Factors Influencing Survival after Resection for Ductal Adenocarcinoma of the Pancreas

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Twenty-three patients with pancreatic cancer who survived ≥3 years after surgical treatment and 56 who survived <12 months were studied. The association of steatorrhea with long survival was significant ($p < 0.05$), and the association of back pain with short survival showed a trend toward significance ($p = 0.06$). Other presenting symptoms, as well as the age, sex, or past medical history of the patients; the gross morphology of the tumor and regional lymph nodes; the operations performed; and the use of postoperative adjuvant therapy had no significant influence on survival. Certain histopathologic characteristics of the resected specimens were significantly associated ($p < 0.05$) with a poor prognosis: malignant infiltration of the pancreatic capsule, proximity of the tumor to lymphatic and blood vessels, a round-cell infiltrate at the tumor margin, and epithelial atypia in the uninvolved pancreatic ducts. The association of Broders' grades 3 and 4 in the primary tumor and metastases to lymph nodes showed a trend toward significance with short survival. Multivariate analysis confirmed that the associations of Broders' grades 3 and 4 in the primary tumor, a round-cell infiltrate at the tumor margin, and atypia of the pancreatic ductal epithelium with short survival were statistically significant.

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CARCINOMA OF THE PANCREAS is increasing in frequency[1] and is now the fourth leading cause of death from cancer in men.[2,3] However, despite efforts at early detection,[4] approximately 85% of symptomatic patients have metastatic disease by the time of diagnosis. In the remaining 10 to 15% in whom the malignant lesion is apparently localized to the pancreas, the results of radical surgery are disappointing: the median survival after resection varies from 10 to 20 months.[5,6] Nevertheless, surgical resection does lead to long-term survival or even to cure for a few patients. It is important to identify this small subpopulation in whom the risks of pancreatoduodenectomy or total pancreatectomy would be justified. It may be equally important to identify those patients with resectable tumors who might survive for only a few months after pancreatectomy. In these patients, radical resection could be avoided and a less dangerous, palliative procedure chosen. Yet, it may not be possible to predict survival from clinical and operative findings before resection is undertaken. Therefore, it is essential to examine resected specimens for microscopic features that might influence survival. These features, if identified, would be a guide to prognosis and may be valuable in assessing the results of adjuvant radiation and chemotherapy.

We reviewed retrospectively the records of 82 patients who underwent resection for ductal adenocarcinoma of the pancreas. A search was made for factors in the clinical history, operative findings, and pathologic features of resected specimens that may have influenced survival.

Patients and Methods

Clinical histories and pathologic specimens from patients undergoing resection for ductal adenocarcinoma of the pancreas at the Mayo Clinic from 1951 to 1980 were reviewed retrospectively. Seventy-nine patients were selected for study. These included 23 patients (approximately 12% of patients undergoing resection) who survived 3 years or more after operation and 56 patients who died within 12 months after resection. None of the 79 patients had received preoperative irradiation or chemotherapy. All hospital deaths (patients who died within 30 days of operation) were excluded. Patients who survived for at least 1 year but less than 3 years after operation also were excluded, to obtain two dichotomous groups of long-term and short-term survivors, with no overlapping.

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TABLE 1. *Presenting Symptoms and Survival of Patients with Ductal Adenocarcinoma of the Pancreas*

Symptoms	Survival	
	Long-term	Short-term
Jaundice		
Percentage of patients	78	86
Mean serum bilirubin (mg/dl)	11.4	13.9
Mean duration (days)	30	30
Loss of weight		
Percentage of patients	83	82
Average loss (kg)	9.5	7.7
Mean duration (days)	90	91
Upper abdominal pain		
Percentage of patients	39	55
Mean duration (days)	61	79
Back pain		
Percentage of patients*	13	34
Mean duration (days)	7	91
Steatorrhea		
Percentage of patients†	43	21
Thrombophlebitis		
Percentage of patients	0	0

Difference between survival groups (χ^2): *p = 0.06; †p < 0.05.

A retrospective review was performed analyzing 33 variables in the past medical history, presenting symptoms, findings at operation, procedure performed, postoperative course, and the use of adjuvant therapy after operation. Resected specimens were re-examined by one of us (L.H.W.) for 38 pathologic variables. Only ordinary adenocarcinomas of ductal origin were included. Carcinoma of the ampulla or periampullary region, cystadenocarcinoma, islet-cell carcinoma, malignant lymphoma, sarcoma, and all other malignant lesions were excluded in an attempt to achieve a histogenetically pure group of carcinomas.

TABLE 2. *Gross Morphology of Tumor and Survival of Patients with Ductal Adenocarcinoma of Pancreas*

Morphology	Survival	
	Long-term	Short-term
Primary tumor		
Site		
Head (% of patients)	96	96
Body (% of patients)	4	2
Diffuse (% of patients)	0	2
Size		
Mean (cm)	2.9	3.2
Range (cm)	1–7	1–11
Local invasion (% of patients)*	41	52
Regional lymph nodes		
Negative (% of patients)	71	76
Positive (% of patients)	29	24

* Invasion of duodenum, common bile duct, and/or capsule of pancreas.

Statistical Analysis

Patients were divided into two groups according to survival (23 long-term and 56 short-term survivors). Comparison of the two groups was performed with the chi square test for discrete variables (or using Fisher's exact test when required) and with two-sample t-tests for continuous variables (or using rank-sum tests when the variables were nongaussian or when the variances were unequal). In addition, associations with short survival were analyzed multivariately with the logistic multiple regression model.[7]

Results

The average age was 63 years for the long-term survivors (range: 50 to 77) and 60 years for the short-term survivors (range: 34 to 77). Both groups had a male-to-female ratio of 2:1. Sixty-five per cent of the long-term survivors had a history of alcohol intake, 58% were smokers, and 4% had a history of pancreatitis. These percentages were similar to those of the short-term survivors, of whom 65% had used alcohol, 70% were smokers, and 8% had a history of pancreatitis. Diabetes of recent onset was identified in 17% and 13% of long- and short-term survivors, respectively. Five long-term survivors (22%) and 19 short-term survivors (34%) had an operation for obstructive jaundice before referral. The operations were usually biliary-enteric anastomoses or T-tube drainage of the common bile duct.

Back pain was a more frequent presenting symptom in the group with a short survival (Table 1). This association showed a trend toward significance (p = 0.06). The short-term survivors had suffered back pain for an average of 91 days, while no long-term survivor had back pain for more than 14 days before admission. Steatorrhea was more frequent in long-term survivors, a difference that was statistically significant (p < 0.05).

Radical pancreatoduodenectomy was performed in 16 long-term survivors (70%) and in 41 short-term survivors (73%). Six long-term (26%) and 15 short-term survivors (27%) underwent total pancreatectomy. One long-term survivor had had a distal pancreatectomy for carcinoma of the body of the pancreas. None of the operative findings related to gross morphology of the tumor or regional lymph nodes was significantly associated with survival (Table 2). The tumor bed was irradiated in 17% of the long-term survivors and 9% of the short-term survivors. Five long-term (22%) and five short-term (9%) survivors received chemotherapy after operation. These differences were not significant.

TABLE 3. *Histopathologic Characteristics of the Primary Tumor and Survival after Radical Resection in Patients with Ductal Adenocarcinoma of Pancreas*

Characteristic	Survival (% of patients)	
	Long-term	Short-term
Broders' grades		
1 and 2	70	46
3 and 4*	30	54
Proximity of tumor margin		
To blood vessels†	39	72
To lymphatic vessels‡	39	67
Infiltration by tumor		
Lines of resection	4	7
Pancreatic capsule†	61	89
Peritumor invasion		
Arteries	9	0
Veins	4	9
Lymphatic vessels	26	32
Neural	91	98
Intrapancreatic spread		
Parenchymal	17	36
Ductal	22	29

Differences between survival groups (χ^2): *p = 0.06; †p < 0.01; ‡p < 0.03.

Significant associations (p < 0.05) were noted between short survival and the following (Table 3): tumor margin adjacent to blood vessels (p < 0.01) and to lymphatic vessels (p < 0.03) and infiltration of the capsule of the pancreas (p < 0.01). There were more Broders' grades 3 and 4 primary tumors in the short-term group than in the long-term group, a difference that showed a trend toward significance (p = 0.06).

In most patients, parenchymal spread was contiguous with the primary tumor, but in 6% of long-term and 5% of short-term survivors, satellite areas of malignant spread were identified beyond the main tumor.

All of the primary tumors were ordinary ductal adenocarcinomas, although the tumors of two long-term and two short-term survivors had areas of adenosquamous carcinoma. Of the primary tumors in the long-term survivors, four contained mucinous elements and one had areas of acinar cell differentiation. Anaplastic or giant-cell pancreatic malignant lesions were not seen. There was no relationship between survival and the variants of pancreatic cancer. A desmoplastic reaction was noted in all tumors.

The pancreatic tissue adjacent to and distant from the tumor was examined (Table 4). There was a statistically significant correlation between round-cell infiltration at the tumor margin and short survival (p < 0.01). The histopathologic characteristics and number of involved lymph nodes in each group are listed in Table 5. Broders' grades 3 and 4 were more common in the lesions metastatic to the lymph nodes of short-term than of long-term survivors; this difference showed a trend toward significance (p = 0.14, Fisher's exact test).

TABLE 4. *Histopathologic Characteristics of the Pancreas and Survival in Patients with Ductal Adenocarcinoma of Pancreas*

Characteristic	Survival (% of patients)	
	Long-term	Short-term
Pancreas adjacent to tumor		
Chronic pancreatitis	59	61
Round-cell infiltrate*	14	50
Pancreas distant from tumor		
Chronic pancreatitis	27	25
Round-cell infiltrate	9	16
Epithelium of duct		
Atypia†	13	41
Carcinoma *in situ*	17	24
Invasive cancer	0	2

Difference between survival groups (χ^2): *p < 0.01; †p < 0.02.

Clinical and histopathologic associations with survival were examined using a logistic multiple regression procedure.[7] This analysis showed that Broders' grades 3 and 4 in the primary tumor (p < 0.03), a round-cell infiltrate at the tumor margin (p < 0.02), and epithelial atypia of the duct (p < 0.04) had a statistically significant correlation with short survival. The incidence of back pain in patients surviving less than 12 months showed a trend toward significance (p = 0.09). Multivariate analysis failed to confirm a significant association between steatorrhea and long survival. A tumor periphery adjacent to blood vessels and lymphatic vessels and infiltration of the pancreatic capsule did not significantly influence survival.

TABLE 5. *Histopathologic Characteristics of Involved Lymph Nodes and Survival in Patients with Ductal Adenocarcinoma of Pancreas*

Characteristic	Survival	
	Long-term	Short-term
Lymph node metastases		
Percentage of patients	43	57
No. of nodes		
Mean	2.6	2.0
Range	1–9	1–6
Broders' grades (% of patients)		
1 and 2	80	48
3 and 4*	20	52
Site in nodes (% of patients)		
Central	0	3
Peripheral	70	45
Diffuse (includes extracapsular growth)	30	52

* Difference between survival groups (Fisher's exact test): p = 0.14.

Discussion

"Early" ductal adenocarcinoma of the pancreas is a relatively silent disease. It spreads insidiously into extrapancreatic tissue and metastasizes readily to lymph nodes. Therefore, by the time patients experience the usual symptoms of pain, jaundice, and loss of weight, most (85% to 90%) are beyond hope of cure.[4] Even when the tumor is resectable, with no obvious regional or distant metastases, only a few patients survive 3 years or more after resection.

Most series[5,8,9] have failed to identify those few patients in whom resection will be followed by prolonged survival, and the role of extirpative surgery in the treatment of pancreatic cancer remains controversial.[10,11] Our study suggests that certain clinical and histopathologic characteristics might influence the prognosis.

Back pain in patients with pancreatic cancer may be due to malignant infiltration of the greater splanchnic nerves or celiac plexus (or both),[12] and its presence suggests that cancer has spread beyond the pancreas. Therefore, the finding that this symptom was associated with short survival was not unexpected. Three of the long-term survivors complained of short periods of back pain, but the presence of back pain for many weeks before diagnosis is a grim prognostic sign.

In patients with pancreatic cancer, steatorrhea can result from near-total interruption to the flow of pancreatic lipase into the duodenum. Clinically obvious steatorrhea suggests that the tumor has obstructed the main pancreatic duct near the ampulla of Vater. Tumors arising at this site may behave like ampullary carcinoma, which has a more favorable prognosis than pancreatic cancer. This difference may explain why steatorrhea was a more frequent presenting symptom in long-term than in short-term survivors. No other clinical features influenced survival. This confirms the results of other series, which have shown that age, sex, preoperative concentration of serum bilirubin, and the incidence of abdominal pain or weight loss have no effect on prognosis.

No morphologic features of the primary tumor or regional lymph nodes could differentiate long-term from short-term survivors. Thus, in the absence of gross extrapancreatic spread, the surgeon cannot rely on the operative findings to identify patients who are not likely to benefit from pancreatic resection. However, certain histopathologic characteristics in the resected specimens had a significant influence on survival. Tumors extending to the outer margin of the pancreas are likely to infiltrate the pancreatic capsule and be closely related to vessels and lymphatic vessels on the surface of the gland. These three interrelated features were significantly more frequent among short-term survivors. A possible explanation is that the more peripheral tumors disseminate at an earlier stage of the disease.

The correlation of short survival to Broders' grades 3 and 4 in the primary tumor and to lymph node metastases showed a trend toward statistical significance. This was not unexpected, as a similar finding has been reported with other visceral malignancies.[13,14] However, retrospective reviews of patients with pancreatic cancer have not reported this association.[5,8] In our series, only patients at either end of the survival curve were studied. Broders' grades may be of no value in predicting survival for all patients undergoing resection for carcinoma of the pancreas.

When uninvolved pancreatic tissue in the resected specimen was examined, atypia of ductal epithelium showed a statistically significant correlation with short survival. There are two possible explanations for this finding. One is that areas of atypia in the ducts of the residual pancreas rapidly progress to invasive cancer. However, a period of less than 12 months probably is not long enough for the induction and spread of pancreatic adenocarcinoma. The second explanation is that frank malignancy has already occurred in the epithelial atypia in the ducts of the body and tail of the pancreas by the time the pancreatic head is resected. If this latter hypothesis is correct, total pancreatectomy should have a favorable influence on prognosis. The Mayo Clinic experience with attempted curative resection for ductal adenocarcinoma of the pancreas was recently reported by Edis et al.[5] In that review, which included most of the patients reexamined in this study, Edis et al. found that total pancreatectomy offered no advantage over the Whipple operation[15] for cancer of the head of the pancreas. These data were confirmed in another study from our institution[9] in which the results of total pancreatectomy in patients with ductal adenocarcinoma were evaluated. However, in the small series reported by Brooks and Culebras,[16] total pancreatectomy was associated with a significantly longer survival in patients with disease localized to the pancreas than in patients without localized disease. Follow-up of a larger number of accurately staged lesions is necessary to determine the advantages of total pancreatectomy over the Whipple operation in terms of 5-year survival—to date, both operations appear to be equal in regard to long-term survival.

In other visceral malignancies, peritumor venous invasion has been correlated with a poor prognosis (Ritts RE, personal communication). In our study, however, peritumor invasion of veins and arteries did not influence survival. Invasion of peritumor lymphatic vessels was frequently observed, and neural invasion was present in almost all cases; neither of these features was related to prognosis.

Round-cell infiltration at the tumor margin was significantly more frequent in patients with a short survival, probably because a more intense host-immune reaction occurs after the cancer is disseminated. Another possible explanation is that a chemotactic influence is exerted by a tumor-associated antigen that either is specific to or elaborated in greater concentration by a malignant pancreatic cancer.[9]

When the features that were shown by univariate analysis to have a statistically significant influence on survival were re-examined using multivariate statistical methods, only three histopathologic characteristics were associated with a poor prognosis: Broders' grades 3 and 4 in the primary tumor, a round-cell infiltrate at the tumor margin, and atypia of uninvolved epithelium of the pancreatic duct. The association of back pain with short survival again showed a trend toward significance. A prospective study is essential to determine which clinical and histopathologic characteristics will be of most value in predicting survival of patients with resectable pancreatic cancer.

Although the current study suffers from the limitations of a retrospective and selected review, the results suggest that radical resection of the pancreas may be inappropriate for the patient with a long history of back pain. Where unfavorable histopathologic characteristics are identified in the resected specimen, the use of adjuvant radiotherapy-chemotherapy should be considered.

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