

Long-Term Survival After Curative Resection for Pancreatic Ductal Adenocarcinoma

Clinicopathologic Analysis of 5-Year Survivors

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Objective

The authors reviewed the clinicopathologic characteristics of patients who underwent resection with curative intent for ductal adenocarcinoma of the pancreas between 1983 and 1989.

Summary Background Data

Recent studies have demonstrated a reduction in the morbidity and mortality of pancreatic resection and improvement in the actuarial 5-year survival for patients with resected ductal adenocarcinoma.

Methods

Resection with curative intent was performed on 118 of 684 patients (17%) with pancreatic cancer admitted to the authors' institution. Clinical, demographic, treatment, and pathologic variables were analyzed. The original pathologic material for all cases was reviewed; nonductal cancers were excluded.

Results

The head of the gland was the predominant tumor site ($n = 102$), followed by the body ($n = 9$), and tail ($n = 7$). Seventy-two percent of the patients underwent pancreaticoduodenectomies, 15% underwent total pancreatectomies, 10% underwent distal pancreatectomies, and 3% underwent distal subtotal pancreatectomies. Operative mortality was 3.4%. Median survival was 14.3 months after resection compared with 4.9 months if patients did not undergo resection ($p < 0.0001$). Twelve patients survived 5 years after surgery (10.2% overall actual 5-year survival rate). Three of the tumors were well differentiated, five were moderately differentiated, and four were poorly differentiated. Extrapancreatic invasion occurred in nine cases (75%), and perineural invasion was present in ten cases (83%). Five tumors exhibited invasion of duodenum, ampulla of Vater, and/or common bile duct, and an additional tumor invaded the portal vein. Lymph node involvement by carcinoma was noted in five cases (42%). Six patients remain alive without evidence of disease at a median follow-up of 101 months (range, 82-133 months). Five patients died of recurrent or metastatic pancreatic cancer at 60, 61, 62, 64, and 64 months, respectively. One patient died at 84 months of metastatic lung cancer without evidence of recurrent pancreatic disease.

Conclusions

This paper emphasizes the grim prognosis of pancreatic ductal adenocarcinoma. Five-year survival cannot be equated to cure. Although pancreatectomy offers the only chance for long-term survival, it should be considered as the best palliative procedure currently available for the majority of patients. This emphasizes the need for the development of novel and effective adjuvant therapies for this disease.

For the majority of patients, ductal adenocarcinoma of the pancreas remains a lethal disease. An estimated 25,000 new cases occur each year in the United States, and almost all patients die of their disease within 2 years of diagnosis.^{1,2} Nonspecificity of symptoms, advanced disease at presentation, and lack of effective adjuvant and systemic therapy explain this grim prognosis. Currently, surgical extirpation for localized disease offers the only chance for long-term survival.

The predominant site for ductal adenocarcinomas is the head of the gland, requiring a pancreaticoduodenectomy for removal.² In 1941, Brunschwig reported the first pancreaticoduodenectomy performed for cancer³; since then, controversy has existed as to the true benefit of resection for invasive ductal adenocarcinoma. Based on results from the 1960s, 1970s and early 1980s, many authors argued that excessive mortality and morbidity associated with surgical resection, coupled with the lack of long-term survivors, indicated that pancreatic resection be abandoned for ductal cancer.⁴⁻⁶ However, recent reports from referral centers, including our own, have demonstrated that pancreatic resections can be performed with operative mortality rates less than 5%.⁷⁻¹⁴ In addition, actuarial 5-year survival rates after resection have been reported in excess of 20%.^{10,13,15} These results suggest that resection is justified and may offer the possibility of cure to a significant proportion of patients.

In contrast, while confirming the reduced perioperative mortality rates, other authors have failed to demonstrate an improved survival.^{16,17} In fact, some reports have failed to demonstrate any 5-year survivors.¹⁸

These conflicting studies prompted us to critically review the clinicopathologic characteristics of our patients who were resected with curative intent for ductal adenocarcinoma of the pancreas between 1983 and 1989, in an attempt to define the true 5-year survival rate.

PATIENTS AND METHODS

Between October 15, 1983 and October 15, 1989, 684 patients were admitted to Memorial Sloan-Kettering

Cancer Center with a histologically confirmed diagnosis of invasive ductal adenocarcinoma of the pancreas. There were 379 male patients and 305 female patients. Resection with curative intent was performed on 118 patients. Clinical, operative, and pathologic data were entered into a prospective database maintained since 1983 by the department of surgery.

Follow-up was obtained by patient interview, letters, hospital charts, or personal contact with the attending physician. Survival was analyzed by the Kaplan-Meier method;¹⁹ differences in survival were compared using the log-rank test. Significance was noted at the 0.05 level.

Twelve patients survived 5 years after their operation, and they are the primary focus of this paper. Clinical, demographic, treatment, and pathologic variables in this group were analyzed. The original pathologic material for all cases was reviewed, including glass slides and gross descriptions. The histologic type of the tumor was determined, and the presence of intraductal carcinoma (carcinoma *in situ*) was specifically noted. The extent of the intraductal component, when present, was graded as focal, multicentric, widespread, or predominant. Other pathologic parameters included tumor size, grade (well, moderately, or poorly differentiated), extrapancreatic spread (present or absent), perineural invasion (present or absent), invasion of adjacent structures (common bile duct, duodenum, ampulla of Vater; present or absent), and invasion of the portal vein (present or absent). The number of involved lymph nodes was noted, and true nodal metastases were distinguished from direct invasion of lymph nodes by carcinoma. Finally, the tumors were staged using the TNM system.²⁰

RESULTS

For all patients admitted to Memorial Sloan-Kettering Cancer Center between October 1983 and October 1989 with a confirmed diagnosis of pancreatic ductal adenocarcinoma, the actual 5-year survival was 1.8%, with a median survival of 6 months (Fig. 1). The median follow-up for 5-year survivors was 83 months.

During the study period, 118 of the 684 patients (17%) underwent pancreatic resections performed with curative intent. There were 59 male patients and 59 female patients. The mean age was 61.2 years (range, 35-82 years). The head of the gland was the predominant tumor site (n = 102), followed by the body (n = 9), and tail

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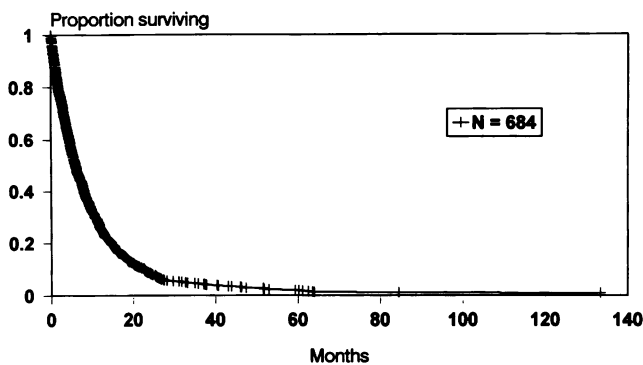


Figure 1. Overall survival for all patients admitted to Memorial Sloan-Kettering Cancer Center with adenocarcinoma of the pancreas between October 15, 1983 and October 15, 1989 (N = 684, median survival = 6 months).

(n = 7). Seventy-two percent underwent pancreaticoduodenectomies, 15% underwent total pancreatectomies, 10% underwent distal pancreatectomies, and 3% underwent distal subtotal pancreatectomies. The median length of the postoperative hospital stay was 22 days (range, 1–125 days). The 30-day operative mortality was 3.4% (4/118 patients). Median survival was 14.3 months after resection compared with the median survival of 4.9 months for those patients who did not undergo resection ($p < 0.0001$; Fig. 2).

Twelve patients survived 5 years after operation, for an actual 5-year survival rate of 10.2%. There were three men and nine women. Clinical details are given in Table 1. Abdominal or back pain was the predominant presenting symptom occurring in seven patients (58%), followed by weight loss (n = 6, 50%) and jaundice (n = 5, 42%). The pancreatic head was the site of disease in nine patients, with the remainder being in the body (n = 1) and tail (n = 2). Seven patients underwent pancreaticoduodenectomies, three patients underwent distal pancreatectomies, and two patients had regional total pancreatectomies. The median estimated operative blood loss was 1400 mL (range, 805–4150 mL). All patients received a blood transfusion in the perioperative period. The median amount of blood transfused was 4 units of packed red cells (range, 2–6 units). Postoperative complications occurred in four patients (33%). Two patients developed pancreatic fistulae, one had gastric outlet obstruction, and one had a wound breakdown. Two patients (17%) required reoperation. Median postoperative stay was 18 days (range, 12–55 days).

The pathologic features of the 12 tumors are listed in Table 2. In 11 of the 12 cases, the tumor was a typical infiltrating ductal adenocarcinoma exhibiting mucin-producing glands, an infiltrating growth pattern, a desmoplastic stroma, and moderate to marked cytologic atypia. In six of these cases, there was an intraductal component that ranged from focal to widespread in dis-

tribution. Although the intraductal component was not predominant in any case, it did constitute approximately 50% of the tumor mass in one case.

One of the tumors exhibited unique histologic features, which will be described in detail elsewhere. The tumor was biphasic, exhibiting a cystic and intraductal component consisting of clear cells, mucin-containing goblet cells, and nonkeratinizing squamous epithelium resembling mucoepidermoid carcinoma of the salivary glands. The second component consisted of an anaplastic spindle cell neoplasm with scattered pleomorphic tumor giant cells and an admixture of reactive lymphocytes and plasma cells. Scattered collections of osteoclastic giant cells were also noted. The sarcomatoid invasive component constituted the majority of the tumor and showed no transitions to the mucoepidermoid-like elements.

Tumor size ranged from 1.0 to 6.5 cm (mean 3.3 cm). Three of the tumors were well differentiated, five were moderately differentiated, and four were poorly differentiated, including one case exhibiting extensive central necrosis. Invasion of extrapancreatic tissues was noted in nine cases, and perineural invasion was present in ten cases. Five of the tumors exhibited invasion of duodenum, ampulla of Vater, and/or common bile duct, and an additional tumor invaded the portal vein. The number of lymph nodes identified in each case ranged from 5 to 31 (mean 16 lymph nodes). There was involvement of lymph nodes by carcinoma in five of the cases. In three of the node-positive cases, the involvement appeared to be metastatic in nature, consisting only of microscopic metastases to a single lymph node in two. The two remaining cases showed only direct invasion of lymph nodes by contiguous spread of the primary carcinoma.

All patients survived at least 5 years from their surgery (Table 3). Currently, six patients remain alive without evidence of disease at a median follow-up of 101 months (range, 82–133 months). One of these patients, although free of pancreatic cancer, currently is alive with meta-

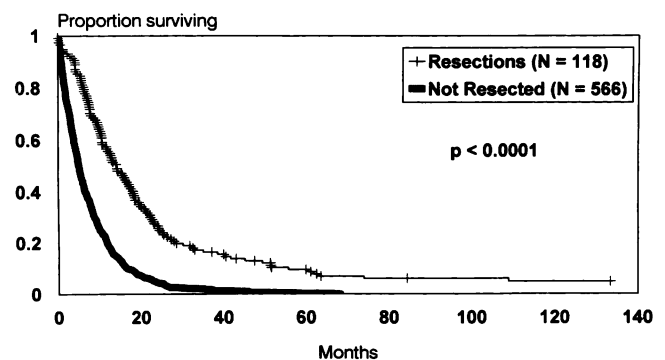


Figure 2. Comparison of survival between patients undergoing resection (N = 118, median survival = 14.3 months) vs. patients who did not undergo resection (N = 566, median survival = 4.9 months; $p < 0.0001$).

Table 1. CLINICAL DETAILS

Patient No.	Sex	Age (yrs)	Presenting Symptoms	Tumor Site
1	Female	57	Pain, nausea/vomiting, weight loss	Tail
2	Female	63	Jaundice	Head
3	Female	68	Asymptomatic (incidental finding)	Body
4	Female	65	Pain, weight loss	Head
5	Male	54	Pain	Head
6	Female	44	Jaundice, nausea/vomiting, weight loss	Head
7	Female	38	Pain, diarrhoea, weight loss	Head
8	Female	47	Pain, weight loss	Tail
9	Female	64	Jaundice	Head
10	Male	73	Pain, jaundice, weight loss	Head
11	Male	70	Jaundice	Head
12	Female	69	Pain, jaundice	Head

static gastric cancer. Five patients died of recurrent or metastatic pancreatic cancer at 60, 61, 62, 64, and 64 months, respectively. The final patient died at 84 months of metastatic lung cancer without evidence of recurrent pancreatic disease.

DISCUSSION

The overall survival rate of 1.8% reported in this paper—confirming the abysmal prognosis of ductal adenocarcinoma—may overestimate survival because our denominator is patients admitted to hospital. However, we do not advocate a nihilistic approach to this disease, as if resectable; the median survival of 14.3 months is superior to the median survival of 4.9 months for those patients who do not undergo resection, and 10% will be true 5-year survivors.

Pancreatic resection can be performed safely in this patient population, many of whom are elderly with comorbid conditions. The 3.4% operative mortality rate reported in this study is similar to those described recently from other tertiary referral centers (Table 4), and is substantially improved from those reported earlier.^{4-14,17-26} Although the reasons for this improvement are multifactorial, the development of tertiary care centers in which a group of surgeons have a particular interest in patients with pancreatic cancer has had a positive impact. A study of all patients admitted to New York State hospitals between 1984 and 1991 with a peripancreatic malignancy who underwent pancreatic resection demonstrated that high-volume hospitals (>81 cases, n = 2) compared with medium- (10-80 cases, n = 56) or low- (<10 cases, n = 124) volume centers had a significantly lower postoperative mortality (4% vs. 12% or 22%, respectively).²⁷ Sim-

Table 2. PATHOLOGICAL FEATURES

Patient No.	Diagnosis	Grade	Size (cm)	Nodal Status	Intraductal Component	Extra Pancreatic Invasion	Perineural Invasion	Invasion of Adjacent Structures
1	Ductal adenocarcinoma	Well	1.0	0/14	Absent	Absent	Present	Absent
2	Ductal adenocarcinoma	Poor	6.5	0/13	Focal	Present	Present	BD, Duod, ampulla
3	Ductal adenocarcinoma	Mod	1.6	0/20	Absent	Absent	Absent	Absent
4	Ductal adenocarcinoma	Mod	1.5	1/31 (M)	Multicentric	Present	Present	BD
5	Ductal adenocarcinoma	Mod	3.0	1/16 (DI)	Focal	Present	Present	Absent
6	Ductal adenocarcinoma	Well	2.5	0/19	Widespread	Present	Present	Portal vein
7	Ductal adenocarcinoma	Mod	2.8	0/12	Absent	Present	Absent	Absent
8	Ductal adenocarcinoma	Poor	6.5	1/16 (DI)	Absent	Present	Present	Absent
9	Ductal adenocarcinoma	Mod	3.5	2/19 (M, DI)	Widespread	Present	Present	Absent
10	Mucoepidermoid*	Poor	5.0	0/5	Multicentric	Absent	Absent	Duod, ampulla
11	Ductal adenocarcinoma	Poor	3.8	0/13	Widespread	Present	Present	BD, Duod
12	Ductal adenocarcinoma	Well	2.0	2/10	Absent	Present	Absent	BD, Duod

BD = bile duct; Duod = duodenum; M = microscopic focus; DI = direct invasion.

* Significant sarcomatoid component.

Table 3. FOLLOW-UP/STATUS

Patient No.	Surgical Procedure	Stage*	Status	Follow-Up (mos)
1	Distal subtotal pancreatectomy	T1aN0	DOD	60
2	Pancreaticoduodenectomy	T2N0	NED	103
3	Distal pancreatectomy	T1aN0	NED	82
4	Distal subtotal gastrectomy			
4	Pancreaticoduodenectomy	T2N1	NED	133
5	Regional total pancreatectomy	T2N1	NED	84
6	Regional total pancreatectomy	T3N0	DOD	64
7	Pancreaticoduodenectomy	T2N0	DOD	62
8	Distal pancreatectomy	T2N1	NED	110
9	Pancreaticoduodenectomy	T2N1	DOD	64
10	Pancreaticoduodenectomy	T2N0	NED	99
11	Pancreaticoduodenectomy	T2N0	DOC	86
12	Pancreaticoduodenectomy	T2N1	DOD	61

NED = no evidence of disease; DOD = dead of disease; DOC = dead of another cause.

* Pathologic stage.

ilarly, an analysis of hospital discharges after pancreaticoduodenectomy reported to the Maryland Health Services Cost Review Commission between 1988 and 1993 showed that hospital mortality, length of stay, and hospital charges were significantly less for a high-volume regional referral center compared with other hospitals with lower volume.²⁸ In contrast, Lea and Stahlgren reported an operative mortality of 30% in a series of ten patients

who underwent resection over a 6-year period by nine different surgeons.²⁹

Historically, the 5-year survival for patients after "curative" resection for ductal carcinoma of the pancreas was reported in the range of 0% to 10%.³⁻⁶ However, many recent reports, including one from our institution, have suggested an improvement in survival (Table 5).^{10,13,15,22,23,28,30,31} Geer and Brennan¹³ reported an actuarial survival of 24% at 5 years for 146 patients undergoing resection; no five-year survivors were seen in 653 patients who did not undergo resection. They identified lymph node-positive tumors, poor histologic tumor differentiation, and a tumor size > 2.5 cm as poor prognostic variables. Cameron and associates¹⁵ reported a 19% actuarial 5-year survival in a group of 89 patients undergoing resection for adenocarcinoma of the pan-

Table 4. OPERATIVE MORTALITY AFTER PANCREATECTOMY

Author	Year	No. of Patients	Operative Mortality (%)
Braasch	1986	71	2.8*†
Grace	1986	45	2.2*
Crist	1987	47	2*
Manabe	1989	74	8.3†
Doerr‡	1990	127	8*†
Trede	1990	118	0*
Miedema	1992	279	4*
Cameron	1993	145	0*
Edge‡	1993	223	6†
Geer	1993	146	3.2†
Baumel‡	1994	794	9.8*
Swope	1994	47	8§
Fernandez del Castillo	1995	231	0.4†
Bramhall‡	1995	145	27.6†
Wade	1995	252	8.3
Present series	1995	118	3.4†

* Includes benign disease and islet cell tumors.

† Includes total and distal pancreatectomies.

‡ Collected series.

§ Total pancreatectomy only.

Table 5. ACTUARIAL SURVIVAL AFTER PANCREATECTOMY FOR DUCTAL ADENOCARCINOMA

Author	Year	No. of Patients	5-Year Survival (%)
Cameron	1991	89	19
Trede	1990	130	24
Geer	1993	146*	24
Willett	1993	72	13
Baumel	1994	787*	12
Bramhall	1995	145*	9.7
Nitecki	1995	174*	6.8
Wade	1995	252	8

* Includes patients with body and tail lesions.

creas. They suggested that tumor factors, such size (>2 cm), positive lymph nodes, and vessel invasion, were adverse prognostic factors. Willett and colleagues²⁸ emphasized the importance of negative pathologic margins, overall 5-year actuarial survival was 13%, but in the group with negative margins (35/72 patients), this was significantly improved to 22%. Similar results were demonstrated by Trede and associates,¹⁰ who reviewed the Mannheim Surgical Clinic's experience between 1972 and 1989. In this retrospective study, the overall actuarial 5-year survival rate was 24%; however, when the tumor was excised both macroscopically and microscopically (the so-called R⁰ resection), actuarial survival increased to 36% for this subgroup of 76 patients. They also demonstrated that 4 of 11 true 5-year survivors ultimately died of their disease. This is similar to the experience described in this paper, in which five (42%) of our true 5-year survivors died of recurrent pancreatic cancer, emphasizing the fact that 5-year survival does not equal cure in this disease.

In contrast to the somewhat optimistic aforementioned reports, a number of recent studies have cast doubt on whether we truly are improving the long-term survival for this disease or whether the disease actually is attenuating, as has been suggested.³² Nitecki and colleagues,¹⁶ reviewing the Mayo Clinic experience between 1981 and 1991, reported an actuarial 5-year survival of 6.8% after resection. Complete resection, with negative lymph nodes, absent perineural or duodenal invasion resulted in a 5-year survival of 23%. However, this subset only accounted for 40% of their patients. Large multicenter studies from Europe and the United States also recently have reported actuarial 5-year survival rates between 8% and 12%.^{17,22,23} Our actual 5-year survival figure of 10.2% is within this range.

Analysis of clinicopathologic variables in our group of 5-year survivors demonstrates the difficulty in prognostication for an individual patient with this disease. Women appeared to do somewhat better than men (actual 5-year survival 15.3% vs. 5.1%), although with the small numbers, this is not statistically significant. Tumor size varied between 1.0 cm and 6.5 cm; both patients with the larger tumors remain free of disease whereas the patient with the smallest tumor in this report died of recurrent disease at 60 months. Similarly, three of four patients with poorly differentiated tumors currently are alive at a median follow-up of 103 months, whereas all three patients with well-differentiated tumors have died, two of recurrent disease. Three patients with positive lymph nodes (1 metastatic, 2 with direct invasion) remain free of recurrent disease at 84, 110, and 133 months, respectively.

Perioperative blood transfusion has been identified as a negative prognostic factor in a number of solid tumors.^{15,33-35} Cameron and associates¹⁵ noted that pa-

tients receiving more than 2 units of blood in the perioperative period after pancreatic resection had significantly worse prognoses, with transfusion proving to be an independent prognostic factor. All of our 5-year survivors received a blood transfusion in the perioperative period (median 4 units), supporting our earlier study, which failed to demonstrate an impact of blood transfusion on survival.¹³

The importance of accurate pathologic confirmation of tumor type and anatomic origin cannot be overemphasized when reporting survival rates after resection for pancreatic ductal carcinoma. In addition to the aforementioned patients, 13 other patients who survived 5-years after pancreatic resection during the same time period were noted to have tumors with either no invasive component, mucinous cystic features, or neuroendocrine differentiation, and thus, were excluded. Nitecki and colleagues¹⁶ noted that of 186 patients who underwent pancreatic resection for ductal pancreatic cancer at the Mayo Clinic between 1981 and 1991, pathologic re-review led to a change in diagnosis in 12 patients. Similarly, Trede and colleagues¹⁰ reclassified 6% of their patients after reviewing the pathologic specimens. Connolly et al.³⁶ reported that of 23 3-year survivors of pancreatic cancer, only 11 had histologically confirmed disease. Inclusion of patients without histologic proof of ductal carcinoma would have resulted in a falsely inflated survival rate. It is worth emphasizing that inclusion of the 13 other patients who survived 5 years from their operation would have increased our 5-year survival rate to 19%. The addition of such patients probably accounts for the discrepancies in reported survival rates.

All of the tumors in this study were invasive carcinomas of ductal origin, and 11 exhibited the typical pathologic features of ductal adenocarcinoma. The remaining case was a patient with an unusual (perhaps unique) tumor with a combination of sarcomatoid carcinoma and mucoepidermoid carcinoma-like patterns. Given the singular nature of this tumor, it is unclear whether there might be an inherently better prognosis for such tumors; however, the prognosis for sarcomatoid pancreatic carcinomas generally is at least as dismal as that of ductal adenocarcinomas.

Seven (58%) of the tumors exhibited an intraductal component, which was widespread in three, but not the predominant component in any case. This frequency of associated carcinoma *in situ* is similar to that reported by us for the entire group (51%).³⁷

We have emphasized the grim prognosis of ductal adenocarcinoma of the pancreas even after "curative" resection. Five-year survival cannot be equated to cure because nearly half of our 5-year survivors died of recurrent or metastatic disease. Although we believe that pancreatectomy offers the only chance for long-term survival for patients with invasive ductal adenocarcinoma

of the pancreas, it should be considered the best palliative procedure currently available for the majority of patients. This emphasizes the need for the development of novel and effective adjuvant therapies for this group of patients.

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