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Six Hundred Fifty Consecutive Pancreaticoduodenectomies in the 1990s

Pathology, Complications, and Outcomes

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Objective
The authors reviewed the pathology, complications, and outcomes in a consecutive group of 650 patients undergoing pancreaticoduodenectomy in the 1990s.

Summary Background Data
Pancreaticoduodenectomy has been used increasingly in recent years to resect a variety of malignant and benign diseases of the pancreas and periampullary region.

Methods
Between January 1990 and July 1996, inclusive, 650 patients underwent pancreaticoduodenal resection at The Johns Hopkins Hospital. Data were recorded prospectively on all patients. All pathology specimens were reviewed and categorized. Statistical analyses were performed using both univariate and multivariate models.

Results
The patients had a mean age of 63 ± 12.8 years, with 54% male and 91% white. The number of resections per year rose from 60 in 1990 to 161 in 1995. Pathologic examination results showed pancreatic cancer (n = 282; 43%), ampullary cancer (n = 70; 11%), distal common bile duct cancer (n = 65; 10%), duodenal cancer (n = 26; 4%), chronic pancreatitis (n = 71; 11%), neuroendocrine tumor (n = 31; 5%), periampullary adenoma (n = 21; 3%), cystadenocarcinoma (n = 14; 2%), cystadenoma (n = 25; 4%), and other (n = 45; 7%). The surgical procedure involved pylorus preservation in 82%, partial pancreatectomy in 95%, and portal or superior mesenteric venous resection in 4%. Pancreatic-enteric reconstruction, when appropriate, was via pancreaticojejunostomy in 71% and pancreaticogastrostomy in 29%. The median intraoperative blood loss was 625 mL, median units of red cells transfused was zero, and the median operative time was 7 hours. During this period, 190 consecutive pancreaticoduodenectomies were performed without a mortality. Nine deaths occurred in-hospital or within 30 days of operation (1.4%

operative mortality). The postoperative complication rate was 41%, with the most common complications being early delayed gastric emptying (19%), pancreatic fistula (14%), and wound infection (10%). Twenty-three patients required reoperation in the immediate postoperative period (3.5%), most commonly for bleeding, abscess, or dehiscence. The median postoperative length of stay was 13 days. A multivariate analysis of the 443 patients with periampullary adenocarcinoma indicated that the most powerful independent predictors favoring long-term survival included a pathologic diagnosis of duodenal adenocarcinoma, tumor diameter <3 cm, negative resection margins, absence of lymph node metastases, well-differentiated histology, and no reoperation.

Conclusions

This single institution, high-volume experience indicates that pancreaticoduodenectomy can be performed safely for a variety of malignant and benign disorders of the pancreas and periampullary region. Overall survival is determined largely by the pathology within the resection specimen.

Halsted[1] performed the first successful resection of a periampullary cancer in 1898, involving a local resection of an ampullary cancer. Kausch[2] is credited with the first successful resection of the duodenum and portion of the pancreas (pancreaticoduodenectomy); he reported this two-stage procedure for ampullary cancer in 1912. More than 20 years later, Whipple et al.[3] reported three cases of pancreaticoduodenal resection to the American Surgical Association in 1935; Whipple generally is credited with popularizing the operation, which now bears his name. In his reminiscence, Whipple documents that he performed 37 pancreaticoduodenectomies during his career, with the operation evolving from a two-stage procedure to a one-stage procedure by the early 1940s.[4,5]

Pancreaticoduodenectomy has been used increasingly in recent years as a safe and appropriate resectional option in selected patients with malignant and benign disorders of the pancreas and periampullary region. The operative mortality rate after pancreaticoduodenectomy is now <4% in many high-volume centers.[6–11] Although a low mortality rate has been observed, the incidence of postoperative morbidity can approach 50%. Common postoperative complications include delayed gastric emptying, disruption of the pancreatic-enteric anastomosis with subsequent pancreatic fistula, wound infection, and hemorrhage.[8,9,12–14] This series reports the experience with pancreaticoduodenectomy at one high-volume center in the 1990s.

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PATIENTS AND METHODS

From January 1990 through July 1996, inclusive, data were collected prospectively on all patients undergoing pancreaticoduodenectomy at The Johns Hopkins Hospital. All pathology specimens were reviewed (RHH) to determine the primary pathologic diagnosis and the extent of disease. For malignant lesions, lymph nodes were considered positive if any lymph node in the resected specimen contained tumor, regardless of whether it was involved by direct extension or was discontinuous with the primary. Resection margins were considered positive if the neoplasm was present at the pancreatic neck, uncinate, bile duct, duodenal, or retroperitoneal soft tissue margin. If the initial margin was positive at frozen section, but further resection yielded a negative margin, the margin was considered negative. The presence of retroperitoneal soft tissue invasion with microscopically negative resection margins was considered a negative margin.

The surgical techniques have been described previously.[15–17] In brief, the biases at our institution have been: 1) to perform standard pancreaticoduodenectomy, without extended retroperitoneal lymph node dissection; 2) to perform a pylorus-preserving resection, reserving distal gastric resection for neoplasms/lesions involving the distal stomach or first portion of the duodenum; and 3) to perform partial pancreatectomy, leaving the body and tail of the pancreas in place unless a neoplasm/lesion extended into the body of the pancreas. Pancreatic-enteric reconstruction was accomplished via either pancreaticojejunostomy or pancreaticogastrostomy.[17] Vagotomy, tube gastrostomy, tube jejunostomy, total parenteral nutrition, and prophylactic octreotide were not used routinely. The overall incidence of postoperative complications was evaluated using standard definitions.[14,18,19]

During the period of this study, patients with a pathologic diagnosis of periampullary adenocarcinoma (e.g., pancreas, distal common bile duct, ampullary or peri-Vaterian duode-

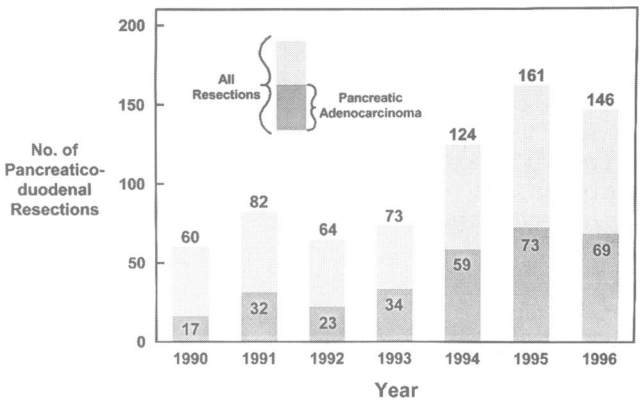

Figure 1. A histogram depicting the number of pancreaticoduodenal resections per year from January 1990 through December 1996 at The Johns Hopkins Hospital. This figure gives the complete number of resections through December 1996, whereas the remainder of the data in this report covers the period January 1990 through July 1996. For each vertical bar, the total number of resections is shown, as is the number of resections performed for pancreatic adenocarcinoma, which was the most common pathologic diagnosis.

nal primaries) were evaluated by a multidisciplinary group (e.g., surgery, radiation oncology, medical oncology, and pathology) and were offered three options for postoperative treatment after pancreaticoduodenectomy: 1) standard therapy consisting of external beam radiation therapy to the pancreatic bed (4000–4500 cGy) given with two 3-day courses of 5-fluorouracil (5-FU) (500 mg/m^2 per day) followed by weekly bolus 5-FU for 4 additional months; 2) intensive therapy consisting of external beam radiation therapy to the pancreatic bed (5040–5760 cGy) with prophylactic hepatic irradiation (2340–2700 cGy) given with and followed by infusional 5-FU (200 mg/m^2 per day) plus leucovorin (5 mg/m^2 per day) for 5 of 7 days a week for 4 months; or 3) no therapy. Details of these postoperative therapies, as well as their toxicities and outcomes, recently have been reported.[20,21]

Patient follow-up was obtained via office records, letter, or telephone contact and was complete up to August 1996. Patient demographics, intraoperative factors, pathologic findings, and postoperative course were evaluated by both univariate and multivariate models to determine their impact on survival. Survival analyses were done by Kaplan–Meier method.[22] Differences in survival between subsets were compared using the log–rank test. Multivariate analysis was performed with the Cox proportional hazards model.[23] Results are reported as mean ± standard deviation. Significance was accepted at the 5% level.

RESULTS

Characteristics of the Entire Cohort (n = 650): Demographics and Intraoperative Factors

In the 6 years and 7 months of this study, 650 patients underwent pancreaticoduodenectomy. The annual distribution of these resections is depicted in Figure 1. Demographics and intraoperative characteristics of this cohort are listed in Table 1. The mean age of the patients was 63 ± 12.8 years and ranged from 18 to 89 years. There were 350 men (54%) and 300 women (46%), with the racial distribution being 589 white (91%), 42 black (6%), and 19 other (3%).

The median intraoperative blood loss was 625 mL, median units of red blood cells transfused was 0, and the median operative time was 7 hours. Pylorus-preserving resection was performed in 532 patients (82%), partial pancreatectomy in 620 patients (95%), and the pancreatic anastomosis was accomplished via pancreaticojejunostomy in 434 patients (67%). Thirty patients were treated with total pancreatectomy and required no pancreatic-

Table 1. 650 CONSECUTIVE PANCREATICODUODENECTOMIES: DEMOGRAPHICS AND INTRAOPERATIVE FINDINGS

	Number	%
Demographics		
Age (yr)		
Mean	63.0 ± 12.8	—
Median	65	—
Range	18-89	—
Gender		
Male	350	54
Female	300	46
Race		
White	589	91
Black	42	6
Other	19	3
Intraoperative factors		
Blood loss (mL)		
Mean	982 ± 1590	
Median	625	
Transfusions (units red cells)		
Mean	1.0 ± 2.7	
Median	0.0	
Operative time (hr:min)		
Mean	7:07 ± 1:41	
Median	7:00	
Type of resection		
Pylorus-preserving	532	82
Classic	118	18
Extent of pancreatectomy		
Partial	620	95
Total	30	5
Anastomosis		
Pancreaticojejunostomy	434	67
Pancreaticogastrostomy	181	28
None	30	5
Vein resection		
Yes	25	4
No	625	96

Table 2. 650 CONSECUTIVE PANCREATICODUODENECTOMIES: PATHOLOGY

	Number	%
Periampullary adenocarcinoma	443	68
Pancreatic	282	43
Ampullary	70	11
Distal bile duct	65	10
Duodenal	26	4
Other	207	32
Chronic pancreatitis	71	11
Neuroendocrine tumor	31	5
Pancreatic cystadenoma	25	4
Ampullary adenoma	21	3
Pancreatic cystadenocarcinoma	14	2
GIST	10	2
Miscellaneous	35	5

GIST = gastrointestinal stromal tumor.

enteric reconstruction. Twenty-five patients (4%) underwent resection of portions of either the portal vein or the superior mesenteric vein.

Pathologic Analysis of the Resected Specimens (n = 650)

Table 2 presents the final pathologic diagnoses of the resected specimens. Periampullary adenocarcinoma was found in 443 (68%) of the patients, with the distribution being 282 patients (43%) with pancreatic cancer, 70 patients (11%) with ampullary cancer, 65 patients (10%) with distal bile duct cancer, and 26 patients (4%) with duodenal cancer. Of the remaining 207 patients (32%) without periampullary adenocarcinoma, chronic pancreatitis was seen in 71 patients (11%), neuroendocrine tumors in 31 patients (5%), pancreatic cystadenoma in 25 patients (4%), ampullary adenoma in 21 patients (3%), pancreatic cystadenocarcinoma in 14 patients (2%), and gastrointestinal stromal tumors in 10 patients (2%). Thirty-five patients (5%) were classified as having a miscellaneous pathologic diagnosis, including 4 patients with metastatic cancer to the head of the pancreas, 3 patients with gallbladder cancer, 2 patients with solid and papillary neoplasms (Hamoudi tumor), 2 patients with lymphoma focally involving the pancreas, and 2 patients with simple cysts.

Detailed pathologic findings from the 443 patients with periampullary adenocarcinoma are listed in Table 3. Tumor diameter was smallest for ampullary and distal bile duct cancers (median, 2 cm) and largest for duodenal tumors (median, 4.8 cm). Less than 10% of the tumors were well differentiated, with moderately differentiated tumors being seen in 63% to 70% of the cases. Node-negative resections were most common for ampullary tumors (56%) and least common for pancreatic tumors (30%). Detailed pathologic results from the patients with less-common neoplasms are listed in Table 4. Malignant islet cell tumors were the smallest of these tumors (median diameter, 3.3 cm) but had the highest incidence of lymph node metastases (69%). Tumor diameter was the largest for the pancreatic cystadenocarcinomas (median, 6.5 cm), which were resected with negative margins in all cases and which had a 36% incidence of positive lymph nodes.

Postoperative Results (n = 650; Table 5)

Nine deaths occurred in-hospital or within 30 days of operation, for an operative mortality rate of 1.4%. In these nine patients, the precipitating cause of death was a leak at the pancreatic-enteric anastomosis in six patients and one patient each having myocardial infarction, hepatic infarction, and hemobilia. At the time of death, all patients had evidence of multisystem organ failure. Twenty-six patients (4%) required reoperation during their index admission, with the indications for reoperation including hemorrhage in 8 patients, intra-abdominal abscess in 8 patients, and fascial dehiscence in 6 patients. Nine of the 26 patients undergoing reoperation died and are included in the 9 in-hospital postoperative deaths. No postoperative complications were observed in 384 patients (59%), whereas 266 patients (41%) had 1 or more postoperative complications. The most common postoperative complications were early delayed gastric emptying (19%), pancreatic fistula (14%), and wound infection (10%). The mean postoperative length of hospital stay was 16.5 ± 10.4 days, with a median of 13 days.

Factors Influencing Survival After Pancreaticoduodenectomy

For the entire cohort of 650 patients, the mean follow-up was 19.2 months and the median follow-up was 12 months. The median survival for the entire cohort of 650 patients was 47 months, with actuarial 1-, 2-, 3-, 4-, and 5-year survival rates of 79%, 61%, 54%, 49%, and 43%, respectively. However, these survival data are not disease specific, and survival is largely dependent on the pathology within the resected specimen. The median survival for patients with pancreatic adenocarcinoma was 18 months, for patients with distal bile duct cancer was 20 months, and for patients with ampullary cancer was 42 months. For duodenal cancer, the median survival has not yet been reached. The actuarial survival curve for all patients with resected periampullary adenocarcinoma is shown in Figure 2. For all of the other major pathologic

Table 3. PATHOLOGIC DETAILS FROM THE 443 PATIENTS WITH RESECTED PERIAMPULLARY ADENOCARCINOMA

	Pancreatic (n = 282)	Ampullary (n = 70)	Distal Bile Duct (n = 65)	Duodenal (n = 26)
Tumor diameter (cm)				
Mean	3.2 ± 1.6*	2.3 ± 1.4	2.1 ± 0.8	4.8 ± 2.8†
Median	3.0	2.0	2.0	4.8
Tumor differentiation (%)				
Well	6	8	3	4
Moderate	63	69	69	70
Poor	31	23	28	26
Margin status (%)				
Negative	71	97	91	96
Positive	29‡	3	9	4
Node status (%)				
Negative	30	56	43	38
Positive	70§	44	57	62

* $p = 0.05$ *vs.* tumor diameter of ampullary and distal bile duct tumors.
† $p = 0.05$ *vs.* tumor diameter of pancreatic, ampullary, and distal bile duct tumors.
‡ $p < 0.05$ *vs.* positive margin status of ampullary, distal bile duct, and duodenal tumors.
§ $p < 0.05$ *vs.* positive nodal status of ampullary and distal bile duct tumors.

categories listed in Table 6, the median survival has not yet been reached, with the exception of gastrointestinal stromal tumors, in which the median survival was 23 months.

Multiple parameters were evaluated by univariate analysis to determine their impact on survival in the 443 patients with periampullary cancer (Table 7). Parameters that did *not* influence survival included age, gender, race, type of resection (pylorus-preserving vs. classic), extent of resection (partial vs. total pancreatectomy), type of pancreatic-enteric anastomosis, venous resection, operative time, transfusion status, postoperative complication status, and postoperative length of stay. Parameters that did influence survival included estimated intraoperative blood loss, site of the primary tumor, tumor diameter,

Table 4. PATHOLOGIC DETAILS FROM PATIENTS WITH OTHER POTENTIALLY MALIGNANT TUMORS

	Malignant Neuroendocrine (n = 26)	Pancreatic Cystadenocarcinoma (n = 14)	GIST (n = 10)
Tumor diameter (cm)			
Mean	4.6 ± 4.5	7.2 ± 4.9	6.7 ± 3.5
Median	3.3	6.5	5.5
Margin status (%)			
Negative	65	100	60
Positive	35	0	40
Node status (%)			
Negative	31	64	60
Positive	89	36	40

GIST = gastrointestinal stromal tumor.

Table 5. 650 CONSECUTIVE PANCREATICODUODENECTOMIES: POSTOPERATIVE RESULTS

	Number	%
Mortality		
Yes	9	1.4
No	641	98.6
Reoperation		
Yes	26	4
No	624	96
Complications		
No	384	59
Yes	266	41
Delayed gastric emptying	124	19
Pancreatic fistula	92	14
Wound infection	66	10
Intra-abdominal abscess	33	5
Cholangitis	31	5
Pneumonia	20	3
Bile leak	17	3
Pancreatitis	12	2
Marginal ulcer	6	1
Postoperative length of stay (days)		
Mean	16.5 ± 10.4	
Median	13	
Range	6–88	

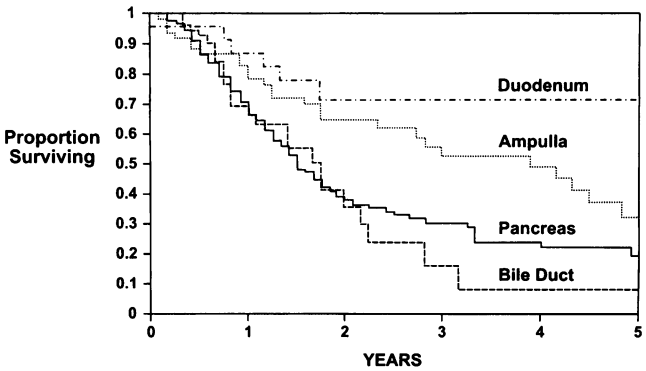

Figure 2. The actuarial survival curves for the 443 patients with periampullary adenocarcinoma resected via pancreaticoduodenectomy. Because the mean follow-up is only 19.2 months (median = 12 months), the curves lose accuracy after the 2-year period.

resection margin status, resected nodal status, tumor differentiation, and need for reoperation. Our analysis could not accurately assess the effects of adjuvant postoperative chemoradiation therapy for the entire group of 443 patients with periampullary adenocarcinoma because of the frequent use of such therapy in patients with pancreatic tumors (70%) and the infrequent use of such therapy in patients with nonpancreatic tumors (<20%).

Using a Cox proportional hazards model, a multivariate analysis was undertaken to determine which of the above univariate factors were independent predictors of survival. The hazard ratios and probability values are listed in Table 8. Two of the factors listed are independent predictors of prolonged survival: presence of a duodenal primary and absence of reoperation; both of these parameters have hazard ratios <1.00 and highly significant probability values. The remaining four factors are all related to the pathologic analysis of the resection specimen. In order of worsening prognosis, they include tumor diameter ≥3 cm (hazard ratio = 1.47), positive resection margin status (hazard ratio = 1.63), lymph node metastases (hazard ratio = 1.93), and poor tumor differentiation (hazard ratio = 3.76).

DISCUSSION

The surgical history of the treatment of periampullary tumors encompasses the past 100 years. Halsted[1] reported the first successful resection of an ampullary tumor in 1899, describing a local ampullary resection with associated reanastomosis of the pancreatic and bile duct into the duodenum. Codivilla, near the turn of the century, performed an en bloc resection of the head of the pancreas and duodenum for periampullary carcinoma, but the patient did not survive the postoperative period.[24] In 1912, Kausch,[2] a German surgeon from Berlin, performed the first successful pancreaticoduodenectomy in two stages. In 1914, Hirschel[25] reported a successful one-stage pancreaticoduodenectomy. Despite these early attempts at combined pancreaticoduodenal resection in the early part of the 20th century, up until 1935, most ampullary cancers were managed by a transduodenal approach similar to that first performed successfully by Halsted. In 1935, a review by Hunt and Budd[26] described 76 patients with periampullary tumors managed by such an approach, with an operative mortality of 40%.

Table 6. FACTORS INFLUENCING SURVIVAL AFTER PANCREATICODUODENECTOMY

	Number	Median Survival (mo)	1-Year Survival (%)	3-Year Survival (%)
Entire cohort	650	47	79	54
Pathologic diagnosis				
Periampullary adenocarcinoma	443	21	71	37
Pancreatic adenocarcinoma	282	18	67	30
Ampullary adenocarcinoma	70	42*	79	53
Distal bile duct adenocarcinoma	65	20	67	16
Duodenal adenocarcinoma	26	NR†	88	72
Other				
Chronic pancreatitis	71	NR	99	96
Neuroendocrine tumor	31	NR	100	89
Pancreatic cystadenoma	25	NR	96	96
Ampullary adenoma	21	NR	100	100
Pancreatic cystadenocarcinoma	14	NR	92	56
GIST	10	23	90	50

NR = not reached; GIST = gastrointestinal stromal tumor.
* p = 0.006 *vs.* pancreatic adenocarcinoma.
† p = 0.002 *vs.* pancreatic adenocarcinoma.

Table 7. UNIVARIATE ANALYSIS FOR 443 PATIENTS WITH PERIAMPULLARY ADENOCARCINOMA

	Hazard Ratio	p
Parameters not influencing survival:		
Age		
Gender		
Race		
Type of resection: pylorus-preserving *vs.* classic		
Extent of resection: partial *vs.* total pancreatectomy		
Type of anastomosis: PJ *vs.* PG		
Venous resection		
Operative time		
Transfusion status		
Postoperative length of stay		
Postoperative complications		
Parameters influencing survival:		
Estimated blood loss		
<700 mL	1.00	0.006
≥700 mL	1.51	
Tumor site		
Pancreas	1.00	—
Bile duct	1.07	0.768
Ampullary	0.56	0.006
Duodenum	0.26	0.002
Tumor diameter		
<3 cm	1.00	0.036
≥3 cm	1.37	
Margin status		
Negative	1.00	<0.001
Positive	2.08	
Node status		
Negative	1.00	<0.001
Positive	2.21	
Tumor differentiation		
Well	1.00	—
Moderate	1.97	0.139
Poor	2.81	0.028
Reoperation		
Yes	1.00	0.003
No	0.36	

PJ = pancreaticojejunostomy; PG = pancreaticogastrostomy.

In 1935, Whipple et al.[3] reported three patients with ampullary cancer treated by a two-stage pancreaticoduodenectomy. In 1937, Brunschwig[27] reported extending the indication for pancreaticoduodenectomy to include cancer of the head of the pancreas. During the 1940s and 1950s, pancreaticoduodenectomy was accomplished routinely as a one-stage procedure, applied to patients with periampullary neoplasms, and was performed with increased frequency. During the 1960s and 1970s, pancreaticoduodenectomy was a formidable operation, which carried a hospital mortality that approached 25% in some series and led some authors to suggest that its use be abandoned.[28,29] There were, however, exceptions to this high mortality rate, notably a report by Howard[30] in 1968 describing 41 consecutive patients treated by pancreaticoduodenectomy without a hospital mortality. In recent years, improved hospital morbidity, mortality, and survival after pancreaticoduodenectomy have been reported.[6,7,11,16] Trede et al.[10] reviewed 118 consecutive resections without an operative death in 1990, whereas a report from our institution in 1993 described 145 consecutive pancreaticoduodenectomies without mortality.[8] In this current series, 190 consecutive patients are reported without mortality. Overall, although pancreaticoduodenectomy remains a formidable operation, many centers now have reported hospital mortality rates <4%, with the mortality rate approaching 1% in selected series.

The patient population presented in this series had a median age of 65 years, with a slight male predominance (54%), and with the majority (91%) being white. These demographic details reflect the patients referred to The Johns Hopkins Hospital, which serves as a tertiary referral center for complex pancreaticobiliary surgery. In recent years, age alone has not been used to determine the appropriateness for pancreaticoduodenal resection. For example, our recent experience with more than 40 patients older than 80 years of age who have undergone pancreaticoduodenal resection has shown comparable morbidity, mortality, and survival results as compared to a younger-aged cohort.[31]

Pancreaticoduodenectomy remains a formidable operation, with a median operative time of 7 hours and a median estimated intraoperative blood loss of 625 mL. The median number of red blood cell transfusions per patient was zero, indicating that more than half of the patients received no blood during their surgery. The pylorus-preserving modification of pancreaticoduodenectomy has been performed preferentially in this series (82% of patients), with distal gastrectomy being reserved for tumor involvement of the distal stomach or first portion of the duodenum. Our bias has been to perform partial pancreatectomy whenever possible (95% of patients), reserving total pancreatectomy for tumors that extended from

Table 8. MULTIVARIATE ANALYSIS FOR 443 PATIENTS WITH PERIAMPULLARY ADENOCARCINOMA

Parameter	Hazard Ratio	p
Duodenal primary	0.29	0.004
No reoperation	0.22	<0.001
Tumor diameter ≥3 cm	1.47	0.02
Margin positive	1.63	0.007
Node positive	1.93	<0.001
Poorly differentiated	3.76	0.008

the head of the gland across the neck and into the body of the pancreas. After partial pancreatectomy, the pancreatic remnant is drained into either the jejunum or the stomach. A prospective, randomized study performed at this institution has shown a pancreatic fistula rate of 11% to 12% after either pancreaticojejunostomy or pancreaticogastrostomy.[18]

In recent years, the indications for pancreaticoduodenectomy have expanded, concomitant with the declining morbidity and improving patient survival. The procedure, whereas applied most commonly with curative intent for periampullary adenocarcinoma, also can be indicated for a variety of other periampullary neoplasms[32–35] as well as for nonneoplastic conditions such as chronic pancreatitis.[36–38] In addition, a recent report has suggested that pancreaticoduodenectomy, when performed with similar perioperative morbidity and mortality rates as can be achieved for palliative bypass procedures, may be associated with improved long-term survival in patients with locally advanced periampullary adenocarcinoma.[39]

In the current series, 68% of all pancreaticoduodenectomies were performed for periampullary adenocarcinoma. The most common pathologic finding in the resection specimen was pancreatic adenocarcinoma, being found in 43% of all cases. The other periampullary tumors were seen in smaller numbers, with ampullary cancer in 11% of specimens, distal common bile duct cancer in 10%, and duodenal cancer in 4%. The pathologic details in the 443 patients with resected periampullary adenocarcinoma are listed in Table 3. In patients with pancreatic adenocarcinoma, the median tumor diameter was 3 cm, and the majority of tumors either were moderately (63%) or poorly (31%) differentiated. There was a 29% incidence of margin positivity, and 70% of patients had node-positive resections. In contrast to those with pancreatic cancer, patients undergoing resection for ampullary, distal bile duct, or duodenal cancer had a significantly lower incidence of positive resection margins (range, 3%–9%) and a lower incidence of node-positive resections (range, 44%–62%). The largest tumor diameters were seen in patients with duodenal cancer, in which the median tumor size was 4.8 cm. The smallest tumor diameters were seen in patients with ampullary and distal bile duct tumors, in which the median tumor diameter was 2 cm.

The multivariate survival analysis performed for the 443 patients with periampullary adenocarcinoma identified several factors that were independent predictors of survival (Table 8). Both the finding of a duodenal primary and the lack of reoperation favored long-term survival, with hazard ratios much less than 1 and highly significant probability values. Four factors were found to adversely effect survival: 1) tumor diameter ≥3 cm; 2) the presence of positive resection margins; 3) the finding of lymph node metastases in the resected specimen; and 4) the presence of a poorly differentiated tumor. These results are similar to those of two recently reported multivariate analyses from our institution that evaluated patients with pancreatic adenocarcinoma.[16,21] In both of these previous analyses, tumor diameter ≥ 3 cm and positive resection margin status served as independent predictors of an adverse outcome. Additionally, these previous analyses identified two other parameters that proved to be highly significant predictors of outcome in patients with pancreatic adenocarcinoma: tumor DNA content and the use of adjuvant postoperative chemoradiation therapy.

Tumor DNA content has been found to be predictive of outcome in several studies of pancreatic cancer.[16,40,41] In these studies, image cytometry has been used to determine tumor DNA content. Patients found to have diploid tumors have been observed to have significantly longer median survival and significantly greater 5-year survival as compared to patients with aneuploid tumors. Unfortunately, in the current study, DNA content measurements were not available for the patients with nonpancreatic periampullary adenocarcinoma, and therefore DNA content could not be evaluated in our statistical analyses.

Adjuvant therapy for patients with resected pancreatic adenocarcinoma has been found to prolong survival in many,[21,42–45] but not all, reported analyses.[46] Two studies from the Gastrointestinal Tumor Study Group in the mid-1980s showed improved survival in patients receiving combined chemoradiation therapy after pancreatic resection.[42,43] Furthermore, the use of radiation therapy alone[44] or chemotherapy alone[45] has been associated with improved postoperative survival. Additionally, a recent study from our institution has evaluated the use of chemoradiation in patients with pancreatic adenocarcinoma treated via pancreaticoduodenectomy.[21] In this study, the use of adjuvant therapy was an independent predictor of improved survival, yielding a median survival of 19.5 months in the group receiving therapy, as compared to a median survival of 13.5 months in the no-therapy group. Although adjuvant treatment for pancreatic adenocarcinoma has gained support based on these and other studies, adjuvant therapy has been used less frequently in patients with ampullary, distal bile duct, and duodenal adenocarcinoma. In the current analysis of 443 patients with periampullary adenocarcinoma, we were unable to assess the role of adjuvant therapy in our survival analyses because of the high frequency of adjuvant treatment in the group with pancreatic adenocarcinoma and the less frequent treatment in the other three tumor types. However, our institutional bias is to recommend adjuvant therapy to all patients with resected periampullary adenocarcinoma in an effort to improve survival.

The overall postoperative mortality in this series was 1.4%, reflecting the dramatic decline in the postpancreaticoduodenectomy mortality rates that have occurred over

the past decades. Many factors may contribute to the declining mortality rate associated with this complex general surgical procedure. There can be no doubt that careful patient preoperative assessment, improved surgical technique, and improvements in perioperative care (including major improvements in interventional radiology and critical care management) all contribute to these declining mortality rates. In addition, recently published data from two large state-wide registries have shown a relation between hospital volume for a complex surgical procedure such as pancreatic resection and perioperative mortality rates. Gordon et al.[47] used data from the Maryland Health Services Cost Review Commission to show that hospital mortality after pancreaticoduodenectomy was six times higher ($p < 0.001$) among patients treated at low-volume facilities as compared with that of a high-volume regional provider. Similarly, Lieberman et al.[48] used data from the New York State Department of Health Statewide Planning and Research Cooperative System to show that both crude and standardized (risk-adjusted) perioperative mortality rates after pancreatic resection were inversely related to hospital volume ($p < 0.001$). These studies have shown that the experience in a high-volume institution is associated with lowered perioperative mortality and duration of hospitalization, when controlling for patient characteristics and comorbidities, and suggest that regionalization of care as concerns complex pancreatic resection would have a substantial impact on both the cost and the outcome for patients undergoing this procedure.

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Discussion

DR. MICHAEL TREDE (Mannheim, Germany): Thank you for giving me this opportunity to congratulate my trans-Atlantic colleagues Dr. Cameron and associates on this superb series. In fact, what else is there left to say, and what is there to ask?

We have come a long way from that discussion held, I believe, in Dr. Harken's department in Denver one Saturday morning in 1986. The motion was (tongue-in-cheek) "that Congress should pass a law making it illegal to do a Whipple operation." Now I propose Congress should pass a law to ensure that Dr. Cameron leaves some patients for other pancreatic surgeons in this country to operate on. We were shown 190 patients operated on consecutively without one death. That is a remarkable achievement. I believe it is a record.

Actually, there are two gentlemen sitting in this audience who did something similar—or even more, because it was done 30 years ago: Dr. John Howard reported on 41 such cases in 1968 and Dr. Kenneth Warren on 68 consecutive Whipple resections without mortality.

Now my question is: What can you do beyond surgery to improve the long-term survival? That seems the main problem today. You can hardly improve the operation. So I would like to hear what adjuvant oncologic methods you are using at Johns Hopkins at present.

DR. ANDREW L. WARSHAW (Boston, Massachusetts): This is an incredible series. No one is going to top this in the next 30 years—mortality of 1.4%, reoperation for complications of 3.5%, and a median length of hospital stay of 13 days. These are about half of what would be considered good in most other institutions. They are not truly unbelievable, however. There are other institutions that are matching these statistics, which are in truth the standard we should be reaching for.

There are some specific lessons that I would like to highlight. One is that the good results are not simply the product of better intensive care and intensive care units. Very few of these patients need to go to the intensive care unit. They are getting more expert operations, and the postoperative care has been simplified. In our institution, 5% of patients who get a Whipple operation spend any time in the intensive care unit. There are fewer postoperative complications, and that is what makes the difference: a 3.5% reoperation rate.

Another lesson in this extensive experience is that different tumors, like different folks, deserve different strokes. Their data comprise different categories of indications for the Whipple operation, and a careful analysis requires more separation of the various groups, but that discussion would take much too long for the present.

Dr. Yeo and his group have suggested that this operation is almost as useful when performed as a palliative operation as it is for potential cure. That does not mean that they are not distressed to find a positive resection margin, as they did in 30%, but it would not stop them prospectively. So the question is, what preoperative tests do you define as crucial? Is it computed tomography (CT) scan and go, or is anything else necessary? We do use laparoscopy for staging of larger tumors of the pancreatic head. I suspect that the Hopkins group does not. Are there any specific criteria that would make you not explore? Too big a tumor? Something other than obvious metastatic disease?

What do you tell your referring physicians about a preoperative biopsy? There are still physicians and surgeons who will not do a Whipple operation without a positive tissue diagnosis. Our own approach has been to avoid a fine-needle aspiration because a negative biopsy, which occurs in 10% to 20% of cases of proven cancer, would not deter us from doing the operation for a small tumor. Since there is a finite risk of disseminating the cancer by needling it, do you advise your referring physicians to avoid needle aspiration of potentially curable pancreatic cancers?

Your length of stay as stated was 13 days. I point out that is median length of stay. That can cover up some significant outliers. Because 80% of your patients were done as pylorus-preserving operations and 20% percent of those had a prolonged length of stay, why are you hanging on to the pylorus-preserving opera-