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Pancreaticoduodenectomy for Cancer of the Head of the Pancreas

201 Patients

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Objective
This single-institution study examined the outcome after pancreaticoduodenectomy in patients with adenocarcinoma of the head of the pancreas.

Summary of Background Data
In recent years, pancreaticoduodenectomy for adenocarcinoma of the head of the pancreas has been associated with decreased morbidity and mortality and, in some centers, 5-year survival rates in excess of 20%.

Methods
Two hundred one patients with pathologically verified adenocarcinoma of the head of the pancreas undergoing pancreaticoduodenectomy at The Johns Hopkins Hospital between 1970 and 1994 were analyzed (the last 100 resections were performed between March 1991 and April 1994). This is the largest single-institution experience reported to date.

Results
The overall postoperative in-hospital mortality rate was 5%, but has been 0.7% for the last 149 patients. The actuarial 5-year survival for all 201 patients was 21%, with a median survival of 15.5 months. There were 11 5-year survivors. Patients resected with negative margins (curative resections: n = 143) had an actuarial 5-year survival rate of 26%, with a median survival of 18 months, whereas those with positive margins (palliative resections: n = 58) fared significantly worse, with an actuarial 5-year survival rate of 8% and a median survival of 10 months ($p < 0.0001$). Survival has improved significantly from decade to decade ($p < 0.002$), with the 3-year actuarial survival of 14% in the 1970s, 21% in the 1980s, and 36% in the 1990s. Factors significantly favoring long-term survival by univariate analyses included tumor diameter < 3 cm, negative nodal status, diploid tumor DNA content, tumor S phase fraction < 18%, pylorus-preserving resection, <800 mL intraoperative blood loss, <2 units of blood transfused, negative resection margins, and use of postoperative adjuvant chemotherapy and radiation therapy. Multivariate analyses indicated the strongest predictors of long-term survival were diploid tumor DNA content, tumor diameter < 3 cm, negative nodal status, negative resection margins, and decade of resection.

Conclusions

The survival of patients with pancreatic adenocarcinoma treated by pancreaticoduodenectomy is improving. Aspects of tumor biology, such as DNA content, tumor diameter, nodal status and margin status, are the strongest predictors of outcome.

Pancreatic cancer is the fifth leading cause of cancer death in the United States. Recent data from the National Cancer Data Base indicate that pancreaticoduodenectomy was the most commonly performed cancer-directed operation, although it was used in only 9% of patients.[1] In this large national database, the 5-year survival rate for patients treated by pancreaticoduodenectomy in 1985 was 3%. In contrast to the national figures, specialized centers have reported decreasing mortality rates and improving survival rates after pancreaticoduodenectomy for pancreatic cancer.[2-5] Many factors are likely to be responsible for the improving safety of pancreaticoduodenal resection, including improvements in intensive and critical care, increased surgical experience with decreases in operative time and blood loss,[2] and regionalization of patient care to specialized centers of excellence.[6]

In addition to the improved safety of pancreaticoduodenal resection, many centers have reported improved survival of patients with adenocarcinoma of the head of the pancreas after the Whipple procedure, with 5-year survival rates of approximately 20%.[7-10] The reasons for the improved 5-year survival rates are not clearly understood and are not fully explained by the decrease in procedure-related mortality. Several studies have analyzed the determinants of long-term survival in patients with resected pancreatic cancer, in an effort to explain the improved survival rates. Factors found to be associated with a favorable prognosis have included diploid tumor DNA content, small tumor size, absence of lymph node metastases, negative resection margins and absence of perioperative blood transfusion, as well as molecular genetic information, such as a low fractional allelic loss pattern and absence of microdeletions in the p53 tumor suppressor gene.[7,9-14]

To determine the factors favoring long-term survival after pancreaticoduodenectomy, the current study analyzed all patients treated by pancreaticoduodenal resection for adenocarcinoma of the head of the pancreas at The Johns Hopkins Hospital from 1970 to April 1994.

METHODS

Between April 1970 and April 1994, 208 patients underwent pancreaticoduodenectomy for adenocarcinoma of the head of the pancreas at The Johns Hopkins Hospital. All resections were standard pancreaticoduodenal resections, with no effort made to perform a radical retroperitoneal lymph node dissection. The bias at this institution has been to perform partial pancreatectomy whenever possible, leaving the pancreatic body and tail in place and drained to either the jejunum or the stomach. Total pancreatectomy was performed for tumors that extended from the head of the gland, across the neck, and into the body of the pancreas. In recent years the pylorus-preserving modification of the classic pancreaticoduodenectomy has been performed preferentially. Distal gastrectomy was reserved for tumor involvement of the distal stomach or first portion of the duodenum. In ten patients with tumor involvement of the superior mesenteric or portal veins, pancreaticoduodenectomy was combined with resections of the involved vein, and venous continuity was restored by primary anastomosis.

All of the histologic sections of the cancers from all patients were reviewed, and the following three previously stated criteria[11] were used for inclusion in the study: 1) tumor origin in the head, neck, or uncinate process of the pancreas, 2) malignant histology, and 3) demonstration of both epithelial and glandular differentiation. The first criterion could be fulfilled in one of two ways—the neoplasm contained an *in situ* component in the pancreatic ducts or the bulk of the neoplasm was present within the head of the pancreas. Cases in which an *in situ* component was identified solely within the bile duct or duodenum were excluded. Occasional cases in which there was apparent *in situ* carcinoma in both the pancreatic and bile ducts were included only if the tumor was clearly centered in the pancreatic parenchyma rather than around the bile duct. To fulfill the second criterion, that of a malignant histology, the neoplasm had to have stromal, perineural, or vascular/lymphatic invasion. To fulfill the third criterion, the neoplasm had to show evidence of epithelial differentiation and lumen formation by light microscopy. In cases in which the carcinoma was

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Table 1. FACTORS INFLUENCING SURVIVAL AFTER PANCREATICODUODENECTOMY: PATIENTS AND DEMOGRAPHICS

Parameter (n)	Median Survival (mo)	5-Year Survival (%)	Log-Rank p Value
Entire series (201)	15.5	21	—
Age (years; median = 65)			
≤65 (108)	17.0	25	
>65 (93)	13.5	14	0.22
Gender			
Male (108)	15.0	23	
Female (93)	15.5	18	0.64
Race			
White (170)	17.0	24	
Black (27)	9.0	10	0.13
Other (4)	N/A	N/A	
Follow-up			
>5 years (74)	11.0	15	
<5 years (127)	17.5	30	0.02

	Median Survival (mo)	1-Year Survival %	3-Year Survival %	5-Year Survival %	
Decade					
1970s (23)	7.5	32	14	9	
1980s (63)	14.0	53	21	15	0.002
1990s (115)	17.5	64	36	N/A	

N/A = Not available.

poorly differentiated, the glandular differentiation was confirmed with the mucicarmine stain. Pancreatic tumors specifically excluded were cystadenocarcinoma, cystadenoma, solid and papillary neoplasms (Hamoudi tumors), and neuroendocrine tumors.

The following factors were analyzed: 1) patient demographics; 2) intraoperative factors, such as type of resection, blood loss, blood transfusion, and operative time; 3) tumor characteristics, including diameter, histologic grade, lymph node status, margin status, DNA content, and S-phase fraction; and 4) postoperative use of adjuvant therapy. The primary outcome variable analyzed was survival. Follow-up was performed by office records, telephone contact, or letter. Tumor DNA content and calculation of S-phase fraction were performed by image cytometry on Feulgen-stained nuclei, as previously described in detail.[11] Survival was analyzed by the method of Kaplan and Meier, which expresses survival by cause-specific tumor mortality, with other observations censored.[15] Differences in survival among these subsets were compared with the log-rank test. Multivariate analysis was performed with the Cox proportional hazards model.[16]

RESULTS

Of the 208 patients undergoing pancreaticoduodenal resection for adenocarcinoma of the head, neck, or uncinate process of the pancreas, accurate survival and outcome data were available in 201; 7 patients had incomplete outcome data and were excluded.

Patients/Demographics (Table 1)

For the group of 201 patients comprising the study population, the postoperative in-hospital mortality rate was 5% (17% for the first 52 patients and 0.7% for the last 149 patients) and the median follow-up was 12 months (range 1–181 months.). The mean age was 62.8 ± 0.7 years, and the median age was 65 years. One hundred eight of the patients were men, and 93 of the patients were women. One hundred seventy patients were white and 27 were black. There were no significant differences in survival based on age, gender, or race.

Survival (Table 1)

The actuarial 1-, 3-, and 5-year survival rates for all 201 patients were 57%, 26%, and 21%, respectively, with a median survival of 15.5 months (Fig. 1). There were 11 5-year survivors, 7 6-year survivors, 3 7-year survivors, and 1 15-year survivor. Five of the 11 5-year survivors remain alive, and 6 have died. Considering only those 74 patients with more than 5 years of follow-up, the 5-year survival rate was 15%, with a median survival of 11 months. In contrast, considering those 127 patients with

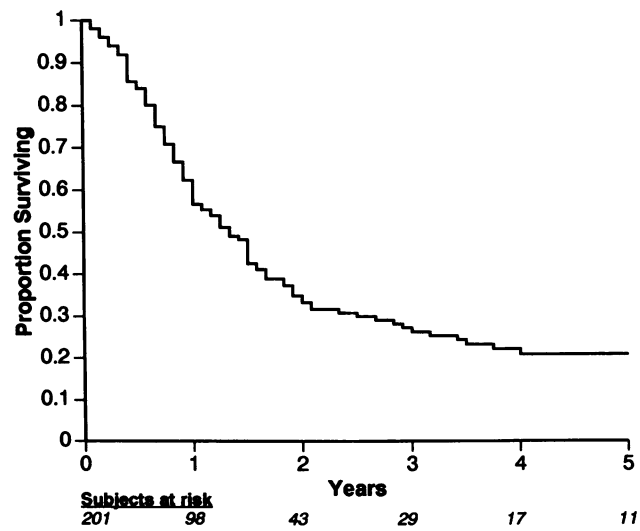

Figure 1. The actuarial survival curve (Kaplan-Meier) for 201 patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma.

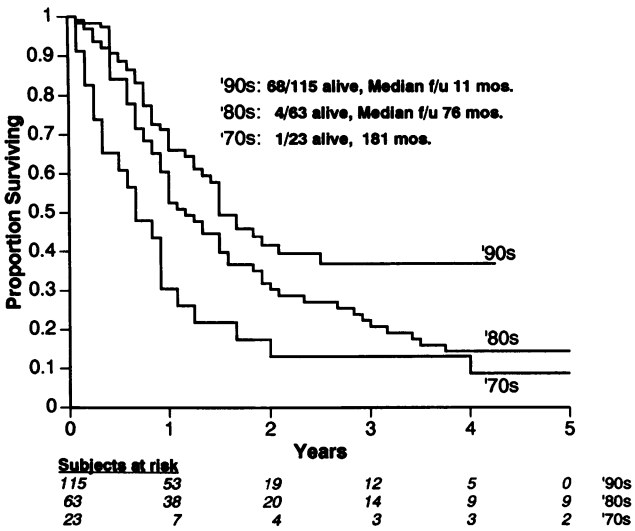

Figure 2. The actuarial survival curves for 201 patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma by decade. A significant improvement ($p = 0.002$) in survival has occurred from the 1970s ($n = 23$), to the 1980s ($n = 63$), to the 1990s ($n = 115$). Median follow-up (f/u) is given for survivors.

less than 5 years of follow-up, the actuarial 5-year survival rate was 30%, with a median survival of 17.5 months. By univariate analysis, a significant improvement in survival has been observed from the decade of the 1970s, to the decade of the 1980s, to the decade of the 1990s ($p = 0.002$). Patients resected in the 1970s had a median survival of 7.5 months and a 3-year survival of 14%; patients resected in the 1980s had a median survival of 14 months and a 3-year survival of 21%; and patients undergoing resection in the 1990s had a median survival of 17.5 months and a 3-year survival of 36% (Fig. 2).

Intraoperative Factors (Table 2)

The type of pancreatectomy performed, partial *versus* total, did not influence the outcome. Of the 181 patients treated by partial pancreatectomy, 165 had the pancreatic remnant drained via pancreaticojejunostomy and 16 had the pancreatic remnant drained via pancreaticogastrostomy. The patients drained via pancreaticogastrostomy all have been resected within the past 2 years, and their survival at short-term follow-up is identical to those patients reconstructed via pancreaticojejunostomy during the same time period. The pylorus-preserving modification of the Whipple procedure was used in 134 patients who underwent partial pancreatectomies, whereas 47 patients underwent distal gastric resection in combination with partial pancreatectomies. Univariate analysis revealed a significantly improved outcome in patients treated via pylorus preservation.

The median intraoperative blood loss for the entire cohort was 800 mL, whereas the median number of units of packed red cells transfused intraoperatively was zero (mean 1.7 ± 0.2 units). Patients with an estimated blood loss of less than 800 mL had significantly better outcomes by univariate analysis compared with those patients with an estimated blood loss equal to or greater than 800 mL ($p = 0.03$). A similar correlation was found between red blood cell transfusions and outcome, with patients receiving less than or equal to 2 units of red blood cells having significantly better outcomes by univariate analysis ($p = 0.002$) compared with those receiving 3 or more units of red blood cells. The median operative time for the entire cohort was 7 hours, with a mean of 7.25 ± 0.12 hours. Operative time was not a significant predictor of survival by univariate analysis ($p = 0.07$). By multivariate analysis, none of these intraoperative factors proved to be independently correlated with patient outcome.

Tumor Characteristics (Table 3)

The diameter of the tumor was an important predictor of survival by univariate analysis (Fig. 3). The median tumor diameter in this series, as determined by assess-

Table 2. FACTORS INFLUENCING OUTCOME AFTER PANCREATICODUODENECTOMY: INTRAOPERATIVE FACTORS

Parameter (n)	Median Survival (mo)	5-Year Survival (%)	Log-rank p Value
Type of resection			
Partial pancreatectomy (181)	16.0	20	0.85
Total pancreatectomy (20)	10.0	30	
Pylorus preserving partial (134)	17.5	24	0.02
Classic partial (47)	12.0	9	
All pylorus preserving (144)	17.5	25	0.009
All classic (57)	10.5	13	
Blood loss (median = 800 mL)			
<800 mL (98)	18.0	27	0.03
≥800 mL (96)	11.5	17	
Packed red cell transfusions			
≤2 units (146)	18.0	26	0.002
>2 units (48)	10.5	10	
Operative time (median = 7 hrs)			
<7 hrs (101)	17.5	30	0.07
≥7 hrs (91)	14.5	10	

Table 3. FACTORS INFLUENCING OUTCOME AFTER PANCREATICODUODENECTOMY: TUMOR CHARACTERISTICS

Parameter (n)	Median Survival (mo.)	5-Year Survival (%)	Log-rank p Value
Diameter (median = 3 cm)			
<3 cm (91)	21.0	28	0.005
≥3 cm (107)	11.5	15	
≤2 cm (58)	23.0	24	0.02
>2 cm (140)	11.5	20	
Histologic grade			
Well differentiated (7)	34.0	48	0.15
Moderately differentiated (156)	15.0	21	
Poorly differentiated (38)	10.5	17	
Lymph node status			
Negative (57)	28.0	36	0.0018
Positive (144)	13.0	14	
Negative (57)	28.0	36	0.004
1-3 (101)	13.5	16	
≥4 (43)	13.0	11	
Margin status			
Negative (143)	18.0	26	0.0001
Positive (58)	10.0	8	
DNA content (ploidy)			
Diploid (51)	24.0	39	0.0002
Aneuploid (68)	11.5	8	
Percent S phase (median = 18)			
≤18 (44)	22.0	30	0.02
>18 (32)	11.5	13	

ment of the pathology specimen, was 3 cm. Patients with tumors less than 3 cm in diameter had significantly longer median survival and 5-year survival (21 months and 28%) compared with patients with tumors 3 cm or more in diameter (11.5 months and 15%; p = 0.005). Further analysis of the tumor diameter data (Table 3) using 2 cm as the breakpoint was performed because some authors have subcategorized pancreatic cancers as "small" if they are ≤2 cm in diameter.[17]

The histologic grade of the tumor was not a significant predictor of outcome by univariate analysis.

The status of the lymph nodes in the resected specimen proved to be a highly significant factor predicting survival (Fig. 4). Lymph nodes were considered positive if any resected nodes contained adenocarcinoma. No distinction was made between those nodes discontinuous with the primary tumor and those infiltrated by direct extension. Lymph nodes were considered negative if all resected lymph nodes were histologically free of tumor.

The status of the resection margins proved to be another highly significant factor, predicting survival by univariate analysis. Margins were considered positive if any of the following had infiltrating adenocarcinoma present at careful microscopic analysis of the resected specimen: pancreatic neck margin, uncinate process margin, retroperitoneal soft-tissue margin, duodenal margin, or bile duct margin. In addition, patients with tumor involvement of the hepatic artery, superior mesenteric vein, or portal vein were considered to have positive margins, even if portions of the vessel were resected. Margins were not considered positive if 1) the initial frozen section pancreatic neck, bile duct, or duodenum margin was positive, but subsequent re-resection of pancreatic parenchyma, bile duct, or duodenum yielded a negative final margin or 2) there was evidence of extrapancreatic soft-tissue extension, but the actual resection margin was negative. Patients resected with negative margins (n = 143) had a median survival of 18 months and a 5-year survival of 26%, whereas those resected with positive margins (n = 58) fared significantly worse (p = 0.0001), with a median survival of 10 months and a 5-year survival of 8%. The subgroup of patients undergoing pancreaticoduodenectomy with both negative lymph nodes and negative resection margins (n = 45) had a median survival of 32 months and a 5-year survival of 40%, indicating a particularly favorable outcome group.

Forty-six patients had primary tumor involvement of the superior mesenteric vein/portal vein region, usually

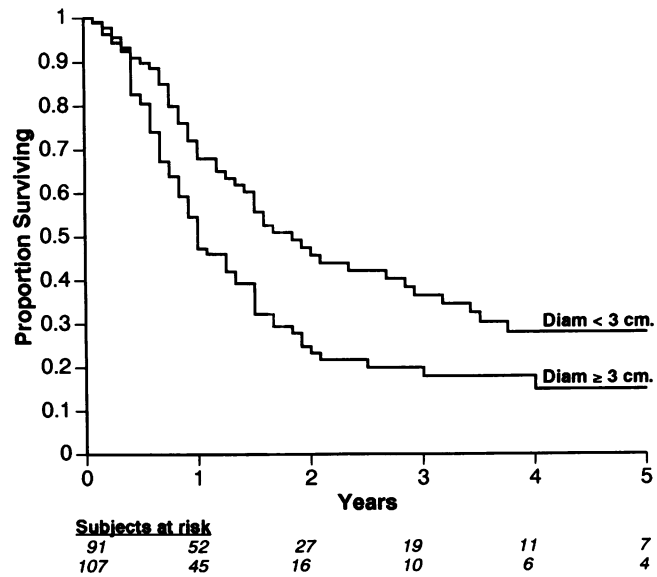

Figure 3. The actuarial survival curves for patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma, comparing patients with tumors < 3 cm in diameter (n = 91) to patients with tumors ≥ 3 cm (n = 107). Survival is significantly better for patients with tumor diameter < 3 cm (p = 0.005).

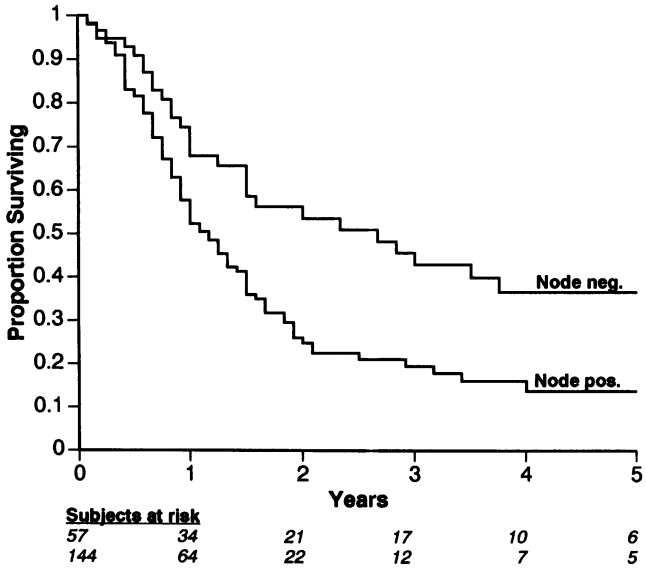

Figure 4. The actuarial survival curves for patients undergoing pancreaticoduodenectomy for pancreatic carcinoma, comparing patients with no lymph node metastases (n = 57) to patients with positive lymph node metastases (n = 144). Survival is significantly better for patients with no lymph node metastases (p = 0.0018).

extending from the uncinate process or neck of the pancreas. Of these 46 patients, 10 underwent resection of a portion of the superior mesenteric vein or portal vein in an effort to resect all tumor, and 36 had no vein resection. The outcomes in these two groups were similar (p = 0.19), with no improvement in survival observed in the group undergoing vein resection (3-year survival = 13%) compared with the group without vein resection (3-year survival = 35%).

The DNA content of the pancreatic cancer cells, as determined by image cytometry, proved to be a highly significant determinant of survival. Of the 119 patients whose tumors were analyzed for DNA content, 51 (43%) had diploid tumors and 68 (57%) had aneuploid tumors. Patients with diploid tumors had a median survival of 24 months and a 5-year survival of 39% (Fig. 5), significantly better than the median survival of 11.5 months and 5-year survival of 8% observed in patients with aneuploid tumors (p = 0.0002). The proportion of pancreatic cancer cells in the synthesis (S) phase of the cell cycle (percent S phase) was calculated in 76 patients, for a median value of 18%. Patients with low percent S phase (≤18) had a median survival of 22 months and a 30% 5-year survival, whereas patients with high percent S phase had a significantly lower median survival of 11.5 months and 5-year survival of 13% (p = 0.02). Covariate analysis indicated that DNA ploidy (diploid *vs.* aneuploid) was a powerful independent prognostic variable, with percent S phase being a codependent variable strongly linked to ploidy, and not predictive alone.

Adjuvant Chemoradiation Therapy

Before October 1991, the treatment of patients with pancreatic cancer using adjuvant combined modality chemoradiation therapy after pancreaticoduodenectomy was not standard at our institution, and only a minority of patients received such adjuvant therapy. Since October 1991, a multidisciplinary team of surgeons, pathologists, medical oncologists, and radiation therapists has evaluated all patients with adenocarcinoma of the pancreas postpancreaticoduodenectomy and recommended adjuvant combined modality chemoradiation therapy, based on data from the Gastrointestinal Study Group, which indicate that such therapy improves survival.[18,19] The adjuvant therapy used in these patients combines external beam radiotherapy to the tumor bed and adjacent tissues (>45 Gy) delivered over the course of 5 to 6 weeks, with 5—fluorouracil-based chemotherapy (given weekly by intravenous bolus at a dose of 350–500 mg/m^2 or via continuous infusion at a dose of 200 mg/m^2) given concurrently during the radiotherapy and for 4 months after the conclusion of the radiotherapy. Details of the combined modality adjuvant therapy protocols have been reported previously.[14] Of 78 patients evaluated since October 1991, 56 patients elected adjuvant therapy and 22 declined such therapy. The two groups were not different (Table 4) with respect to age,

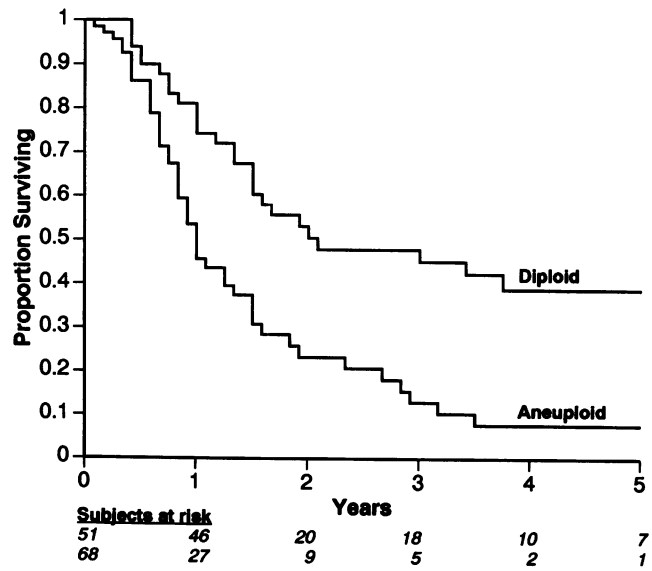

Figure 5. The actuarial survival curves for patients undergoing pancreaticoduodenectomy for pancreatic carcinoma, comparing patients with diploid tumors (n = 51) to patients with aneuploid tumors (n = 68). Survival is significantly better for patients with diploid tumors (p = 0.0002).

Table 4. COMPARISON OF 78 PATIENTS FOLLOWED PROSPECTIVELY SINCE OCTOBER 1991, BASED ON TREATMENT *VERSUS* NO TREATMENT WITH POSTOPERATIVE ADJUVANT COMBINED MODALITY CHEMORADIATION THERAPY

	Treatment (n = 56)	No Treatment (n = 22)
Mean tumor diameter (cm)	3.2	2.9
Positive lymph nodes	73%	73%
Positive resection margins	23%	29%
Mean red cells transfused (units)	0.6	1.4
Percent aneuploid DNA content	59%	22%
Median survival (mo)	20	12
Actuarial 2-yr survival	35%	0%

The median survival and 2-yr survival data are significantly different (p = 0.001).

gender, race, tumor diameter, lymph node status, or margin status. The treatment group had a higher proportion of unfavorable aneuploid tumors. The early results demonstrate a significant outcome difference between the two groups (p = 0.001), with a median survival of 20 months and an actuarial 2-year survival of 35% in the group receiving adjuvant therapy, compared with a median survival of 12 months and an actuarial 2-year survival of 0% in the group receiving no therapy (Fig. 6).

Multivariate Analysis

A multivariate survival analysis was performed to determine which univariate prognostic relationships were independent predictors and which were probably the result of confounding. These results are shown in Table 5. Analyses of two cohorts were done—the 201 subjects in the full cohort, and a subcohort of 119 subjects who had ploidy data. In the full cohort, in which 128 deaths occurred, three pathologic variables were identified as being prognostically important: presence of positive nodes, positive margins, and tumor diameter ≥ 3 cm. All had approximately equal effects on prognosis, with relative risks of approximately 1.5. No intraoperative variables had substantive prognostic value, indicating that their univariate relationship to prognosis was the result of their relationships to tumor size, node positivity, or the likelihood of incomplete resection. In the subcohort of 119 subjects (76 deaths), ploidy had a much stronger prognostic import that any other variable, measured both by the risk ratio (2.7) and statistical significance (p = 0.0001). All of the factors found to be important in the full cohort remained important in this subgroup analysis, although the statistical significance of positive margins was weakened (p = 0.09).

The decade in which surgery was performed was an independent predictor in both cohorts with a relative risk of 0.70 per decade (p = 0.005) in the full cohort, and a relative risk of 0.58 per decade (p = 0.05) in the subcohort (n = 119). However, those results must be considered preliminary because follow-up of subjects treated in the 1990s is limited; of the 115 subjects operated on in the 1990s, 68 (59%) are still alive, with a median follow-up of only 11 months. In addition, with only 23 subjects seen in the 1970s, comparisons to that era are complicated by the limited ability to adjust for confounders. Nonetheless, both by univariate and multivariate analyses, survival of patients with pancreatic cancer appears to be improving over time. This observation needs confirmation when further follow-up information is available from recently treated patients.

DISCUSSION

During the 1960s and 1970s, some authors suggested that pancreaticoduodenectomy for pancreatic cancer be abandoned because of high complication and mortality rates and low survival rates.[20,21] In recent years, the surgical treatment of adenocarcinoma of the head, neck, or uncinate process of the pancreas via pancreaticoduodenectomy has been associated with falling postoperative

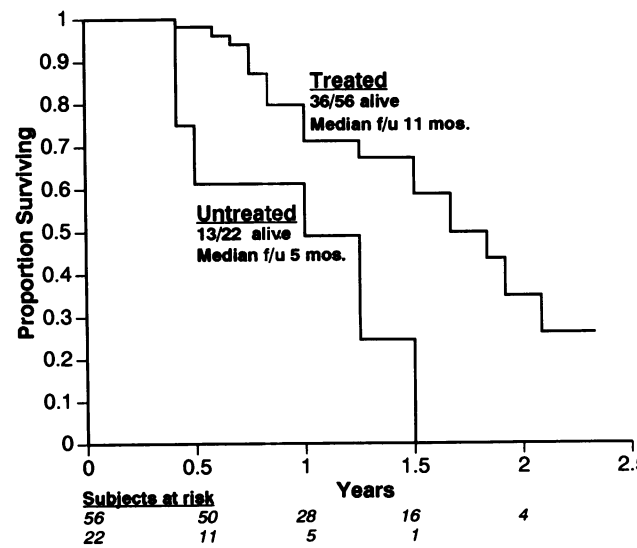

Figure 6. The actuarial survival curves for patients undergoing pancreaticoduodenectomy for pancreatic carcinoma since October 1991, comparing patients receiving combined modality adjuvant therapy (n = 56) with patients receiving no adjuvant therapy (n = 22). Survival is significantly better for patients receiving adjuvant therapy (p = 0.001). Median follow-up (f/u) is given for survivors.

Table 5. MULTIVARIATE ANALYSIS

Parameter	Relative Risk	95% CI	p Value
Full cohort (n = 201)			
Positive nodes	1.6	1.1–2.5	0.02
Positive margins	1.7	1.1–2.5	0.01
Diameter ≥3 cm	1.4	1.0–2.0	0.06
Positive nodes	1.6	1.1–2.6	0.02
Positive margins	1.4	1.0–2.0	0.08
Diameter ≥3 cm	1.5	1.0–2.3	0.05
Decade (per 10 yr)	0.70	0.54–0.90	0.005
Subcohort with tumor DNA content (n = 119)			
Positive nodes	1.7	1.0–2.9	0.04
Positive margins	1.6	0.9–2.6	0.09
Diameter ≥3 cm	2.2	1.3–3.7	0.003
Aneuploidy	2.7	1.6–4.5	0.0001
Positive nodes	1.5	0.9–2.6	0.14
Positive margins	1.5	0.9–2.5	0.13
Diameter ≥3 cm	2.3	1.4–3.9	0.001
Aneuploidy	2.5	1.5–4.2	0.0003
Decade (per 10 yr)	0.58	0.33–0.99	0.05

CI = confidence interval.

morbidity and mortality rates and improving long-term survival.[2–5,22,23] The results from the current single-institution experience demonstrate an actuarial 5-year survival rate of 21% for all 201 patients undergoing pancreaticoduodenal resection for adenocarcinoma of the pancreas. Importantly, the actuarial 5-year survival is improved for patients resected with tumors less than 3 cm in diameter (28%), negative margins (26%), negative nodal involvement (36%), or diploid tumor DNA content (39%). Multivariate analysis has indicated that the parameters that serve as the strongest independent predictors of favorable outcome are tumor DNA content and diameter, status of resected lymph nodes, margin status, and decade of resection.

A stepwise improvement in outcome has been observed in our series from the 1970s through the 1980s, up to the 1990s. An analysis of some of the most important univariate predictors of outcome is given by decade in Table 6. The comparisons are confounded somewhat by the small number of patients and high in-hospital mortality in the 1970s, the short length of follow-up in the 1990s, and the increased use of what is now considered standard postoperative adjuvant therapy in the 1990s.[18,19] Nonetheless, there appears to be a demonstrable significant improvement in overall outcome now, compared with the outcomes observed in the 1970s and 1980s.

The outcomes reported in the current series represent results obtained using standard pancreaticoduodenal resection, without radical (extended) retroperitoneal lymph node dissection. Although some groups have advocated such a radical procedure,[24–26] the accumulated data have failed to demonstrate a survival advantage for radical resection.[27] For example, Satake et al. recently have reported on 185 patients undergoing resection for pancreatic cancers less than 2 cm in diameter from 59 institutions in Japan.[28] There was no difference in overall survival between the radical and standard resection groups, with a 5-year survival of 27% observed in each. Similar results have been reported by Geer and Brennan, with no differences noted in median survival between patients treated by radical *versus* standard resection.[9] We continue to maintain that standard pancreaticoduodenectomy is the appropriate surgical procedure for patients with resectable ductal adenocarcinoma of the head, neck, or uncinate process of the pancreas.

The current data support the performance of pylorus-preserving resections in the treatment of cancer of the pancreatic head. Although pylorus preservation has gained favor in recent years, based on results that show no decrement in survival when comparing classic (partial gastrectomy) to pylorus-preserving pancreaticoduodenectomy,[7,29,30] some groups have advocated against pylorus preservation because of the possibility of microscopic spread of tumor into the proximal duodenum[31] and because pylorus preservation does not allow lymph node dissection in the peripyloric and perigastric groups.[32] Our current data (Table 2) indicate that a significant improvement in survival was observed by univariate analysis when comparing pylorus-sparing to classic (distal gastrectomy) resections. These data appear to favor the pylorus-preserving resection. In fact, multivariate analysis indicates that pylorus preservation is not an independent prognostic parameter, suggesting that the

Table 6. FACTORS INVOLVED IN OUTCOME BY DECADE

	1970s (n = 23)	1980s (n = 63)	1990s (n = 115)
Mean tumor diameter (cm)	3.1	3.0	3.2
Positive lymph nodes	83%	70%	70%
Positive resection margins	43%	29%	26%
Mean red cells transfused (units)	5.6	2.0	0.9
Adjuvant therapy*	0%	<25%	>65%
In-hospital mortality (%)	30%	3%	0.9%
Median survival (mo)	7.5	14.0	17.5

* Refers to percentage of patients receiving postoperative 5-FU based chemotherapy plus ≥40 Gy external beam radiotherapy.

statistical improvement in outcome seen with the univariate analysis is a reflection of the increased popularity of pylorus preservation over the last 10 years, largely skewing the data to a more favorable subgroup analysis. We continue to favor pylorus-preserving pancreaticoduodenectomy because it shortens the operative time, retains the entire stomach as a reservoir, and maintains a more normal gastrointestinal hormone milieu.[33,34]

The tumor DNA content results add to prior reports on the importance of image cytometric DNA measurements as a prognostic factor in pancreatic adenocarcinoma.[11,35,36] In our series, patients undergoing resection with diploid tumors had a median survival of 24 months and an actuarial survival of 39%, significantly better ($p = 0.0002$) than the 11.5-month median survival and 8% actuarial 5-year survival seen with aneuploid tumors. Additionally, tumor DNA content was the most powerful prognostic parameter favoring long-term survival in our multivariate analysis (Table 5). Importantly, these data have been obtained using image cytometry on Feulgen-stained, paraffin-embedded nuclei, not by the use of flow cytometry. The inaccuracies involved with flow cytometry have been reported previously,[35] as has the lack of correlation of flow cytometric data with patient outcome.[37]

The appropriate place of portal vein or superior mesenteric vein resection in the management of patients with cancer of the head of pancreas cannot be fully answered by the available data. Although several authors have supported resection of these venous structures when locally infiltrated by tumor,[24,38,39] such a venous resection, and the requisite venous reconstruction, can add considerably to the morbidity and mortality of pancreaticoduodenectomy. Our data comparing 10 patients undergoing such venous resection with 36 patients with tumor involvement near the portal or superior mesenteric veins but without venous resection indicate that no survival advantage was conferred by venous resection in this setting. Although these subgroups are small and not entirely identical, and treatment was not randomly assigned, these data suggest that venous resection may not favorably influence outcome.

Although it appears that a number of factors are responsible for the improvement in survival for resected pancreatic cancer (reduced in-hospital mortality rates, lower proportion of patients resected with positive lymph nodes, and positive resection margins), one factor that deserves special mention is the increased use of adjuvant combined modality chemoradiation therapy. The initial reports from the Gastrointestinal Tumor Study Group were published in 1985 and 1987,[18,19] reporting an improved survival in patients undergoing pancreaticoduodenectomy for pancreatic cancer when treated postoperatively with fluorouracil-based chemotherapy and external beam radiotherapy. Since these reports, the percentage of our patients receiving such adjuvant therapy has increased, with 56 of our last 78 patients who were observed prospectively since October 1991 choosing to receive therapy. Comparisons between the adjuvant treatment *versus* no treatment groups (Table 4) indicate no significant differences between the two groups in the important parameters known to determine prognosis (tumor diameter, nodal involvement, margin status, and DNA content), and the groups also were similar with respect to age, gender, and Karnovsky performance status. The majority of patients who chose to receive no therapy were candidates for therapy, but chose to receive no therapy based on personal preference or difficult access to treatment facilities. There is a significantly longer median survival and an improved actuarial 2-year survival in the group choosing to receive adjuvant therapy ($p = 0.001$). Although the groups are nonrandomized, these data add further support to the observation that the administration of postoperative adjuvant combined modality chemoradiation therapy improves survival in patients undergoing pancreaticoduodenectomy for adenocarcinoma of the head of the pancreas. Our data allow no conclusions regarding the use of neoadjuvant chemoradiation therapy[40,41] or preoperative and intraoperative radiotherapy[42,43] because none of these techniques have been used in our patient population.

We have previously reported, from a smaller cohort of 81 patients, that the number of units of red cells transfused perioperatively was an independent factor influencing long-term survival.[7] This relationship linking perioperative blood transfusion to a poor prognosis has been reported for other cancers, such as colon and breast cancer,[44,45] and has been speculated to involve transfusion-induced immunosuppression, which may put patients receiving blood at greater risk for tumor dissemination and growth.[46] The present analysis has increased the size of our evaluable cohort to 201, added analyses of such important prognostic features as tumor DNA content and margin status, and re-evaluated the role of blood transfusions and other intraoperative factors, such as type of resection, estimated blood loss, and operative time (Table 2). Although univariate analysis of the current data indicate that type of resection (pylorus-preserving *vs.* classic), estimated blood loss, and blood transfusion all are significant by univariate analysis; all these factors fail to achieve prognostic significance when included in our multivariate analysis.

This large series from a single institution provides for cautious optimism in the treatment of pancreatic adenocarcinoma. There appears to be an overall improvement in patient survival in recent decades, associated with but not fully explained by the increasing safety of pancreaticoduo-

denal resection. Factors that appear to be the most important predictors of long-term survival include diploid tumor DNA content, small tumor size, absence of lymph node metastases, and resection with negative resection margins. The increasing use of postoperative combined modality chemoradiation therapy appears to be another factor favoring long-term survival. The development of more promising adjuvant therapies, such as strategies combining chemoradiation with immunotherapy, may further enhance survival. Additionally, developments in the field of molecular genetics hold promise for the earlier detection of pancreatic carcinogenesis and its genetic alterations,[12,13,47] using gene-based diagnostic modalities on easily accessible specimens such as stool,[48] duodenal juice, or blood.

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Discussion

DR. R. SCOTT JONES (Charlottesville, Virginia): President McDonald, Secretary Copeland, thank you very much for the privilege of the floor. The discussion of this presentation should be fairly brief, I think. This represents probably the standard that we should look to for management of patients with this dread disease. I don't know of a larger or more effectively managed or carefully evaluated population of patients ever reported. My first recommendation to the membership about this presentation is that we all listen very carefully.

I think this represents focused attention of a well-organized group of experts. The data speak to us clearly—decreasing mortality, decreasing blood transfusion, decreasing length of operation, decreasing hospital stay. And if there have been any debates or reservations about pancreaticoduodenectomy as a treatment for carcinoma of the pancreas, this should basically put them to rest, with certain reservations.

Obviously, one reservation is that none of the rest of us in this room have this same level of experience with this disease. But, nonetheless, this is the standard we should seek.

I can't really ask a lot of questions about the survival or the technique or the results. That's all been presented very clearly. I would ask the authors to tell us how they approach the patient with recurrent disease.

Of this group of patients, undoubtedly, many will recur because they are not all cured. And so what is your approach to recurrence or progression?

Many of your patients obviously have had the Whipple operation, and they have had radiation therapy already—some have and some haven't. You might break that up. But what are the strategies that are available to us and to you for the detection and management of locally recurrent disease and, if you have time, distant disease as well?

The other comment I would make is that probably resection represents the best palliation available. And I would like for you to comment on that, if you would.

And if there is time left after the other discussants have spoken, I would appreciate if you would comment on the approach to the patient who may not be operable or, I should say, may not be resectable. We have an array of techniques that are available presently to relieve jaundice and some of the other consequences of cancer of the head of the pancreas—endoscopic stents, percutaneous stents, operative biliary bypass. And I would be particularly interested in hearing your thoughts about what you believe to be the best techniques of palliation.

I'd like to close my comments by thanking the Society for the privilege of the floor, but also, again, acknowledging the excellence of this paper. Thank you very much for your informing us about this.

DR. EDWARD L. BRADLEY III (Buffalo, New York): Dr. McDonald, Dr. Copeland, Ladies and Gentlemen, good morning.

I think we are all indebted to Dr. Cameron and the Hopkins group for the prodigious effort to collect this kind of data. This is the finest paper it has ever been my privilege to read on pancreatic adenocarcinoma, and I commend it to your attention when it appears in print.

There are so many things that one can discuss in this paper. I choose to pick just three of the many things that we could speak about.

The first point is that the strongest predictors of survivorship in these patients are a diploid DNA content, once again suggesting that good genes assist all forms of therapy—negative nodes, negative margins, and a size less than 3 cm.

Under this set of conditions, if a patient had these factors, the overall 5-year survival rate was 40%. This, once again, emphasizes the necessity for early diagnosis in this malignancy and, I believe, probably approaches the maximum that we will be able to do in the treatment of the type of pancreatic adenocarcinomas that we see currently.

The second point that I think deserves emphasis is the data that were generated by the adjuvant chemoradiation therapy. This emphasizes that the original data from the gastrointestinal tumor study group were, in fact, correct—that adjunctive therapy for these patients is extremely important. For those of you who may be seeing these types of patients without adding adjunctive therapy, I think that must now be reconsidered on the basis of these data.

My first question to the authors is: While I believe you have very clearly demonstrated the efficacy of chemoradiation therapy in operated patients, could you share with us whether you have any information on the group of patients that you did not