PAPER

Pancreaticoduodenectomy

A 20-Year Experience in 516 Patients

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Hypothesis: Pancreaticoduodenectomy (PD) is a safe procedure for a variety of periampullary conditions.

Design: Retrospective review of a prospectively collected database.

Setting: Academic tertiary care hospital.

Patients: A total of 516 consecutive patients who underwent PD.

Main Outcome Measures: Patient outcomes and survival factors.

Results: Pathological examination demonstrated 57% periampullary cancers, 22% chronic pancreatitis, 12% cystic neoplasms, 4% islet cell neoplasms, and 5% other. Fifty-one percent of patients underwent pylorus preservation. Median operating time was 5 hours; blood loss, 1300 mL; and transfusion requirement, 1.5 U. Postoperative complications occurred in 43% of patients, including cardiopulmonary events (15%), fistula (9%), delayed gastric emptying (7%), and sepsis (6%). Additional surgery was required in 3% of patients, most commonly because of bleeding. Perioperative mortality was 3.9% overall but only 1.8% in patients with chronic pancreatitis; 25% of patients who died had preoperative complications associated with their periampullary condition. Three-year survival was 15% after resection for pancreatic cancer, 42% for duodenal cancer, 53% for ampullary cancer, and 62% for bile duct cancer. Univariate predictors of long-term survival in patients with periampullary adenocarcinoma included elevated glucose levels, liver function test results, abnormal tumor markers, blood loss, transfusion requirement, type of operation, and pathologic findings (periampullary adenocarcinoma type, differentiation, and margin and node status). Multivariate predictors were serum total bilirubin level, blood loss, operation type, diagnosis, and lymph node status.

Conclusions: Pancreaticoduodenectomy continues to be associated with considerable morbidity. With careful patient selection, PD can be performed safely. Long-term survival in patients with periampullary adenocarcinoma can be predicted by preoperative laboratory values, intraoperative factors, and pathologic findings.

Arch Surg. 2004;139:718-727

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PANCREATICODUODENECTOMY (PD) has its origins in the late 1800s. Although William Halsted[1] performed the first transduodenal local excision of a tumor of the ampulla of Vater in 1898, Alessandro Codivilla, in that same year, was the first to perform a PD, in Imola, Italy. In 1909 in Berlin, Walter Kausch[2] performed the first successful 2-stage PD. Allen Whipple et al[3] reported the first series of PDs in 1935, and since that time, the operation has been known as the "Whipple" operation. Operative mortality from the original report of Whipple to well into the 1970s was in excess of 25%.[4-10] More recently, however, several series[11-14] have reported large numbers of consecutive Whipple procedures without mortality. In addition, the procedure has gained wide acceptance such that in the past decade, some centers have reported large series of Whipple procedures for a variety of benign and malignant periampullary conditions.[15,16] In such high-volume centers, with the standardization of perioperative care, advances in surgical technique, and interventional radiology and intensive care support, the procedure has become considerably safer.[17-19] Nonetheless, the long-term outcome of PD in patients with periampullary adenocarcinoma continues to be poor. A benchmark study[15] from Johns Hopkins reported multivariate predictors of long-term survival in patients with periampullary adenocarcinoma that included diagnosis, number of additional surgeries, tumor size (>3 cm), tumor differentiation, tumor margin, and node sta-

tus. Similarly, in this article we report a high-volume, single-institution experience during the past 20 years with PD in which we examined the effects of preoperative, perioperative, and pathological variables on long-term survival.

METHODS

This is a retrospective review of a prospectively collected database of patients who underwent PD between March 23, 1980, and January 7, 2002. All patients underwent surgical treatment at University Hospital at the Indiana University School of Medicine. The purpose of this review is to investigate outcomes after PD for a variety of benign, premalignant, and malignant periampullary conditions. In addition, this review aims to determine whether there were preoperative or perioperative predictors of long-term survival in patients with periampullary adenocarcinoma. All data in this study were collected and reported in strict compliance with patient confidentiality guidelines put forth by the Indiana University institutional review board.

DATA COLLECTION

Data were prospectively collected and analyzed from the principal investigator's (J.A.M) database. All patients underwent a baseline history and physical examination. The diagnosis of jaundice was based on the presence of scleral icterus on examination. The presence of new-onset diabetes mellitus was defined as the existence of glucose intolerance necessitating diet modification and oral hypoglycemic drug or insulin use within 2 years of the diagnosis of a periampullary pathologic disorder without another obvious explanation. The diagnosis of diarrhea was made if patients experienced 3 or more bowel movements per day or if the total volume of their movements in a day was 0.5 L or greater. Weight loss was quantified by the patient at the time of the preoperative visit. Serum chemistry studies, hematologic studies, and tumor markers were analyzed from routine preoperative phlebotomy samples. Perioperative variables were recorded from the anesthesiologists' records at the time of the operation. Necessary radiographic and endoscopic procedures were performed to confirm a diagnosis of a periampullary disorder. All patients underwent PD (performed by C.M.S., D.F.C., E.A.W., J.A.M., L.E.J., R.J.G., T.A.B., or T.J.H.), with patients who underwent total pancreatectomy excluded from this study. All specimens were primarily reviewed by the staff pathologist at University Hospital. Most of these specimens were also reviewed by a single pathologist (O.W.C.). Margins routinely analyzed included the common bile duct margin, pancreatic neck margin, and duodenal or stomach margin. Uncinate and retroperitoneal margins were not routinely analyzed. Pancreaticocutaneous fistula was defined as a persistent amylase-rich fluid postoperatively from surgical drains or other cutaneous sites more than 1 week after surgery (>10 mL/d of the same at 1 week in closed-suction drains). Survival was determined from the most recent encounter at University Hospital and was cross-referenced with the Clarian Cancer Registry Database and the Social Security Database up until July 2002.

OPERATIVE TECHNIQUES

Patients underwent either pylorus-preserving or classic (hemigastrectomy) PD. Pancreaticoduodenectomy was performed via subcostal or midline incision. After thorough abdominal exploration and a generous Kocher maneuver, the gallbladder was removed and the common bile duct was transected. The anterior aspect of the portal vein was then dissected free of the overlying pancreatic neck. Subsequently, the duodenum (in the pylorus-preserving procedure) or the stomach (in the classic procedure) was transected, followed by transection of the pancreatic neck, uncinate process, and jejunum distal to the ligament of the Treitz. Truncal vagotomy was performed in most patients undergoing hemigastrectomy. Reconstruction was undertaken with an isoperistaltic limb of jejunum in retrocolic fashion and anastamosed with an end-to-side pancreaticojejunostomy, followed by an end-to-side choledochojejunostomy and an (antecolic or retrocolic) end-to-side duodenojejunostomy or gastrojejunostomy. The pancreaticojejunostomy was performed using a duct-to-mucosa anastomosis or, alternatively, an invaginated anastomosis. No pancreaticogastrostomies were performed in this series. The pancreaticojejunostomy and hepaticojejunostomy were drained routinely with Penrose or closed-suction drains. Prophylactic octreotide was not routinely used. Finally, some patients in the series underwent prophylactic gastrostomy placement for postoperative stomach decompression and alimentation.

Table 1. Demographic and Diagnostic Data for 516 Patients Who Underwent Pancreaticoduodenectomy

Variable	Patients, No. (%)
Age, mean (range), y	58 (15-93)
Males	298 (58)
Diagnosis	
Periampullary adenocarcinoma	**295 (57)**
Pancreatic	202 (39)
Ampullary	47 (9)
Duodenal	31 (6)
Bile duct	15 (3)
Pancreatitis	**112 (22)**
Cystic neoplasms	**61 (12)**
Intraductal papillary mucinous neoplasms	52 (10)
Mucinous cystadenoma	5 (1)
Serous cystadenoma	4 (1)
Islet cell neoplasms	**19 (4)**
Functional	11 (2)
Nonfunctional	8 (2)
Other	**29 (5)**

STATISTICAL ANALYSIS

Statistical associations between categorical factors were assessed using the Fisher exact test. The association of categorical factors with survival was assessed using the Kaplan-Meier (KM) method and was tested using the log-rank test. The association of continuous variables with survival was analyzed using a Cox proportional hazards regression model and was tested via the Wald test. Median values of continuous data were compared using the Kruskal-Wallis test. Statistical significance was set at $P \leq .005$ owing to the large number of variables being tested.

RESULTS

Demographic and diagnostic data for this series are presented in **Table 1**. Of 516 patients, only 65 underwent PD in the 1980s. The remaining patients underwent PD in the latter 12 years. The age of the patients recorded at the time of the operation in this series ranged from 15 to 93 years (median, 60 years; mean, 58 years). The male-female ratio was 58:42. Periampullary adenocarcinoma was the most common indication for PD (57%), with chronic pancreatitis being the second most common

Table 2. Serum Chemistry, Hematologic, and Tumor Markers Values in 516 Patients Who Underwent Pancreaticoduodenectomy

Variable	Patients, No.	Value		
		Mean	Median	Range
Total bilirubin, mg/dL	426	3.1	0.9	0.1-32
Alkaline phosphatase, U/L	429	297.8	154	0.5-13 860
Aspartate aminotransferase, U/L	426	75.2	42	6.0-668
Total protein, g/dL	410	7.0	7.1	4.7-16
Albumin, U/L	425	3.7	3.7	0.9-6.1
Amylase, U/L	314	100.1	62.5	6.8-943
Glucose, mg/dL	433	132.4	111	15.0-535
Calcium, mg/dL	417	9.1	9.2	4.4-12
Phosphorus, mg/dL	413	3.7	3.6	0.7-24
PT, s	423	12.4	12	10.3-21.3
aPTT, s	417	28.7	27.9	18.9-64.3
Hemoglobin, g/dL	457	13.0	12.9	7.6-22.0
Hematocrit, %	459	38.0	38	22.8-64.8
WBC, cells/mL	452	8.4	7.8	2.7-25.7
CEA, serum ng/mL	215	8.0	2.6	0-628
CA 19-9, serum U/mL	208	5563	80.9	10.0-544 100
CA 125, serum U/mL	73	23.0	15.0	3.0-157

Abbreviations: aPTT, activated partial thromboplastin time; PT, prothrombin time; WBC, white blood cell count.

SI conversion factors: To convert bilirubin to micromoles per liter, multiply by 17.1; calcium to millimoles per liter, multiply by 0.25; glucose to millimoles per liter, multiply by 0.05551; phosphorus to millimoles per liter, multiply by 0.323.

Table 3. Pathologic Findings in 295 Patients With Periampullary Adenocarcinoma

Variable	Periampullary Adenocarcinoma			
	Pancreatic (n = 202)	Ampullary (n = 47)	Bile Duct (n = 15)	Duodenal (n = 31)
Diameter, mean ± SD, cm	3.2 ± 1.5	2.5 ± 1.2	2.6 ± 0.7	3.7 ± 1.7
Differentiation, %				
Well	6	15	8	12
Moderate	44	33	38	19
Poor	38	13	0	27
No indication	12	41	54	42
Margin status, %				
Negative	80	100	83	90
Positive	20	0	17	10
Node status, %				
Negative	40	57	50	54
Positive	60	43	50	46

(22%). Of the periampullary adenocarcinomas, pancreatic adenocarcinoma was the most common (39%), followed by ampullary (9%), duodenal (7%), and distal bile duct (3%) adenocarcinomas. Cystic neoplasms (12%), islet cell tumors (4%), and other disorders (5%) composed 21% of the series. Cystic neoplasms consisted of 52 intraductal papillary mucinous neoplasms (40 benign and 12 malignant), 5 mucinous cystadenomas, and 4 serous cystadenomas. Islet cell tumors were benign in 7 patients and malignant in 12. Of the 19 patients with islet cell tumors, 11 (58%) were functional (4 vipomas, 2 somatostatinomas, 1 gastrinoma, and 4 unspecified). Other periampullary indications for PD included trauma (n=8), metastasis (n=11: 5 colon, 2 stomach, 2 renal, 1 testicular teratoma, and 1 neuroectodermal), ampullary adenoma (n=5), abscess (n=2), schwannoma (n=1), and neoplasm not otherwise specified (n=2).

Of the 12 patient preoperative symptoms, physical signs, and associated conditions recorded in our prospective database, the most common were abdominal pain (n=288; 56%), weight loss (n=227; 44%), and jaundice (n=223; 43%), followed by nausea and vomiting (n=164; 32%), abdominal tenderness (n=135; 26%), back pain (n=105; 20%), diabetes mellitus (n=95; 18%), pancreatitis (n=76; 15%), diarrhea (n=68; 13%), hemepositive stool samples (n=24; 5%), abdominal mass (n=22; 4%), and organomegaly (n=17; 3%).

Also recorded in the database were 9 preoperative serum chemistry values, 5 hematologic study results, and 3 serum tumor marker values (CEA, CA 19-9, and CA 125) (**Table 2**). Most patients had their preoperative complete blood cell count, serum chemistry values, and coagulation profile recorded. Of the 426 patients in whom the serum bilirubin level was measured, 42% had an elevated level, suggesting that many patients had a component of obstructive jaundice. This reflects our preoperative sign "jaundice" (43%). Biliary stasis can lead to poor synthetic function in the liver, and, correspondingly, 31% of 423 patients tested had an elevated serum prothrombin time. Serum albumin concentration was below the reference range in 24% of the patients tested.

Pylorus-preserving PD was performed in 263 patients (51%), and classic PD was performed in 252 patients (49%); for 1 patient, the type of operation performed was not specified. Pancreaticojejunostomy technique was reported in 406 patients. Duct-to-mucosa pancreaticojejunostomies were performed on 345 patients (85%), and the remaining 61 (15%) underwent an invaginated anastomosis (except 3 patients who underwent a lateral pancreaticojejunostomy or Peustow-type anastomosis). Operative time was a median of 5 hours and 6 minutes (mean, 5 hours and 46 minutes). Operations required a median transfusion of 1.5 U of packed red blood cells (mean, 2.8 U). The median blood loss was 1300 mL (mean, 1922 mL). Median blood loss has been steadily decreasing in the series by approximately 80 mL yearly. Median length of hospital stay was 13 days (mean, 18 days).

We performed a subset analysis of the pathologic features of the periampullary adenocarcinomas. **Table 3** provides the tumor characteristics of resected periampullary adenocarcinomas, including average tumor diameter, differentiation, and margin and lymph node status. Average tumor diameter ranged from 2.5 to 3.7 cm. Median (range) tumor diameter was different (Kruskal-Wallis, $P=.03$) based on periampullary adenocarcinoma type: duodenal, 3.5 cm (1.5-8.0 cm); pancreatic, 3.0 cm (0.8-11.0 cm); distal bile duct, 2.3 cm (1.9-3.8 cm); and ampullary, 2.25 cm (0.4-5.3). There was a dramatic difference in differentiation status according to periampullary adenocarcinoma diagnosis. The least differentiated tumors were the pancreatic adenocarcinomas (Kruskal-Wallis, $P<.001$). Margin status was negative in greater than 79% of patients. Positive margins were high-

est in the pancreatic adenocarcinoma group (20%) and the distal bile duct cancers (17%). Node-positive status ranged from 43% in ampullary cancers to 60% in pancreatic adenocarcinoma. There was no difference in margin or lymph node status according to periampullary adenocarcinoma diagnosis ($P=.13$ and $P=.26$, respectively).

In general, 57% of patients undergoing PD (n=293) had no perioperative complications, whereas 43% (n=223) experienced complications. The most common category of complication was cardiopulmonary in 15% of the patients (n=78), followed by pancreatic anastomotic leak or fistula in 9% (n=46). Less common were complications of delayed gastric emptying (7%; n=38), sepsis (6%; n=32), wound infection (5%; n=24), intra-abdominal abscess (3%; n=13), and bleeding (3%; n=18). Only pancreatic leak or fistula complications were associated with diagnosis. This complication was particularly frequent in cases of duodenal (23%) and ampullary (17%) neoplasms. Delayed gastric emptying was more common in pylorus-preserving PD vs classic PD, although this difference did not reach statistical significance (10% vs 6%; $P=.13$ for all patients and 11% vs 5%; $P=.07$ for patients with adenocarcinoma). Median length of hospital stay was 20 days for patients with postoperative complications vs 10 days for patients without postoperative complications ($P<.001$).

Overall 30-day in-hospital mortality in the series was 3.9%. However, mortality in patients with periampullary adenocarcinoma was slightly higher (4.7%), whereas the mortality rate in patients with chronic pancreatitis was only 1.8%. Patients with cystic neoplasms and islet cell tumors had mortality rates of 3.4% and 5.3%, respectively. These differences in perioperative mortality are not statistically significant. The causes of perioperative mortality include sepsis/multisystem organ failure (9 patients), disseminated intravascular coagulation/coagulopathy (4 patients), myocardial infarction (3 patients), pulmonary embolus (2 patients), and hemorrhage (2 patients). Five patients (25%) who had perioperative mortality had significant preoperative complications of their periampullary condition, including sepsis, hemorrhage, and failure to thrive. Thirty-five percent of patients who had perioperative mortality received preoperative total parenteral nutrition.

The long-term survival outcomes are presented in **Table 4** (proportional method) and the **Figure** (KM method). The KM method is probably a more accurate estimate of actual survival because it accounts for the fact that not all participants have been followed for exactly 1-year intervals. One can appreciate this as the 2 estimators (proportional and KM) become increasingly divergent in the later periods (2 and 3 years), where many patients have been followed for less than that period and thus are not accounted for by the method of proportions (which simply excludes them from analysis). The KM method adjusts the analysis for these patients, however, using all available information. For all 516 PDs, 1-year survival was 74% (KM, 74%) and 3-year survival was 53% (KM, 57%). For periampullary adenocarcinoma, 1-year survival was 63% (KM, 64%) and 3-year survival was 27% (KM, 35%). Pancreatic adenocarcinoma carries the worst prognosis of the 4 periampullary adenocarcinomas in this series, with 1-year survival of 55% (KM, 56%) and 3-year survival of 15% (KM, 27%). In our series, distal bile duct adenocarcinoma had the best prognosis at the 3-year interval among periampullary adenocarcinomas at 62% (KM, 64%). Survival after PD for chronic pancreatitis at 3 years was 91% (KM, 93%). Survival after resection of cystic neoplasms at the 3-year interval was 86% (KM, 87%). Patients with intraductal papillary mucinous neoplasms had 3-year survival of 87%. The median follow-up in this group was 25 months (mean, 50 months).

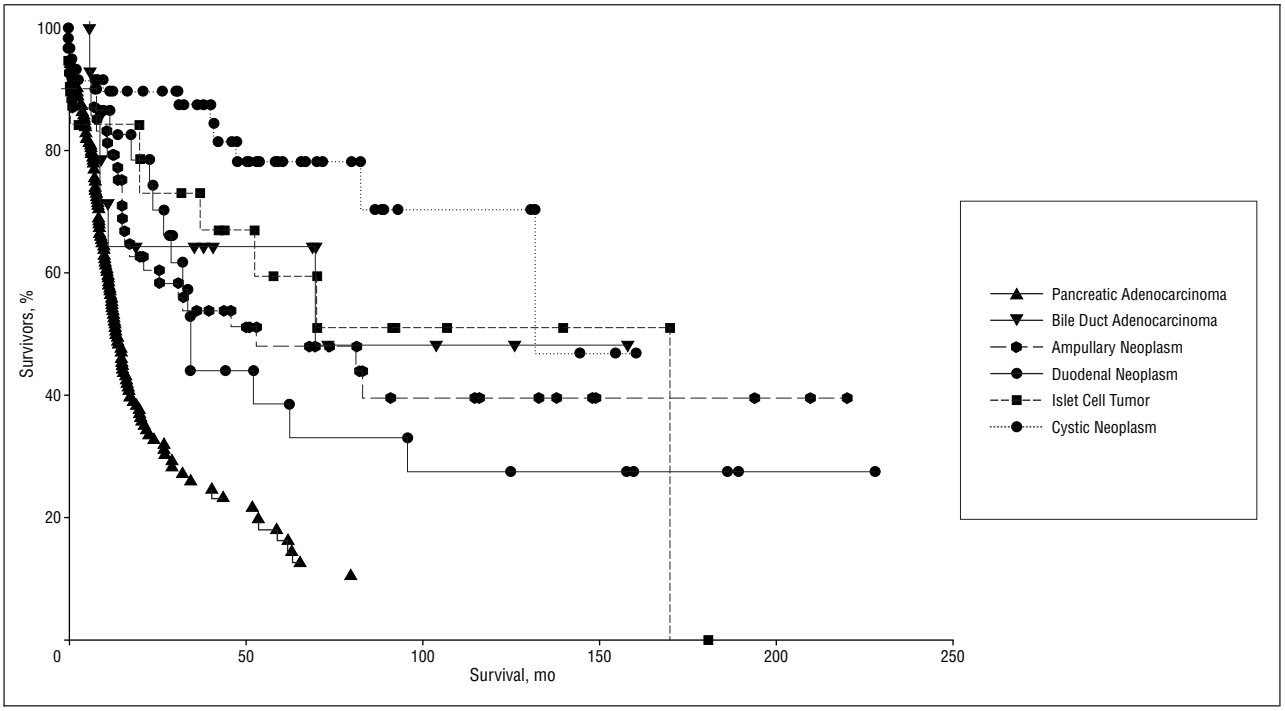
Table 4. Actual Long-term Survival Rates by Diagnosis

Patient Group	Patients, No.	Survival, %		
		1 y	2 y	3 y
Periampullary adenocarcinoma				
Pancreatic	202	55	25	15
Distal bile duct	15	71	64	62
Ampullary	47	84	60	53
Duodenal	31	81	69	42
Subtotal	**295**	63	38	27
Pancreatitis	112	92	92	91
Cystic neoplasms	61	89	88	86
Islet cell tumors	19	84	78	67
Total	**516**	74	59	53

Survival in the subset of 236 patients with periampullary adenocarcinoma whose adjuvant treatment status was known is given in **Table 5**. Most patients with known follow-up did not have adjuvant treatment (67%). Most patients who underwent adjuvant therapy received combined chemotherapy and radiotherapy (26%). Only 15 patients (7%) received chemotherapy alone. Chemotherapy involved predominantly fluorouracil and gemcitabine-based regimens. One-year survival was highest in patients who underwent adjuvant chemoradiotherapy (72%) vs chemotherapy alone and no adjuvant therapy (both 62%). Two-year survival was similar in patients who underwent chemoradiotherapy vs those with no adjuvant treatment, but at 3 years, there was a slight but nonsignificant advantage in patients who received no treatment (28% vs 23%). All comparisons of these 3 treatment groups fell short of statistical significance ($P=.28$).

All factors were analyzed for their effecton long-term survival in the subgroup of patients with periampullary adenocarcinoma. Univariate analysis of demographic factors using a Cox proportional hazards regression model showed that age and sex were not associated with survival. Similarly, no symptoms, signs, or associated conditions were associated with survival in the subgroup of patients with periampullary adenocarcinoma.

Preoperative laboratory values associated with survival were serum total bilirubin, alkaline phosphatase, aspartate aminotransferase, glucose, CA 19-9, and CEA levels (**Table 6**). Elevation of any of these laboratory values reflected poorer survival. Serum total bilirubin level was statistically the most significant factor of all preoperative laboratory values ($P<.001$). The other liver function test values, aspartate aminotransferase level ($P=.008$) and alkaline phosphatase level ($P=.02$), were less significant but were highly associated with serum total bi-



Kaplan-Meier survival curves by diagnosis.

Table 5. Actual Survival by Adjuvant Therapy in 236 Patients With Periampullary Adenocarcinoma Whose Adjuvant Treatment Status Was Known

Adjuvant Therapy	Patients, No.	Survival, %		
		1 y	2 y	3 y
Chemotherapy + radiotherapy	62	72	38	23
Chemotherapy alone	15	62	33	18
None	159	62	37	28

lirubin level. Despite diabetes mellitus not being a significant predictor of survival ($P=.15$), glucose level as a continuous variable was a significant predictor of survival ($P=.003$). Glucose level was correlated with total bilirubin level ($P<.001$) and, separately, with a diagnosis of pancreatic adenocarcinoma ($P=.003$). Patients with elevated levels of CA 19-9 and CEA had statistically significant poorer survival than patients with normal levels ($P=.007$ and $P=.008$, respectively).

Type of operation was strongly associated with survival ($P=.001$). Pylorus-sparing PD was associated with significantly longer survival vs non–pylorus-sparing PD (median survival, 32.2 vs 14.0 weeks; 95% confidence interval, 18.9-53.6 vs 12.1-18.0 weeks). The duration of the operation was not a significant factor with respect to long-term survival, with the trend favoring longer operations ($P=.11$). Excluding patients with perioperative mortality in the analysis, this is even more suggestive ($P=.06$). Blood loss was also a significant factor associated with poor survival ($P=.002$). Correspondingly, blood replacement had a weaker association with survival ($P=.03$). There is a significant correlation between the amount of blood lost and the amount of blood replaced (Spearman correlation $r=61\%$; $P<.001$).

Among the perioperative complications, only bleeding was associated with shorter survival ($P=.03$). Bleeding was also associated with perioperative death ($P=.02$). With perioperative deaths excluded, bleeding was not significantly associated with survival ($P=.18$). No perioperative complications were associated with survival in the subgroup of patients with periampullary adenocarcinomas. The small frequency of specific complications, however, resulted in reduced power to perform these comparisons.

Periampullary adenocarcinoma type was a significant survival predictor, with pancreatic cancer having a significantly lower survival than the other 3 periampullary adenocarcinomas ($P<.001$). The existence of positive lymph nodes was associated with significantly lower survival ($P<.001$). Margin-positive status ($P<.001$) and poor differentiation ($P<.02$) were also significant negative predictors of survival. Size (tumor diameter) was not associated with survival as a continuous variable ($P=.15$).

Long-term survival predictors in the entire series in general mirrored those of the periampullary adenocarcinomas. Exceptions are that blood loss was not significant in patients without periampullary adenocarcinoma ($P=.45$) or any other subgroups (eg, pancreatitis; $P=.66$). Also, as might be expected, preoperative pancreatitis, abdominal pain, and tenderness were significantly associated with longer survival ($P<.001$). These latter findings may be explained by the high degree of association between abdominal pain and tenderness and pancreatitis vs any other pathologic diagnosis ($P<.001$).

Multivariate analysis of all statistically significant predictors of survival as identified in the univariate analysis involved stepwise model selection. A candidate variable was entered into the model if it was significant

Table 6. Univariate Variables Negatively Affecting Survival in Patients With Periampullary Adenocarcinoma

Univariate Variable	Hazard Ratio	*P* Value
Glucose (mg/dL)*	1.004	.003
Serum total bilirubin	1.908	<.001
Aspartate aminotransferase	1.668	.008
Alkaline phosphatase	1.499	.02
Elevated CA 19-9	1.961	.007
Elevated CEA	1.709	.008
Classic pancreaticoduodenectomy	1.614	.001
Blood loss (mL)*	1.370	.002
Transfusions (mL)*	1.001	.03
Positive lymph nodes	1.905	<.001
Positive margins	2.857	<.001
Poor tumor differentiation	1.481	<.02
Diagnosis (pancreatic cancer vs other)	5.811	<.001

*Continuous variables (the hazard ratio represents an increase in risk for every unit increase); blood loss is log-transformed.

(adjusted for all other variables already in the model) at the 20% level of significance, and it remained in the model if it attained statistical significance of at least 10%. Cox proportional hazards regression was again the analysis vehicle. Of all the factors that were statistically significant in the univariate analysis, serum total bilirubin level, blood loss, operation type, diagnosis, and lymph node status were jointly predictive of long-term survival (**Table 7**).

Table 7. Multivariate Variables Negatively Affecting Survival in 281 Patients With Periampullary Adenocarcinoma

Predictive Factor	Hazard Ratio	*P* Value
Diagnosis (pancreatic adenocarcinoma vs other)	2.350	<.001
Elevated total bilirubin level	1.676	.007
Positive lymph node status	1.667	.007
Classic pancreaticoduodenectomy	1.533	.02
Blood loss*	1.329	.02

*Log-transformed.

COMMENT

In this study, we cite our experience during the past 20 years with 516 PDs. This single academic tertiary referral center experience in many ways confirms the experience of other large centers with this operation. Pancreaticoduodenectomy continues to be a challenging and substantially morbid procedure. In our series, 43% of patients undergoing PD had a complication. Nonetheless, these complications, for the most part, were minor and not life threatening. Furthermore, there were no specific postoperative complications associated negatively with survival, including additional surgical procedures.

In this series, 57% of patients had a diagnosis of periampullary adenocarcinoma. Patients with periampullary adenocarcinoma had a greater incidence of perioperative mortality compared with patients with benign conditions. Patient selection remains an important factor in minimizing the perioperative mortality from this operation. Although cardiopulmonary complications were the most common in this series, sepsis/multisystem organ failure and bleeding were the commonest causes of perioperative mortality. At least 25% of patients with perioperative mortality in this series had experienced complicated preoperative courses, suggesting that operating on patients with recent sepsis, hemorrhage, or other considerable preoperative complications puts these patients at high risk of perioperative mortality. Despite the increased risk of perioperative mortality in the subgroup of patients with periampullary adenocarcinoma, they were not at increased risk of complications (43%). In addition, patients with periampullary adenocarcinoma (compared with patients with benign or premalignant conditions undergoing PD) were generally older (but age was not a negative predictor of long-term survival in patients with periampullary adenocarcinoma).

Long-term survival after PD for periampullary adenocarcinoma remains poor. Univariate predictors of long-term survival in this subgroup included serum glucose level, liver function test results, serum tumor marker levels (CEA and CA 19-9), blood loss, transfusion requirement, type of operation, and pathologic findings (periampullary adenocarcinoma type, differentiation, and margin and node status). Multivariate predictors were serum total bilirubin level, blood loss, operation type, diagnosis, and lymph node status.

Periampullary adenocarcinoma type and lymph node status were the most important predictors of survival outcome in univariate and multivariate analyses. These multivariate predictors of survival were also identified by the Johns Hopkins benchmark study[15] looking at long-term survival outcomes in a similar population of patients. With mean follow-up of 50 months (median, 25 months), patients with pancreatic cancer had 2-year survival of 25%. Two-year survival in patients with other periampullary adenocarcinomas was 60% or greater. Patients with nonpancreatic periampullary adenocarcinomas and node-negative status tended to survive longer, placing the emphasis on early detection or prevention. Efforts at cessation of smoking, screening of high-risk groups, and research into chemopreventive strategies are warranted.

In contrast to the Johns Hopkins study[15] and absent from our multivariate analysis are tumor size, tumor differentiation, and margin-positive status. Tumor size was a continuous variable in our univariate analysis and was not statistically significant. The Hopkins study used an arbitrary cutoff value of 3 cm and found that tumors 3 cm or larger carried a worse prognosis. When we use an arbitrary cutoff value of 3 cm and treat this as a categorical variable, tumor size is not a statistically significant univariate or multivariate predictor of survival among patients with a periampullary adenocarcinoma diagnosis. Tumor grade (differentiation) was a statistically significant univariate predictor, but it did not reach significance in the multivariate model because tumor differentiation is strongly associated with a diagnosis of pancreatic adenocarcinoma. Of patients with pancreatic adenocarcinoma, 86% had poor tumor differentiation vs 52% of the remaining patients with periampullary adenocarcinoma. Similarly, margin status was a statistically sig-

nificant univariate predictor, but it did not reach significance in the multivariate model. The reason for this is that positive margin status was statistically significantly correlated with lymph node status. The proportion of procedures with positive margins was 3-fold higher in lymph node–positive individuals vs lymph node–negative individuals, explaining its absence from the multivariate model. In addition, a complete margin status (retroperitoneal, uncinate, neck, bile duct, and duodenum/stomach) was not present in many patients, so margin status as opposed to lymph node status was preferentially excluded from the multivariate analysis. If we include margin status and perform the model selection on this subsample of patients, lymph node status and operation type fall out. Multivariate predictors then become margin status, blood loss, a diagnosis of pancreatic adenocarcinoma, and total bilirubin level.

Statistically significant multivariate predictors of long-term survival in the present study that were not common to the Johns Hopkins series[15] included blood loss, type of operation, and serum total bilirubin value. In our series, we treated blood loss as a continuous variable, and it reached statistical significance as a univariate and multivariate predictor. In the Johns Hopkins series, blood loss was treated as a categorical variable with an arbitrary cutoff value of 700 cm^3 and was found to be statistically significant as a univariate predictor but not as a multivariate predictor. If we use this 700-cm^3 cutoff value, blood loss is no longer statistically significant in our multivariate model. Blood loss and transfusion requirement were not statistically significant predictors in the nonadenocarcinoma PD subgroups. Operations that minimize blood loss through preoperative and postoperative measures may give people with periampullary adenocarcinoma a survival advantage. Correspondingly, duration of surgery was not a statistically significant survival predictor, which would further encourage a meticulous approach to hemostasis. Classic PD was a univariate and multivariate predictor of poorer survival. Operation type was not associated with diagnosis, lymph node status, or tumor size, suggesting that operation type (as opposed to its indication) may have some effect on long-term survival. Pylorus-preserving PD was performed more commonly later in the series; however, adjusting by the effect of the year of operation did not explain away any of the effect of operation type on long-term survival. These data are intriguing as 2 smaller randomized controlled trials looking at radical vs standard PD[20] and pylorus-preserving vs standard PD[21] did not demonstrate a survival advantage to patients undergoing pylorus preservation. Finally, serum total bilirubin level was found to be a preoperative predictor in our multivariate model of long-term survival. Aside from pathologic findings, serum total bilirubin level remained the most statistically significant predictor of survival in our multivariate analysis. Often, pathologic features on the periampullary tumor before surgery are limited. Aside from pathologic findings, bilirubin level may be helpful in counseling patients about the chances of long-term survival before surgery. It is unclear what role stenting and timing of stenting may have in affecting these patients' risk profile. Accordingly, in patients with abnormally elevated bilirubin levels in this series, there was no survival difference in patients who were preoperatively stented or unstented.

Other preoperative blood tests worth mentioning are tumor markers CEA and CA 19-9. Tumor markers are a univariate predictor but not a multivariate predictor in our model. Elevated levels of tumor markers (CEA and CA-19-9) are statistically significantly associated with a diagnosis of pancreatic adenocarcinoma, which was entered into the model as a separate category and thus superceded and summarized all these markers (which were thus excluded from the final model). We believe that explicitly modeling this diagnosis as a predictor of survival and stating factors that are associated with it is a more direct method of presenting the results. Conversely, not accounting for the impact of this diagnosis in multidiagnosis models may produce artifactual risk predictors for survival, which are merely predictors of the diagnosis itself. Once this diagnosis is established, no incremental information on subsequent survival is supplied by these serum tumor markers (in addition to knowledge of the pancreatic adenocarcinoma diagnosis). This is why they are significant univariate predictors but fall out of the multivariate analysis. It is important to note, however, that in the preoperative evaluation of patients it is not always known whether the diagnosis is pancreatic vs other periampullary adenocarcinoma, so we believe that preoperative CEA and CA19-9 values have a role in stratifying patients' long-term prognosis.

Chemotherapy, radiotherapy, or combined chemoradiotherapy for periampullary adenocarcinomas in general, without any subgroup analysis, did not seem to confer a survival advantage to those with known follow-up. There may have been a slight increase in survival at the 1-year interval for patients undergoing adjuvant treatment, but this is counterbalanced by a slight decrease in survival at the 3-year interval. It is unclear whether this is related to selection bias. These results should be interpreted with caution.

Although resection of periampullary adenocarcinoma does not seem amenable to alternative approaches, resection of benign conditions may indeed be amenable to operations other than PD. Short-term results[22] of duodenal-sparing pancreatic head resection are promising for patients with pancreatitis predominantly in the head of the pancreas. In addition, there are also small series of patients who have undergone enucleation of cystic-type lesions, both cystadenomas[23] and branch-type intraductal papillary mucinous neoplasms.[24] Whether these less invasive options of resecting benign or premalignant periampullary processes are equivalent to PD awaits longer-term follow-up.

In high-volume centers, PD can be conducted with acceptable mortality. Currently, PD continues to be the best approach to a variety of benign and malignant periampullary conditions. Proper patient selection and careful technique continue to be the most important factors in minimizing morbidity and perioperative mortality from this operation. In patients with complications of periampullary adenocarcinoma before surgery, PD should be approached with caution. In patients with periampullary adenocarcinoma, efforts to minimize perioperative blood loss and transfusion seem important in prolong-

ing patient survival. Negative margins should be achieved at surgery if possible, and pylorus preservation should be preferred. Preoperative laboratory studies, in particular serum bilirubin, CEA, and CA 19-9 levels, are simple but powerful tests that may be used before surgery to stratify survival outcome in patients with periampullary adenocarcinoma. Periampullary adenocarcinoma type and lymph node status remain the 2 most important predictors of long-term survival.

Accepted for publication February 24, 2004.

This study was presented at the annual meeting of the Western Surgical Association; November 12, 2003; Tucson, Ariz, and is published after peer review and revision. The discussions that follow this article are based on the originally submitted manuscript and not the revised manuscript.

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DISCUSSION

Gerard V. Aranha, MD, Maywood, Ill: Dr Schmidt has done an excellent job in presenting a summary of the experiences of the past 20 years with the Whipple operation at Indiana University. So when one has such a paper, one cannot be too critical, especially when the morbidity rates are the same as in any major center and the mortality is less than 2%, which I think all of us are aiming for. I would like to ask some questions to tease out some data and to expound on some of the problems that they may have had in their patients and ask what they have learned from these 516 patients. These questions are going to be in chronological order from the "Methods" and "Comment" sections. I didn't see any mention of sarcomas in your histological types. Did you have any and how did they do? You say that increased bilirubin is an increased hazard. Do you believe now that you are going to put stents in the future in your patients prior to the operation? What is the best preoperative test? You talk about the ultrasound, CT, ERCP? Should we use all? How should we use them? In what combination? And, when did you do laparoscopy in this disease?

You say that the patients who had the pylorus-preserving Whipple did better than those who had the traditional Whipple. Did both groups have the same histology? In your paper you state that you looked at several margins: the cut body margin of the pancreas, the cut biliary margin, and the cut duodenal margin. But you don't mention the posterior margin. That is the most likely to be positive. Why didn't you look at the posterior margin in your series?

You had 11 patients in whom you did a Whipple in the presence of metastasis. I had difficulty in understanding that. Were the metastases to the pancreas or were they patients who had primary pancreatic tumors that had metastasized? In 11 patients you had 1 death (9%) and an 8-month survival. Is it worthwhile doing the operation in those patients?

Your major complication was cardiac. In my practice, all patients above the age of 70 are taken past 1 cardiologist who clears the patients for me. Some people have needed coronary stents, and nobody had a bypass yet. Do you do that for your patients?

Two deaths occurred in cystic tumors. Last year we presented our paper here on cystic tumors. The deaths that we had were only in those who had a total pancreatectomy that you had excluded. What were the causes of the deaths in those 2 patients with cystic tumors? What was the histology and what was the operation?

And, of course the final question, do you have any thoughts on the use of somatostatin for this operation?

Dr Madura: I will go through the questions one by one. We did not have any pancreatic sarcomas in this series of patients, and we have no information for you on that. The increased bilirubin was a statistically significant increased hazard: we are currently looking at that. Dr Schmidt has been busy sorting that out. Of the 180 patients who were jaundiced, half

of those were stented and half were not. I cultured the bile in all of those patients who had gallbladders and in those patients who we could retrieve bile from the common duct. Patients who had an endoscopically placed stent all had infected bile, and that mirrored the organisms in infection complications. Some of those patients had wound and abdominal infections, and the organisms were the same as cultured in the bile and may have contributed to postoperative sepsis and multisystem organ failure in a few patients.

Is a pylorus-preserving Whipple better than the classic Whipple? It seems that way, but our series is not a prospective randomized trial, and we eventually utilized the pylorus-preserving procedure. There was no difference in those groups as far as histology, nodal metastasis, size of tumor, or anything else.

You specifically asked about posterior margins: this is a problem like Dr Farley had with many anesthesiologists. We had many pathologists looking at these specimens over the years, and there was not a specific reporting protocol. I think that they looked at posterior margins but were not fastidious in reporting this. We did not biopsy the retroperitoneum in a routine fashion, and some patients had frozen sections of all of the margins and some of them we did not. Additionally, some patients were reported to have clear margins on frozen and subsequently were reported to have tumor cells at the posterior margin on the permanent sections, and we did not go reoperate on those patients.

In the 11 patients with metastatic disease, none of these were patients who metastasized from a primary pancreatic tumor to anywhere else. There were several colon cancer patients, renal cancer patients, and other primary extra pancreatic lesions which had metastasized to the pancreas as well as other places. The colon cancer patients did reasonably well, and these were patients with colon tumors, which had occluded the duodenum and invaded the pancreas, and as a last resort therapy we did a Whipple en bloc in conjunction with the removal of the colon tumor. Those patients did reasonably well. It improved the quality of their life for what survival they had.

You inquired about the cardiac complications: 7% of those patients had cardiac problems. When the cardiac history was suspicious, they were seen by cardiologists. None of those patients underwent coronary artery stenting, and no cardiac surgeon would do an open procedure on somebody with pancreatic cancer. Several of the patients were high-risk patients with heavy smoking history. There was no history of previous MIs [myocardial infarctions], however, and several of them had died of postoperative myocardial infarction, but not many.

The cystic tumors that resulted in postoperative mortality had low–malignant potential IPMNs [intraductal papillary mucinous neoplasms]. Both died of sepsis; 1 of a florid pneumonia and 1 who had significant intraoperative bleeding, multisystem organ failure, and eventually died.

We did not use somatostatin routinely. Some of our colleagues used it if there was a pancreatic fistula in some patients, but nothing in a strict protocol fashion.

William W. Turner, Jr, MD, Jackson, Miss: Did you find any value in using serum CEA, CA 19-9, and CA-125 preoperatively or in postoperative follow-up? Could you tell us about the selection of ductal anastomoses vs invaginated pancreatic anastomoses?

Dr Madura: We are also looking at CEA. What I also did when we were collecting bile for culture was to analyze it for biliary and, in many cases, pancreatic duct fluid tumor markers. It looks as though elevated CEA levels predicted poor long-term survival. It is related to tumor size and length of presence of malignancy preoperatively, and those are both bad things for survival. The CA 19-9 and the CA 125 did not seem to have any prognostic influence. The pancreaticoenteric anastomosis was done pretty much at the discretion of the individual surgeon. When I first started doing these, I did some invaginated ones, but it became very clear to me that doing a precise duct-to-mucosa anastomosis was better. My patients were all done without stents because I could never keep a stent in the duct and I usually did not use a T-tube because the bile ducts were sufficiently large.

My younger colleagues came along and utilized that technique as well. We had very few leaks from the pancreatic enteric duct-to-mucosa anastomosis.

Thomas A. Stellato, MD, Cleveland, Ohio: Jim, this is a spectacular series. Once again, the pancreatic anastomosis—did you note a difference in the fistula rate between your early experience with the invagination technique vs the mucosal technique. Second, regarding biopsies, do you have any data about the patients who were biopsied preoperatively and their subsequent survival data? Finally, you indicated that stents are associated with infection, which we are all aware of. I take it you try to avoid stenting these patients if you can, even endoscopically. Do you have an absolute value for bilirubin where you will be more likely to push for a stent or not?

Dr Madura: To answer your last question first, that is kind of out of our control because many of these patients came to us already having been endoscopically stented. When patients were first seen with a markedly high bilirubin, and while they were being studied, a stent would be placed either at a referring institution or by our own endoscopists. So we really had very little control over that. If I would see a patient initially and their bilirubin was 10 mg/dL, I would prefer not to have a stent and just simply go ahead and operate without preoperative contamination of an obstructed biliary tree. The leak rate was higher with the invagination techniques, and after everybody got used to doing a nice 2-layered anastomosis, duct-to-mucosa, the leaks essentially disappeared, so much so that we didn't think that we could find any difference in doing a double-blind study with somatostatin, for example.

One other question I forgot to answer for Dr Aranha was the most efficient way to study these patients preoperatively. We have currently submitted a prospective study to the *Annals of Internal Medicine*, and it should be published soon, evaluating endoscopic ultrasound vs helical CT done several weeks before surgery in a strict prospective double-blinded fashion. Our results suggest that the best study is endoscopic ultrasound. It offers the advantage of detecting abnormal-looking lymph nodes and biopsying both primary tumor and lymph nodes transgastrically or transduodenally, and it gives you the most accurate prognostic information. There is still a small group of patients who you really can't tell if the tumor is abutting the portal venous system or if it is in fact invading it, and these patients need surgery to solve that dilemma. We currently think that if you can only do 1 study, we would select the endoscopic ultrasound.

Richard A. Prinz, MD, Chicago, Ill: A number of surgeons were involved in this study. I realize Dr Madura did the bulk of the operations, but was there any difference in the type of operation performed or the outcome according to the operating surgeon? I ask this because I am intrigued by the difference in the outcome with pylorus preserving and a standard Whipple. It seems to me that your group is a proponent of pylorus preserving, and there had to be some reason why the standard Whipple procedures were performed. Was that due to things that might affect the outcome, such as a larger tumor size or more nodal involvement around the celiac axis?

The second thing is in Chicago any jaundiced patient who reaches a surgeon is going to have a stent in place. I realize your study took place over a number of years. Did you have patients who were jaundiced that you could compare who did not have a stent with those who did have a stent, and were there differences in those 2 groups?

Dr Madura: Your question regarding the classic vs the pylorus-preserving Whipple must be tempered by the fact that this is a 20-year experience. Early in the series, when I did most of them, I did what I had learned to do, the standard Whipple. I had some hesitation in doing a pylorus-preserving procedure, but about 10 or 15 years ago I sustained courage from reported series showing no difference in outcome. Now most of us are doing a pylorus-preserving [procedure] unless the duodenum or antrum is involved. In the early years, we saw large tumors, which was a direct result of lack of accurate preoperative studies. So in those patients I felt that with the possibility of positive peripancreatic and the peripyloric nodes, it was probably better from a curative standpoint to do the classic Whipple. And I might add that I always did a vagotomy with those because I was worried about postoperative ulceration and bleeding.

Regarding your question about the jaundiced vs nonjaundiced patient, it's not apples vs apples but apples vs oranges because, like you, we don't get new patients very often with a bilirubin of 1 or 2 mg/dL. Many present deeply jaundiced with pruritis, and they come to us after being sorted out. If the gastroenterologists see them first, they all get stented. It's interesting that there are a few patients who had percutaneous transhepatic stents and their bile samples were sterile. As I mentioned previously, in those with enteric-placed stents, their bile is all infected. So we are going to look at that very carefully and see if stenting has some difference in survival. Right now it doesn't look as though there is a difference in survival between the 2 groups, but it is clear that a history of elevated bilirubin is a statistically significant prognostic factor.

Sachinder Hans, MD, Warren, Mich: I have the same question or concern as Dr Aranha had regarding preoperative cardiac testing. Some of these patients who do undergo these extensive operations should have a thorough preoperative cardiac evaluation, and in particular patients with diabetes mellitus and some of the cancer of the pancreas patients who have diabetes, abnormal EKG [electrocardiogram], history of angina, and patients with history of MI. If preoperative noninvasive cardiac testing is positive, those patients should undergo coronary arteriography and angioplasty or stenting if it is indicated. This approach may improve your results even further.

Dr Madura: We did not routinely send these patients to have nuclear cardiac scans, stress tests, or cardiac catheterization. The patients who had a suspicious cardiac history were all seen and cleared by their own cardiologist, or, if they did not have one, one of the University cardiologists saw them. We have seen patients with other surgical diseases who successfully went through cardiac stress testing and then would have some procedure and die of a myocardial infarction. So I don't think that routine cardiac investigation totally eliminates the risk, but I agree with you that we need to look at these patients perhaps in a little more specific and structured way.

Arthur J. Donovan, MD, Los Angeles, Calif: Did you observe a higher mortality in the early years, and could that have explained the higher mortality for the standard or classic Whipple?

Dr Madura: I think that probably some of the early patients had a little bit higher mortality and that experience, improved technique, and better postoperative care ironed that out, but we still have patients with malignant lesions, and, as you saw from the presentation, 25% had significant problems preoperatively, particularly the jaundiced ones. That affects patient outcome, but in many of these patients with large tumors and jaundice, you can't really delay the operation. If you are going to do this procedure for attempted cure, you must get the show on the road. Our mortality has gotten better over the years, but still, statistically we still have an occasional death, and the morbidity certainly hasn't changed that much. This is a very morbid procedure.

Michael B. Farnell, MD, Rochester, Minn: Your delayed gastric emptying rate of only 7% really intrigued me. The literature would suggest a rate of 20%, and in my own experience it's about 20%. Did you define delayed gastric emptying differently or do you have some kind of herb that you give in Indianapolis that makes these patients empty much better than they do in Minnesota?

Dr Madura: It is a matter of interpretation. Many of these patients had gastrostomy tubes placed, and so that wasn't an issue. We looked at length of hospital stay as far as delayed gastric emptying and actually looked for mention of delayed gastric emptying related to length of hospital stay from the discharge summaries, and it did not seem to be a major problem. Particularly as time goes on, these people are being discharged more quickly. It does not seem to be a problem. They are all placed on prokinetic agents, so I have no other real explanation for you.

Fabrizio Michelassi, MD, Chicago: What was the incidence of vessel resections in pancreaticoduodenectomy, and, over the 20 years, did you do just venous resections or at times attempted arterial resections? And knowing you as a fastidious collector and investigator, do you know whether the vessel wall was actually invaded by tumor, and was there a prognostic significance to that?

Dr Madura: We resected very few major vessels. I can't even think of a single artery that was resected. Only a few side-byte portal or superior mesenteric vein resections were performed, and we really did not look at that as far as a prognostic indicator, although you might predict that it would make them worse. We did not usually go after these tumors that were invading vessels. In our prospective study that is going to be published, true invasion of those vessels eliminated the patient from the study, so they didn't even get operated on. It was difficult to cull out those patients in whom the portal vein was abutted by tumor or inflammatory response, so we don't have long-term outcome in those patients.