Experience with 647 Consecutive Tumors of the Duodenum, Ampulla, Head of the Pancreas, and Distal Common Bile Duct

FABRIZIO MICHELASSI, M.D., F.A.C.S.,* FRANCESCA ERROI, M.D.,* PETER J. DAWSON, M.D., F.R.C.PATH.,† ANDREA PIETRABISSA, M.D.,* SEIICHI NODA,* MARK HANDCOCK,‡ and GEORGE E. BLOCK, M.D., F.A.C.S.*

From the Departments of Surgery, Pathology,† and Statistics,‡ University of Chicago, Chicago, Illinois*

Between 1946 and 1987, 647 patients with periampullary tumors were diagnosed at the University of Chicago Medical Center. These included 549 tumors located in the head of the pancreas, 40 in the distal common bile duct, 29 in the duodenum, and 29 at the ampulla of Vater. Ninety-eight per cent of all tumors were adenocarcinoma, with 93% of the remaining being duodenal carcinoid or sarcoma. Operability rate ranged from 81% to 97%, according to the tumor location and histologic type. A combination of laparotomy, biopsy, and bypass was performed in 433 patients and only one survived 5 years (0.2%). Resectability rate ranged from 16.5% for pancreatic adenocarcinoma to 89.3% for ampullary tumors. Of the 133 resections, 80 were pancreatoduodenectomies, 29 total pancreatectomies, 7 duodenectomies, 2 gastrectomies, 8 common bile duct resections, and 7 local excisions. Overall 19% of patients who underwent radical resection died in the immediate postoperative period, although mortality has decreased to 5% since 1981. Mortality was 20% after a standard pancreatoduodenectomy and 24.1% after a total pancreatectomy. Five-year actuarial survival rates, including perioperative deaths, were 8.8%, 20%, and 32% for pancreatic, duodenal, and ampullary adenocarcinoma, respectively. One half of patients with sarcoma and two thirds with carcinoid of the duodenum survived 5 years. No patient with distal common bile duct adenocarcinoma achieved a 5-year survival rate. Multivariate analysis on all patients operated on (n = 566) revealed that the 5-year survival rate was significantly related to intent of operation (palliative 0.2%, curative 12%; $p < 0.001$), histologic type (adenocarcinoma 2%, carcinoid and sarcoma 31%; $p < 0.0001$), and site (ampullary and duodenal 21%, biliary and pancreatic 0.9%; $p < 0.001$). A second multivariate analysis, evaluating only those patients with adenocarcinoma who survived the perioperative period of the radical resection (n = 97) analyzed the influence of tumor size and differentiation, lymphatic, capillary, and perineural microinvasion, lymph node status, and type of procedure (pancreatoduodenectomy *vs.* total pancreatectomy) on 5-year survival. None of these additional variables was significantly associated with long-term survival rates. In addition we evaluated the presence of local or distant recurrence after resection by analyzing the findings from all autopsies performed on these patients (n = 49): 29.4% of patients died with local recurrence alone, 23.5% with distant recurrence alone, and 47.1% had both local and distant recurrences. The occurrence of multicentricity in pancreatic adenocarcinoma was investigated in 36 patients in whom the entire gland was examined histologically. Multicentricity was noted in only one instance (2.8%). These results suggest that intent of operation, tumor site, and histologic type determine the outcome of patients with periampullary tumors. Although a curative resection offers the best chance for long-term survival, our results emphasize the limitation of our staging and selection. Multicentricity occurs rarely and total pancreatectomy does not achieve a lower perioperative mortality or better survival rates than standard pancreatoduodenectomy, indicating that the latter is the resection of choice unless multicentricity is obvious at exploration.

ALLEN O. WHIPPLE SUCCESSFULLY performed and described a radical operation for the treatment of ampullary carcinomas in 1935.[1] Two years later, Alex Brunschwig[2] from the University of Chicago reported a patient with carcinoma of the head of the pancreas treated by a pancreatoduodenectomy. Since then this operation has been applied also to tumors of the duodenum and distal common bile duct. Today one half a century later, the debate still continues on the proper selection of patients for such radical procedure. In an effort to improve our ability to select the appropriate candidates for radical resection of tumors of the duodenum, ampulla, head of the pancreas, and distal bile duct, we analyzed our experience at the University of Chicago with such cancers. By using multivariate regression analysis, we tried to identify any significant clinical or pathologic variable that could be used to aid in this selection.

Presented at the 109th Annual Meeting of the American Surgical Association, Colorado Springs, Colorado, April 10–12, 1989.

Correspondence and reprint request to: Fabrizio Michelassi, M.D., The University of Chicago Medical Center, Department of Surgery, 5841 South Maryland Avenue, Chicago, Illinois 60637.

Supported in part by grant RO1 CA45249-02 of the National Cancer Institute and by award 87–100 of the American Cancer Society.

Accepted for publication: April 17, 1989.

Materials and Methods

Between 1946 and 1987, 647 patients with periampullary tumors were diagnosed at the University of Chicago Medical Center. These included 549 tumors located in the head of the pancreas, 40 in the distal common bile duct, 29 in the duodenum, and 29 at the ampulla of Vater. The clinical records of all of these patients were reviewed, and in all cases complete follow-up to December 1987 was obtained through our Registry of Neoplastic Diseases. Data on age, sex, race, tumor location, size, type of operation performed, and hospital deaths were specifically sought in each instance. Autopsy records, when available, were retrieved.

Histologic slides from all ampullary, duodenal, and biliary tumors and from resected pancreatic tumors were retrieved for determination of histologic tumor type, differentiation degree, vascular and/or lymphatic and/or perineural invasion by one pathologist (PJD) who was unaware of the patient's clinical course.

Long-term survival, using 5-year survival rate as the dependent variable, was analyzed by logistic regression analysis.[3] All patients who were operated on (n = 566) were analyzed. The following independent variables were entered into the multivariate analysis: age, sex, race, intent of operation (palliative *vs.* curative), histologic type (adenocarcinoma *vs.* carcinoid and sarcoma), and tumor location (ampullary and duodenal *vs.* biliary and pancreatic).

A second multivariate analysis evaluated only those patients with adenocarcinoma who survived a radical resection with curative intent (n = 97). Five-year survival was used again as the dependent variable, while the following independent variables were considered: tumor size, differentiation degree, presence of vascular and/or lymphatic and/or perineural invasion, lymph node status, and type of operative procedure used (pancreaticoduodenal resection *vs.* total pancreatectomy). Operative deaths were defined as those deaths occurring after operation in the hospital or within 30 days after discharge.

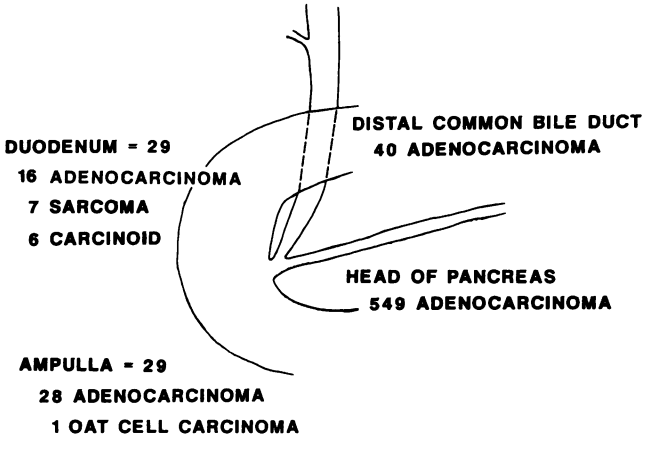

FIG. 1. Histology and location of 29 ampullary, 29 duodenal, 40 distal common bile duct, and 549 pancreatic tumors diagnosed at the University of Chicago Medical Center between 1946 and 1987.

TABLE 1. *Operability Rate*

Location	Histology	Operability Rate n (%)
Ampulla (n = 29)	Adenocarcinoma (n = 28) Oat cell carcinoma (n = 1)	28 (96.6)
Duodenum (n = 29)	Adenocarcinoma (n = 16) Carcinoid (n = 6) Sarcoma (n = 7)	13 (81.3) 5 (83.3) 6 (85.7)
Distal common bile duct (n = 40)	Adenocarcinoma (n = 40)	36 (90)
Head of pancreas (n = 549)	Adenocarcinoma (n = 549)	478 (87)

Results

Figure 1 summarizes the histology and the location of the 647 tumors. As expected most of the tumors were found in the head of the pancreas (85%), and almost all were adenocarcinomas (98%). Only in the duodenum was there a substantial likelihood (almost 50%) that the tumor would be another cell type: 6 of 29 were carcinoids and 7 of 29 were sarcomas.

The operability rates, as outlined in Table 1, depended largely on location, with the highest rate of 97% found for patients with tumors of the ampulla and the lowest rates of 81% to 86% associated with tumors of the duodenum. Eighty-one patients did not undergo any operative procedure.

Of the 566 patients operated on, 433 underwent nonresectional treatment. Table 2 summarizes the rate of nonresectional treatment, its associated hospital mortality and 5-year survival, classified by location and histology. The rate of nonresectional surgical treatment varied dramatically depending on the tumor site. Only 11% of patients with ampullary adenocarcinoma underwent nonresectional treatment, compared to 84% of patients with adenocarcinoma in the head of the pancreas. The outcome was uniformly poor with a high postoperative mortality rate and only one 5-year survivor.

The primary tumor was resected in the remaining 133 patients, 84 men and 49 women. The mean age at the time of operation was 60.5 years, with a range from 10 to 85 years. Ninety-six patients were white and 37 were black. Table 3 summarizes the demographic characteristics by tumor site.

Of the 133 patients whose tumors were resected, 126 (95%) patients underwent a radical resection of the tumor, and seven patients had a local excision. The majority of

TABLE 2. *Nonresectional Treatment*

Location	Histology	n and % of All Patients with Same Tumor Type		Hospital Mortality n (%)	5-Year Survival n (%)
Ampulla	Adenocarcinoma	3	10.7	2 (67)	0 (0)
Duodenum	Adenocarcinoma	3	23.1	0 (0)	0 (0)
	Carcinoid	1	20	0 (0)	0 (0)
	Sarcoma	1	16.7	0 (0)	0 (0)
Distal common bile duct	Adenocarcinoma	26	72.2	5 (19.2)	0 (0)
Head of pancreas	Adenocarcinoma	399	83.5	53 (14.3)	1 (0.2)
Total		433			

radical resections performed were pancreaticoduodenectomies (n = 80) and total pancreatectomies (n = 29). Table 4 details the resectability rate and the procedure according to the location and the histology of the primary tumor for all 133 patients.

Nineteen per cent (n = 24) of the 126 patients who underwent a radical resection died during the immediate postoperative period, although only one of 20 patients resected since 1981 died in the postoperative period, yielding a recent mortality rate of 5%. Overall, mortality was 20% after a standard pancreatoduodenectomy and 24.1% after a total pancreatectomy; none of the patients with local resections died after operation. Long-term survival was improved by radical resection as compared to nonresectional procedures. Nineteen of 126 patients who had radical resections were alive at follow-up and 14 patients (11%) were alive at least 5 years after operation; only one of the nonresected patients survived 5 years. Of the seven patients with local resection, four were alive at follow-up and of those, two were alive 5 years after operation. Table 5 delineates the hospital mortality and the long-term survival rates, classified by the extent of operation performed and by the location and histology of the primary tumor for all 133 patients.

A multivariate logistic regression analysis was performed to evaluate statistically significant relationships between clinical and pathologic features and patient survival in the group of 566 patients who underwent an operation. Only three independent variables, intent of operation, histologic type, and site were found to correlate significantly with 5-year survival (Fig. 2). As observed above, patients undergoing a curative operation had a significantly improved 5-year survival rate compared to patients undergoing palliative surgery (16 of 33 patients = 12% *vs.* 1 of 433 patients = 0.2%, respectively; $p < 0.001$). In addition there was a significantly increased ($p < 0.001$) rate of survival for patients with tumors of the ampulla or duodenum as compared to patients with tumors of the bile duct or head of the pancreas (12 of 52 patients = 21% *vs.* 5 of 514 patients = 0.9%, respectively). The few patients with carcinoids or sarcomas fared significantly better than did patients with adenocarcinomas (4 of 11 patients = 31% *vs.* 13 of 555 patients = 2%, respectively; $p < 0.0001$).

The second multivariate analysis, evaluating only those 97 patients with adenocarcinoma who survived the perioperative period after a radical resection, analyzed the influence of other pathologic characteristics on long-term survival. Data for these variables were not available for all patients and are summarized in Table 6. The multivariate analysis showed that none of these additional variables influenced long-term survival.

To present our results in a clinically useful manner, survival rates based on life table analysis were calculated. Figure 3 displays the differences among histologic types of duodenal tumors in 5- to 10-year survival rates after

TABLE 3. *Age, Sex, and Race of Patients with Resected Tumors*

Tumor Type	n	Age			Sex		Race	
		Mean	Min	Max	M	F	White	Black
All Patients	133	60.5	10	85	84	49	96	37
Ampulla	25	60.1	43	76	14	11	23	2
Pancreas	79	60.7	31	83	51	28	56	23
Duodenal adenocarcinoma	10	62.8	49	72	6	4	5	5
Duodenal carcinoid	4	52.7	44	65	3	1	1	3
Duodenal sarcomas	5	54.7	10	85	3	2	3	2
Distal common bile duct	10	64.8	47	74	7	3	8	2

TABLE 4. *Type of Procedure for Resected Tumors*

Location	Resectability Rate n (%)	Radical Resections: Pancreatico-duodenectomy	Total Pancreatectomy	Duodenal Resection	Gastrectomy	CBD resection	Local Excisions
Ampulla	25 (89.3)	20	3	—	—	—	2
Duodenal adenocarcinoma	10 (76.9)	5	—	5	—	—	—
Duodenal carcinoid	4 (80)	1	—	1	1	—	1
Duodenal sarcoma	5 (83.3)	—	—	1	1	—	3
Distal common bile duct	10 (27.8)	1	—	—	—	8	1
Pancreas	79 (16.5)	53	26	—	—	—	—
Total	133	80	29	7	2	8	7

radical resections. Patients with duodenal adenocarcinoma had a poorer long-term prognosis than patients with carcinoids or sarcomas.

Figure 4 compares the 5- to 10-year survival rates by tumor site for all four periampullary sites. Patients with ampullary and duodenal tumors fared better after a curative resection than patients with tumors in the head of the pancreas or distal common bile duct. Five-year actuarial survival rates, including perioperative deaths, were 8.8%, 20%, and 32% for pancreatic, duodenal, and ampullary adenocarcinoma, respectively. No patient with distal common bile duct adenocarcinoma achieved a 5-year survival. Of note, one patient with ampullary and two patients with pancreatic adenocarcinoma died of recurrent disease between 5 and 10 years after their curative procedure.

The development of local or distant recurrence after resection was analyzed by reviewing available autopsy findings. Of 49 autopsies, 15 were performed on patients who had not undergone resection. Of the remaining 34 autopsies, 19 were performed on patients with pancreatic adenocarcinomas, 2 with biliary carcinomas, 7 with ampullary, and 6 with duodenal carcinomas (see Table 7). Sixteen autopsies were performed in the immediate postoperative period and metastatic tumor was found in only one instance. The remaining 18 autopsies were performed after a mean survival of 9.1 months (range, 2 to 28.3 months). Ten autopsies followed resection of a pancreatic cancer and eight followed resection of an ampullary or duodenal cancer. One patient with pancreatic cancer died 86 days after operation from massive hemorrhage due to a marginal ulcer and no tumor was found at autopsy. In the remaining 17 patients, 29.4% had only local recurrence, 23.5% had only distant disease, and 47.1% had both local and distant recurrences.

The question of multicentricity in pancreatic adenocarcinoma was investigated in 36 patients in whom the entire gland was examined histologically (Table 8). In one patient (2.8%), multicentricity was evident at operation and the patient underwent a total pancreatectomy. In 25 additional patients treated by a total pancreatectomy, no evidence of multicentricity was found on histologic examination of the resected specimen. In the remaining ten patients who initially underwent a Whipple procedure and later an autopsy, histologic examination of the entire gland failed to show any evidence of multicentricity.

TABLE 5. *Resectability and Hospital Mortality Rates*

Location	Histology	Radical Resections: Total (n)	Hospital Mortality (n) (%)	5-Year Survivors	Alive with F/U < 5 yrs.	Local Resections: Total (n)	Hospital Mortality (n)	5-Year Survivors	Alive with F/U < 5 yrs.
Ampulla	Adenocarcinoma	23	5 (22)	6	1	1	0	1	0
	Oat cell carcinoma	—	—	—	—	1	0	0	0
Duodenum	Adenocarcinoma	10	1 (10)	1	1	—	—	—	—
	Carcinoid	3	0	2	0	1	0	0	0
	Sarcoma	2	0	1	0	3	0	1	2
Distal common bile duct	Adenocarcinoma	9	2 (22)	0	0	1	0	0	0
Head of pancreas	Adenocarcinoma	79	16 (20)	4	3	—	—	—	—
Total		126	24 (19)	14	5	7	0	2	2

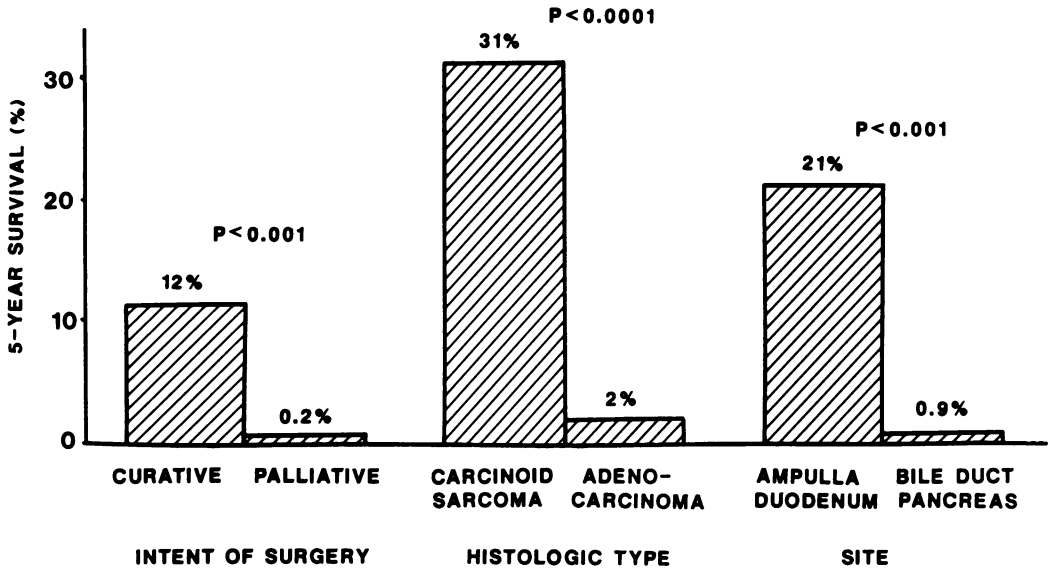

FIG. 2. Factors influencing 5-year survival in tumors of the ampulla, duodenum, distal common bile duct, and head of the pancreas.

Discussion

The results of our analysis of the 647 patients with periampullary tumors diagnosed at our institution during the past 40 years indicate that outcome depends largely on the site of the tumor, its histology, and its resectability. The prognosis for long-term survival was significantly better for patients with cancer of the duodenum and ampulla and worse for those with cancer of the pancreas and common bile duct.

With the exception of one oat cell carcinoma of the ampulla, all tumors outside of the duodenum were adenocarcinomas. In patients with tumors of the duodenum, almost 50% were another cell type. Although the nonadenocarcinomas were few in number (n = 14), cell type significantly influenced outcome: patients with carcinoids or sarcomas fared significantly better than patients with adenocarcinomas.

We determined that once the diagnosis was made, patients whose tumors were resected had significantly better

TABLE 6. *Clinicopathologic Characteristics of Resected Tumors in Patients Surviving the Perioperative Period*

Size (n = 78 cm)	Mean	Min	Max
Ampullary (18)	1.77	0.3	5.5
Pancreatic (47)	3.71	0.8	9.0
Duodenal (7)	5.6	3.0	11.0
Distal common bile duct (6)	2.2	1.0	3.7
Differentiation Degree (n = 85)	**Well**	**Moderate**	**Poor**
Ampullary (18)	15	2	1
Pancreatic (50)	19	22	9
Duodenal (10)	5	3	2
Distal common bile duct (7)	4	2	1

Invasion (n)	Lymphatic (n = 68)		Perineural (n = 65)		Capillary (n = 45)		No Invasion
	+	−	+	−	+	−	
Ampullary (18)	15	3	12	6	2	16	3
Pancreas (50)	27	6	25	5	9	6	2
Duodenal (10)	6	4	2	8	2	7	3
Common bile duct (7)	5	2	1	6	1	2	1

Lymph Node Status (n = 86)	positive	negative
Ampullary (18)	9	9
Pancreatic (54)	31	23
Duodenal (10)	3	7
Distal common bile duct (4)	1	3

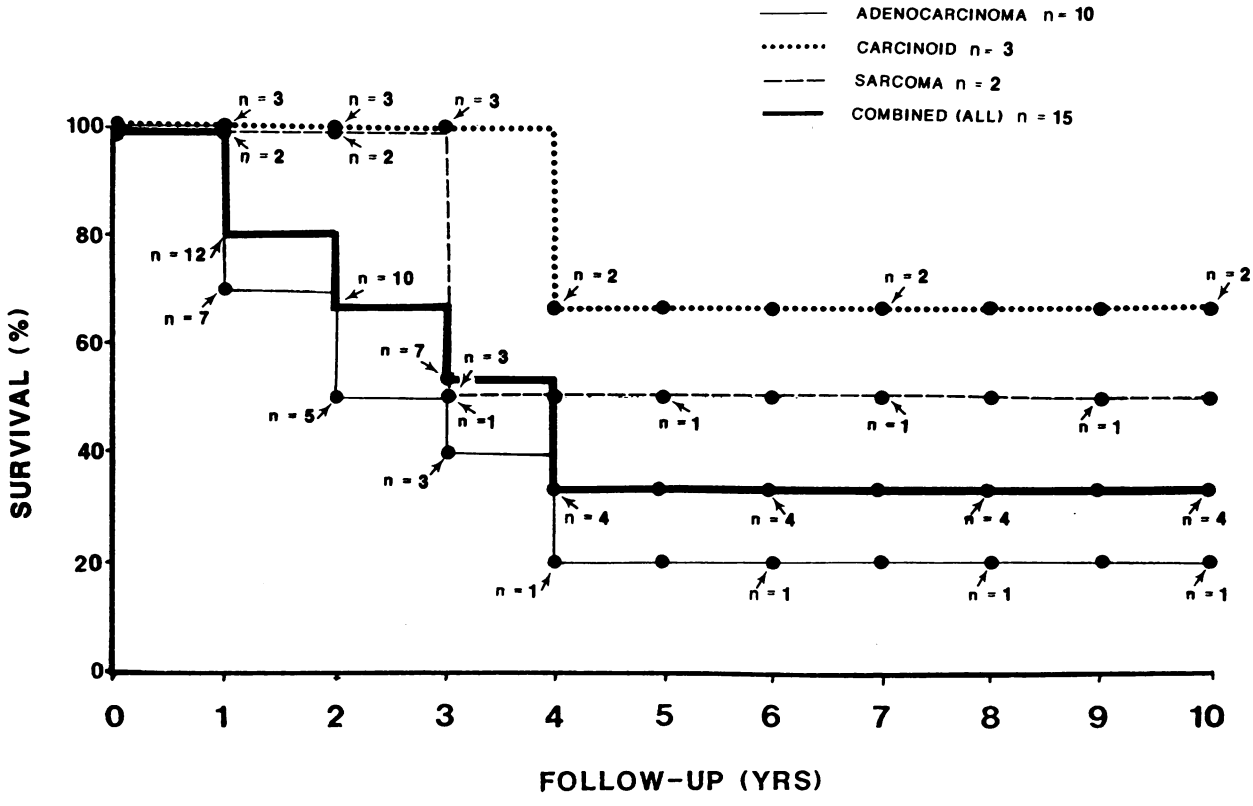

FIG. 3. Long-term survival rates in patients after radical resection of a duodenal tumor. Patients who died of intercurrent disease were censored at the time of the last known follow-up.

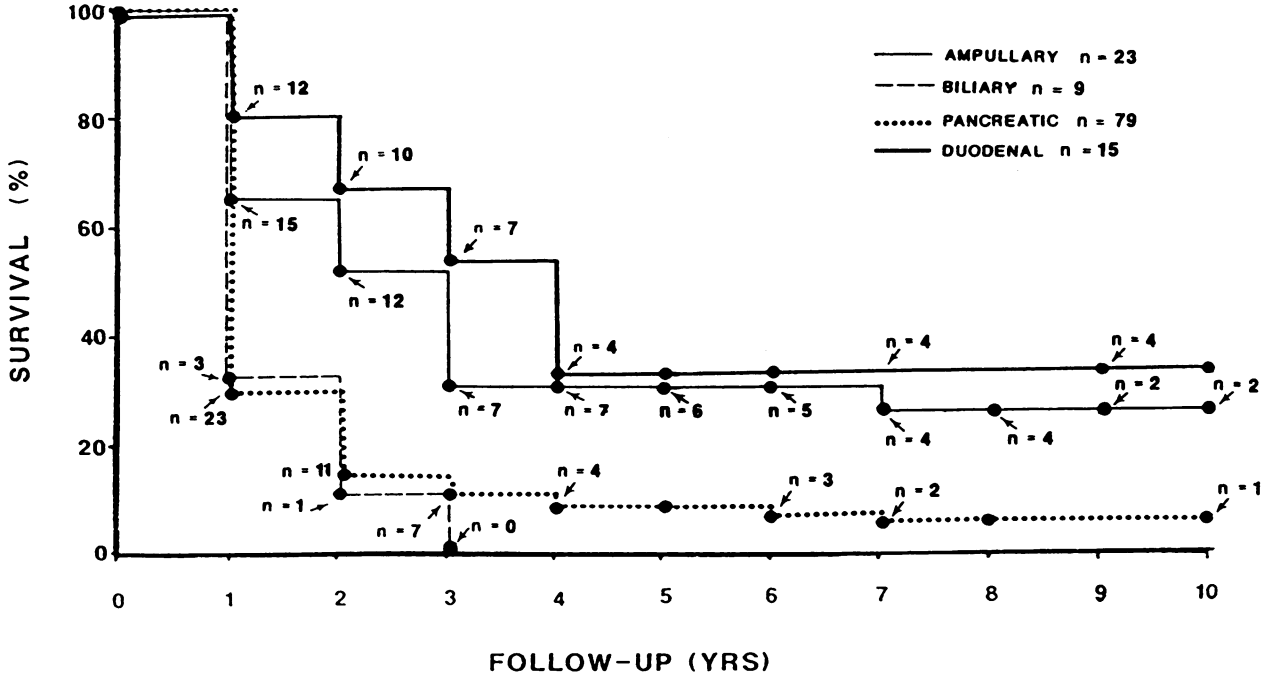

FIG. 4. Long-term survival in patients after radical resection of a tumor of the ampulla, duodenum, distal common bile duct, and head of the pancreas. Patients who died of intercurrent disease were censored at the time of the last known follow-up.

TABLE 7. *Autopsy Findings After Resection*

Tumor Site	Perioperative Deaths	Late Deaths			
		No Recurrence	Distant	Local	Distant and Local
Pancreas (n = 19)	9	1	1	3	5
Ampulla (n = 7)	4	—	2	—	1
Duodenum (n = 6)	1	—	1	2	2
Common bile duct (n = 2)	2	—	—	—	—

prognoses than patients who underwent palliative operations. Although the site of the tumor influenced resectability rates, using a multivariate analysis, our results suggested that the type of operation performed (resection or palliation) significantly influenced outcome for all sites.

Our results are consistent with other series reported in the literature. Table 9[4–9] outlines the distribution by site of resectable periampullary tumors described in the literature during the past decade. Although our series included a higher percentage of resected pancreatic tumors (61%), the differences were not large and our distribution was quite similar to that reported by Grace in 1986.[8]

When the operability and 5-year survival rates were compared to other series reported by site of tumor, our results were similar. Table 10[10–46] details the operability, resectability, operative mortality, and 5-year survival rates of patients with adenocarcinoma of the head of the pancreas extracted from reports in which such information was specifically stated. These series varied in the number of patients analyzed, from 27 patients to 1819. Operative mortality rates ranged from a low of 0% to a high of 64%, while 5-year survival was uniformly poor, varying from 0% to 17%. Regardless of the number of patients followed, no series reported more than five[40] patients surviving for 5 years. We averaged the results reported in the literature and found that our figures were comparable: the averaged operative mortality rate was 21% compared to ours of 19%, while the averaged crude 5-year survival was 2.4% compared to ours of 5%.

Carcinoma of the extrahepatic bile duct is located in the distal common bile duct in approximately one third of instances. Because our 40 cases were limited to the distal common bile duct, we compared the results with other similarly defined series reported in the literature during the past decade (see Table 11)[47–53]. Because the tumor is uncommon, most series, including our own, report on a small number (ranging from five to 15) of patients undergoing resection; we report on ten. Because of the small numbers, there is wide variability in the resectability, operative mortality, and 5-year survival rates. Our findings are consistent with those reported, although the 5-year survival rate for our patients is one of the lowest: none of the ten patients survived. Although most of the other series reported a better long-term outcome, few patients survived. Including our series in an averaged 5-year survival, only 17.5% of patients survived 5 years.

Tables 12[54] and 13[55–57] summarize similar results reported in the literature for adenocarcinomas of the ampulla and of the duodenum. Our results are consistent with these reports, but as noted with common bile duct tumors, the numbers from the series are very small, and so there is a marked variability in operative mortality and 5-year survival.

Of our 433 patients with periampullary tumors who did not undergo a resectional procedure, only one survived 5 years. This finding is also consistent with other reported cases of histologically proved adenocarcinoma of the pancreas having a long-term survival in the absence of radical resection. Gudjonsson,[46] in an extensive review of the world literature, found 12 5-year survivors among 33,000 unresected patients (0.04%). The unexpected nature of these findings suggests that, although pancreatic adenocarcinoma is a very aggressive tumor with a hopeless prognosis when unresected, on rare occasions, its behavior may be unpredictable.

Of the 133 patients who underwent resection, seven had a local excision. With the exception of one bile duct tumor, local excision was performed only in ampullary (n = 2) and duodenal (n = 4) cancers. At follow-up four patients were alive and of those, two were alive 5 years after operation. The limited number of local excisions does not allow us to comment on the validity and indications for such approach. The first reported local excision of an ampullary lesion is attributed to Halstead in 1898.[58] Recently several authors have reported their experience with local excisions and their 5-year survival rates have ranged from 17% to 41%.[7,9,59–61] Tarazi[9] reported on 11 adenocarcinomas of the ampulla of Vater treated by local

TABLE 8. *Multicentricity in Pancreatic Adenocarcinoma: Data from Clinical and Histologic Observations*

Procedure (N = 36)	Multicentricity		
	Exploration	Histologic Examination of Specimen	Autopsy
Total Pancreatectomy (n = 26)	one*	one*	—
Whipple Procedure (n = 10)		None	
5 Postoperative deaths			None
5 Survivors (2 to 28 months)			None

* Same case.

TABLE 9. *Per cent Distribution of Resected Pancreatic, Ampullary, Duodenal, and Distal Biliary Adenocarcinoma in Recent Representative Series*

		Pancreatic		Ampullary		Duodenal		Distal CBD	
Author		n	%	n	%	n	%	n	%
Cohen[4]	1982	36	42.3	22	25.9	16	18.8	11	12.9
Herter[5]	1982	75	52.1	44	30.6	15	10.4	10	6.9
Kellum[6]	1983	18	46.7	17	37.8	3	8.9	3	6.6
Jones[7]	1985	34	34.7	40	40.8	12	12.2	12	12.2
Grace[8]	1986	37	56.9	18	27.7	5	7.7	5	7.7
Tarazi[9]	1986	26	26.0	45	46.0	17	17.0	11	11.0
Michelassi	1989	79	61.2	25	20.9	10	10.1	10	7.7

resection; three patients later required another excision for a local recurrence and one patient underwent a total of three local re-excisions and eventually died of systemic disease 2 years later. Local excision, therefore, although associated with a low perioperative mortality rate, appears to have a high local recurrence rate. In addition its long-term therapeutic value is questionable if a disappointingly low 17% to 41% 5-year survival rate is achieved when

TABLE 10. *Operability, Resectability, Mortality, and Crude 5-Year Survival Rates in Adenocarcinoma of the Head of the Pancreas*

			Operability Rate		Resectability Rate			5-Year Survival	
Author/Year		Patients n	n	%	n	%	Operative Mortality %	n	%
Broadbent[10]	1951	72	66	92	7	11	NA	NA	NA
Brintnall[11]	1952	67	58	87	15	26	13	NA	NA
Cliffton[12]	1952	122	89	73	12	13	33	2	16.7
McDermott[13]	1953	112	75	67	0	0	NA	0	0
		136	100	74	33	33	33	0	0
Stafford[14]	1954	37	37	100	11	30	27	0	0
Gullick[15]	1959	65	49	75	7	14	64	0	0
Dancer[16]	1965	28	23	82	6	26	0	1	16.7
Halbert[17]	1965	74	46	62	13	28	30.7	0	0
Collins[18]	1966	67	57	85	11	19	18	0	0
Morris[19]	1966	121	109	90	26	24	38.5	2	7.7
Salmon[20]	1966	203	163	80	38	23	33.3	1	2.6
Rastogi[21]	1967	49	42	86	2	5	NA	0	0
Richard[22]	1969	190	163	86	45	28	NA	2	4.4
Vijayanager[23]	1970	61	49	80	NA	NA	NA	NA	NA
Pope[24]	1971	114	104	91	10	10	20	0	0
Elmslie[25]	1972	27	26	96	NA	NA	NA	NA	NA
Parkash[26]	1972	48	41	85	0	0	NA	0	0
Richards[27]	1973	152	136	89	27	20	15	0	0
Douglass[28]	1974	81	59	73	10	17	25	1	10
Hertzberg[29]	1974	193	181	94	12	7	13	0	0
Wilson[30]	1974	103	93	89	13	14	23	0	0
Shapiro[31]	1975	297	162	55	24	15	8	0	0
Webster[32]	1975	75	58	77	8	14	38	0	0
Balasegaram[33]	1976	66	64	97	7	11	43	0	0
Hines[34]	1976	115	108	94	22	20	7	0	0
Nakase[35]	1977	1819	1635	90	322	20	25.3	0	0
Sato[36]	1977	95	82	85	22	27	14	2	9.1
Stephenson[37]	1977	222	192	86	35	18	17	NA	NA
Bergstrand[38]	1978	271	238	88	34	14	25	0	0
Bungay[39]	1980	56	47	84	NA	NA	NA	NA	NA
Bjorck[40]	1981	480	NA	NA	62	13	10	5	8.1
Deschamps[41]	1984	106	75	71	15	20	20	0	0
Rosenberg[42]	1985	461	365	79	24	7	9	3	12.5
Parker[43]	1985	142	120	85	10	8	20	0	0
Matsuno[44]	1986	172	164	96	38	23	12.7	2	5.3
Ubhi[45]	1986	98	83	85	1	1	NA	0	0
Gudjonsson[46]	1987	196	165	84	8	5	0	1	12.5
Total		6793	5323	78	930	17.5	21	22	2.4
Michelassi	1989	549	478	87	79	16.5	20	4	5.0

TABLE 11. *Percentage of Extrahepatic Biliary Tumors in Distal Portion of the Common Bile Duct, Resectability Rate, Operative Mortality, and Crude 5-Year Survival Rate in Representative Series Published in the Last Decade*

Author	% of Extrahepatic Biliary Tumors in Distal CBD	Resectability Rate		Operative Mortality %	5-Yr. Survival	
		n	%		n	%
Lees[47] 1980	40.5	6	19	0	1	16.7
Takasan[48] 1980	40	15	75	33	3	16
Rodgers[49] 1981	69.5	6	12.5	—	0	0
Tompkins[50] 1981	19	12	67	8	3	25
Alexander[51] 1984	13	14	100	21	2	14
Langer[52] 1984	23	12	47	—	4	33
Adkins[53] 1986	18	5	50	—	1	20
Michelassi 1989	NA	10	25	10	0	0
Total		80		—	14	17.5

only the most favorable, potentially curable lesions are selected as reported above.[7,9,59–61]

The primary purpose of this study was to identify clinical or pathologic characteristics that might predict long-term prognosis in patients with periampullary tumors. Because the operability and survival characteristics of our cohort of patients are similar to those reported by others, the results of our multivariate analysis should be relevant for others as well.

The principal findings from the multivariate analysis were previously summarized: only site, histology, and resectability were significantly associated with long-term survival. Other clinical and pathologic characteristics, including the type of resection, status of regional lymph nodes, degree of differentiation, invasiveness of the tumor and its size, were not predictive of high-risk or low-risk patients. Many other series have demonstrated this lack of clinically useful identifying characteristics. For example survival in node- positive patients is essentially similar to that of node-negative patients, an observation also noted by others.[62,63]

TABLE 12. *Resectability Rate, Operative Mortality, and Crude 5-Year Survival Rate for Ampullary Adenocarcinoma in Recent Representative Series*

Author	Resectability Rate		Operative Mortality		5-Yr. Survival	
	n	%	n	%	n	%
Cohen[4] 1982	22	—	—	23.8	—	30.0
Herter[5] 1982	44	—	—	—	10	22.7
Kellum[6] 1983	17	—	2	11.8	—	50.0
Jones[7] 1985	36	100	—	—	13	32.0
Tarazi[8] 1986	46	—	6	13.0	—	37.2
Hayes[54] 1987	31	88	8	25.8	12	38.7
Michelassi 1989	25	89.3	5	20	6	24.0

TABLE 13. *Resectability Rate, Operative Mortality, and Crude 5-Year Survival Rate for Duodenal Adenocarcinomas in Representative Series*

Author	Resectability Rate		Operative Mortality		5-Yr. Survival	
	n	%	n	%	n	%
Crane[55] 1973	6	100	4	67	1	16.7
Alwmark[56] 1980	32	65.3	7	21.9	9	28.1
Joesting[57] 1981	—	—	12	11.6	21	35.6
Michelassi 1989	10	76.9	1	10	1	10

These results are not surprising. Pancreatic adenocarcinomas are known for their aggressive course. The retroperitoneal location provides little margin for growth before invasion occurs. The proximity of the portal vein, hepatic and superior mesenteric arteries may preclude removal of the tumor even in its early stages. Moreover the location of the pancreas at an anatomic water-shed with drainage to multiple lymph node basins invites early and widespread dissemination of tumor and makes a curable lesion an uncommon event. Conversely ampullary tumors have been long recognized to have a better prognosis.

In agreement with our results, several authors have shown that resection is associated with longer survival than bypass or biopsy only. The better prognosis of patients who undergo tumor resection compared to those who undergo palliative therapy could be due to a selection of patients with earlier disease. This argument could support the thesis that pancreatoduodenectomy has not proved successful and should not be used in the treatment of cancer of the head of the pancreas. However because the prognosis and quality of life for nonresected tumors is so poor, and resectional therapy is the only potentially curative procedure, we favor selected resections in the presence of the low postoperative mortality rates achieved in these recent years.

Another argument in favor of surgical resection is that it is sometimes difficult to differentiate between tumors of the ampulla, duodenum, and lower third common bile duct and tumors arising from the pancreas. An aggressive approach in these doubtful cases is justifiable because of the better long-term prognosis of duodenal and ampullary cancers.

Total pancreatectomy has been advocated because of fear of pancreatic cancer multicentricity, spillage of neoplastic cells along the pancreatic duct with implantation in the body and tail of the pancreas, fear of margin involvement by tumor, and the avoidance of the pancreaticojejunal anastomosis. However our data indicate that perioperative mortality was comparable for both procedures and multivariate analysis showed no significant difference in long-term survival after a standard pancreaticoduodenectomy or a total pancreatectomy.

Our analysis also does not justify performance of total pancreatectomy on the basis of multicentricity. We found multicentricity evident at exploratory laparotomy in only one patient. In the other 35 cases, in which the whole gland was eventually examined histologically, no evidence of multicentricity was found. These cases included ten patients who initially underwent a Whipple procedure and a later autopsy. Herter[5] found similar results: one case of multicentricity and two cases of cellular atypia in the tail of the pancreas among 42 total pancreatectomy specimens. In contrast Tryka and Brooks[64] analyzed specimens from 25 patients undergoing a total pancreatectomy for adenocarcinoma of the head of the pancreas and found that in 38% there was tumor spread beyond the local palpable tumor mass. Ross[65] in 1954 described multicentricity in one of his four patients undergoing total pancreatectomy, and Ihse,[66] Levin,[67] Pliam,[68] and Edis[62] reported multicentricity rates varying between 17% and 32%. Although we cannot explain the differences in the incidence of multicentricity reported, considering the increased postoperative morbidity associated with a total pancreatectomy, the similar perioperative mortality and the comparable long-term survival rates between total pancreatectomies and pancreatoduodenectomies, we would recommend a Whipple procedure unless multicentricity is obvious at exploration.

In conclusion, our results suggest that intent of operation, site, and histologic type determine the outcome of patients with periampullary cancers. Although a curative resection offers the best chance for long-term survival, our results emphasize the limitation of our ability to stage and select. Unless multicentricity is documented during exploration, a pancreatoduodenectomy is the resection of choice.

Acknowledgments

The authors thank Valerie Spiro of the Registry of Neoplastic Diseases of the University of Chicago Medical Center for her assistance in gathering follow-up data on all patients, and Roberta Carden for her expert secretarial help.

References

1. Whipple AO, Parsons WB, Mullins CR. Treatment of carcinoma of the ampulla of Vater. Ann Surg 1935; 102:763–779.
2. Brunschwig A. Resection of the head of the pancreas and duodenum for carcinoma-pancreaticoduodenectomy. Surg Gynecol Obstet 1937; 65:681–684.
3. Meier P. The anatomy and interpretation of the Cox Regression Model. ASAIO Trans 1985; 8:1–20.
4. Cohen JR, Kuchta N, Geller N, et al. Pancreaticoduodenectomy. A 40-year experience. Ann Surg 1982; 195:608–617.
5. Herter FP, Cooperman AM, Ahlborn TN, Antinori C. Surgical experience with pancreatic and periampullary cancer. Ann Surg 1982; 195:274–280.
6. Kellum JM, Clark J, Miller HH. Pancreatoduodenectomy for resectable malignant periampullary tumors. Surg Gynecol Obstet 1983; 157:362–366.
7. Jones BA, Langer B, Taylor BR, Girotti M. Periampullary tumors: which ones should be resected? Am J Surg 1985; 149:46–51.
8. Grace PA, Pitt HA, Tompkins RK, et al. Decreased morbidity and mortality after pancreatoduodenectomy. Am J Surg. 1986; 151: 141–149.
9. Tarazi RY, Hermann RE, Vogt DP, et al. Results of surgical treatment of periampullary tumors: a thirty-five-year experience. Surgery 1986; 100:716–723.
10. Broadbent TR, Kerman HD. One hundred cases of carcinoma of the pancreas. A clinical and roentgenologic analysis. Gastroenterology 1951; 17:163–176.
11. Brintnall ES. An evaluation of surgical treatment of carcinoma of the head of the pancreas. Cancer 1952; 5:908–910
12. Cliffton EE. Carcinoma of the pancreas: symptoms, signs and results of treatment in one-hundred-twenty-two cases. Arch Surg 1952; 65:290–306.
13. McDermott MV, Bartlett MK. Pancreaticoduodenal cancer. NEJ Med 1953; 248:927–931.
14. Stafford ES, Trimble R, Classen JN. Results of treatment of carcinoma of the pancreas. Ann Surg 1954; 139:800–803.
15. Gullick HD. Carcinoma of the pancreas. A review and critical study of 100 cases. Medicine 1959; 38:47–81.
16. Dancer JT, Duval MK. Carcinoma of the head of the pancreas. A reappraisal and report of a five year cure. Am J Surg 1965; 110: 704–708.
17. Halpert B, Makk L, Jordan GL. A retrospective study of 120 patients with carcinoma of the pancreas. Surg Gynecl Obstet 1965; 121: 91–96.
18. Collins JS, Craighead JE, Brooks JR. Rationale for total pancreatectomy for carcinoma of the pancreatic head. N Engl J Med 1966; 274:599–602.
19. Morris PJ, Nardi GL. Pancreatoduodenal cancer. Experience from 1951 to 1960 with a look ahead and behind. Arch Surg 1966; 92:834–837.
20. Salmon PA. Carcinoma of the pancreas and extrahepatic biliary system. Surgery 1966; 60:554–565.
21. Rastogi H, Brown CH. Carcinoma of the pancreas: a review of 100 cases. Cleve Clin Q 1967; 34:243–263.
22. Richard L, Cohn I. Cancer of the pancreas. Am Surg 1969; 335:95–103.
23. Vijayanager R, Tolins SH. Evaluation of palliative operations for carcinoma of the head of the pancreas: a ten year study. Mt Sinai J Med 1970; 37:115–118.
24. Pope NA, Fish JC. Palliative surgery for carcinoma of the pancreas. Am J Surg 1971; 121:271–272.
25. Elmslie RG, Slavotinek AH. Surgical objectives in unresected cancer of the head of the pancreas. Br J Surg 1972; 59:508–512.
26. Parkash O. On the statistical and clinical evaluation of carcinoma of the pancreas: a survey of 68 cases. Digestion 1972; 6:152–164.
27. Richards AB, Sosin H. Cancer of the pancreas. The value of radical and palliative surgery. Am Surg 1973; 177:325–331.
28. Douglass HO, Holyoke ED. Pancreatic cancer. Initial treatment as the determinant of survival. JAMA 1974; 229:793–797.
29. Hertzberg J. Pancreaticoduodenal resection and bypass operation in patients with carcinoma of the head of the pancreas, ampulla and distal end of the common bile duct. Acta Chir Scand 1974; 140:523–527.
30. Wilson SM, Block GE. Periampullary carcinoma. Arch Surg 1974; 108:539–544.
31. Shapiro TM. Adenocarcinoma of the pancreas: a statistical analy is of biliary bypass vs. Whipple resection in good risk patients. Ann Surg 1975; 182:715–721.
32. Webster DJT. Carcinoma of the pancreas and periampullary and periampullary region: a clinical study in a district general hospital. Br J Surg 1975; 62:130–134.
33. Balasegaram M. Carcinoma of the periampullary region: a review of a personal series of 87 patients. Br J Surg 1976; 63:532–537.
34. Hines LH, Burns RP. 10 year's experience treating pancreatic and periampullary cancer. Arch Surg 1976; 42:441–447.
35. Nakase A, Matsumoto Y, Uchida K, Honjo I. Surgical treatment of cancer of the pancreas and the periampullary region. Cumu-

lative results in 57 institutions in Japan. Ann Surg 1977; 185: 52–57.
36. Sato T, Saitoh Y, Noto N. Matsuno S. Follow-up studies of radical resection for periampullary cancer. Ann Surg 1977; 186:581–588.
37. Stephenson LW, Blackstone EH, Aldrete JS. Radical resection for periampullary carcinomas. Results in 53 patients. Arch Surg 1977; 112:245–249.
38. Bergstrand O, Ahlberg J, Ewerth S, et al. A retrospective study of carcinomas of the pancreas with special reference to the results of surgical treatment. Acta Clin Scad 1978; 482:26–28.
39. Bungay K, Dennistone S, Hunt PS. Duodenal obstruction and carcinoma of the head of pancreases. Med J Aust 1980; 2:150–151.
40. Bjorck S, Svensson JO, Macpherson S, Edlund Y. Cancer of the head of the pancreas and choledochoduodenal junction: a clinical study of 88 Whipple resections. Acta Clin Scand 1981; 147:353–359.
41. Deschamps G, Bourbeau D. Pancreatic carcinoma: surgical treatment. Can J Surg 1984; 27:559–560.
42. Rosenberg JM, Welch JP. Macaulay WP. Cancer of the head of the pancreas: an institutional review with emphasis on surgical therapy. J Surg Oncol 1985; 28:217–221.
43. Parker GA, Postlethwait RW. The continuing problem of carcinomas of the pancreas. J Surg Oncol 1985; 28:36–38.
44. Matsuno S, Sato I. Surgical treatment for carcinomas of the pancreas. Experience in 272 patients. Am J Surg 1986; 152:499–503.
45. Ubhi CS, Doran J. Palliation for carcinomas of the head of the pancreas. Ann R Coll Surg Engl 1986; 68:159–162.
46. Gudjonsson B. Cancer of the pancreas. 50 years of surgery. Cancer 1987; 60:2284–2303.
47. Lees CD, Zajdonski A, Cooperman AM, Hermann RE. Carcinoma of the bile ducts. Surg Gynecol Obstet 1980; 151:193–198.
48. Takasan H, Kim CI, Arii S, et al. Clinicopathologic study of seventy patients with carcinoma of the biliary tract. Surg Gynecol Obstet 1980; 150:721–726.
49. Rogers CM, Adams JT, Schwartz SI. Carcinoma of the extrahepatic bile ducts. Surgery 1981; 90:596–601.
50. Tompkins RK, Thomas D, Wile A, Longmire WP, Jr. Prognostic factors in bile duct carcinoma. Analysis of 96 cases. Ann Surg 1981; 194:447–455.
51. Alexander F, Rossi RL, O'Bryan M, et al. Biliary Carcinoma. A review of 109 cases. Am J Surg 1984; 147:503–509.
52. Langer JC, Langer B, Taylor BR, et al. Carcinoma of the extrahepatic bile ducts: results of an aggressive surgical approach. Surgery 1985; 98:752–759.
53. Adkins RB, Jr., Dunbar LL, McKnight WG, Farringer JL, Jr. An aggressive surgical approach to bile duct cancer. Am Surg 1986; 52:134–139.
54. Hayes DH, Bolton JS, Willis GW, Bowen JC. Carcinoma of the Ampulla of Vater. Ann Surg 1987; 206:572–577.
55. Crane JM, Gobbel WG, Jr., Scott HW, Jr. Surgical experience with malignant tumors of the ampulla of Vater and duodenum. Surg Gynecol Obstet 1973; 137:937–940.
56. Alwmark A, Andersson A, Lasson A. Primary carcinoma of the duodenum. Ann Surg 1980; 191:13–18.
57. Joesting DR, Beart RW, Jr., van Heerden JA, Weiland LH. Improving survival in adenocarcinoma of the duodenum. Am J Surg 1981; 141:228–231.
58. Halstead WS. Contributions to the surgery of the bile passages, especially of the common bile duct. Boston Med Surg J 1899; 141: 645–654.
59. Newmann RJ, Pittam MR. Local excision in the treatment of carcinoma of the ampulla of Vater. J R Coll Surg Edinburgh 1982; 27:154–157.
60. Wise L, Pizzimbono C, Dehner L. Periampullary cancer. A clinicopathological study of sixty-two patients. Am J Surg 1976; 131: 141–146.
61. Isaksson G, Ihse I, Andren-Sandberg A, et al. Local excision for ampullary carcinoma. An alternative treatment for patients unfit for pancreatectomy. Acta Chir Scand 1982; 148:163–165.
62. Edis AJ, Kiernan PD, Taylor WF. Attempted curative resection of ductal carcinoma of the pancreas: review of Mayo Clinic experience 1951–1975. Mayo Clin Proc 1980; 55:531–537.
63. Forrest JF, Longmire WP, Jr. Carcinoma of the pancreas and periampullary region: a study of 279 patients. Ann Surg 1979; 189: 129–139.
64. Tryka AF, Brooks JR. Histopathology in the evaluation of total pancreatectomy for ductal carcinoma. Ann Surg 1979; 190:373–381.
65. Ross DE. Cancer of the pancreas. A plea for total pancreatectomy. Am J Surg 1954; 87:20–23.
66. Ihse I, Lilja P, Arnesjo B, et al. Total pancreatectomy for cancer: an appraisal of 65 cases. Ann Surg 1977; 186:675–682.
67. Levin B, ReMine WH, Hermann RE, et al. Panel: cancer of the pancreas. Am J Surg 1978; 135:185–191.
68. Pliam MB, ReMine WH. Further evaluation of total pancreatectomy. Arch Surg 1975; 110:506–511.

Discussion

PROFESSOR M. TREDE (Mannheim, Germany): I thank you very much for this chance to compliment Dr. Michelassi and Dr. George Block and his group from Chicago for this presentation. It is an excellent, very clear, very honest albeit dismal picture that they have painted. But as their experience spans 41 years, I wonder if this is the whole true story as of today in 1989. If it were, that would be water on the mills of the pessimists who question the cost-effectiveness of this surgery and of those who, perhaps with tongue in cheek, are suggesting that "Congress pass a law making it illegal to do a Whipple operation." Sometimes I think the history of pancreatic resection is a bit like climbing Everest. It took more than 30 years and many costly expeditions to put two men on the summit. Today, on a fine day, 12 at a time will make it, including 60-year olds (and even women!) and no one really knows the reason. The equipment has improved a little. I don't think the men are really any better. It is as though a spell has been broken, and so our more recent experience in Mannheim makes us cautiously optimistic.

Looking at the late results, we can plot the survival curve of 106 patients whose true ductal adenocarcinoma of the pancreas was resected, according to Kaplan-Meier. All patients are included here, whether the resection was partial or total, and whether they survived the operation (and 2 of these 106 did not). This curve crosses the magic 5-year limit at 37%.

Now you may not trust "actuarial survival," and I think you would probably be right. So let us drop all statistical gimmicks and just look at the fate of those 50 patients whose resection for adenocarcinoma of the pancreas, be it partial or total, took place more than 5 years ago before October 1983; (Slide) you can see that 41 have died since. But nine patients are still alive, which is a 5-year survival rate of 18%. For papillary carcinoma, by the way, it amounts to 47%. I hasten to add that the histologies of these nine survivors were reviewed by two independent pathologists, and they were confirmed. But I must also admit that 2 of these 9 patients have died after crossing the 5-year line. And it is a sobering thought that these two died of late recurrent pancreatic cancer.

That brings me to my two questions. First have you considered adding some adjuvant radio- and chemotherapy to your surgery? Second if you break up your 40-year experience into time periods, have you not seen some improvement in the last decade with surgery alone?

DR. JOHN W. BRAASCH (Boston, Massachusetts): We noted yesterday after Dr. Moore's superb discussion of Dr. Starzl's paper a complete lack of other discussants, and I must say I felt the same pangs in following Professor Trede this morning.

We have just heard a monumental 40-year experience on the surgical treatment of periampullary malignancy with a multivariant analysis of