Sofía Cáceres. *La Sombra del Quijote (Quixote's Shadow)*. Oil on table, 42″ × 62″.

Pancreatectomy with curative intent offers the possibility of long-term survival to patients with this usually lethal disease.

Outcomes Following Resection of Pancreatic Adenocarcinoma: 20-Year Experience at a Single Institution

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Background: *Pancreatectomy for ductal adenocarcinoma has been performed with increasing frequency since the late 1980s as postoperative mortality decreased and long-term survival became more common. However, the belief persists among some clinicians that pancreatectomy offers little survival benefit. This report reviews our institutional experience with pancreatectomy for pancreatic adenocarcinoma and provides a critical overview of the controversies regarding the benefits of surgical intervention for patients who are candidates for curative resection.*

Methods: *We determined the survival of 142 patients who underwent pancreatectomy for ductal adenocarcinoma with curative intent (stage IA–IIB) at Moffitt Cancer Center during the last two decades by using data obtained from review of the medical record, the Moffitt Cancer Registry, and the Social Security Death Index. Histologic diagnosis was confirmed by expert review of stained sections cut from fixed surgical specimens.*

Results: *In the 137 patients who survived at least 30 days after surgery, the median survival was 21.2 months after resection, with Kaplan-Meier 3- and 5-year disease-specific survival rates of 36% and 32%, respectively. One patient has survived without evidence of recurrent disease for more than 15 years after pancreatectomy. Survival for patients greater than 75 year of age did not differ from that of younger patients. The postoperative mortality rate was 1.5% during the most recent years of highest operative volume (2003 to 2006) and 3.5% for the entire patient cohort.*

Conclusions: *Review of our 20-year experience with resection of pancreatic adenocarcinoma indicates that pancreatectomy with curative intent offers a real chance of long-term survival to patients with this highly lethal disease for which there is no other curative modality.*

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Introduction

About 37,600 new cases of pancreatic cancer and nearly as many deaths from the disease are expected in the United States in 2008.[1] Although only the eleventh most common cancer in the United States, pancreatic cancer is the fourth most common cause of cancer death after lung, colorectal, and breast cancer. No more than 5% of all patients with pancreatic cancer will survive 5 years, the lowest long-term survival rate of any cancer.[1] The majority of pancreatic cancers are ductal adenocarcinomas, which most often present at an advanced stage with a poor prognosis because there are no early symptoms. Patients with localized disease in whom a potentially curative resection can be performed have the only real chance of long-term survival. Our experience has been that only about 15% of patients with ductal cancer will have a tumor amenable to resection, which is consistent with other estimates reported in the literature.[2,3]

Literature reviews have found that pancreatectomy for cancer has been described in reports dating to as early as the 1890s.[4-6] Until relatively recently, pancreatectomy was done infrequently because of excessive surgical morbidity and mortality and also because of the lack of a clear survival benefit. Long-term survival was uncommon in the early years of pancreatic resection for cancer. It was not until nearly a century after pancreatectomy was first described that advances in surgical technique and postoperative care allowed the procedure to be done with acceptably low morbidity and mortality. Pancreatectomy was performed more frequently for cancer in the late 1980s, and long-term survival became increasingly more common. Nevertheless, the belief persists among some clinicians that pancreatectomy offers little survival advantage to those with pancreatic cancer.

Recent studies offer evidence that only a minority of pancreatic cancer patients with potentially curable disease undergo resection, and the most common reason cited in one of these reports was that surgery was not offered to the patient.[7-10] We reviewed the outcomes of pancreatic cancer patients who underwent resection at our institute to validate the experience of other institutions indicating that pancreatectomy is the treatment of choice for patients with resectable local or regional disease. We found that pancreatectomy for ductal adenocarcinoma amenable to resection offers a 1-in-3 chance of disease-specific, long-term survival to patients who otherwise would have no real chance of such benefit.

Methods

We identified 238 patients who underwent pancreatic resection for a primary pancreatic cancer or premalignant neoplasm at our institute from January 1987 through December 2006. Patients who underwent pancreatic resection were identified from surgical and pathology administrative databases and from the Moffitt Cancer Registry. The *World Health Organization International Classification of Diseases for Oncology*[11] was used to classify all pancreatic neoplasms based on the dominant histologic appearance described in the original interpretation by the pathologist of record.

We then focused on the 149 patients who underwent resection of invasive ductal pancreatic cancer or a variant thereof. A pathologist with expertise in pancreatic cancer (B.A.C.) confirmed the histologic diagnosis by review of stained sections cut from fixed surgical specimens. Patients with premalignant lesions, neuroendocrine tumors, and nonductal pancreatic cancers were excluded from further study since their clinical outcomes likely would differ substantially from those with ductal pancreatic cancer. Tumors arising from the ampulla of Vater and the common bile duct were also excluded. Data from the Moffitt Cancer Registry, the patient's medical record, and the Social Security Death Index were reviewed to determine each patient's clinicopathologic characteristics, tumor stage, and survival following surgery. We also determined if the patient was deceased as of most recent knowledge and if there was evidence of disease at that time. Disease stage for all patients was defined by the present-day tumor-node-metastasis (TNM) classification of the American Joint Committee on Cancer (AJCC).[12] This study was approved by the University of South Florida Institutional Review Board.

Disease-specific survival was estimated by the Kaplan-Meier method, using death with evidence of disease as the endpoint rather than death from all causes. Death within 30 days of surgery was considered to be perioperative mortality associated with the surgery itself rather than cancer. Median survival, as well as 3- and 5-year probabilities of survival, was determined. The log-rank test was used to compare Kaplan-Meier survival curves.

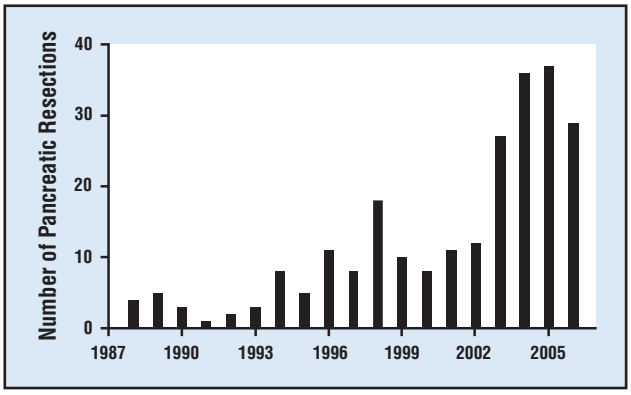

Fig 1. — Frequency distribution of 238 pancreatic resections done for primary pancreatic cancer or premalignant neoplasms at our institute during the 20-year period of 1987 through 2006. Prior to 1994, data were available only for primary pancreatic cancers and did not include premalignant neoplasms.

Results

Series Overview

A total of 238 patients underwent resection of a primary pancreatic cancer or premalignant neoplasm during the past 20 years. Fig 1 shows the frequency distribution of pancreatic resections done for these indications by year. In the last 4 years, about 30 to 35 such resections were performed each year. Ten surgeons performed pancreatic resections, with 3 surgeons having performed 80% of the 238 resections done during this 20-year period. Of these 238 resections, 67.6% were pancreaticoduodenectomies, with or without pylorus preservation, 27.3% were distal pancreatectomies, 1.7% were total pancreatectomies, and the remaining 3.4% were local or central pancreatectomies.

Table 1 shows the distribution of histologic diagnoses in the 238 patients who underwent pancreatic resection. Invasive ductal pancreatic cancers accounted for 62.6% of resections. Another 22.3% of resections were done for premalignant or other neoplasms, with 38% of these lesions being benign intraductal papillary mucinous neoplasms. The remaining 15.1% of resections were done for neuroendocrine tumors.

Table 1. — Histologic Diagnoses in 238 Patients Who Underwent Resection of Pancreatic Neoplasms During the 20-Year Period of 1987–2006

ICD-O	Histology	n
Invasive	**Ductal Pancreatic Cancers and Variants**	
8140	Ductal adenocarcinoma	133
8560	Adenosquamous carcinoma	4
8020	Undifferentiated (anaplastic) carcinoma	3
8453	Invasive intraductal papillary-mucinous carcinoma	3
8470	Mucinous cystadenocarcinoma	3
8480	Mucinous adenocarcinoma	2
8500	Infiltrating ductal carcinoma	1
		149 (62.6%)
Premalignant and Other Neoplasms		
84531	Intraductal papillary mucinous neoplasm with moderate dysplasia	17
84410	Serous cystadenoma	10
84701	Mucinous cystic neoplasm with moderate dysplasia	5
84532	Noninvasive intraductal papillary mucinous carcinoma	4
84700	Mucinous cystadenoma	4
8470	Mucinous cystadenocarcinoma, not otherwise specified	2
8453	Intraductal papillary mucinous carcinoma, not otherwise specified	4
84530	Intraductal papillary mucinous adenoma	3
8452	Solid pseudopapillary carcinoma	2
8000	Pancreatoblastoma	1
84521	Solid pseudo-papillary neoplasm	1
		53 (22.3%)
Neuroendocrine Tumors		**36 (15.1%)**

ICD-O: Fritz AG, Percy C, Jack A, et al, eds. *International Classification of Diseases for Oncology.* 3rd ed. Geneva, Switzerland: World Health Organization; 2000.

Clinicopathologic Features

Of the 238 patients who underwent pancreatic resection, 149 had invasive ductal pancreatic cancers. Of these 149 patients, 142 underwent resection with curative intent by present-day stage criteria (AJCC stage IA–IIB). The 7 other patients who underwent resection for ductal pancreatic cancer would not be considered operative candidates by these same stage criteria (stage III–IV), and these patients were not considered further in this analysis. Those who underwent pancreatic resection for stage III or IV disease generally did so in the early years of our series. In a more recent case, however, the surgeon did a pancreatectomy in the belief that the patient had lesser-stage disease, only to determine subsequently that fixed histologic slides showed evidence of metastatic disease that was not evident on intraoperative frozen sections. The overall mortality rate within 30 days of surgery was 3.5% (5 of 142 patients). Four postoperative deaths occurred in the first 76 patients who underwent pancreatectomy, for a postoperative mortality rate of 5.3% during the years 1987 to 2002. One postoperative death occurred in the next 66 patients who underwent resection during the years of highest operative volume (2003 to 2006), for a postoperative mortality rate of 1.5%.

Table 2. — Stage of 137 Patients Who Underwent Resection of Stage IA–IIB Ductal Pancreatic Cancer With Curative Intent and Survived at Least 30 Days After Surgery*

Stage Group	n
IA – tumor ≤ 2 cm, confined to pancreas, no nodes positive	9 (7%)
IB – tumor > 2 cm, confined to pancreas, no nodes positive	21 (15%)
IIA – local extrapancreatic extension without celiac axis or superior mesenteric artery involvement, no nodes positive	44 (33%)
IIB – regional node metastasis	63 (45%)
T Stage	
T1 – tumor ≤ 2 cm, confined to pancreas	14 (10%)
T2 – tumor > 2 cm, confined to pancreas	28 (21%)
T3 – local extrapancreatic extension without celiac axis or superior mesenteric artery involvement	95 (69%)
N Stage	
N1 – regional node metastases	65 (48%)
R Stage	
R1 – microscopically positive resection margin	37 (27%)

* Stage as per Greene FL, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Manual.* 6th ed. New York, NY: Springer-Verlag, 2002:157-164.

In order to separate death attributable to recurrent disease from mortality associated with the surgery itself, we focused the remainder of our analysis on the 137 patients with stage IA–IIB ductal pancreatic cancer who survived at least 30 days after surgery. Eighty (58%) of these 137 patients were women. The median age at time of surgery was 67.8 year (range 24.6–88.3). Of the 137 resections, 117 (85.4%) were pancreaticoduodenectomies with or without pylorus preservation, 18 (13.1%) were distal pancreatectomies, and the remaining 2 (1.5%) were total pancreatectomies. Five of the pancreatectomies involved resection of the superior mesenteric vein, the portal vein, or in one instance, both. At least 61 patients received adjuvant chemotherapy, radiation therapy, or both. The median primary tumor size was 3.0 cm (range 0.6–14.7). Table 2 shows the AJCC staging for all 137 patients with stage IA–IIB ductal pancreatic cancers who survived at least 30 days after pancreatectomy.

Survival

The disease-specific Kaplan-Meier survival estimate for the 137 stage IA–IIB patients who underwent resection of ductal pancreatic cancer and survived at least 30 days after surgery is shown in Fig 2. The sum of the number of years that each patient was at risk for death due to recurrent pancreatic cancer (total analysis time at risk) was 254.8 years, and 70 of the 137 patients died with evidence of disease. Median survival time was 21.2 months after resection. The probability of surviving 3 years after resection was 0.36 (95% confidence interval [CI] 0.26, 0.46), while the 5-year probability was 0.32 (95% CI 0.22, 0.43). Two of the 13 patients who survived at least 5 years died later with evidence of disease. The patient who survived longest after pancreatectomy has remained alive without evidence of recurrent disease for almost 16 years. The Kaplan-Meier survival curve for those patients who underwent a distal pancreatectomy did not differ from that of patients who underwent a pancreaticoduodenectomy ($P = .93$). Survival for the 65 patients undergoing resection during the recent years of highest operative volume, 2003 to 2006, was greater than for those 72 patients who underwent surgery in earlier years, 1987 to 2002 ($P < .05$) (Fig 3). The Kaplan-Meier survival curve for those patients greater than 75 year of age did not differ from that of younger patients ($P = .64$) (Fig 4), with median survivals of 1.54 years and 1.77 years, respectively.

Discussion

Pancreatectomy for primary cancers and premalignant neoplasms was done with increasing frequency at our institute in the late 1980s, as at other institutions. We reviewed our 20-year experience with pancreatectomy, focusing on the outcomes of surgery in patients with ductal adenocarcinoma amenable to resection as defined by the current TNM classification of the AJCC.[12] In this classification, patients are deemed unresectable if there is involvement of the celiac axis or superior mesenteric artery (stage III) or if metastatic

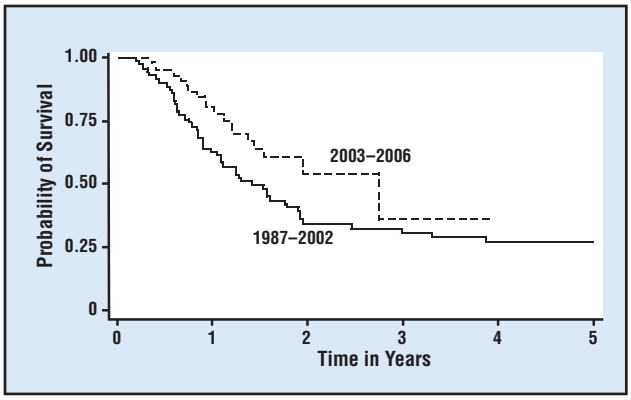

Fig 3. — Kaplan-Meier survival estimate by year of surgery for 137 patients who underwent resection of stage IA–IIB ductal pancreatic cancer with curative intent and survived at least 30 days after surgery. Survival for 65 patients undergoing resection during the recent years of highest operative volume, 2003–2006, was greater than for those 72 patients who underwent surgery in earlier years, 1987–2002 ($P < .05$).

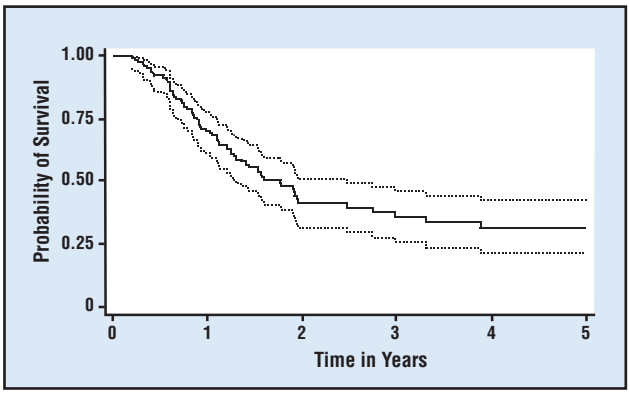

Fig 2. — Kaplan-Meier survival estimate for 137 patients who underwent resection of stage IA–IIB ductal pancreatic cancer with curative intent and survived at least 30 days after surgery. Dotted lines represent the 95% confidence interval. Surgeries were done at our institute during the 20-year period of 1987 through 2006.

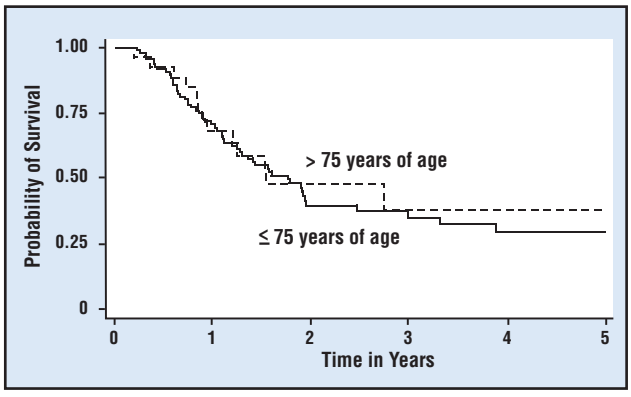

Fig 4. — Kaplan-Meier survival estimate by age at time of surgery for 137 patients who underwent resection of stage IA–IIB ductal pancreatic cancer with curative intent and survived at least 30 days after surgery. Survival for the 29 patients greater than 75 years of age did not differ from the 108 patients who were younger ($P = .64$).

Table 3. — Outcomes of Pancreatectomy for Ductal Adenocarcinoma of the Pancreas in Selected Case Series Reported Since 2000

Institution (Year of Publication)	n	Median Survival (yrs)	Probability of Survival		Postoperative Mortality (%)	
			3 Year	5 Year	Recent Years	Entire Series
Kansai Medical University, Osaka (2003)[13]	94	0.9	0.22	0.13	–	3.2
University Hospital Mannheim (2003)[14]	194	1.3	–	0.25	–	3.1
Indiana University Hospital (2004)[15]	202	–	0.27	–	–	4.7
Samsung Medical Center, Seoul (2006)[3]	94	1.0	0.16*	0.16	–	2.1
Seoul National University Hospital (2006)[16]	123	1.2	0.28	0.12	–	0.8
Johns Hopkins Hospital (2006)[4]	1175	1.6	0.27*	0.18	1	2
Moffitt Cancer Center	142	1.8	0.36	0.32	1.5	3.5

* Estimated from published Kaplan-Meier survival curve.

disease is present (stage IV). Current AJCC staging classifies cancer with local extension to the superior mesenteric or portal veins as being a potentially resectable T3 lesion because such tumors are considered resectable in some centers.

We found that patients with ductal adenocarcinoma of the pancreas who underwent resection with curative intent had a 32% chance of avoiding death attributable to recurrent disease for 5 years, as estimated by the Kaplan-Meier method. The survival curve that describes the experience of our specific group of patients can be generalized to the larger population of such patients, of which our patients are but a sample. The point estimate of 32% is our best estimate of the true 5-year probability of avoiding death attributable to recurrent disease in the larger population, while the 95% CI represents the range within which the true probability lies with a specified degree of assurance. Thus, we are 95% confident that the true 5-year disease-specific survival in the larger population is no less than 22% and no greater than 43%. Similar to others, we found a modest improvement in survival for patients undergoing resection during the recent years of highest operative volume compared to patients who underwent surgery in earlier years.[4]

Series published since the year 2000 exhibit variability in the probability of long-term survival for patients undergoing resection of pancreatic ductal adenocarcinoma (Table 3).[3,4,13-16] The probability of surviving 3 years varied from 16% to 36% in these studies, as determined by the Kaplan-Meier method, while the probability of 5-year survival ranged from 12% to 32%. We do not know if studies other than our own estimated disease-specific survival, ie, the probability of surviving death attributable to recurrent disease rather than all-cause mortality. The survival probability will be less if survival from all-cause mortality rather than disease-specific survival is estimated. Only our case series specified 95% CI for the survival curve. At least in part, variability in survival rates among studies could be explained by between-study differences in details of analysis as well as by factors such as patient selection for surgery, disease stage, and operative procedures. No true control groups exist against which these survival rates can be compared. Nevertheless, surgery offers a chance for long-term disease-specific survival to patients who otherwise would not be expected to survive 5 years, with the only question being the true magnitude of the survival benefit.

All forgoing evidence to the contrary, a degree of credence is still given to the belief that pancreatectomy offers little survival advantage to those with pancreatic cancer.[2,4,10,17-19] This belief is rooted primarily in the observation that the number of patients who have been observed to actually survive 5 years is less than would be expected from the probability of survival determined by the Kaplan-Meier method. As a result, Gudjonsson[17] concluded that Kaplan-Meier and other actuarial methods "have contributed to the misinterpretation of results and the continuation of resections, with a concomitant waste of resources." This conclusion is unexpected, as survival analysis is a widely accepted statistical method for studying the occurrence and timing of many kinds of events in the biomedical and social sciences, engineering, and economics. The estimation of disease-specific survival after cancer resection is a classic application of the Kaplan-Meier method for survival analysis.

Guðjónsson[17] has argued that the survival rate should be calculated as the proportion of resected patients who are documented 5-year survivors rather than according to the Kaplan-Meier method. If we were to use this approach, termed the "method of proportions," in our patient population, we would find a 10% (13/137) documented, actual 5-year survival rate in the 137 patients who underwent resection and survived at least 30 days, whereas the Kaplan-Meier method yields a 32% disease-specific probability of surviving 5 years. While the method of proportions may seem intuitive, it does not use information from patients who died early without evidence of recurrent pancreatic cancer, from those who were "lost" to follow-up before 5 years of observation, or from those who were alive at last contact but not yet 5 years out

from pancreatectomy. This method effectively treats all such patients as if they had died with evidence of recurrent cancer. In the language of survival analysis, these patients are referred to as being "censored." [20,21] All methods of survival analysis allow for censoring. Conceptually, the Kaplan-Meier method involves the recalculation of survival probability at each time after pancreatectomy that a death attributable to recurrent disease occurs. All patients who were alive and at risk at each time are used in determining the survival probability, and no information is discarded. If enough patients are censored, then the method of proportions can grossly underestimate survival probability and introduce bias.[21] In total, 67 of our 137 patients were censored and, for purposes of calculating the 5-year survival rate by the method of proportions, were effectively treated as if they died with recurrent disease.

To illustrate the difficulties encountered in interpreting and comparing survival rates from different studies when different measures of survival are used, we compared our findings to those of a recently published series by Riall et al[22] of patients who underwent pancreaticoduodenectomy for periampullary adenocarcinoma, all of whom were followed for at least 5 years or until death. The "actual" 5-year survival rate of 17% reported for the 564 patients with periampullary adenocarcinoma of the pancreas in this series is greater than the 10% "actual" 5-year survival rate calculated by the method of proportions in our own series. Because all patients in this series were followed for at least 5 years or until death from all causes, 17% is also the all-cause mortality survival rate. The authors state that they did not have disease-specific survival for their patients; however, the disease-specific Kaplan-Meier estimate of 5-year survival in their patients would be greater than the "actual" 5-year survival rate of 17%, although how much greater would depend on how many patients died before 5 years without evidence of recurrent disease. We found that the Kaplan-Meier all-cause mortality survival rate was 23% in our series, in which we had patients who were either lost to follow-up or who were alive at last contact but not yet 5 years out from pancreatectomy. As we have already noted, the disease-specific 5-year survival estimate in our patients was 32%. We suspect that because disease-specific survival is not specified in many studies, the survival estimates reported in these studies are all-cause mortality survival, which are expected to be lower.

In considering the survival advantage offered by pancreatectomy, the probability of long-term survival must be weighed against postoperative mortality. Prior to 1970, postoperative mortality exceeded 25%.[5,7] In our patients, the 30-day postoperative mortality was 3.5% for the entire series but 1.5% in the most recent years of highest operative volume. Postoperative mortality in our patients is comparable to the 1% to 3% mortality reported for other case series published since the year 2000 (Table 3), a dramatic improvement from the rates observed prior to the 1980s. Factors shown to be associated with reduced morbidity and mortality include shorter operative times, reduced intraoperative blood loss, experience of surgeons, and the higher operative volume found in centers with a particular interest in the care of patients with pancreatic cancer.[23-25] One study found that the risk of perioperative mortality in hospitals with fewer than 5 pancreatic resections performed annually was nearly 20 times that in hospitals where more than 20 pancreatectomies were done.[25] Our low postoperative mortality and favorable long-term survival are due at least in part to surgeon experience and the volume of pancreatic resections. Three surgeons experienced in pancreatic surgery performed 80% of the pancreatectomies done at our institute during the past two decades, and between 30 and 35 pancreatic resections were done in each of the last 4 years, a time when the number of clinicians and investigators focused on the care of patients with pancreatic cancer has increased.

Recent large case series of pancreaticoduodenectomies done for cancer in the elderly have shown that age alone should not preclude resection of a pancreatic cancer with curative intent.[26,27] Age was not an independent risk factor for increased postoperative mortality in these studies. Our findings are consistent with these studies in that the survival curve for patients who were older than 75 years of age did not differ from that of younger patients.

Conclusions

In the history of surgery for pancreatic adenocarcinoma, the earliest efforts were focused on achieving acceptably low perioperative morbidity and mortality and on determining the technical factors important in achieving this outcome. The emphasis of more recent reports in the literature has shifted toward demonstrating the survival advantage offered by pancreatectomy and identifying readily available clinicopathologic measures that may be predictive of survival. Review of our 20-year experience with resection of pancreatic adenocarcinoma confirmed the findings of others that pancreatectomy with curative intent offers the only real chance of long-term survival to patients who otherwise would have none. Further studies are needed to determine histologic, molecular, and genetic markers of tumor behavior that not only may be more predictive of survival, but also may guide adjunctive therapy for patients undergoing pancreatectomy for ductal adenocarcinoma.

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