (17.5% vs 8.6%, P = 0.017, Table 2).

The postoperative complication rates (46.7% vs 47.2%, P = 0.919) and severity (20.5% vs 17.9% with Clavien Grade \geq 3a complications, P = 0.572) between the low and high drain amylase groups were similar despite a significantly lower PF rate in the low drain amylase group. This was mainly attributed to the higher incidence of ileus in the low drain amylase group (6.8% vs 1.4%, P = 0.02). Although not meeting statistical significance, the mortality in the high drain amylase group was more than twofold higher when compared to the low drain amylase group (1.6% vs 0.6%, P = 0.366). The overall length of hospital stay was not different between both groups (median 7 days vs 7 days, P = 0.882). The overall readmission rate was significantly lower in the low drain amylase group (17.1% vs 25.7%, P = 0.048, Table 3).

Predictors of PF

Specific predictors of postoperative PF formation were then analyzed (Table 4). Univariate variables that were statistically significant predictors of PF were included in the multivariate model. On multivariate analysis, POD 1 drain amylase level of lower than 600 U/L was the strongest independent predictor of the absence of PF (OR = 0.0192, P < 0.0001). Hard pancreatic gland texture (OR = 0.193, P = 0.002) and pancreatic adenocarcinoma pathology (OR = 0.496, P = 0.031) were the other predictors of absence of PF, with PD diameter losing significance on the multivariate analysis.

DISCUSSION

Starting in the 1950s, prophylactic intraperitoneal drainage after abdominal surgery became routine.³¹ Intraperitoneal drains serve to drain intra-abdominal free fluid (blood, bile, pancreatic juice, chyle) postoperatively and may also serve as a useful indicator of complications (intra-abdominal hemorrhage, anastomotic failure) before the clinical decline of the patient. In more recent years, however, prophylactic intraperitoneal drainage has been abandoned almost universally across general surgery (cholecystectomy, colectomy, hepatectomy, splenectomy) with the exception of PD.³² This is mostly explained by persistent high rates of leaks from the pancreatojejunostomy, despite

TABLE 1. Demographics and Preoperative Variables of Patients Undergoing PD Dichotomized According to POD1 Drain
Amylase Value

	All Patients (n = 369), %	POD 1 Drain Amylase <600 U/L (n = 229), %	POD 1 Drain Amylase ≥600 U/L (n = 140), %	Р
Male	50.4	51.9	47.9	0.444
Age, yr	66 ± 12.1	66 ± 12.2	65.6 ± 11.9	0.409
Body mass index	25.7 ± 5.9	25.0 ± 5.2	27.4 ± 6.5	0.0001
$ASA \ge 3$	41.3	42.0	38.5	0.689
Age-adjusted Charlson index	5 ± 2.3	5 ± 2.3	4 ± 2.1	0.001^{*}
Surgeon volume				
High (>25 cases/yr)	72.6	68.9	78.6	0.06
Intermediate (5–25 cases/yr)	21.4	23.1	18.6	
Low (<5 cases/yr)	6.0	8.0	2.9	
Pathology				
Pancreatic adenocarcinoma	52.0	64.6	31.4	$< 0.001^{*}$
Cholangiocarcinoma	4.1	3.9	4.3	0.867
Ampullary adenocarcinoma	7.1	6.9	7.1	0.955
Duodenal adenocarcinoma	1.9	0.9	3.6	0.065
Chronic pancreatitis	3.5	3.5	3.6	0.969
Intraductal papillary mucinous neoplasm	13.3	9.2	20.0	0.003*
Pancreatic neuroendocrine tumor	5.7	4.4	7.9	0.160

TABLE 2. Intraoperative Variables of Patients Undergoing PD Dichotomized According to POD 1 Drain Amylase Value

	All Patients (n = 369), %	POD 1 Drain Amylase <600 U/L (n = 229)	POD 1 Drain Amylase ≥600 U/L (n = 140)	Р
Duration of surgery, min	329.5 ± 101.9	344 ± 107.5	308 ± 89.4	0.006*
Anastomosis type				
Duct-to-mucosa	96.9	97.4	96.4	0.596
Invagination	0.8	0.4	1.4	
Pancreaticogastrostomy	2.2	2.2	2.1	
Hard pancreatic gland	52.6	77.1	32.9	< 0.001*
PD diameter, mm	3.0 ± 2.2	3.5 ± 2.5	2.5 ± 1.7	< 0.001*
Vessel resection	10.1	13.3	5.0	0.01*
Estimated blood loss, mL	600 ± 626.4	600 ± 688.7	450 ± 494.5	0.002*
Blood transfusion	14.1	17.5	8.6	0.017*

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TABLE 3. Postoperative Outcomes of Patients Undergoing PD Dichotomized According to POD 1 Drain Amylase
Value

	All Patients (n = 369), n (%)	POD 1 Drain Amylase <600 U/L (n = 229)	POD 1 Drain Amylase ≥600 U/L (n = 140)	Р
Median POD 1 drain amylase (U/L)	209 ± 11912.8	117 ± 12233.5	4856 ± 8241	0.0001*
Morbidity	151 (46.9)	91 (46.7)	60 (47.2)	0.919
Pancreatic fistula	46 (12.5)	2 (0.9)	44 (31.4)	< 0.0001*
Class A	23 (6.2)	1 (0.45)	22 (15.7)	0.619
Class B	12 (3.3)	1 (0.45)	11 (7.9)	
Class C	11 (3.0)	0 (0)	11 (7.9)	
Intra-abdominal abscess	26 (7.2)	16 (7.2)	10 (7.1)	0.982
DGE	29 (8.0)	20 (9.0)	9 (6.4)	0.378
Ileus	17 (4.7)	15 (6.8)	2 (1.4)	0.02*
Intra-abdominal hemorrhage	13 (3.6)	3 (2.1)	10 (4.5)	0.240
DVT/PE	7 (1.9)	5 (2.3)	2 (1.4)	0.579
Clavien Grade $\geq 3a$	61 (18.9)	35 (17.9)	26 (20.5)	0.572
LOS, d	7 ± 6.6	7 ± 6.7	7 ± 6.6	0.882
Need for ICU	20 (5.5)	11 (4.9)	9 (6.4)	0.550
Reoperation	9 (2.5)	7 (3.2)	2 (1.4)	0.305
Mortality	3 (0.9)	1 (0.6)	2 (1.6)	0.366
Readmission	74 (20.4)	38 (17.1)	36 (25.7)	0.048

*Statistical significance was achieved at the P < 0.05 level.

DGE indicates delayed gastric emptying; DVT/PE, deep venous thromboembolism/pulmonary embolism; ICU, intensive care unit.

TABLE 4. Multivariate Anal	vsis of Predictors of	f Postoperative Pancreatic	Fistula Formation After PD
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	Odds Ratio	95% CI	Р
POD 1 drain amylase < 600	0.0192	0.00457-0.0809	< 0.0001
Hard pancreatic gland	0.193	0.0686-0.544	0.002
Pancreatic adenocarcinoma pathology	0.496	0.262-0.938	0.031
PD diameter	0.861	0.669-1.110	0.247

major improvement in overall mortality. In PD, intraperitoneal drains are left mainly to detect PF, and should this occur, to funnel egress of the pancreatic juice and enteric contents, thereby preventing their accumulation, which in turn may lead to infection and/or vessel wall damage.

The Verona group has contributed much to our understanding of intraperitoneal drainage in PD and has set the benchmark for PD drain management. In a prospective controlled trial, Bassi et al¹⁵ randomized 114 patients undergoing pancreatectomy to drain removal on POD 3 and POD 5 or beyond and demonstrated that earlier drain removal on POD 3 was associated with decreased rate of PF (1.8% vs 26.5%, P = 0.0001), length of stay (8.7 days vs 11.3 days, P = 0.018), and hospital costs ($\notin 10,071$ vs $\notin 12,140$, P = 0.02), and based on these results implemented early (day 3) drain removal in their practice. The value of earlier drain removal was also shown by Kawai et al,¹⁸ who hypothesized that intraperitoneal drains serve as a rout for ascending infection when demonstrating a higher incidence of postoperative abscess in patients with drains removed on POD 8 compared to those removed on POD 4 (38% vs 8%, P = 0.0003).

The use of drains after PD, regardless of whether they are removed early or late, is by no means a universal practice. Proponents of not using closed suction drains after PD, in addition to the risk of infection, cite the detrimental impact of the vacuum exerted by the negative bulb suction (-75 to -175 mm Hg),³³ possibly eroding the pancreaticojejunostomy anastomosis and by itself causing a PF. To date, the Memorial Sloan Kettering group has provided the majority of the data supporting abandonment of routine drainage after PD. They initially described their retrospective experience of patients undergoing PD without intraperitoneal drains, reporting no difference in incidence of PF, intra-abdominal abscess, reoperation rates, or need for computed tomography–guided intervention between the drain and no-drain group.¹¹ The group went on to validate the findings in a trial that randomized 179 patients to drain versus no drain after pancreatectomy. They reported no difference in complication rate between the groups (63% vs 57% in the no-drain group, P > 0.05) and also a higher incidence of PF or intra-abdominal collection in the drained group (21.6% vs 8.8%, P < 0.02).¹² A subsequent study retrospectively evaluating the evolution of their practice of abandoning intraperitoneal drains after PD corroborated their previous findings. However, the practice did not even become generalized in their institution, because intraperitoneal drains were still used in more than half of their patients.¹³

The limitation to the aforementioned data, as with any single institutional study, is its external validity. In an attempt to add clarity to the debate, a multi-institutional, prospective randomized controlled trial was recently conducted. In the trial, Van Buren and colleagues randomized 137 patients across 9 high-volume pancreatic centers to PD with and without intraperitoneal drainage. The no-drain group was associated with a higher incidence of gastroparesis (42% vs 24%, P = 0.021), intra-abdominal fluid collection (12% vs 2%, P = 0.033), intra-abdominal abscess (26% vs 12%, P = 0.033), need for postoperative percutaneous drain (23% vs 9%, P = 0.022), and a prolonged length of stay (8 days vs 7 days, P = 0.016). The trial was terminated by the Data Safety Monitoring Board because of a fourfold increase in mortality in the no-drain group compared to patients who underwent routine intraperitoneal drainage (12% vs 3%). The reoperation rate was also higher in the no-drain group (9% vs 3%). Although neither of these 2 latter endpoints reached statistical significance, their clinical relevance is major when compared to standard outcomes.¹⁴ In the study's routine drainage group, the authors defined the criteria for drain removal to be when the drain amylase level (drawn POD 3 and later) was less than 3 times the upper limit of serum amylase level, or the output being 20 mL per day or less for 2 consecutive days. The latter criterion is incongruent with that as described by the ISGPF, which obviates the drain volume, inevitably resulting in most of the drains being removed as late as postoperative day 7. Given the evidence that early drain removal result in less morbidity,^{15,18} we wonder if the disparity in the results would have been even more apparent if drains were removed earlier.

Intuitively, defining a cohort at low risk of developing PF that would benefit from early drain removal would be a reasonable strategy.34 The correlation between drain amylase level and incidence of PF has been previously investigated, but interest in its utility to predict PF has peaked of late. In one of the earliest studies (n =137), Molinari et al³⁵ prospectively analyzed the correlation of drain amylase level and incidence of PF and found that a POD 1 drain amylase level of higher than 5000 U/L was highly predictive of PF on multivariate analysis (OR = 68.4, P < 0.001). Several subsequent studies have corroborated these findings, with suggested drain fluid amylase cutoff levels ranging from 100 to 5000 U/L yielding negative predictive value ranges of 84% to 100% and AUC ranges of 0.797 to 0.962 in detecting PFs.^{16,17,19–23,35} More recent studies have focused on lower drain amylase cutoff levels (100,16 100,20 and 35021) as they have shown to have a higher sensitivity and negative predictive value. In a recently published study correlating drain amylase level with incidence of PFs, the Wisconsin group identified a cutoff value of 100 U/L, which resulted in impressive sensitivity and negative predictive values of 96%,¹⁶ although the study sample size was only 63 patients, and the identified cutoff value of 100 U/L had a relatively low applicability, encompassing less than 40% of the study cohort.

In this study, we attempted to correlate drain amylase levels with PFs in a large cohort with prospective validation. To our knowledge, this is the largest study to date of consecutive patients with standardized drain management strategy that addresses this issue. We identified a POD 1 drain amylase level of higher than 612 U/L, which demonstrated the best accuracy, sensitivity, and specificity (Fig. 1). From the training cohort analysis, we then utilized a POD 1 drain amylase level of 600 U/L and successfully demonstrated a reproducible ROC curve, prospectively validating the cutoff value in a separate cohort (Fig. 2), and was, in fact, a much stronger predictor than well-established variables like pancreatic gland texture and duct diameter on multivariate analysis.

Despite the low drain amylase group having a higher ageadjusted Charlson index, longer duration of surgery, more vessel resections and a higher estimated blood loss, morbidity, and mortality was no different between both groups, with the low drain amylase group demonstrating a lower readmission rate. We hypothesize that in this low-risk group, drain removal as early as POD 1 is safe and may lead to decreased intra-abdominal infection. Importantly, the variable has high applicability, consisting of up to 62% of our study cohort that may benefit from earlier drain removal. Of course, to prove this hypothesis, we need to manage a large cohort of patients with early drain removal based on the drain amylase value on POD 1. We have begun this process and are currently removing the closed suction drains on postoperative days 1 and 2 if the amylase is less than 600 U/L.

One of the limitations to this study, as with any single institutional cohort analysis, is the external validity of our results. Our institution's PF rate of 12.5% is low when compared to historic rates, and akin to the external validity of the Memorial Sloan Kettering group's data on drain abandonment, utilizing POD 1 drain amylase of less than 600 U/L as an early stratification of patients to guide drain removal should not be assumed to be a universally safe practice. Similarly, our group's preference of pancreaticojejunostomy duct-to-mucosa anastomosis and utilizing external pancreatic stent is institution-specific. External pancreatic duct stents have been shown in several randomized controlled trials to reduce PF, morbidity, and delayed gastric emptying rates in high-risk patients (soft pancreatic gland, small pancreatic duct) and may have implications in postoperative outcomes.^{36–38}

We believe that the debate of current intraperitoneal drain management after PD should not be "to drain or not to drain" but rather "who and when can we stop draining." This study validates the Verona group's initial model of utilizing POD 1 drain amylase measurement as an early stratification of patients to high- or low-risk groups allowing for early drain removal and suggests that selective early drain removal may represent a safe strategy in minimizing patient discomfort and morbidity of prolonged intraperitoneal drainage with little consequences. After PD, the risk of PF is less than 1% if POD 1 drain amylase level is lower than 600 U/L. We propose that in this group, which comprises more than 60% of patients, intraperitoneal drains should be removed on PODs 1 and 2 and are currently validating this strategy in our practice. This has important implications in accelerating postoperative recovery and potentially further shorten anticipated length of stay in critical postoperative pathways.

REFERENCES

- Fernandez-del Castillo C, Morales-Oyarvide V, McGrath D, et al. Evolution of the Whipple procedure at the Massachusetts General Hospital. *Surgery*. 2012;152(3, suppl 1):S56–S63.
- Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. J Gastrointest Surg. 2006;10:1199–1210; discussion 1210–1211.
- Cameron JL, Riall TS, Coleman J, et al. One thousand consecutive pancreaticoduodenectomies. *Ann Surg.* 2006;244:10–15.
- Fong ZV, Ferrone CR, Thayer SP, et al. Understanding hospital readmissions after pancreaticoduodenectomy: can we prevent them? a 10-year contemporary experience with 1,173 patients at the Massachusetts General Hospital. *J Gastrointest Surg.* 2014;18:137–144; discussion 144–145.
- Veillette G, Dominguez I, Ferrone C, et al. Implications and management of pancreatic fistulas following pancreaticoduodenectomy: the Massachusetts General Hospital experience. *Arch Surg.* 2008;143:476–481.
- Correa-Gallego C, Brennan MF, D'Angelica MI, et al. Contemporary experience with postpancreatectomy hemorrhage: results of 1,122 patients resected between 2006 and 2011. J Am Coll Surg. 2012;215:616–621.
- Kennedy EP, Rosato EL, Sauter PK, et al. Initiation of a critical pathway for pancreaticoduodenectomy at an academic institution–the first step in multidisciplinary team building. *J Am Coll Surg.* 2007;204:917–923; discussion 923–924.
- Nagakawa Y, Matsudo T, Hijikata Y, et al. Bacterial contamination in ascitic fluid is associated with the development of clinically relevant pancreatic fistula after pancreatoduodenectomy. *Pancreas*. 2013;42:701–706.
- Gervais DA, Fernandez-del Castillo C, O'Neill MJ, et al. Complications after pancreatoduodenectomy: imaging and imaging-guided interventional procedures. *Radiographics*. 2001;21:673–690.
- Singh AK, Gervais D, Mueller P. Pancreatoduodenectomy: imaging and imageguided interventional treatment. Semin Ultrasound CT MR. 2004;25:252–260.
- Heslin MJ, Harrison LE, Brooks AD, et al. Is intra-abdominal drainage necessary after pancreaticoduodenectomy? J Gastrointest Surg. 1998;2:373–378.
- Conlon KC, Labow D, Leung D, et al. Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. *Ann Surg.* 2001;234:487–493; discussion 493–494.
- Correa-Gallego C, Brennan MF, D'Angelica M, et al. Operative drainage following pancreatic resection: analysis of 1122 patients resected over 5 years at a single institution. *Ann Surg.* 2013;258:1051–1058.
- Van Buren G, 2nd, Bloomston M, Hughes SJ, et al. A randomized prospective multicenter trial of pancreaticoduodenectomy with and without routine intraperitoneal drainage. *Ann Surg.* 2014;259:605–612.
- Bassi C, Molinari E, Malleo G, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. *Ann* Surg. 2010;252:207–214.

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- Israel JS, Rettammel RJ, Leverson GE, et al. Does postoperative drain amylase predict pancreatic fistula after pancreatectomy? J Am Coll Surg. 2014;18:978– 987.
- El Nakeeb A, Salah T, Sultan A, et al. Pancreatic anastomotic leakage after pancreaticoduodenectomy. Risk factors, clinical predictors, and management (single center experience). World J Surg. 2013;37:1405–1418.
- Kawai M, Tani M, Terasawa H, et al. Early removal of prophylactic drains reduces the risk of intra-abdominal infections in patients with pancreatic head resection: prospective study for 104 consecutive patients. *Ann Surg.* 2006;244: 1–7.
- 19. Moskovic DJ, Hodges SE, Wu MF, et al. Drain data to predict clinically relevant pancreatic fistula. *HPB (Oxford)*. 2010;12:472–481.
- Nissen NN, Menon VG, Puri V, et al. A simple algorithm for drain management after pancreaticoduodenectomy. Am Surg. 2012;78:1143–1146.
- Sutcliffe RP, Battula N, Haque A, et al. Utility of drain fluid amylase measurement on the first postoperative day after pancreaticoduodenectomy. *World* J Surg. 2012;36:879–883.
- Tsujie M, Nakamori S, Miyamoto A, et al. Risk factors of pancreatic fistula after pancreaticoduodenectomy: patients with low drain amylase level on postoperative day 1 are safe from developing pancreatic fistula. *Hepatogastroenterology*. 2012;59:2657–2660.
- Yamaguchi M, Nakano H, Midorikawa T, et al. Prediction of pancreatic fistula by amylase levels of drainage fluid on the first day after pancreatectomy. *Hepatogastroenterology*. 2003;50:1155–1158.
- Warshaw AL, Thayer SP. Pancreaticoduodenectomy. J Gastrointest Surg. 2004;8:733–741.
- Charlson M, Szatrowski TP, Peterson J, et al. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47:1245–1251.
- Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40:373–383.
- Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg.* 2009;250:187–196.

- 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.
- 29. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery*. 2005;138:8–13.
- Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142:761–768.
- Reynolds JT. Intraperitoneal drainage, when and how? Surg Gynecol Obstet. 1955;101:242–244.
- Petrowsky H, Demartines N, Rousson V, et al. Evidence-based value of prophylactic drainage in gastrointestinal surgery: a systematic review and meta-analyses. *Ann Surg.* 2004;240:1074–1084; discussion 1084– 1085.
- Grobmyer SR, Graham D, Brennan MF, et al. High-pressure gradients generated by closed-suction surgical drainage systems. *Surg Infect (Larchmt)*. 2002;3:245–249.
- Miller BC, Christein JD, Behrman SW, et al. A multi-institutional external validation of the fistula risk score for pancreatoduodenectomy. *J Gastrointest Surg.* 2014;18:172–179; discussion 179–180.
- Molinari E, Bassi C, Salvia R, et al. Amylase value in drains after pancreatic resection as predictive factor of postoperative pancreatic fistula: results of a prospective study in 137 patients. *Ann Surg.* 2007;246:281–287.
- Pessaux P, Sauvanet A, Mariette C, et al. External pancreatic duct stent decreases pancreatic fistula rate after pancreaticoduodenectomy: prospective multicenter randomized trial. *Ann Surg.* 2011;253:879–885.
- Poon RT, Fan ST, Lo CM, et al. External drainage of pancreatic duct with a stent to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. *Ann Surg.* 2007;246:425–433; discussion 433–435.
- Hong S, Wang H, Yang S, et al. External stent versus no stent for pancreaticojejunostomy: a meta-analysis of randomized controlled trials. *J Gastrointest* Surg. 2013;17:1516–1525.