ANNALS OF SURGERY
Vol. 236, No. 3, 355–368

Pancreaticoduodenectomy With or Without Distal Gastrectomy and Extended Retroperitoneal Lymphadenectomy for Periampullary Adenocarcinoma, Part 2

Randomized Controlled Trial Evaluating Survival, Morbidity, and Mortality

Charles J. Yeo, MD,* John L. Cameron, MD,* Keith D. Lillemoe, MD,* Taylor A. Sohn, MD,* Kurtis A. Campbell, MD,* Patricia K. Sauter, RN,* JoAnn Coleman, RN,* Ross A. Abrams, MD,† and Ralph H. Hruban, MD‡

*From the Departments of *Surgery, †Oncology, and ‡Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland*

Objective
To evaluate, in a prospective, randomized single-institution trial, the end points of operative morbidity, operative mortality, and survival in patients undergoing standard versus radical (extended) pancreaticoduodenectomy.

Summary Background Data
Numerous retrospective reports and a few prospective randomized trials have suggested that the performance of an extended lymphadenectomy in association with a pancreaticoduodenal resection may improve survival for patients with pancreatic and other periampullary adenocarcinomas.

Methods
Between April 1996 and June 2001, 299 patients with periampullary adenocarcinoma were enrolled in a prospective, randomized single-institution trial. After intraoperative verification (by frozen section) of margin-negative resected periampullary adenocarcinoma, patients were randomized to either a standard pancreaticoduodenectomy (removing only the peripancreatic lymph nodes en bloc with the specimen) or a radical (extended) pancreaticoduodenectomy (standard resection plus distal gastrectomy and retroperitoneal lymphadenectomy). All pathology specimens were reviewed, fully categorized, and staged. The postoperative morbidity, mortality, and survival data were analyzed.

Results
Of the 299 patients randomized, 5 (1.7%) were subsequently excluded because their final pathology failed to reveal periampullary adenocarcinoma, leaving 294 patients for analysis (146 standard vs. 148 radical). The two groups were statistically similar with regard to age (median 67 years) and gender (54% male). All the patients in the radical group underwent distal gastric resection, while 86% of the patients in the standard group underwent pylorus preservation ($P < .0001$). The mean operative time in the radical group was 6.4 hours, compared to 5.9 hours in the standard group ($P = .002$). There were no significant differences between the two groups with respect to intraoperative blood loss, transfusion requirements (median zero units), location of primary tumor (57% pancreatic, 22% ampullary, 17% distal bile duct, 3% duodenal), mean tumor size (2.6 cm), positive lymph node status (74%), or positive margin status on final permanent section (10%). The mean total number of lymph nodes resected was significantly higher in the radical group. Of the 148 patients in the radical group, only 15% (n = 22) had metastatic adenocarcinoma in the resected retroperitoneal lymph nodes, and none had retroperitoneal nodes as the only site of lymph node involvement. One patient in the radical group with negative pancreaticoduodenectomy specimen lymph nodes had a micrometastasis to one perigastric lymph node. There were six perioperative deaths (4%) in the standard group versus three perioperative deaths (2%) in the radical group (P = NS). The overall complication rates were 29% for the standard group versus 43% for the radical group ($P = .01$), with patients in the radical group having significantly higher rates of early delayed gastric emptying and pancreatic fistula and a significantly longer mean postoperative stay. With a mean patient follow-up of 24 months, there were no significant differences in 1-, 3-, or 5-year and median survival when comparing the standard and radical groups.

Conclusions
Radical (extended) pancreaticoduodenectomy can be performed with similar mortality but some increased morbidity compared to standard pancreaticoduodenectomy. The data to date fail to indicate that a survival benefit is derived from the addition of a distal gastrectomy and retroperitoneal lymphadenectomy to a pylorus-preserving pancreaticoduodenectomy.

Pancreaticoduodenectomy (the Whipple procedure) is the traditional resectional procedure for patients with periampullary adenocarcinoma (carcinoma of the head, neck, or uncinate process of the pancreas; ampulla of Vater; distal common bile duct; or peri-Vaterian duodenum). The outcomes of patients undergoing surgical resection depend on various tumor-specific factors[1–7] (e.g., primary tumor location, tumor size, status of resection margins and the presence or absence of lymph node metastases), tumor DNA content,[8] molecular genetics of the tumor,[9] postresection CA 19-9 levels,[10] and the use of postoperative chemotherapy or chemoradiation.[7,11–14] In the last several years, an unanswered question has arisen regarding patient survival after pancreaticoduodenectomy: Does radical (extended) pancreaticoduodenectomy improve patient outcome?

In 1973 Fortner proposed radical pancreatic resection as a means of increasing resectability and improving the outcome for pancreatic cancer patients.[15] Initially presented as "regional resection of the pancreas," the operation typically involved a total pancreaticoduodenectomy with subtotal gastrectomy, accompanied by resection of the transpancreatic portion of the portal vein, and occasionally further vascular resection and reconstruction.[16–18] In the last several years, radical resection has evolved to be most commonly defined as a wide en bloc pancreaticoduodenal resection, incorporating a wide soft tissue resection margin, combined with harvesting of specific lymph node stations and a retroperitoneal lymphadenectomy.

Currently, most studies in support of radical pancreaticoduodenectomy are nonrandomized retrospective studies,[19–21] which are limited by their lack of concurrent controls and lack of random allocation to standard versus radical resection. Contrary to many of these published reports, a nonrandomized comparison by Henne-Bruns et al. found no survival advantage to extended retroperitoneal lymphadenectomy.[22] However, one prospective, randomized multicenter Italian study by Pedrazzoli et al.[23] suggested a survival advantage. This study accrued 81 patients with pancreatic adenocarcinoma over 3 years and allocated patients to standard versus radical lymphadenectomy. While the two groups were similar with respect to multiple preoperative parameters, morbidity, and overall survival, a posthoc subgroup analysis suggested that patients with node-positive tumors had a significantly ($P < .05$) better survival after radical lymphadenectomy.

Presented at the 122nd Annual Meeting of the American Surgical Association, April 24–27, 2002, The Homestead, Hot Springs, Virginia.
Supported in part by grants from the National Institutes of Health (R01-CA56130 and P50-CA62924).
Correspondence: Charles J. Yeo, MD, Professor of Surgery and Oncology, The Johns Hopkins Hospital, 600 N. Wolfe Street, Blalock 606, Baltimore, MD 21287.
E-mail: cyeo@jhmi.edu
Accepted for publication April 24, 2002.
DOI: 10.1097/01.SLA.0000027272.08464.0B

We present here a follow-up report extending our interim analysis[24,25] of a prospective, randomized single-institution study designed to evaluate the impact of standard versus radical (extended) pancreaticoduodenal resection on postprocedure morbidity, mortality, and long-term survival.

METHODS

Protocol

Our previous report detailed the recruitment, surgical technique, postoperative management, data collection, pathologic review, and statistical analyses.[24] Briefly, patients were recruited into the study before surgery on the basis of the anticipation of pancreaticoduodenectomy for adenocarcinoma of the periampullary region (primary tumor in the right side of the pancreas, ampulla, distal common bile duct, or peri-Vaterian duodenum). This study was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins University School of Medicine. Informed consent was obtained preoperatively on all participating patients. Specific exclusion criteria included absence of informed consent, preoperative chemotherapy or chemoradiation, pathology revealing tumor other than adenocarcinoma primary to the periampullary region, or presence of gross tumor left behind at the conclusion of the standard pancreaticoduodenal resection. During the period that this trial was open for accrual (April 1996 through June 2001), 983 patients underwent pancreaticoduodenal resection at the Johns Hopkins Hospital, with 672 of these patients undergoing resection for periampullary adenocarcinoma. Of these, 299 patients were enrolled into this study.

Assignment

Using a computer-generated random number pattern, eligible, consented patients were randomized intraoperatively after completion of a standard, margin-negative pancreaticoduodenal resection. Randomization was between two procedures: standard pancreaticoduodenal resection or radical (extended) pancreaticoduodenal resection.

For the standard resection pylorus preservation was preferred, and lymph node groups resected en bloc included the anterior pancreaticoduodenal lymph nodes (lymph node station 17 in the Japanese system; Table 1[20]), the posterior pancreaticoduodenal lymph nodes (station 13), nodes in the lower hepatoduodenal ligament (station 12b2 and 12c), and nodes along the right lateral aspect of the superior mesenteric artery and vein (some station 14b and 14v). The standard, pylorus-preserving resection involved division of the duodenum 2 to 3 cm distal to the pylorus with resection of all duodenum distal to the transection site, removal of the gallbladder (if present) and common bile duct (from the level of the cystic duct junction with the common hepatic duct caudally), removal of 10 to 20 cm of the proximal jejunum beyond the ligament of Treitz, resection of the

Table 1. LYMPH NODE STATIONS RESECTED

Number	Name	Standard	Radical
3	Gastric lesser curve	No[A]	Yes[B]
4	Gastric greater curve	No[A]	Yes[B]
5	Superior pyloric	No[A]	Yes
6	Inferior pyloric	No[A]	Yes
8	Common hepatic artery	No	No
9	Celiac origin	No	Yes[C]
12	HEPATODUODENAL LIGAMENT		
12a2	Proper hepatic artery near GDA	No[D]	No[D]
12b2	Bile duct below cystic duct	Yes[E]	Yes[E]
12c	Around cystic duct	Yes	Yes
12p2	Retro portal vein-below cystic duct	No[D]	No[D]
13	Posterior pancreaticoduodenal	Yes	Yes
14	SMA AND SMV NODES		
14a	Origin of SMA	No	No
14b	Right side of SMA	Yes[E]	Yes[E]
14c	Anterior SMA at middle colic	No	No
14d	Left side of SMA at first jejunal branch	No	No
14v	SMV nodes	Yes[E]	Yes[E]
16	AORTO-CAVAL NODES		
16a2	Celiac to left renal vein	No	Yes[F]
16b1	Left renal vein to IMA	No	Yes
17	Anterior pancreaticoduodenal	Yes	Yes

[A] Unless a distal gastrectomy is performed as part of the standard resection.
[B] Some of these nodes may accompany the distal gastrectomy specimen.
[C] Sampled only.
[D] Not formally resected.
[E] Some of these nodes may accompany the pancreaticoduodenectomy specimen.
[F] Some of these nodes, cephalad to the left renal vein, but not required to dissect to celiac axis origin.
(From Japanese Pancreas Society. Classification of Pancreatic Carcinoma, 1st English edition. Tokyo: Kanehara and Co, Ltd, 1996:11.)

head, neck, and uncinate process of the pancreas (with the pancreas being divided ventral to the superior mesenteric vein [SMV]-portal vein axis), and removal of the periampullary tumor. For the standard resection, if pylorus preservation was thought not to be appropriate because of an inadequate local duodenal margin (tumor proximity) or duodenal cuff ischemia, then a distal gastrectomy varying from 10% to 40% was performed.

For the radical (extended) resection (Figs. 1 and 2), the standard resection was extended to include a 30% to 40% distal gastrectomy (to include lymph node stations 5 and 6, and some station 3 and 4, including portions of the greater omentum and lesser omentum along the course of the right gastroepiploic artery and right gastric artery, respectively) and a retroperitoneal lymph node dissection extending from the right renal hilum to the left lateral border of the aorta in the horizontal axis, and from the portal vein to below the third portion of the duodenum in the vertical axis (the origin of the inferior mesenteric artery is a near-constant anatomical landmark for the inferiormost aspect of the dissection). This retroperitoneal lymph node dissection harvests lymph nodes from stations 16a2 and 16b1 and samples a celiac lymph node (station 9).

For both the standard and radical resections, the uncinate process was removed from underneath the superior mesenteric vein, flush with the superior mesenteric artery (SMA). This results in clearing of lymphatic and neural tissues from the ventral and right lateral aspects of the SMA for about a 90° to 180° circumference. All resections were performed favoring partial pancreatectomy, and nearly all reconstructions were performed to a single retrocolic jejunal limb, with a proximal pancreaticojejunostomy, downstream hepaticojejunostomy, and further downstream duodeno- or gastrojejunostomy. Vagotomy, tube gastrostomy, and feeding jejunostomy were not used.

Postoperative Management

All patients were managed using a standard postoperative critical pathway. Histamine H_2-receptor antagonists were administered to all patients postoperatively as prophylaxis for marginal or stress ulceration. Most patients received erythromycin lactobionate as prophylaxis against early delayed gastric emptying.[26] As part of a now-completed clinical trial evaluating pancreatic fistula, less than 15% of patients received perioperative octreotide.[27] Operatively

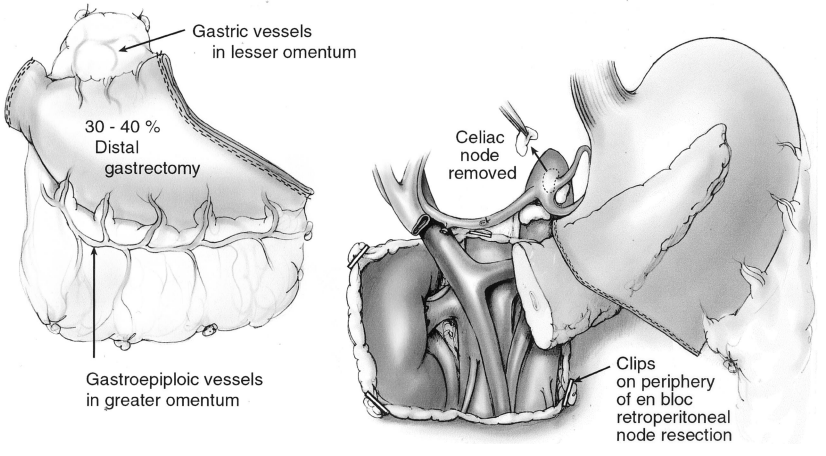

Figure 1. Components of the radical procedure. At the left is the 30% to 40% distal gastrectomy specimen, which includes the pylorus and 1- to 2-cm cuff of the duodenum. At the right is the retained stomach, the pancreatic body and tail, and an overview of the retroperitoneal dissection. Titanium clips have been placed to mark the extent of the retroperitoneal dissection. A celiac node is removed for histologic analysis. (Yeo CJ, Cameron JL, Sohn TA, et al. Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma: Comparison of morbidity and mortality and short-term outcome. Ann Surg 1999; 229:613–624, with permission.)

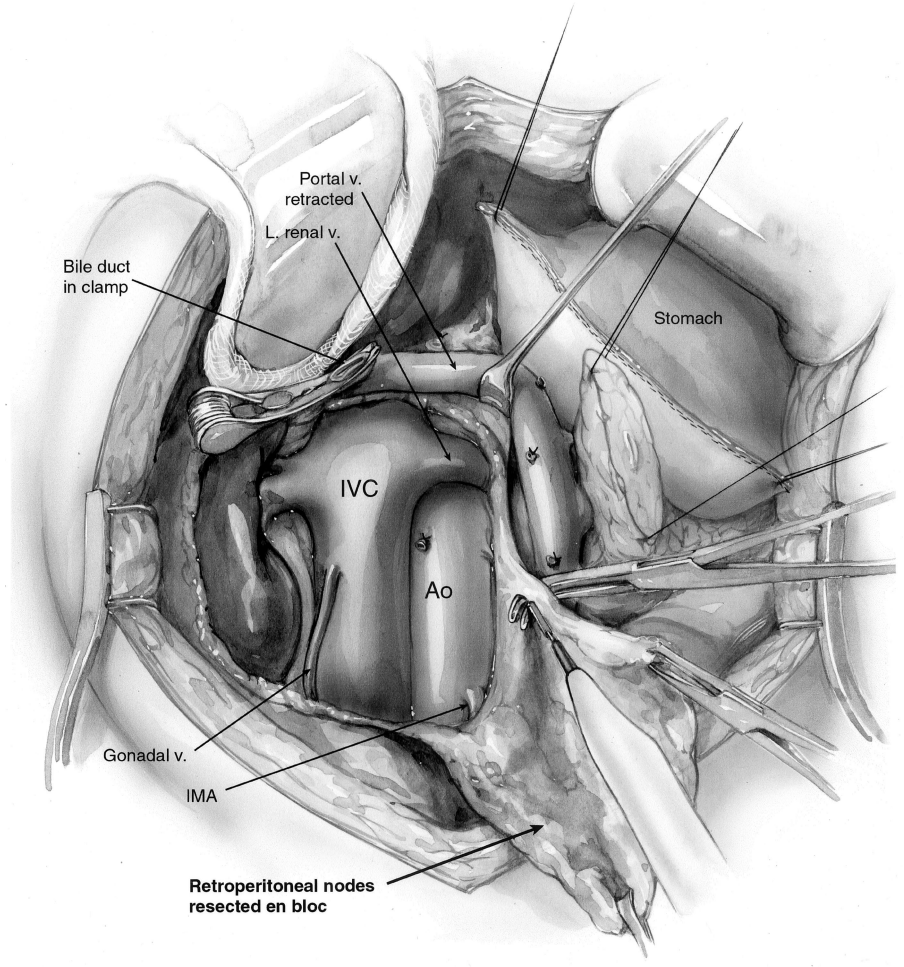

Figure 2. Retroperitoneal dissection component of the radical procedure. The retroperitoneum is dissected from the hilum of the right kidney to the left lateral border of the aorta (Ao) in the horizontal axis, exposing the left renal vein. In the vertical axis the dissection extends from the level of the portal vein to below the level of the third portion of the duodenum (level of the inferior mesenteric artery [IMA] origin). Here the gastric staple line and pancreatic remnant are being retracted toward the upper right. The inferior vena cava (IVC) and aorta (Ao) are fully exposed, and the right gonadal vein has been preserved. A curved vascular clamp gently occludes the inferior aspect of the bile duct. The retroperitoneal fat and lymph nodes are being resected en bloc (bottom right). (Yeo CJ, Cameron JL, Sohn TA, et al. Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma: Comparison of morbidity and mortality and short-term outcome. Ann Surg 1999; 229: 613–624, with permission.)

placed drains left in the area of the pancreatic and bile duct anastomoses were removed under the direction of the attending surgeon, usually between postoperative days 5 and 8. All patients were evaluated postoperatively by medical oncology and radiation oncology consultants and were given recommendations regarding treatment with adjuvant chemoradiation[11,28,29] and immunotherapy.[30,31] Approximately 78% of the patients in each group received postoperative chemoradiation using various protocols. Eight patients (2.7%) were treated with immunotherapy (three standard, five radical) as part of a phase I immunotherapy trial.[31]

Pathologic Review

All pathology specimens were reviewed as previously described[2] to determine the site of the primary tumor, margin status, lymph node status, and overall pathologic staging. Two criteria were used to define the site of tumor origin: location of the bulk of tumor (grossly and microscopically) and identification of in situ tumor components. The retroperitoneal lymph node specimens were submitted in their entirety for histologic examination.

Study End Points

Multiple end points are evaluable from this study. Primary end points include postoperative survival, perioperative complications, and length of hospital stay. Our previous interim report focused on intraoperative parameters, postoperative complications, and length of postoperative hospital stay but could not meaningfully address long-term survival.[24]

A secondary end point of postoperative quality of life assessment, using a subgroup of pancreaticoduodenectomy survivors, will be reported separately.[32]

Data Collection and Statistical Analysis

Data were collected prospectively on all patients and included details of the operative procedure, a surgeon questionnaire detailing the operative findings, and other relevant clinical information. Follow-up was obtained from hospital and office records or telephone contact or from the U.S. Social Security Administration, and was complete through February 2002.

Assessors were blinded to the allocation group (i.e., standard vs. radical resection).

Table 2. PATIENT DEMOGRAPHICS AND INTRAOPERATIVE FACTORS

		Standard (n = 146)	Radical (n = 148)	*P* Value
Age (years)	Mean	66.2 ± 0.9	65.2 ± 0.9	.46
	Median	68	66	
Gender	Male	58%	51%	.19
	Female	42%	49%	
Race	Caucasian	89%	95%	.02
Type of resection	Pylorus-preserving	125 (86%)	0 (0%)	<.0001
	Classic	21 (14%)	148 (100%)	
Extent of pancreatic resection	Partial	141 (97%)	145 (98%)	.46
	Total	5 (3%)	3 (2%)	
Type of pancreatic anastomosis	PJ	140 (99%)	141 (97%)	.42
	PG	1 (1%)	4 (3%)	
	None	5	3	
Vein resection	Yes	4 (3%)	4 (3%)	.98
Intraoperative blood loss (mL)	Mean	740 ± 40	800 ± 40	.30
	Median	600	700	
Red blood cells transfused intraoperatively (units)	Mean	0.5 ± 0.1	0.5 ± 0.1	.96
	Median	0	0	
Operative time (hr)	Mean	5.9 ± 0.1	6.4 ± 0.1	.002
	Median	5.5	6.2	

PJ, pancreaticojejunostomy; PG, pancreaticogastrostomy; Classic, distal gastrectomy.

The study design at the time of initial study planning (1995) determined that the number of patients necessary for statistical validity (one-sided) to improve the 5-year survival rate from 20% to 35% (α set at 0.05; β set at 0.2; power = 80%) was 121 patients per arm, for a total projected study population of 242 patients. At an interim statistical analysis (1999) this initial study design was modified to adjust the 5-year survival rates from 30% to 40%, calculating that 300 patients per arm were needed, yielding a total projected study population of 600 patients. A subsequent interim statistical analysis (2001) revealed that 1-, 2-, and 3-year survivals did not differ between the standard and radical groups. After review by the JCCI (Institutional Review Board), the trial was closed for new patient accrual in June 2001.

For statistical purposes, comparability of the standard and radical groups was verified using Student *t* test and chi-square statistics. Differences in survival between subsets were compared using the log-rank test. Results are reported as mean ± SEM. Significance was accepted at the 5% level.

RESULTS

The study population consisted of 299 patients with periampullary adenocarcinoma who were randomized to either standard or radical pancreaticoduodenectomy. Of the 299 patients randomized, 5 (1.7%) were subsequently excluded because their final pathology results failed to reveal an invasive periampullary adenocarcinoma. The final pathology results in these five patients was (one each): gallbladder adenocarcinoma, small cell carcinoma, undifferentiated carcinoma, intraductal papillary mucinous neoplasm without an invasive carcinoma, and chronic pancreatitis with an incidental islet cell adenoma. After these five exclusions, 294 patients were left for analysis, with 146 undergoing standard resection and 148 undergoing radical resection (Table 2). The mean patient age was 65.7 ± 0.6 years (median 67 years), with 54% of the patients being male. Ninety-two percent of patients were white, 4% were African American, and 4% were of other races. The age and gender distributions were not significantly different between the two groups. However, despite the randomization, there were significantly more whites ($P = .02$) in the radical group.

Intraoperative factors are depicted in Table 2. Eighty-six percent of patients in the standard group underwent pylorus preservation, while all patients in the radical group (by design) had distal gastrectomy ($P < .0001$). The two groups were comparable with respect to extent of pancreatic resection (98% had partial pancreatectomy), type of pancreatic anastomosis (98% via pancreaticojejunostomy), intraoperative blood loss (mean 770 mL), and units of red blood cells transfused (median 0). The mean operative time was significantly longer in the radical group (6.4 hours vs. 5.9 hours standard; $P = .002$) because of the additional time needed for the distal gastrectomy and retroperitoneal lymphadenectomy.

The final pathology results in the resected specimens are depicted in Table 3. The two groups were comparable with respect to site of tumor origin (57% pancreatic), differentiation (42% poorly differentiated), tumor diameter (mean 2.6 cm), resected lymph node status (74% positive), margin status (10% microscopically positive), perineural invasion, and vascular invasion. Of the 28 patients (10%) with mi-

Table 3. PATHOLOGIC ANALYSES

	Standard (n = 146)	Radical (n = 148)	*P* Value
Site of origin			
Pancreas	84 (58%)	83 (56%)	.40
Ampulla	35 (24%)	28 (19%)	
Distal bile duct	23 (16%)	28 (19%)	
Duodenum	2 (1%)	7 (5%)	
IPMN of pancreas with carcinoma	2 (1%)	2 (1%)	
Poor tumor differentiation	39%	45%	.27
Mean tumor diameter (cm)	2.6 ± 0.1	2.5 ± 0.1	.42
Resected lymph node status			
Positive	107 (73%)	110 (74%)	.76
Negative	39 (27%)	38 (26%)	
Resection margin status			
Positive*	18 (12%)	10 (7%)	.11
Negative	128 (88%)	138 (93%)	
Perineural invasion			
Positive	93 (70%)	99 (77%)	.17
Negative	40 (30%)	29 (23%)	
Vascular invasion			
Positive	55 (44%)	57 (45%)	.89
Negative	69 (56%)	69 (56%)	

IPMN, intraductal papillary mucinous neoplasm.
* All positive margins were only microscopically positive on permanent section. No patient was randomized with microscopically positive resection margins by frozen section or with gross tumor left behind (macroscopically positive margin).

croscopically positive resection margins on permanent section, 20 had carcinoma involving the margin at the level of the uncinate process (adjacent to the SMV, portal vein, or SMA), 4 patients had a positive microscopic margin at the pancreatic neck–body transection site, 2 patients in the standard group had microscopic involvement at or near the duodenal margin, and 2 patients had a positive microscopic margin at the bile duct margin.

Table 4 details the analysis of resected lymph nodes. For the standard group, 73% of patients had histologically positive lymph node metastases in the resection specimen, and the mean total number of resected lymph nodes was 17. For the radical group, 74% of patients had histologically positive lymph node metastases in the resection specimen, and the mean total number of resected lymph nodes was significantly greater at 28.5 ($P = .001$). In only one patient was there histologic evidence of metastatic adenocarcinoma in a perigastric lymph node, without lymph node metastases being identified in the pancreaticoduodenectomy specimen. Thus, the performance of the radical (extended) resection altered the TNM pathologic staging in only 1 of 148 patients (0.6%), changing the TNM classification in this patient from $T_3N_0M_0$ to $T_3N_1M_0$ and from stage 2 to stage 3 disease.

Postoperative complications and hospital course are depicted in Table 5. There were six perioperative deaths in the standard group (4%) and three in the radical group (2%), for an overall perioperative mortality rate of 3%. The predominant causes of death were sepsis and multiple organ dysfunction syndrome, which accounted for seven of the nine deaths. One patient died following a myocardial infarction, and one died of hepatic failure due to hepatic artery thrombosis. Twelve patients underwent reoperation during their index admission: five for surgical wound problems, two for anastomotic disruptions and sepsis, and one each for postoperative bleeding, hepatic artery thrombosis, late gastrointestinal bleeding, unexplained acidosis, and sepsis.

The overall complication rate was 36%; it was 29% in the standard group and significantly higher at 43% in the radical group ($P = .01$). The most common complications were early delayed gastric emptying, pancreatic fistula, and wound infection. The radical group had significantly higher rates of early delayed gastric emptying (16% vs. 6%; $P = .006$) and pancreatic fistula (13% vs. 6%; $P = .05$) and more than twice the incidence of wound infection (11% vs. 5%; $P = .06$) compared to the standard group. Four patients in the radical group and one in the standard group were identified as having postoperative lymph collections several weeks after discharge; these were managed via percutaneous drainage. The mean postoperative length of hospital stay was 11.3 days in the standard group and significantly longer at 14.3 days in the radical group ($P = .003$).

The actuarial survival curves for the 285 patients surviving the immediate postoperative period are depicted in Figures 3 to 6, with the data being given in Table 6. For these survival analyses, the mean length of follow-up for all patients was 24 months, and the mean length of follow-up for all surviving patients was 31.5 months. One hundred

Table 4. DETAILS OF RESECTED LYMPH NODE ANALYSES

		Standard (n = 146)	Radical (n = 148)	*P* Value
Resected lymph node status	Positive	107 (73%)	110 (74%)	.76
	Negative	39 (27%)	38 (26%)	
Total lymph nodes resected	Mean	17.0 ± 0.6	28.5 ± 0.6	.001
	Median	16	26	
Nodes in pancreaticoduodenectomy specimen	Positive	107 (73%)	109 (74%)	.83
	Negative	39 (27%)	39 (26%)	
	Mean number LN	17.0 ± 0.6	16.4 ± 0.6	
	Mean number positive LN	3.3 ± 0.3	3.0 ± 0.3	
Nodes in retroperitoneal lymphadenectomy specimen	Positive	N/A	22 (15%)*	—
	Negative		126 (85%)	
	Mean number LN		7.0 ± 0.3	
	Mean number positive LN		0.4 ± 0.1	
Nodes in distal gastrectomy specimen	Positive	N/A	8 (5%)†	—
	Negative		140 (95%)	
	Mean number LN		4.1 ± 0.4	
	Mean number positive LN		0.1 ± 0.02	
Nodes in celiac region	Positive	N/A	5 (3%)‡	
	Negative		143 (97%)	
	Mean number LN		0.8 ± 0.1	
	Mean number positive LN		0.04 ± 0.02	

LN, lymph node.
* In 22 patients there were positive LN in the retroperitoneal lymphadenectomy specimen. In all 22, LN were also positive in the pancreaticoduodenectomy specimen.
† In 8 patients there were positive LN in the distal gastrectomy specimen. In all but one of these patients, LN were also positive in the pancreaticoduodenectomy specimen. One patient in the radical group had negative pancreaticoduodenectomy specimen LN and one positive lymph node in the distal gastrectomy specimen.
‡ In 5 patients there were positive LN in the celiac region. In all 5 patients, LN were also positive in the pancreaticoduodenectomy specimen.

fifty-two of the 285 patients remained alive at the time of the February 2002 survival analysis.

Figure 3 depicts the survival curves for the entire cohort of patients (all pathologic diagnoses), comparing the standard resection group (n = 140) to the radical resection group (n = 145). The 1-, 3-, and 5-year survival rates were comparable between the two groups, with a median survival of 30 months in the standard group and 28 months in the radical group (see Table 6).

Figure 4 depicts the survival curves for all patients with pancreatic adenocarcinoma. The 1-, 3-, and 5-year actuarial survival rates were 77%, 36%, and 10% for the standard group and 74%, 38%, and 25% for the radical group (P = .57). Figure 5 depicts the survival curves for the subgroup of patients with lymph node-positive pancreatic adenocarcinoma, and Figure 6 shows the survival curve for the subgroup of patients with lymph node-negative pancreatic adenocarcinoma. There were no significant differences in

Table 5. POSTOPERATIVE COMPLICATIONS AND HOSPITAL COURSE

	Standard (n = 146)	Radical (n = 148)	*P* Value
Perioperative mortality	6 (4%)	3 (2%)	.30
Reoperation	6 (4%)	6 (4%)	.98
Any complication			
Yes	42 (29%)	64 (43%)	.01
No	104 (71%)	84 (57%)	
Early delayed gastric emptying	9 (6%)	24 (16%)	.006
Pancreatic fistula	9 (6%)	19 (13%)	.05
Wound infection	7 (5%)	16 (11%)	.06
Intraabdominal abscess	5 (3%)	6 (4%)	.77
Bile leak	3 (2%)	7 (5%)	.21
Cholangitis	2 (1%)	3 (2%)	.66
Lymphocele	1 (1%)	4 (3%)	.57
Postoperative length of hospital stay (days)			
Mean	11.3 ± 0.5	14.3 ± 0.8	.003
Median	9	10	

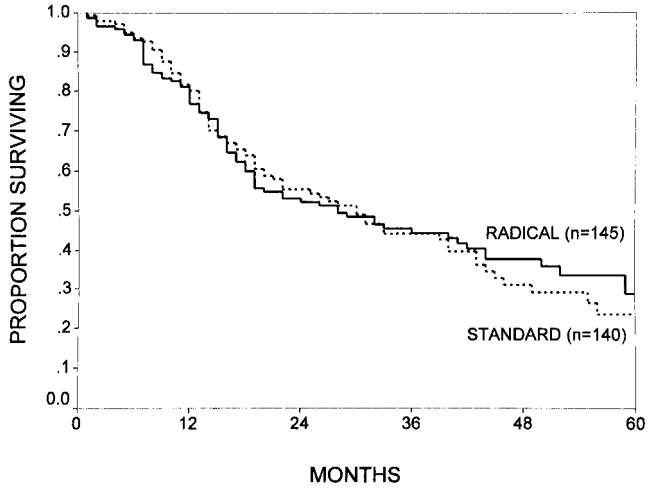

Figure 3. The actuarial survival curves for all patients (all pathologic diagnoses) who survived the immediate postoperative period, comparing the standard resection group (n = 140; dashed line) to the radical resection group (n = 145; straight line). The 1-, 3-, and 5-year survival rates are 80%, 44%, and 23% for the standard group and 77%, 44%, and 29% for the radical group (P = .79).

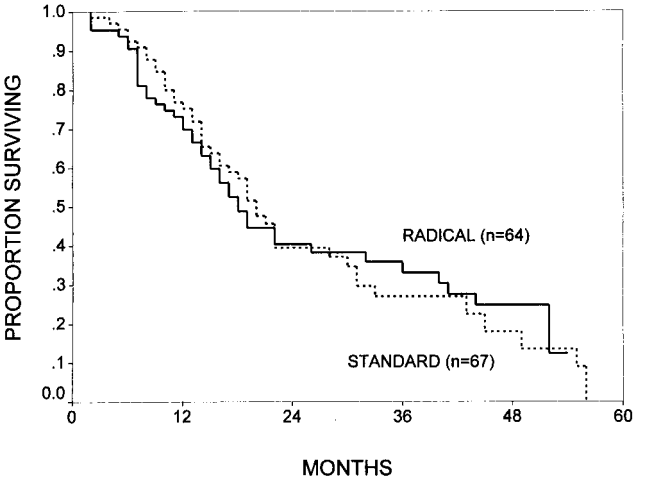

Figure 5. The actuarial survival curves for patients with node-positive pancreatic adenocarcinoma who survived the immediate postoperative period, comparing the standard resection group (n = 67; dashed line) to the radical resection group (n = 64; straight line). The 1- and 3-year survival rates are 75% and 27% for the standard group and 70% and 33% for the radical group (P = .98).

survival between the standard and radical groups in any subgroup of patients with pancreatic adenocarcinoma. In node-positive pancreatic adenocarcinoma patients undergoing radical resection (n = 64), the 51 patients with uninvolved retroperitoneal nodes had 1- and 3-year survival rates of 76% and 38% and a median survival of 20.5 months. In contrast, the 13 patients with involved retroperitoneal nodes had 1- and 3-year survival rates of 46% and 15% and a median survival of 11.5 months (P = .07), indicating a survival disadvantage with second-order nodal involvement.

For patients with primary tumors of the ampulla and distal bile duct, the survival data are shown in Table 6. Patients with ampullary adenocarcinoma (n = 62) had similar 5-year actuarial survival rates of 56% for the standard resection and 60% for the radical resection (P = .72). Patients with distal bile duct cancer (n = 49) had survival rates comparable to patients with pancreatic tumors, with no significant differences in outcome comparing standard to radical resection. Only nine patients in this series were treated for duodenal adenocarcinoma (two via standard resection and seven via radical resection), and all remained alive at last follow-up.

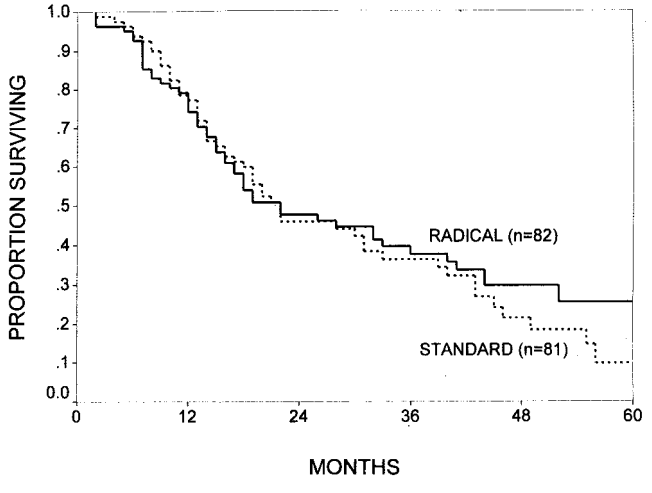

Figure 4. The actuarial survival curves for patients with pancreatic adenocarcinoma who survived the immediate postoperative period, comparing the standard resection group (n = 81; dashed line) to the radical resection group (n = 82; straight line). The 1-, 3-, and 5-year survival rates are 77%, 36%, and 10% for the standard group and 74%, 38%, and 25% for the radical group (P = .57).

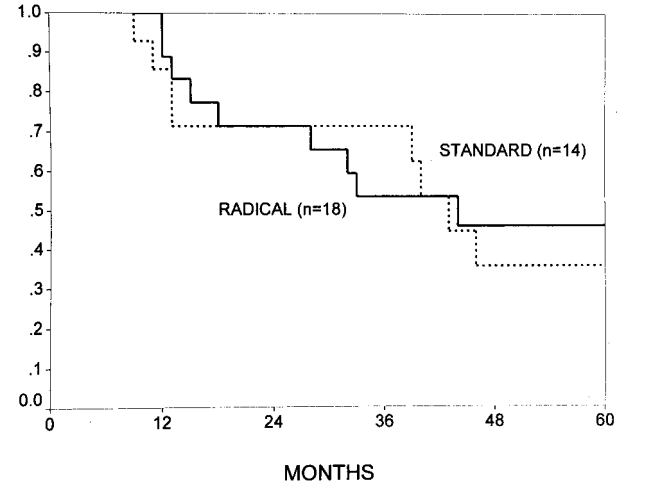

Figure 6. The actuarial survival curves for patients with node-negative pancreatic adenocarcinoma who survived the immediate postoperative period, comparing the standard group (n = 14; dashed line) to the radical group (n = 18; straight line). The 1-, 3-, and 5-year survival rates are 86%, 71%, and 36% for the standard group and 89%, 54%, and 46% for the radical group (P = .73).

Table 6. ACTUARIAL SURVIVAL RATES FOLLOWING STANDARD VERSUS RADICAL PANCREATICODUODENECTOMY

	1 Year	3 Years	5 Years	Median	*P* Value
Entire cohort					
Standard (n = 140)	80%	44%	23%	30 mo	.79
Radical (n = 145)	77%	44%	29%	28 mo	
Pancreatic adenocarcinoma					
Standard (n = 81)	77%	36%	10%	21 mo	.57
Radical (n = 82)	74%	38%	25%	20 mo	
Node-positive pancreatic adenoca.					
Standard (n = 67)	75%	27%	—	19 mo	.98
Radical (n = 64)	70%	33%	—	17.5 mo	
Node-negative pancreatic adenoca.					
Standard (n = 14)	86%	71%	36%	41 mo	.73
Radical (n = 18)	89%	54%	46%	43 mo	
Ampullary adenocarcinoma					
Standard (n = 34)	85%	65%	56%	NYR	.72
Radical (n = 28)	89%	60%	60%	NYR	
Distal bile duct cancer					
Standard (n = 22)	81%	34%	23%	22 mo	.74
Radical (n = 27)	78%	41%	11%	24 mo	

NYR, not yet reached.

DISCUSSION

One proposed strategy to improve outcome in patients with resectable pancreatic and periampullary adenocarcinoma involves extension of the operation and increased lymph node clearance. This large single-institution randomized controlled trial was designed to evaluate the end points of postoperative survival and complications, comparing standard and radical (extended) pancreaticoduodenal resection. Our analyses to date (with a mean follow-up of 31.5 months for all surviving patients) fail to indicate a survival benefit associated with the more radical procedure. As presented in Table 6, the 1-, 3-, and 5-year actuarial survival rates as well as the median survival are not statistically different when comparing patients with pancreatic adenocarcinoma, ampullary adenocarcinoma, and distal bile duct adenocarcinoma who underwent standard or radical resection. Furthermore, no significant differences in survival were observed when evaluating subgroups of patients with pancreatic cancer stratified by resected lymph node status, comparing standard to radical resection (node-positive median survival approximately 18 months; node-negative median survival approximately 42 months). While it may be tempting to examine the data for all patients with pancreatic adenocarcinoma (see Fig. 4 and Table 6), which projects an actuarial 5-year survival of 25% in the radical group (vs. 10% in the standard group), and suggest that radical resection may have a survival benefit that becomes apparent only after years of follow-up, this conclusion is not supported by the current statistical analyses. In fact, the median survival was 21 months in the standard group and 20 months in the radical group, and the survival curves were identical well beyond the 31.5 months of mean follow-up for all surviving patients. It is our intention to continue to follow these study patients and to update our survival results when appropriate. However, the current survival results indicate no benefit to radical resection and are largely concordant with previous smaller prospective trials comparing differing extents of pancreaticoduodenal resection.

The type of radical (extended) resection varied among past trials.[33] For example, Henne-Bruns et al.[34] from Germany reported a prospective nonrandomized study in patients with pancreatic adenocarcinoma, comparing 26 patients undergoing a lesser regional lymphadenectomy (including removal of lymph nodes in the hepatoduodenal ligament, proximal celiac trunk, right side of the SMA, and ventral surface of the inferior vena cava) to 46 patients undergoing a more extensive retroperitoneal lymphadenectomy (adding removal of all lymphatic, connective, and neural tissue along the left side of the SMA and the aorta, from the inferior mesenteric artery to the diaphragm). On average, 14 lymph nodes were harvested in their lesser procedure and 24 lymph nodes in their more extensive procedure. Their analyses failed to reveal a survival benefit for the more extensive procedure, with a median survival of only approximately 12 months in each group. A second trial by Pedrazzoli et al. from Italy randomized 81 patients with pancreatic adenocarcinoma to pancreaticoduodenectomy with two different extents of lymphadenectomy.[23] In one group of 40 patients a standard resection was performed, while 41 patients underwent extended lymphadenectomy to include circumferential clearance of the celiac and superior mesenteric arteries and removal of lymph nodes from the

hepatic hilum and along the aorta from the diaphragmatic hiatus to the inferior mesenteric artery (laterally to both renal hila). In this study an average of 13 lymph nodes were retrieved in the standard group, compared to 20 lymph nodes in the extended group. While the overall survival was not different between the two groups, the subgroup of node-positive patients had a significantly better survival rate after the extended operation, implying a potential benefit for extended resection. A third trial, by Seiler et al., randomized pancreaticoduodenectomy with or without pylorus preservation (no extended lymphadenectomy) and evaluated long-term follow-up in 61 patients with pancreatic or periampullary adenocarcinoma.[35] Survival analyses revealed no differences in 1-year or 2-year survival rates or median survival when comparing the 33 patients undergoing classic pancreaticoduodenectomy (which includes a distal gastrectomy) to the 28 patients treated via pylorus-preserving pancreaticoduodenectomy.

The current study differs as regards the extent of resection from the previous prospective studies of Henne-Bruns et al.[22,34] and Pedrazzoli et al.[23] The current study randomized 294 patients, and, as designed, used a pylorus-preserving pancreaticoduodenectomy as the lesser (or control) procedure, and then added distal gastrectomy plus retroperitoneal lymphadenectomy to the group randomized to the extended procedure. The average number of lymph nodes retrieved was 17 in the standard group and 28.5 in the radical group. There was no circumferential clearance of the SMA or celiac axis in the current study, nor was there extensive nodal harvesting from the hepatoduodenal ligament or the region of the common hepatic artery. The survival data appear to indicate that the addition of a distal gastrectomy (attended by harvesting of the respective perigastric lymph nodes) and retroperitoneal lymphadenectomy to the pylorus-preserving pancreaticoduodenectomy provides no survival benefit. The failure of extended surgical strategies to provide survival benefit is not limited to pancreatic and periampullary adenocarcinoma. For example, most of the data from prospective randomized trials in gastric adenocarcinoma (a tumor with comparable lymph node drainage, molecular genetics, and histologic appearance) have failed to reveal a survival advantage for extended lymphadenectomy (designed to remove second-order or third-order lymph nodes).[36–39] Furthermore, a mathematical model recently outlined by Pisters et al. appears to validate the lack of survival benefit for extended resections in pancreatic adenocarcinoma.[40] In this model the authors make the following three assumptions: complete gross and microscopic tumor resection (R_0) is required for extended resection to confer a survival benefit; only patients with second-order lymph node involvement will benefit when extended resections remove those nodes; and only node-positive patients without metastatic disease outside the resection zone will derive a benefit from extended resection. By assuming an R_0 resection rate of 80%, second-order nodal involvement of 10%, and node positive-M_0 rate of 5%, the authors calculated that only 0.4% ($0.8 \times 0.1 \times 0.05 \times 100\%$) of patients undergoing extended resections may achieve a survival benefit. While these assumptions may be challenged as inaccurate (the second-order retroperitoneal nodal involvement rate in the current study was 15%) and their analysis fails to consider that extended resection may reduce tumor burden sufficiently to allow meaningful responses to chemotherapy, radiotherapy, or novel immunotherapy, the general argument appears sound: current data fail to support that a strategy of extended resection improves survival in patients with pancreatic (and other periampullary) adenocarcinoma.

In addition to the end point of survival, other primary end points in this study include operative mortality, operative morbidity, and length of postoperative hospital stay. As has been observed in several previous studies, extended resections (here distal gastrectomy plus retroperitoneal lymphadenectomy) do not appear to increase the operative mortality rate. In our cohort, the operative mortality was 4% (6/146) in the standard group and 2% (3/148) in the radical group. However, the radical group was observed to have significantly higher rates of early delayed gastric emptying (16% vs. 6%; $P = .006$) and pancreatic fistula (13% vs. 6%; $P = .05$) and a higher wound infection rate of 11% (compared to 5% in the standard group; $P = .06$). Since all three of these complications typically increase the length of hospital stay, it is not surprising that we observed a significantly longer hospital stay in the radical group (mean 14.3 days) compared to the standard group (mean 11.3 days; $P = .003$). The reasons for the increased rates of early delayed gastric emptying and pancreatic fistula in the radical group are not clear. We acknowledge that our definition of early delayed gastric emptying is broad and clinically based,[26] and that some patients with nausea, vomiting, and difficulties with oral intake after distal gastrectomy may have a component of bile reflux gastritis, and not a gastric dysmotility problem. Perhaps pylorus preservation, with a retained sphincter, reduces the magnitude or incidence of bile reflux and the resulting symptoms. The higher rate of pancreatic fistula in the radical group also is not clearly explainable, since the usual factors contributing to pancreatic fistula (underlying pathology, pancreatic texture, surgical technique) were comparable between the two groups. We have noted, using our method of reconstruction, that following pylorus preservation the anterior aspect of the pancreaticojejunostomy is typically covered by the distal stomach and the duodenojejunostomy. In contrast, following distal gastrectomy, the anterior aspect of the pancreaticojejunostomy is less likely to be covered by overlying viscera, perhaps rendering the pancreatic–enteric anastomosis more prone to a failure of healing.

From the data in this study, it appears that the widespread use of extended resections for patients with pancreatic and related periampullary adenocarcinoma will not be associated with improved long-term survival. These data further support the use of pylorus preservation, since its use was attended by significantly lower rates of early delayed gastric

emptying and pancreatic fistula, and with a significantly shorter postoperative hospital stay, without a negative impact on survival. There remain multiple avenues of investigation that may prove fruitful in treating patients with or at risk for pancreatic and related cancers. For example, a better understanding of tumor genetics and neoplastic progression models[41,42] may lead to progress in early detection and perhaps chemoprevention. This may be particularly true as additional observations are made using global gene expression technology and protein biochip technology.[43,44] Improvements in abdominal imaging and the recognition of imageable precursor lesions may improve our ability to detect smaller, lower-staged neoplasms.[45] Based on data from a recent large epidemiologic study that linked obesity and physical inactivity with pancreatic cancer,[46] changes in eating habits and additional physical exercise may be encouraged as a specific means of decreasing the risk of pancreatic cancer. Genetic epidemiology, combined with large tumor registries, now allows for the identification of individuals at high risk for these tumors.[45,47] Further large trials of postoperative adjuvant therapies or preoperative neoadjuvant strategies may identify improved combinations with particular activity against these tumors.[11–14,31]

At no time in the past has there been as much activity in the field of pancreatic adenocarcinoma. It is hoped that future developments in many areas currently under active study will improve the overall prognosis for patients with pancreatic or periampullary adenocarcinoma.

Acknowledgments

This study would not have been possible without the support of the surgical housestaff and nurses of the Johns Hopkins Hospital. Their dedication to the care of our pancreaticoduodenectomy patients is critical for our success.

References

1. Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. Am J Surg 1993; 165:68–73.
2. Yeo CJ, Sohn TA, Cameron JL, et al. Periampullary adenocarcinoma: Analysis of 5-year survivors. Ann Surg 1998; 227:821–831.
3. Delcore R, Rodriquez FJ, Forster J, et al. Significance of lymph node metastases in patients with pancreatic cancer undergoing curative resection. Am J Surg 1996; 172:463–469.
4. Conlon KC, Klimstra DS, Brennan MF. Long-term survival after curative resection of pancreatic ductal adenocarcinoma. Clinicopathologic analysis of 5-year survivors. Ann Surg 1996; 223:273–279.
5. Yeo CJ, Cameron JL. Review topic: Prognostic factors in ductal pancreatic cancer. Langenbeck's Arch Surg 1998; 383:129–133.
6. Nakeeb A, Pitt HA, Sohn TA, et al. Cholangiocarcinoma: A spectrum of intrahepatic, perihilar and distal tumors. Ann Surg 1996; 224:463–475.
7. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas—616 patients: Results, outcomes, and prognostic indicators. J Gastrointest Surg 2000; 4:567–579.
8. Allison DC, Piantadosi S, Hruban RH, et al. DNA content and other factors associated with ten-year survival after resection of pancreatic carcinoma. J Surg Oncol 1998; 67:151–159.
9. Tascilar M, Skinner HG, Rosty C, et al. The SMAD4 protein and prognosis of pancreatic ductal adenocarcinoma. Clin Cancer Res 2001; 7:4115–4121.
10. Montgomery RC, Hoffman JP, Riley LB, et al. Prediction of recurrence and survival by post-resection CA19–9 values in patients with adenocarcinoma of the pancreas. Ann Surg Oncol 1997; 4:551–556.
11. Yeo CJ, Abrams RA, Grochow LB, et al. Pancreaticoduodenectomy for pancreatic adenocarcinoma: Postoperative adjuvant chemoradiation improves survival. A prospective, single institution experience. Ann Surg 1997; 225:621–636.
12. Nukui Y, Picozzi VJ, Traverso LW. Interferon-based adjuvant chemoradiation therapy improves survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. Am J Surg 2000; 179:367–371.
13. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg 1999; 230:776–784.
14. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomized controlled trial. Lancet 2001; 358:1576–1585.
15. Fortner JG. Regional resection of cancer of the pancreas: A new surgical approach. Surgery 1973; 73:307–320.
16. Fortner JG. Recent advances in pancreatic cancer. Surg Clin North Am 1974; 54:859–863.
17. Fortner JG, Kim DK, Cubilla A, et al. Regional pancreatectomy: En bloc pancreatic, portal vein and lymph node resection. Ann Surg 1977; 186:42–50.
18. Fortner JG, Klimstra DS, Senie RT, et al. Tumor size is the primary prognosticator for pancreatic cancer after regional pancreatectomy. Ann Surg 1996; 223:147–153.
19. Satake K, Niskiwaki H, Yokomatsu H, et al. Surgical curability and prognosis for standard versus extended resections for T_1 carcinoma of the pancreas. Surg Gynecol Obstet 1992; 175:259–265.
20. Kayahara M, Nagakawan T, Veno K, et al. Surgical strategy for carcinoma of the pancreas head area based on clinicopathologic analysis of nodal involvement and plexus invasion. Surgery 1995; 117: 616–623.
21. Manabe T, Ohshio G, Baba N, et al. Radical pancreatectomy for ductal cell carcinoma of the head of the pancreas. Cancer 1989; 64:1132–1137.
22. Henne-Bruns D, Vogel I, Luttges J, et al. Ductal adenocarcinoma of the pancreas head: survival after regional versus extended lymphadenectomy. Hepato-Gastroenterology 1998; 45:855–866.
23. Pedrazzoli S, DiCarlo V, Dionigi R, et al. Standard versus extended lymphadenectomy associated with pancreaticoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas. A multicenter, prospective, randomized study. Ann Surg 1998; 228:508–517.
24. Yeo CJ, Cameron JL, Sohn TA, et al. Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma: Comparison of morbidity and mortality and short-term outcome. Ann Surg 1999; 229:613–624.
25. Yeo CJ. The Johns Hopkins experience with pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma. J Gastrointest Surg 2000; 4:231–232.
26. Yeo CJ, Barry MK, Sauter PK, et al. Erythromycin accelerates gastric emptying following pancreaticoduodenectomy: A prospective, randomized placebo-controlled trial. Ann Surg 1993; 218:229–238.
27. Yeo CJ, Cameron JL, Lillemoe KD, et al. Does prophylactic octreotide really decrease the rates of pancreatic fistula and other complications following pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. Ann Surg 2000; 232:419–429.
28. Abrams RA, Grochow LB, Chakravarthy A, et al. Intensified adjuvant therapy for pancreatic and periampullary adenocarcinoma: Survival results and observations regarding patterns of failure, radiotherapy dose and CA 19–9 levels. Int J Radiat Oncol Biol Phys 1999; 44: 1039–1046.

29. Chakravarthy A, Abrams RA, Yeo CJ, et al. Intensified adjuvant combined modality therapy for resected periampullary adenocarcinoma: Acceptable toxicity and improved 1-year disease-free survival. Int J Rad Oncol Biol Phys 2000; 48:1089–1096.
30. Jaffee EM, Abrams R, Cameron J, et al. A phase I trial of lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene for the treatment of pancreatic adenocarcinoma. Hum Gene Ther 1998; 9:1951–1971.
31. Jaffee EM, Hruban RH, Biedzycki B, et al. Novel allogeneic granulocyte-macrophage colony-stimulating factor-secreting tumor vaccine for pancreatic cancer: A phase I trial of safety and immune activation. J Clin Oncol 2001; 19:145–156.
32. Nguyen TC, Sohn TA, Cameron JL, et al. Standard versus radical pancreaticoduodenectomy for periampullary adenocarcinoma: A prospective randomized trial evaluating quality of life in pancreaticoduodenectomy survivors. J Gastrointest Surg (In Press).
33. Traverso LW, Kawarada Y, Isaji S, et al. Extended lymphadenectomy during pancreaticoduodenectomy for cancer of the pancreas: Summary of "How I Do It" Session. J Gastrointest Surg 2000; 4:225–232.
34. Henne-Bruns D, Vogel I, Lüttges J, et al. Surgery for ductal adenocarcinoma of the pancreatic head: Staging, complications, and survival after regional versus extended lymphadenectomy. World J Surg 2000; 24:595–602.
35. Seiler CA, Wagner M, Sadowski C, et al. Randomized prospective trial of pylorus-preserving vs. classic duodenopancreatectomy (Whipple procedure): Initial clinical results. J Gastrointest Surg 2000; 4:443–452.
36. Dent DM, Madden MV, Price SK. Randomized comparison of R_1 and R_2 gastrectomy for gastric carcinoma. Br J Surg 1988; 75:110–112.
37. Robertson CS, Chung SCS, Woods SDS, et al. A prospective randomized trial comparing R_1 subtotal gastrectomy with R_3 total gastrectomy for antral cancer. Ann Surg 1994; 200:176–182.
38. Bonenkamp JJ, Hermans J, Sasako M, et al. Extended lymph-node dissection for gastric cancer. N Engl J Med 1999; 340:908–914.
39. Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D_1 and D_2 resections for gastric cancer: Long-term results of the MRC randomized surgical trial. Br J Surg 1999; 79:1522–1530.
40. Pisters PWT, Evans DB, Leung DHY, et al. Letter to the editor. World J Surg 2001; 25:523–534.
41. Sohn TA, Yeo CJ. The molecular genetics of pancreatic ductal carcinoma: A review. Surgical Oncol 2000; 9:95–101.
42. Wilentz RE, Iacobuzio-Donohue CA, Argani P, et al. Loss of expression of DPC4 in pancreatic intraepithelial neoplasia: Evidence that DPC4 inactivation occurs late in neoplastic progression. Cancer Res 2000; 60:2002–2006.
43. Iacobuzio-Donahue CA, Maitra A, Shen-Ong GL, et al. Discovery of novel tumor markers of pancreatic cancer using global gene expression technology. Am J Pathol 2002; 160:1239–1249.
44. Rosty C, Christa L, Kuzdzal S, et al. Identification of hepatocarcinoma-intestine-pancreas/pancreatitis-associated-protein I as a biomarker for pancreatic ductal adenocarcinoma by protein biochip technology. Cancer Res 2002; 62:1868–1875.
45. Hruban RH, Canto MI, Yeo CJ. Prevention of pancreatic cancer and strategies for management of familial pancreatic cancer. Dig Dis 2001; 19:76–84.
46. Michaud DS, Giovannucci E, Willett WC, et al. Physical activity, obesity, height, and the risk of pancreatic cancer. JAMA 2001; 286: 921–929.
47. Tersmette AC, Peterson GM, Offerhaus GJA, et al. Increased risk of incident pancreatic cancer among first-degree relatives of patients with familial pancreatic cancer. Clin Cancer Res 2001; 7:738–744.

DISCUSSION

DR. ANDREW L. WARSHAW (Boston, MA): Dr. Yeo, this is another superb randomized trial from you and your colleagues at Johns Hopkins. Your group has demonstrated almost a unique capability to conduct these large single-institution trials, this one to study whether more extensive lymph node dissection can provide better cancer control for pancreatic head cancer and other periampullary cancers.

The biology of pancreatic cancer is particularly challenging, not only because of the late presentation of the disease but especially because of the somewhat atypical pathways of spread through the peritoneal cavity, perineural channels, and bloodstream dissemination.

The Japanese have claimed improved survival after wider extension of the tissues removed. However, their operation is different and more radical than the one that the Hopkins group has used in this study. The Japanese remove more lymph node groups in a wider circumference and perform a circumferential cleaning of the nerve plexuses around the superior mesenteric artery. The price for this dissection is significant morbidity due to diarrhea, malnutrition, and rehospitalization.

In the more limited dissection used in this study, similar to the operation commonly performed elsewhere in this country and the West, the retroperitoneal nodes and antropyloric tissues are removed only after proving negative margins of the standard lesser resection. The specific principle being tested is whether there is some survival benefit to removing the retroperitoneal lymphoid tissues located behind the pancreas and in the aortocaval sulcus. As a point of fact, only 15% of your patients had positive retroperitoneal nodes, and none were uniquely positive when the nodes immediately closer to the pancreas were negative. What you have clearly proven is that these nodes are not a primary site for pancreatic metastases and are, rather, another index of disseminated disease. Tumor biology is the determining factor.

I have three questions for you, Dr. Yeo.

What specific margins were tested by frozen section during the operation to determine negativity? How often were the negative margins on frozen section found to be positive on permanent section, especially if you might have used immunohistochemistry for cytokeratins or PER for K-ras?

Second, do you worry that the discontinuous rather than en-bloc dissection, commonly used by the Japanese, violates the integrity of the specimen and may contaminate by dissemination a highly implantable cancer? Could this factor have contributed to your failure to show a benefit for the retroperitoneal dissection?

Third, there was significant early morbidity for the extended resection in your experience. Did you see any evidence of the late diarrhea and malnutrition that the Japanese found with the more extended dissection?

I congratulate you on taking on an important and debated issue and for pointing us back at the biological factors which are more important in pancreatic cancer than local circumstances.

PRESENTER DR. CHARLES J. YEO (Baltimore, MD): Thank you, Dr. Warshaw, for your insightful questions.

First, the requisite obligation in this study was that by frozen section, all margins—and the margins that were tested were the bile duct, the retroperitoneum, the pancreatic neck, and the duodenal margins—were all negative prior to randomization. So four frozen sections were done, all were negative, in order for a patient to be randomizeable after informed consent. It turns out on permanent section, with additional sampling, 10% of patients ended up with positive margins histologically. We did not look at immunohistochemistry, we did not look at PCR, et cetera. Of the 28 patients with positive margins at permanent section, 20 were retroperitoneal margins positive at the uncinate process or in the vascular groove.

The second question is the issue of en bloc versus discontinuous resection. This was a major issue when we set up the trial. It became a major issue when we discussed a possible trial for the American College of Surgeons Oncology Group. We thought doing it this way was cleanest oncologically and allowed to us get a true randomization between patients who could undergo a margin-negative pylorus-preserving resection and those who could have an extended resection. While I can't speak specifically to the issue of whether this operation has caused dissemination of tumor, I doubt it. There certainly seemed to be no decrement in survival with the radical operation here.

Third, the late morbidity and quality of life issues are very important. We have analyzed a group of 105 pancreaticoduodenectomy survivors,

randomized 55 to standard and 50 to radical resection. Their health-related quality of life as measured by the FACT-Hep tool, which includes the FACT-G and the FACT-Hep subscales, is identical. So, the survivors of this radical pancreaticoduodenectomy have no decrement in quality of life when compared to patients with the standard resection. Additionally, there were no differences in pancreatic enzyme use or number of bowel motions per day, when comparing the standard to the radical group.

DR. MURRAY F. BRENNAN (New York, NY): Dr. Yeo is to be complimented for a very lucid presentation. Certainly the authors are to be complimented on an attempt at a surgical randomized trial. Not surprisingly, I would find that, as with all well-intended trials, there are some difficulties here.

Some might consider the procedure they call an extended operation to be the standard operation; i.e., the clearance of the tissue in front of the vena cava and the aorta is, in my opinion, the easiest way to do the operation, as the vascular structures are clearly identified.

Whether pylorus preserving or sacrifice of the antrum is an important issue has been debated by many. But to me, no clear benefit was demonstrated in the long term, although this study certainly suggests an increase in delayed gastric emptying if the pylorus is resected.

More importantly, one might question the basic premise beyond morbidity. How can such an operation alter long-term survival?

Lymph node positivity is considered a negative prognostic factor in pancreatic adenocarcinoma. While that may be statistically significant at 5 years, the variation between node positive and node negative is measured in single digits. If there was a benefit to removing unknown positive nodes, it would take a truly enormous number of patients to define a difference, as overall mortality is bad, independent of lymph node status.

The high prevalence of histological positive nodes in this study, 74%, emphasizes the diligence with which the authors look for the nodes, but again raises the question of whether or not you can improve survival by taking more nodes when at least three quarters are already positive. As the authors showed, only one patient with negative peripancreatic nodes had a positive node in the more extended operation. So it would be theoretically impossible to show a benefit.

The present study, therefore, is an important study in perioperative morbidity, and the difference here was a difference in pancreatic fistula rate. My first question: How can the extent of gastric resection or node dissection influence pancreatic fistula?

Clearly, operative mortality is excellent in the hands of these investigators, and we cannot expect it to be improved. The operative time was prolonged by half an hour, which in our hospital is the time it takes to complete randomization in any procedure! The more extensive operation had a greater incidence of wound infection. That may be due to the division of the stomach as opposed to the duodenum.

My second question was: Were the wound infection organisms the same as was in the bile culture? Because if they were, that would disprove the possibility of the gastric resection causing the morbidity. It is not clear at all, Dr. Yeo, why patients with an extended procedure should have a greater pancreatic fistula rate, and it would be interesting to hear your comments.

Some will take solace and claim benefit based on the manuscript's improved 5-year survival, 25% versus 10%. These are actuarial numbers and can be expected to be overestimates. Dr. Yeo has clearly pointed out, as evidenced by the equivalent median survival, that will not take place.

So what can we take from the manuscript? We certainly admire the diligence and fortitude of the authors in putting forward randomized trials. I might take some umbrage that the study as designed would only address perioperative morbidity, as no potential survivor benefit could possibly be obtained in this rather dismal disease. So the strength of the trial is that it was done at all. And the difficulty is, as the authors point out, we need better ideas rather than minor variations in technique, a subject that the Hopkins group is continuing to exercise.

And finally, perhaps lightheartedly, as a long-term admirer of the Hopkins group I was impressed to see that they too have occasional perioperative demise. We continue to struggle to emulate them.

DR. CHARLES J. YEO (Baltimore, MD): Dr. Brennan, you struck upon two of the results that are statistically dissimilar between the groups. The pancreatic fistula rate was higher in the radical group. We don't have a good explanation for that observation, because when we compare the two groups as concerns the pathology, texture of the gland, type of anastomosis, all is comparable. The one speculation I can make—and it is purely speculation, but it is a true observation—is that when you do the radical operation, the pancreaticojejunostomy is typically not covered by the posterior wall of the stomach, because you have done a distal gastrectomy. On the other hand, when you have a pylorus-preserving resection, the antrum of the stomach sits right upon the pancreaticojejunostomy. It is possible that the failure of healing of the pancreatic–enteric anastomosis is related to the lack of this anterior coverage.

The wound infection issue, I think, is driven by several things. The higher rates of pancreatic fistula and the longer operative time in the radical group certainly drive the wound infection rate upward. We do not routinely culture typical postop wounds or bile. The wounds are simply opened and packed and hospitalization is delayed perhaps a day, perhaps not at all. So I can't address the issue of whether the bacteria in the bile were the same as the bacteria in the wound.

DR. JOSEPH G. FORTNER (New York, NY): I am very grateful to Dr. Yeo for giving me his paper to review of this very nice study. At first I was surprised to find that his somewhat limited lymphadenectomy was not done en bloc with a primary tumor. Then I remembered that the Halstedian principles have been discredited, so it didn't make any difference. But is it all right with pancreatic cancer, which is nearly all advanced when first diagnosed?

Dr. Yeo and Dr. Cameron and their colleagues found perienteral invasion in 75% of their cases. The incidence of microscopic soft tissue involvement is even greater in some series. Nearly 75% of their patients had positive nodes. Undoubtedly, pancreatic cancer cells were in the lymphatics, capillaries, and fibrous tissues of the peripancreatic region. And cutting across these to do a preliminary pancreaticoduodenectomy before the node dissection carries a very high risk of spreading these cancer cells.

The second problem is the extent of the resection. Twenty patients had positive margins where the specimen was removed from the portal venous system or SMA. Four patients had disease where the pancreatic duct was transected.

My question is: Haven't you proven the need for a valid trial of monoblock resection of the regional lymph nodes with portal vein resection and transection of the pancreas to the left of the portal vein, a regional pancreatectomy, which is the operation that Dr. Warshaw referred to that the Japanese were doing? It is not a staging procedure and needs a mindset which intends to cure, and the game is up if you get into the cancer even just a little bit.

A related question is: Does the hope of possible improved survival of patients who have adjuvant chemoradiation obviate the need for new surgical efforts? Most patients still die after pancreaticoduodenectomy and chemoradiation, so I hope that the surgical attempts will continue.

DR. CHARLES J. YEO (Baltimore, MD): Dr. Fortner, thank you very much for your questions. Much of your early work was the stimulus for us to proceed with this study, in what we believed was a thoughtful, scientific fashion.

Again, the issue of en bloc versus discontinuous resection has been raised. I would just say as a reminder, the pyloric-preserving resection that was done as the standard resection was margin negative by frozen section at the time of the resection. And when we report positive perineural invasion, that is in the specimen, that is not around the SMA. Obviously, this study cannot distinguish between the value of en bloc versus discontinuous resection, since we did all radical operations in two steps, by design. My opinion is that the decrement in survival seen after both types of resection is due to the tumor biology itself, and not the method of resection.

I can only comment that the operation that Dr. Fortner so nicely wrote about in the 1970s, 1980s, and the last publication in 1996, is really a mega-operation. Regional pancreatectomy excising the portal vein, elevating the SMV to restore portal venous continuity, at times resecting arterial

structures, is an operation that even in the best of hands is attended by significantly increased morbidity and mortality. It is our contention that more extensive surgery is probably not the answer for this particular disease. Rather, the answer may come with earlier detection, molecular genetics, and adjuvant trials.

And so the question dealing with adjuvant trials. I would call everyone's attention to the ESPAC-I trial which was recently published in *Lancet* and shows (although there are many critics of that trial) that chemotherapy does prolong survival postpancreatic resection. The issue of postop chemoradiation remains somewhat more controversial. We believe that postop chemoradiation is beneficial, and we continue to pursue such therapies in the adjuvant setting.

DR. J. HANS JEEKEL (Rotterdam, Netherlands): I think we have long waited for this study. I have three quick questions.

One question is: Was the radical operation radical enough? If you look at your data in the group of patients with originally negative margins by frozen biopsy, 10% appeared to be positive. Shouldn't you have extended at that area your resection? And if you would do it again, wouldn't you do a more extended resection at those areas where your pathology specimen showed positive margins?

Second question: You have a difference in delayed gastric emptying, to my surprise. We have just recently completed a prospective randomized study comparing pylorus-preserving versus distal gastrectomy and we didn't find any difference in delayed gastric emptying in a group of 171 patients. So what was your definition of delayed gastric emptying?

Third question: If it is true that the removal of lymph nodes in the retroperitoneal area is not important, then you expect that retroperitoneal metastases are a part of systemic disease. Where did you find your recurrences? How much local recurrence did you find and where?

DR. CHARLES J. YEO (Baltimore, MD): Dr. Jeekel first asks, was the radical resection radical enough? I think the answer really remains to be seen. Our feeling is that this was a radical resection. We harvested 28 lymph nodes in the radical group versus 17 in the standard group. I would remind you that in the previous studies, for example by the Italian group, their radical resection only harvested 20 lymph nodes. In the data from Henne-Bruns from Germany, their radical resection only harvested 24 lymph nodes. So, compared to most of the previous trials we have actually harvested more lymph nodes in this operation than have been previously reported. And I think it is very important to keep Dr. Brennan's issue in mind. There was a wonderful letter to the editor by Pisters et al. in the *World Journal of Surgery* that nicely presented a mathematical model predicting that radical resection would not be the answer for pancreatic cancer.

We defined delayed gastric emptying (DGE) by criteria that we have used for about 8 years now, based on our initial erythromycin data. In brief, DGE requires that the NG tube be in place for 10 days or be reinserted and that the patient fail to progress to a normal diet by postoperative day 10. It is a fairly strict definition. Our findings of 16% versus 6% are actually lower than they have been in the past. One of my theories is that DGE is not just gastric dysmotility, but it is also bile reflux gastritis. Thus, some patients that vomit bile really don't have gastric dysmotility but have bile reflux gastritis.

The site of tumor recurrence issue I can't specifically deal with. We do not have adequate data regarding site of recurrence, since many of our patients develop recurrent disease and never return to Baltimore. We have little in the way of autopsy data; we simply have survival data. I can tell you that, by observation, most patients recur intra-abdominally, locally, or in the liver. Past autopsy data have shown that at demise, most have extensive evidence of tumor dissemination.