

Results of Total Pancreatectomy for Adenocarcinoma of the Pancreas

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Hypothesis: Total pancreatectomy for infiltrating ductal adenocarcinoma is not superior to pancreaticoduodenectomy or distal pancreatectomy.

Design: A retrospective analysis of a prospective database of patients.

Setting: Memorial Sloan-Kettering Cancer Center, New York, NY.

Patients: All patients (n=488) undergoing pancreatic resection.

Main Outcome Measures: Duration of operation, estimated blood loss, complications, length of stay, number of positive lymph nodes, presence of a positive margin, and survival times were analyzed.

Results: Thirty-five patients were identified who underwent total pancreatectomy, 28 of whom had adenocarcinoma. Median length of stay was 32 days; 19 (54%) developed postoperative complications, of which 63% were infectious. Thirty-day mortality was 3% (1 patient). Median survival was 9.3 months (range, 0.6-172 months).

There was no significant difference between patients with and without adenocarcinoma in terms of duration of operation, estimated blood loss, complications, length of stay, or number of readmissions. In patients with adenocarcinoma, margin or nodal status were not significant survival variables. Patients undergoing total pancreatectomy for adenocarcinoma had a significantly worse overall survival than those undergoing total pancreatectomy for other reasons ($P < .001$), or compared with a contemporaneous cohort with adenocarcinoma undergoing pancreaticoduodenectomy (n=409) and distal pancreatectomy (n=51) (7.9 vs 17.2 months; $P < .002$).

Conclusions: Total pancreatectomy can be performed safely with low mortality; survival is predicted by the underlying pathologic findings: patients undergoing total pancreatectomy for adenocarcinoma have a uniformly poor outcome. Those undergoing total pancreatectomy for benign disease or nonadenocarcinoma variants can have long-term survival. In patients who require total pancreatectomy for ductal adenocarcinoma, the survival is so poor as to bring into question the value of the operation.

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ALTHOUGH THERE have been substantial improvements in morbidity and mortality for surgical resection of cancer of the pancreas, improvements in survival have been small,¹⁻⁴ with the majority of patients dying in less than 2 years after "curative resection."⁵ A number of adverse prognostic factors have been identified, including lymph node status, tumors with poor histologic differentiation, and tumor size.⁶ While the extent of operation has not been shown to be a significant predictor of outcome, some have suggested that pancreatic adenocarcinoma is a multicentric disease and resections less than total are suboptimal. Thus, the concept of total pancreatectomy with wide regional lymphadenectomy is intellectually appealing.

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The first total pancreatectomy was reported in 1943 by Rockey,⁷ who performed the procedure for carcinoma. Unfortunately, the patient died within 1 month of resection. Priestly et al,⁸ in 1944, performed the procedure for hyperinsulinism, resulting in long-term survival; Ross,⁹

See Invited Critique at end of article

in a 1954 report of a total pancreatectomy for carcinoma, was a strong advocate of the procedure. Support for the procedure grew in the early 1970s because the results of pancreaticoduodenectomy were so poor. The results of total resection, however, were not significantly better, with few long-term survivors.^{10,11} Further interest in total pancre-

PATIENTS AND METHODS

We analyzed a prospective database of patients undergoing pancreatic resection at Memorial Sloan-Kettering Cancer Center, New York, NY, from October 15, 1983, to November 30, 1998. Clinical and operative details were recorded, and pathologic findings were reviewed. Resections were performed by experienced pancreatic surgeons. The extent of nodal dissection was at the surgeon's discretion. Patients undergoing total pancreatectomy for infiltrating ductal adenocarcinoma were compared with those undergoing total pancreatectomy for other tumors or benign diseases. We also compared survival of patients undergoing total pancreatectomy for adenocarcinoma with those undergoing either distal pancreatectomy or pancreaticoduodenectomy (Whipple) for adenocarcinoma. Follow-up was obtained by patient interview or hospital charts and correspondence with the attending physician.

Clinical characteristics were compared by means of Fisher exact test and Wilcoxon rank sum test for categorical and continuous data. Survival was analyzed by the Kaplan-Meier method, with differences in survival compared by the log-rank test. Significance was defined at the .05 level.

atectomy has been generated because of the literature on extended lymphadenectomy for pancreatic resections.¹² A recent randomized trial from Italy showed a trend toward a survival benefit from extended lymphadenectomy.^{11,13}

The true role of total pancreatectomy for adenocarcinoma is controversial. Advocates have suggested that the increased morbidity associated with total pancreatectomy is compensated for by a potential improvement in survival.⁹ Detractors have reported that the morbidity and brittle diabetes subsequent to complete resection of the gland overshadow any marginal benefits. To clarify the role of total pancreatectomy, we examined the outcome of patients undergoing total pancreatectomy, analyzing the safety of the procedure and factors associated with long-term survival.

RESULTS

During the study period, 488 patients underwent exploration and resection for adenocarcinoma of the pancreas: 51 patients underwent distal pancreatectomy, 409 patients underwent pancreaticoduodenectomy, and 28 patients underwent total pancreatectomy. An additional 7 patients underwent total pancreatectomy for other diseases (3 for benign disease, 3 for intraductal papillary-mucinous neoplasms, and 1 for adenocarcinoma of the common bile duct). Of the 28 patients with adenocarcinoma who underwent total pancreatectomy, 15 were men and 13 were women, with a median age of 61 years (range, 45-82 years). Eight patients (29%) had undergone exploration before presentation at our institution. Of these, 6 patients had exploration without resection; 1 patient had a distal pancreatectomy but subsequently developed recurrent disease. Data were unavailable for the remaining patient.

Table 1. Operative and Postoperative Characteristics of Patients Undergoing Total Pancreatectomy

Characteristic	No		P
	Adenocarcinoma (n = 28)	Adenocarcinoma (n = 7)	
Age, (median), y	61.7	61.7	.71
Sex, No. (%) M	15 (54)	3 (43)	.69
Estimated blood loss, median, mL	2800	2100	.12
Duration of procedure, median (range), h	8.2 (4.5-11.3)	8.0 (4.5-12.3)	.36
Complications, No. (%) of patients	17 (61)	2 (29)	.21
Sepsis, No. (%) of patients	10 (36)	2 (29)	1.00
Length of stay, median (range), d	32 (14-131)	14 (11-51)	.18
Readmitted to hospital, No. (%) of patients	15 (54)	4 (57)	1.00
No. of readmissions, median (range)	2 (1-4)	1 (0-4)	.49
Postoperative survival, median (range), mo	7.9 (0.6-120.0)	31.8 (7.9-179.0)	<.001*

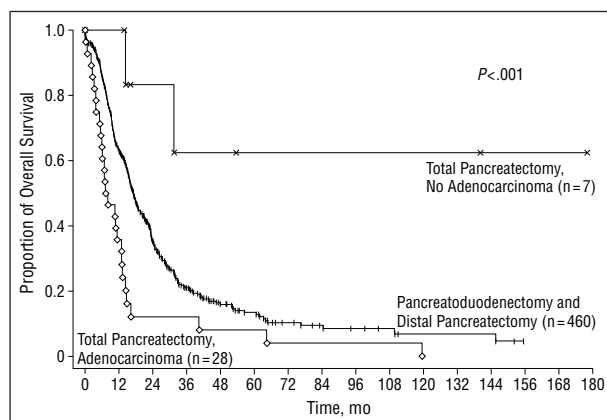
*By Kaplan-Meier test.

Median duration of the procedure for all patients (n=35) undergoing total pancreatectomy was 8.1 hours (range, 4.5-12.1 hours), with a median estimated blood loss of 2500 mL (range, 350-7600 mL). Previous exploration correlated with a significantly longer procedure ($P<.03$) and greater estimated blood loss ($P<.02$). Nineteen (54%) developed postoperative complications, 12 (63%) of which were infectious. Median length of stay was 32 days. The perioperative mortality (30 days) was 3% (1/35). One patient died at 71 days and 1 died at 131 days postoperatively, without having been discharged. Nineteen patients (55%) who underwent total pancreatectomy were readmitted postoperatively, with a median hospital stay of 22 days (range, 2-136 days).

Despite total pancreatectomy, 18% (5/28) of patients with adenocarcinoma had a positive margin. Positive lymph nodes were seen in 29% (8/28). Histologic examination of the primary tumor demonstrated good differentiation in 25% (7/28), moderate differentiation in 36% (10/28), and poor differentiation in 39% (11/28). Ninety-six percent (27/28) of patients with adenocarcinoma had recurrences, and all died. One patient was alive and free of disease 13 months after operation before becoming unavailable for follow-up. Median survival for this group was 7.9 months (range, 0.63-120 months). In patients with adenocarcinoma, there was no apparent effect of number of positive nodes ($P=.97$), positive margins ($P=.08$), or differentiation ($P=.30$) on outcome.

There was no significant difference between ductal adenocarcinoma and nonadenocarcinoma groups in terms of age, sex, duration of operation, estimated blood loss, complications, length of stay, or number of readmissions (**Table 1**). However, patients undergoing total pancreatectomy for ductal adenocarcinoma had a significantly worse overall survival than those undergoing total pancreatectomy for other reasons ($P<.001$).

We then compared survival of patients undergoing total pancreatectomy for ductal adenocarcinoma with a contemporaneous cohort with adenocarcinoma undergoing pancreaticoduodenectomy (n=409) or distal pancreatectomy (n=51) and found those undergoing total pancreatectomy to have a significantly worse survival (7.9 vs 17.2 months; $P<.002$) (Figure). When compared separately, patients undergoing total pancreatectomy for adenocarcinoma had a shorter survival than those undergoing pancreaticoduodenectomy (7.9 vs 17.2 months; $P<.001$) or distal pancreatectomy (7.9 vs 15.8 months; $P=.02$). Even when patients who underwent total pancreatectomy were compared with the subset of all patients who underwent resection with pancreaticoduodenectomy or distal pancreatectomy with a pathologically positive surgical margin (n=100) (ie, patients who were not rendered free of disease), survival for total pancreatectomy was worse (7.9 vs 14.2 months; $P<.03$).



Results of pancreatic resection. Patients undergoing total pancreatectomy for adenocarcinoma had a significantly worse survival than patients undergoing other pancreatic resections or total pancreatectomy for nonadenocarcinoma pathologic findings.

Although the operative morbidity and mortality of all varieties of pancreatic resection have decreased markedly in the past 2 decades, no inroads have been made in improving overall survival in patients with adenocarcinoma.^{1,4} The poor survival has been attributed to the advanced disease state at diagnosis, the presence of microscopic positive margins, and positive nodal disease.^{1,14} Total pancreatectomy offers the theoretical advantage of complete surgical extirpation of the gland and consequent elimination of multicentric disease. It also may allow a wider lymphadenectomy¹⁵ and improve the rate of resectability, as indicated in a study by Launois et al.¹⁶ Initial reports of total pancreatectomy for hyperinsulinism⁸ and carcinoma⁷ demonstrated the feasibility of total resection, and Ross⁹ in 1954 urged that total pancreatectomy be a standard for resection. **Table 2** provides a summary of the larger series of total pancreatectomies.

To be useful, total pancreatectomy must be done safely, and there are differing reports in the literature as to the safety of this procedure. Some reports indicate that total pancreatectomy can be performed safely^{19,23-25} and with no different morbidity than with Whipple resection.^{11,15} Other reports in the literature, however, show significant mortality rates for total pancreatectomy, as high as 28% in one series.¹⁸ Another report indicated the complication rate with total pancreatectomy to be 3-fold higher than with pancreaticoduodenectomy.²⁶ Ihse et al¹⁰ showed that patients undergoing total pancreatectomy had significantly increased perioperative morbidity and mortality compared with those undergoing less radical surgery, but many of these patients underwent surgery before the "modern" era, and more recent studies have shown total pancreatectomy to be relatively safe. In our study, performed in the modern era of pancreatic surgery, there was only a 3% perioperative (30-day) mortality rate and a 55% morbidity rate. Length

Table 2. Results of Total Pancreatectomy: Collected Series

Source	Years of Study	No. of Patients	Operative Mortality, %	Operative Morbidity, %	Median Length of Stay, d	5-y Survival, %	Median Survival, mo	Pathologic Findings*
Current series	1983-1998	35	3†	55	32	11	11.6	Mix
		28	4	63	26	7	7.9	Cancer
Brooks et al ¹¹	1970-1986	48	18‡	27	21-28§	14	12-24	Cancer
Cooper et al ¹⁷	1977-1986	83	5	46	NA	NA	NA	Benign
Cooperman et al ¹⁸	1940-1978	58	26	NA	NA	14	NA	Mix
		47	28	NA	NA	5	NA	Cancer
Fleming and Williamson ¹⁹	1978-1994	40	5	38	NA	38	43	Benign
Cubilla et al ²⁰	1949-1972	19	26	NA	NA	NA	NA	Cancer
Fortner ²¹	1979-1983	20	10	56	29	NA	NA	Cancer
Grace et al ⁴	1975-1984	22	14	59	NA	0	NA	Cancer
Ihse et al ¹⁰	1959-1992	89	27	52	27	4.5	7	Cancer
Launois et al ¹⁶	1968-1986	47	13¶	53	31	8	8	Cancer
Swope et al ¹⁵	1987-1991	47	8	39	NA	NA	17.4	Cancer
van Heerden et al ²²	1951-1978	51	14	NA	26	2.3	13	Cancer

*Mix indicates all pathologic findings; cancer, any cancer.

†Thirty-day mortality.

‡Zero in last 15 years.

§Fifty percent discharged within 3 to 4 weeks; 25%, in greater than 4 weeks.

||NA indicates not available.

¶Zero after 1981 (n = 19).

of stay was markedly prolonged, emphasizing the greater morbidity associated with total pancreatectomy.

The reported efficacy of total pancreatectomy varies widely, for some have claimed a survival advantage for total pancreatectomy,²⁷ whereas other reports find the results of pancreaticoduodenectomy to be superior.²⁸ Swope et al,¹⁵ in a review of the Veterans Affairs database, found an improved survival in patients with stage I and stage II disease undergoing total pancreatectomy compared with Whipple resection ($P = .06$),¹⁵ but this was not seen in stage III and IV disease. These results may simply be due to stage migration. A study by van Heerden et al²² showed a 3-year survival rate of 9% and a 5-year survival rate of 2.3%. In the current study, only 2 of 28 patients survived 5 years.

Most of the theoretical advantages of total pancreatectomy over subtotal resection are not borne out. The advantage resulting from the multicentric nature of the disease is not realized, for studies show that multicentric disease is actually uncommon, seen in only 9% of cases.^{18,29} In addition, the theoretical advantage of total pancreatectomy in eliminating a pancreatic anastomosis²² is often not realized; although the leak rates after anastomosis are substantial, occurring in 10% to 20%, pancreatic leaks are most often not life threatening.³

Total pancreatectomy has been advocated as an alternative in selected cases of benign pancreatic disease,^{18,24,30} and these reports indicate favorable outcomes. Dresler et al³¹ examined the metabolic consequences of total pancreatectomy and found that, although patients become diabetic and have some alterations in lifestyle, most are able to resume a reasonable level of activity. Only 1 of 49 patients died of metabolic disarray, with no other patients having serious diabetic sequelae. Other reports after total pancreatectomy have shown good performance status postoperatively, with intermittent hypoglycemia being the most frequent complication.³² In the current study, all 3 patients with benign disease were alive, with follow-up of 4.5, 12, and 14 years. Two of the 3 patients with intraductal papillary lesions were alive, with a median follow-up of 16 months.

Prognosis of patients undergoing total pancreatectomy appears to be based more on underlying pathologic features than type of resection. In the current series, patients undergoing total pancreatectomy for ductal adenocarcinoma had a significantly worse overall survival than those undergoing total pancreatectomy for other pathologic conditions. In fact, 96% of patients with adenocarcinoma died of their disease, whereas 86% of patients undergoing total pancreatectomy for other disease were still alive at last follow-up. These results are in accord with those of Assan et al,³² who showed long-term survival after total pancreatectomy for benign disease but none for cancer.

Total pancreatectomy for adenocarcinoma offers no survival advantage over less-than-total resection. Furthermore, a positive margin of resection at the time of pancreaticoduodenectomy for adenocarcinoma should not cause the surgeon to perform a total pancreatectomy, as the morbidity is greater and the outcome no better. Total pancreatectomy may play a role in patients with other disease, such as benign disease or intraductal papillary lesions of the pancreas. These patients can have prolonged survival.

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The development, evolution, and eventual abandonment of total pancreatectomy for cancer of the head of the pancreas is analogous to the earlier historic fate of total gastrectomy for gastric cancer. Total extirpation of both organs was originally thought to be incompatible with life, but major surgical, scientific, and technical advances in the second quarter of the past century allowed the surgeon to completely excise both organs with impunity. Such radical operations were, however, reserved exclusively for advanced tumors with high morbidity and mortality and negligible long-term survival. In the past 25 years, our understanding of the resulting derangements in gastrointestinal tract function and metabolic processes have led to a more selective, realistic, and conservative approach to operations on both organs.

During the 1960s, dissatisfaction with the early results of Whipple pancreaticoduodenectomy for cancer of the head of the pancreas led to the recommendation by some that the entire gland be removed. The following arguments for total pancreatectomy were rational, even though they could not be subjected to statistical validation:

- **To decrease the complications emanating from the pancreatic remnant.** In the 1960s and 1970s, at least 40% of the postoperative mortality after a Whipple resection was attributable to leakage at the pancreaticojejunal anastomosis. However, this anastomosis is no longer a true "Achilles heel" of the operation, as our technical ability to avoid this complication has improved appreciably. Even if a postoperative leak occurs, we now have an armamentarium, consisting of percutaneous drainage under computed tomographic guidance, octreotide acetate (Sandostatin) to suppress pancreatic secretion, antibiotics, and total parenteral nutrition, such that we rarely, if ever, have to operate on the patient a second time.
- **The multicentricity of pancreatic cancer.** Recent evidence suggests that multicentric disease exists at a much lower rate than previously reported and cannot be advanced as an argument for routine total extirpation of the gland. The associated, possibly premalignant, dysplastic histological changes seen in the body and tail of the gland have an unpredictable natural history, and it is impossible to predict how long, if ever, these microscopic changes will take to evolve into a frankly invasive cancer.
- **More extensive lymphadenectomy when the total gland is removed.** While this is true, the lymph nodes around the body and tail of the gland are rarely involved with a resectable cancer of the pancreatic head.
- **Decreased risk of tumor growth at the resection margin.** The true risk of a positive resection margin at the site of glandular transection is much smaller than was originally feared. In addition, postoperative local recurrence seems to be more frequent in the peripancreatic tissues than in the pancreatic margin itself, as ascertained by autopsy studies. An acceptable alternative to total pancreatectomy is a subtotal resection removing the entire neck and proximal body of the gland, thereby reducing the risk of tumor extension at the resection margin.
- **The issue of diabetes mellitus.** Many patients with pancreatic cancer are already diabetic at the time of presentation. However, total pancreatic extirpation ensures endocrine insufficiency in 100% of cases. The diabetes mellitus is then sometimes difficult to manage, the main problem being hypoglycemia, which can be lethal.

In this issue, Karpoff et al report their experience with total pancreatectomy; their results were disappointing compared with pancreaticoduodenectomy of the Whipple type. However, a word of caution should be expressed. This is a large retrospective review that includes patients with various tumor stages. Nonetheless, it confirms the impression of others during the past 2 decades.^{1,2} In institutions where both operations have been practiced, no statistical difference in survival has been found between the 2 operations.^{3,4} Although it is unlikely that a prospective randomized study could ever be organized to answer this question, we have to conclude that long-term survival in cancer of the head of the pancreas does not depend entirely on whether a Whipple operation or a total pancreatectomy is done, but depends on such factors as the stage and biological behavior of the tumor, the surgeon's experience and expertise with the operation, and the functional status of the patient. It is also clear that excision of the surrounding soft tissue and regional lymph nodes and skeletonization of the major vessels confer more benefit than does removal of the entire gland. Although the Whipple resection remains the first and best option for cancer of the head of the gland and periampullary region, total pancreatectomy should still be considered in rare specific instances for patients with long-standing diabetes who require insulin, such as: (1) when there is obvious tumor growth along the main pancreatic duct or when multicentricity is suspected clinically; (2) when the pancreatic remnant is atrophic, soft, and friable and does not hold sutures; and (3) when a postoperative pancreaticojejunal leak cannot be controlled and reexploration necessitates a complete pancreatectomy.

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