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Total Pancreatectomy for Ductal Adenocarcinoma of the Pancreas with Special Reference to Resection of the Portal Vein and Multicentric Cancer

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Between March 1, 1968 and March 1, 1986, 323 patients underwent surgery for cancer of the pancreas or the periampullary region. Extirpative procedures were performed in 91 patients, of whom 51 had ductal carcinoma of the pancreas. Forty-seven patients had total pancreatectomy, 9 associated with resection of the portal vein and 1 with total gastrectomy. Operative mortality was 15% but fell to zero for the 19 total pancreatectomies performed after 1981. With the introduction of total pancreatectomy, the resectability rate increased from 15% to 32%. Overall mean survival was 14.4 months. Actuarial survival was 42.4% at 1 year, 25.6% at 2 years, 11.9% at 3 years, and 8% at 5 years. Six patients are alive 7, 11, 14, 30, 30, and 73 months, respectively, after operation. Survival was calculated according to the classifications of Hermreck, Tryka and Brooks, and the TNM system. Ductal carcinoma was multifocal in 32% of patients, and 25% had epithelial dysplasia of the pancreatic duct. When portal vein resection was necessary, mean survival was 6.1 months, compared with 18.25 months when it was not performed. We conclude that total pancreatectomy has increased our resectability rate, mainly in patients with tumor spread beyond the usual margins of division for Whipple's procedure. However, the procedure does not appear worthwhile when portal vein resection is necessary or when multicentric cancer or neoplastic emboli are observed in the operative specimen.

The mortality rate for pancreatic carcinoma has increased in industrialized nations over the last 30 years. In the United States it is the fourth leading cause of death due to cancer in men and the fifth leading cause of death in women.

Mortality due to this disease in France is lower than in the United States but may be increasing [1]. Improved detection of pancreatic cancer by ultrasonography, computed tomography (CT) scans, and endoscopic retrograde cholangiopancreatography (ERCP) should result in treatment at an earlier stage. The modalities of treatment, however, have been the object of a long series of controversies.

Under Crile's influence [2], palliative bypass was long preferred. Brooks and Culebras [3], Fortner et al. [4], Ihse et al. [5], Lawrence and Ghosh [6], Moossa et al. [7], Pliam and Remine [8], and Matsui et al. [9] have endorsed excision as the treatment of choice. The results of total pancreatectomy, however, have been disappointing [10]. The aim of this study is to present the results after total pancreatectomy in patients with cancer of the pancreas.

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Patients and Methods

Between March 1, 1968 and March 1, 1986, 323 patients underwent surgery for cancer of the pancreas or the periampullary region. Exploratory laparotomy was performed in 49 patients (15.2%), palliative decompression in 183 (56.7%), and extirpative procedures in 91 (28.1%), 51 of whom had ductal carcinoma of the pancreas. Three patients underwent Whipple's procedure, 1 splenopancreatectomy, and 47 total pancreatectomy; the latter patients form the basis of this report.

There were 33 men and 14 women with a mean age of 59 ± 10.6 years (range 26–73 years); 25 patients (52%) were > 60 years of age. Asymptomatic jaundice was the presenting feature in 43 of 47 patients (91.5%), deteriorated general health in 26 (55%), pain in 22 (47%), weight loss in 38 (81%), and steatorrhea in 13 (28%). Diabetes was associated in only 3 patients (6%). In 3 patients, the tumor had caused gastrointestinal bleeding.

Diagnostic methods have advanced considerably during the period of review, which explains why ultrasonography, a relatively recent technique, was performed in only 38 of the 47 patients. Findings were positive in 89% of cases. ERCP was carried out in 15 of the 47 patients and was positive in 86%. Percutaneous transhepatic cholangiography (PTC) was performed in 9 of the patients and was positive in all of them. Mesenteric-celiac angiograms were obtained in 5 patients to assess vascular involvement and arterial abnormalities. Biologic findings were cholestatic jaundice with increased alkaline phosphatase in 43 patients (91%), γ-glutamyl transpeptidase in 34 of 37 (92%), 5′-nucleotidase in 30 of 33 (91%), and bilirubin in 43 of 47 (91.5%). Increased serum glutamic oxalacetic transaminase and glutamic pyruvic transaminase levels were found in 38 of 42 patients (90.5%) and 37 of 41 (90%), respectively. The carcinoembryonic (CEA) antigen was measured in 13 patients and was found to be increased in 7.

Operative Procedure

Total pancreatectomy was carried out with en bloc removal of the pancreas, skeletonization of the celiac axis, hepatic artery,

superior mesenteric artery, portal vein with complete retroperitoneal node dissection, cholecystectomy, and high transection of the common bile duct. Portal vein resection was necessary in 9 cases. Direct suture was possible in 7 cases, whereas in 2 a saphenous vein graft or arterial prosthesis was used for venous repair. Preoperative discovery of a right hepatic artery did not preclude pancreatic resection. One total pancreatectomy was combined with total gastrectomy because of spread to the stomach.

Segmental portal hypertension was observed during surgery in 4 cases (9%), capsular spread in 3 (6%), retroperitoneal invasion in 6 (13%), and both capsular and retroperitoneal invasion in 4 (9%). Juxtapancreatic and regional lymph node involvement was demonstrated intraoperatively in 2 patients.

Postoperative Management

After total pancreatectomy, postoperative diabetes was managed by regular insulin for the first 2 weeks followed by NPH insulin. Exocrine insufficiency was compensated by 20 to 35 grams of pancreatic extract per day started as soon as oral feeding became possible. Antacids were given to prevent marginal ulceration.

Follow-up

Survival data were assessed according to the Hermreck et al. [11], Tryka and Brooks [12], and TNM [13] classifications (Table 1). Survival was determined from clinical files, autopsy data, and follow-up inquiries to patients and their doctors. Standard statistical analyses were used. The p values are given only for statistically significant results. Postoperative quality of life was assessed according to the following criteria: diabetes under control, no diarrhea, no pain, and normal social life. The result was regarded as excellent with four items present, fair with three items, and poor with fewer than three items.

Table 1. Classifications for pancreatic disease.

Hermreck classification [11]	
I	Local disease only
II	Invasion into surrounding tissue (duodenum portal vein and mesenteric vessels)
III	Lymph node metastases
IV	Generalized carcinoma (liver metastases and peritoneal implants)
Tryka and Brooks classification [12]	
I	Tumor spread along the common bile duct
II	Tumor spread into the body of the pancreas to and beyond the usual site of transection for a Whipple procedure
III	Multicentric carcinoma and intraluminal pancreatic carcinomatosis
TNM classification [13]	
T_0	No evidence of primary tumor
T_1	Tumor limited to the pancreas
T1a	Tumor 2 cm or less in greatest dimension
T1b	Tumor more than 2 cm in greatest dimension
T_2	Tumor extends directly to the duodenum bile duct or peripancreatic tissues
T_3	Tumor extends directly to the stomach, spleen, colon, or adjacent large vessels
N_0	No regional lymph node metastasis
N_1	Regional lymph node metastasis
M_0	No distant metastasis
M_1	Distant metastasis
Stage I	T_1, N_0, M_0; T_2, N_0, M_0
Stage II	T_3, N_0, M_0
Stage III	Any T, N_1, M_0
Stage IV	Any T, any N, M_1

Results

Operative Mortality

Perioperative mortality (30 days) for total pancreatectomy was 13% (6 of 47 patients). No deaths occurred among the 19 patients with total pancreatectomy performed after 1981 or in those with total pancreatectomy combined with resection of the portal vein (9 cases) or with total gastrectomy (1 case). Three patients died from septicemia and one each from hemoperitoneum, hypoglycemic coma, and myocardial infarction associated with intestinal hemorrhage.

The patients spent an average of 12 days in the intensive care unit (range 1–53 days), and overall hospitalization lasted 30.5 days (up to 85 days). The patient's age (i.e., according to whether they were > 60) and bilirubin level had no effect on mortality. There was no mortality among 7 patients in whom jaundice had developed within 15 days before their operation. This result was significantly different from those with jaundice of longer standing ($p < 0.05$).

Similarly, there was no mortality among 11 patients without preoperative weight loss compared with 25% postoperative mortality in 35 patients with preoperative loss of weight ($p <$ 0.05). Mortality increased progressively with an increasing level of malnutrition, as assessed by the protein level in the serum.

Postoperative Morbidity

Nonmetabolic Complications. Postoperative complications occurred in 25 of 47 patients (53%); there were 7 fistulas (2 biliary, 5 digestive), 3 upper gastrointestinal tract hemorrhages, and 20 infections, the main complication. Infection was generalized in 11 patients, of whom 2 had isolated episodes of unexplained fever, 7 septicemia, 2 suppurative empyema. Six had intraabdominal sepsis, and 3 wound infection. Two patients had pulmonary complications associated with cardiac failure. Eleven patients underwent 16 relaparotomies: 3 for digestive fistulas, 2 for hemoperitoneum, 2 for upper gastrointestinal hemorrhage, 3 for septicemia of unknown origin, 3 for subphrenic abscess, 1 for burst abdomen, 1 for thoracotomy for pleural empyema, and 1 for intestinal obstruction.

Functional Results

Surgery was associated with pain relief in 23 patients. During the 30-day postoperative period, 4 patients had severe hypoglycemia, 4 hyperosmolarity, 1 ketoacidosis, and 2 brittle diabetes that responded well to intravenous insulin. Diabetes later became uncontrolled in 4 patients and required several hospital admissions. Previously well controlled diabetes became brittle, and recurrence of tumor was suspected because of the severity of pain, weight loss, and a rise in the CEA titer in 7 patients.

The quality of life, as defined previously, was judged excellent or fair in 62% of the patients.

Pathology Findings

In 42 of 47 cases there were well differentiated ductal adenocarcinomas (89%) and 5 undifferentiated lesions (11%). Three tumors were < 2 cm in diameter. Duodenal involvement was present in 41% of the cases and capsular involvement in 42%. In 57.7%, the nerve sheaths were involved. There was no lymph node spread in 57% of patients. Lymph node extension was present in 20 cases; it was juxtatumoral in 8 cases (40%), peripancreatic in 8 (40%), and distal in 4 (20%). Ductal adenocarcinoma was multifocal in 15 of 47 patients (32%). Twelve patients had epithelial dysplasia of the pancreatic duct.

Resectability Rate

Of the 323 periampullary and pancreatic tumors, 91 were resectable. Between 1968 and 1977, only 13 resections (3 total pancreatectomies and 10 Whipple procedures) were performed in 87 patients, for a resectability rate of 15%. Between 1977 and March 1, 1986, 78 of 246 patients underwent extirpative surgery (47 total pancreatectomies and 20 Whipple procedures), a resectability rate of 32%. According to Tryka and Brooks' classification of ductal carcinoma of the pancreas, 12 (58.7%) of the patients had carcinoma that spread beyond the classic margin for a Whipple procedure and required total pancreatectomy.

Survival Data

Median survival time was 8 months (range 1–73 months). Actuarial survival was 42.4% at 1 year, 25.0% at 2 years, 11.9% at 3 years, and 8.0% at both 4 and 5 years. Six patients are alive 7, 11, 14, 30, 30, and 73 months, respectively, after surgery. The involvement of lymph nodes brings the actuarial curve close to statistical significance. In patients with lymph node involvement, 40% of the nodes were juxtatumoral and were found only when the excised specimen was examined by the pathologist. In several instances, lymph node involvement would have been missed if we had relied only on lymph node biopsy. Age and tumor differentiation did not influence survival.

In relation to Hermreck's classification for ductal adenocarcinoma of the pancreas, median survival was 11 months (range 1–73 months) for the 13 stage I patients, 7 months (range 1–48 months) for the 18 stage II patients, and 8 months (range 1–30 months) for the 16 stage III patients. The difference in survival times between stage I and stages II and III combined was not significant. Likewise, there was no significant difference in actuarial survival (Fig. 1). Median survival according to the Tryka and Brooks classification was 10 months (range 1–34 months) for the 20 type I patients, 10 months (range 1–73 months) for the 12 type II patients, and 6 months (range 1–23 months) for the 15 type III patients. There was no significant difference in actuarial survival (Fig. 2).

Median survival time according to the TNM classification, once operative mortality was excluded, was 12 months (range 1–73 months) for the 38 stage I and II patients and 6.5 months (range 1–30 months) for the 8 stage III patients. Actuarial survival was 51.5% at 1 year, 36.4% at 2 years, 18.7% at 3 years, 12.5% at 4 years, and 12.5% at 5 years for the stage I patients and 32.6% at 1 year, 13% at 2 years, and 0% at 3 years for the stage III patients. This difference was not significant (log rank χ^2 test 2.85) (Fig. 3).

En bloc portal vein resection with the pancreas, as in Fortner's type I operation, was performed as necessary for resection rather than as an elective procedure. Mean survival for the 9 patients who underwent resection of the portal vein was 6.1 months. In comparison, mean survival, excluding

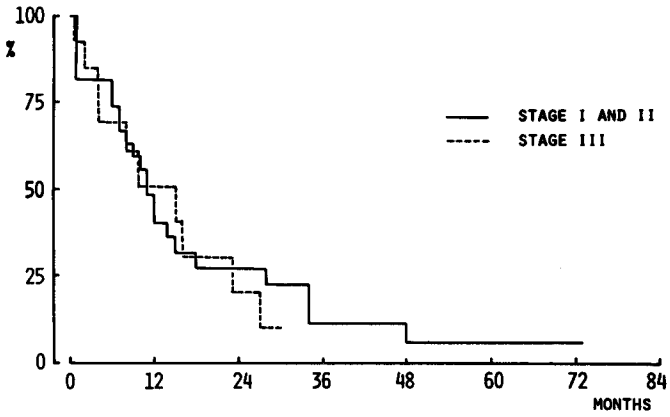

Fig. 1. Long-term survival related to the Hermreck classification.

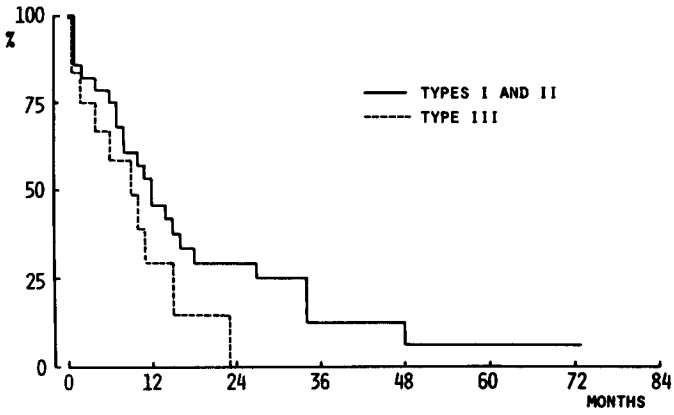

Fig. 2. Long-term survival related to the Tryka and Brooks classification.

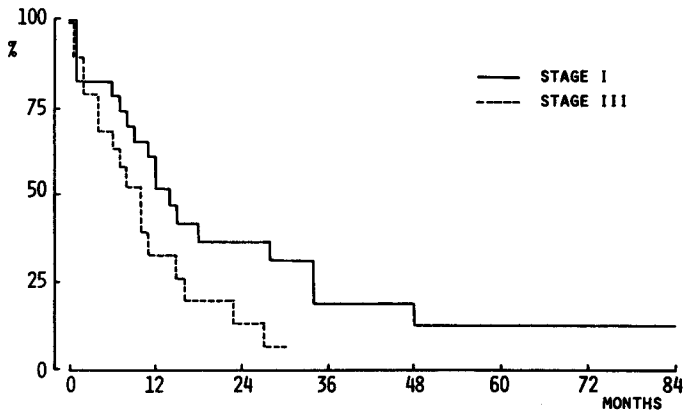

Fig. 3. Actuarial survival related to the TNM classification.

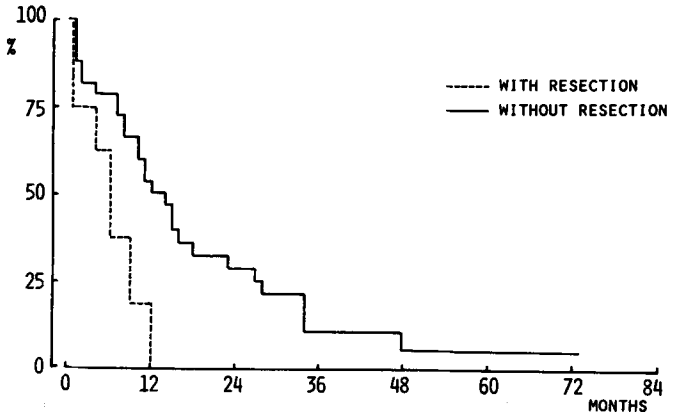

Fig. 4. Long-term survival related to portal vein resection.

operative mortality, for the 35 patients who had extensive en bloc resection without removal of a portal vein segment was 18.25 months. Actuarial survival is 50.4% at 1 year, 29% at 2 years, 10.4% at 3 years, and 5.4% at 5 years without resection, compared with 0% at 1 year with resection (Fig. 4).

Discussion

The choice between performing a Whipple procedure and total pancreatectomy for ductal carcinoma of the pancreas remains a subject of controversy [10–19]. Only three Whipple procedures were performed in our series. One patient survived 8 years [17]. If total pancreatectomy had not been performed in this patient population, 27 of the 47 patients would have been left with residual tumor, as 12 of the patients had tumor extension beyond the usual resection margin for the Whipple procedure and multifocal carcinoma or emboli were present in the ducts of the body and the tail of the pancreas in 15 more.

The rate of multicentric carcinoma or widespread carcinoma (32%) was higher than the 20% to 25% rate commonly reported, probably due to routine use of total pancreatectomy for pancreatic carcinoma in our institution. Unfortunately, another unpropitious factor emerged: the presence of a multifocal tumor or of ductal emboli in the surgical specimen removed during total pancreatectomy (type III, Tryka and Brooks). The prognosis was poor, as median survival was 6 months in these cases. Thus one of the arguments in favor of total pancreatectomy disappears, but these unfavorable findings can be disclosed only if the entire pancreas is removed for pathology examination.

Malpighian metaplasia and in situ tumors were often found in these type III neoplasms. This observation is in concordance with that of Mannell et al., who noted that there was a statistically significant correlation between atypical ductal epithelioma and short survival [20].

Regional pancreatectomy as described by Fortner et al. [4, 21] was not performed in this series. On the other hand, portal vein resection was necessary in 9 cases but was of little benefit to these patients, as the average survival was 6 months when the portal vein was resected; none of these patients lived for more than 12 months.

The quality of life after total pancreatectomy is often a subject of debate. Almost two-thirds of the patients considered the quality of their lives to be fair to excellent. The severe pain experienced before surgery disappeared; and when abdominal pain heralded the onset of recurrence, it was often less intense.

These results, with regard to both operative mortality and the length and quality of survival, must be compared with those obtained using palliative endoscopic cholangiography. In a review of the literature by Andreani et al. [22], including 10 series covering 1342 patients, insertion of a prosthesis was successful in 78% to 92% of the patients. Only one series, however, mentioned mortality at 30 days; all the others included immediate mortality only. The average duration of survival, presented in only four series, ranged from 63 to 144 days [22].

This study does not answer the question of whether it is better to undertake a Whipple procedure or a total pancreatectomy for ductal cancer of the head of the pancreas. It does show, however, that to be certain of removing all of the cancer in the pancreas it is necessary to perform total pancreatectomy. It shows as well that this procedure can be done with acceptable mortality and morbidity.

Total pancreatectomy has increased our resectability rate, which doubled as a whole, although the average duration of survival was comparable to that already reported. Twelve patients (i.e., one-fourth of this population) underwent complete excision, although the neoplastic lesion extended beyond the usual resection margin of a Whipple procedure (type II, Tryka and Brooks). Median survival for these patients was 10 months, which is comparable to the median survival after "curative" resection for pancreatic cancer. The procedure does not appear worthwhile, however, when portal resection is necessary or if the cancer is multicentric or neoplastic emboli (type III, Tryka and Brooks) are present.

Update

Since the writing of this paper, the results from 11 more patients with total pancreatectomy have confirmed our original data.

Acknowledgment

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Résumé

Entre le 1 Mars 1968 et le 1 Mars 1986, 323 patients ont été opérés d'un cancer du pancréas ou de la région périampullaire. Une exérèse a été réalisée chez 91 patients parmi lesquels 51 avaient un cancer glandulaire (adénocarcinome) du pancréas. Parmi ceux-ci, 47 ont eu une pancréatectomie totale dont 9 combinées à une résection de la veine porte et une associée à une gastrectomie totale. La mortalité périopératoire a été de 13%, mais est tombée à 0% pour les 19 pancréatectomies totales réalisées après 1981. Lorsque la pancréatectomie totale a pu être menée à bien, le taux de résecabilité est passé de 15% à 32%. La survie globale a été de 14.4 mois. La survie actuarielle a été de 42.4% à un an, de 25.6% à 2 ans, de 11.9% à 3 ans, et de 8% à 5 ans. Six patients sont en vie 7, 11, 14, 30, 30 et 73 mois après résection. La survie a été calculée en fonction de la classification de Hermreck, Tryka, Brooks et TNM. Le cancer était multifocal dans 32% des cas, et 25% des patients avaient une dysplasie épithéliale du système canalaire. Lorsqu'une ré-

section de la veine porte a été nécessaire, la suvie moyenne a été de 6.1 mois, comparée à 18.25 mois lorsqu'elle n'a pas été réalisée. Nous concluons que la pancréatectomie totale a augmenté notre taux de résécabilité, principalement chez les patients qui aurait eu une résection incomplète si une duodénopancréatectomie céphalique avait été effectuée. Cependant, la pancréatectomie totale ne se justifie pas lorsque la résection concomitante de la veine porte est nécessaire ou lorsque le cancer est multifocal, ou encore lorsque des embols néoplasiques sont présents dans la pièce opératoire.

Resumen

Trescientos veintitrés pacientes fueron sometidos a cirugía por cáncer del páncreas o de la región periampular en el periodo marzo 1 de 1968 a marzo 1 de 1986. Se practicaron procedimientos extirpativos en 91 pacientes, 51 de los cuales presentaban carcinoma del páncreas. Se practicó pancreatectomía total en 47, en 9 de ellos acompañada de resección de la vena porta y en uno combinada con gastrectomía. La mortalidad operatoria fue 13%, pero descendió a cero en las 19 pancreatectomías totales practicadas después de 1981. Con la introducción de la pancreatectomía total se incrementó la tasa de resectabilidad de 15% a 32%. El promedio de sobrevida fue 14.4 meses. La sobrevida actuarial fue de 42.4% a 1 año, 25.6% a 2 años, 11.9% a 3 años y 8% a 5 años. Seis pacientes están vivos a 7, 11, 14, 30, 30 y 73 meses después de la operación. La sobrevida fue calculada de acuerdo a las clasificaciones de Hemreck, Tryka y Brook, así como a la clasificación TNM. El carcinoma ductal apareció multifocal en 32% de los pacientes y en 25% exhibió displasia epitelial del canal pancreático. En los casos en que fue necesario resecar vena porta la sobrevida promedio fue 6.1 meses, en comparación con 18.25 meses cuando ésto no fue necesario. Nuestra conclusión es que la pancreatectomía total ha venido a aumentar la tasa de resecabilidad, especialmente en pacientes con tumores que sobrepasan los límites usuales de la operación de Whipple. Sin embargo, el procedimiento no parece que merezca ser emprendido cuando sea necesario resecar vena porta o en presencia de cáncer multicéntrico o de émbolos tumorales.

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Invited Commentary

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The controversial issue in surgical treatment of cancer of the head of the pancreas is how radical should the extirpative procedure be? Current arguments center around two points: (1) the extent of the pancreatic resection; and (2) the extent of the peripancreatic excision.

1. *Extent of the pancreatic resection*: Extending the Whipple operation into a total pancreatectomy is intended to: (1) remove multifocal disease; (2) eradicate direct extension into the distal pancreas, seeding along the dilated main pancreatic duct, and tumor permeation along the rich lymphatic network of the gland; (3) achieve a better cancer operation by en bloc tissue excision, avoiding confusion over a pancreatic transection level, eliminating multiple frozen section histologic examinations, and obviating a pancreatojejunal anastomosis. Objections