Tumor Size Is the Primary Prognosticator for Pancreatic Cancer After Regional Pancreatectomy

Joseph G. Fortner, M.D.,* David S. Klimstra, M.D.,† Ruby T. Senie, Ph.D.,*
and Barbara J. Maclean, B.A.*

From the Departments of Surgery* and Pathology,† Memorial Sloan-Kettering Cancer Center,
New York, New York

Objective
The purpose of this study was to evaluate the regional pancreatectomy as surgical therapy for ductal adenocarcinoma of the pancreas and to evaluate potential prognostic factors.

Summary Background Data
Regional pancreatectomy was developed as a more adequate surgical procedure for pancreatic cancer in an attempt to improve the cure rate for this highly lethal disease. Few studies have evaluated large numbers of patients treated with this technique, and in recent years the emphasis has been on more limited surgery for pancreatic cancer.

Methods
Fifty-six patients with ductal adenocarcinoma of the pancreatic head were treated by regional subtotal or total pancreatectomy. Clinical and pathologic parameters were reviewed and potential prognostic factors were compared statistically. The three patients who died within 30 days of the operation were excluded from the survival analysis.

Results
Primary tumor size was the strongest determinant of prognosis. The mean tumor size was 3.9 cm (range, 1–7 cm). Eighty-five percent of patients had peripancreatic soft tissue invasion microscopically, and 58% had regional lymph node metastasis. Kaplan-Meier survival curves indicated a 33% 5-year survival for patients with tumor 2.5 cm or less in diameter (n = 12) and 12% for patients with larger tumors (n = 39). No patient with a tumor larger than 5 cm survived more than 5 years. Mean tumor size was not significantly associated with lymph node metastases, but 5 of 12 patients (42%) with primary tumor ≤2.5 cm had lymph node metastases. Twenty-four percent of patients with negative lymph nodes and 14% with positive lymph nodes survived 5 years. The difference was not statistically signifcnat (p = 0.3), but this is likely related to sample size. The 30-day operative mortality was 5.3%. The most common complications were infection, gastrointestinal bleeding, and gastric stasis.

Conclusions
After regional pancreatectomy, tumor size is the strongest predictor of prognosis. A multi-institutional randomized prospective trial of regional pancreatectomy versus pancreaticoduodenectomy is warranted in previously untreated, noninfected cases.

Regional pancreatectomy was described about 20 years ago[1,2] in an attempt to improve the results of surgical treatment of pancreatic cancer as well as invasive ampullary cancers. Principles found to be essential for cure of other intra-abdominal cancers were applied to this anatomically challenging area. A subtotal or total pancreatic resection, usually with resection and reconstruction of the pancreatic segment of the portal vein, is done *en bloc* with a regional lymph node dissection. In highly selected cases, a locally involved segment of a major artery is resected and reconstructed.

The operation has been viewed skeptically for various reasons, including a widespread belief that lymph node dissection for cancer is not therapeutic, because involvement is thought to be a manifestation of generalized disease. The current trend, generally, is for more limited surgery rather than extensive surgery. Furthermore, the operation has not been reported to cure advanced cancer. Only Nagakawa's series[3,4] has confirmed the value of a regional pancreatectomy for controlling pancreatic cancer. Impetus to use the operation may have been lessened by recent reports[5,6] of improved survival rates with a routine pancreaticoduodenectomy.

In the current report, we evaluated further the therapeutic potential of regional pancreatectomy for pancreatic cancer. Our analysis revealed that size of the primary cancer was the single most important determinant of surgical cure. This information could provide a useful basis for selecting patients who might benefit from surgical resection. The validity of the concept of a wide excision of the primary cancer, as permitted by the operation, is supported by the survival of some patients who had extension of the primary cancer into surrounding soft tissue and the relatively large size of the cancer of some patients who were 5-year survivors. That this could include resection and reconstruction of the portal vein was evident from the absence of complications attributed to this. The need for a regional lymph node dissection was apparent from the high proportion of microscopically positive lymph nodes even from small lesions and the long-term survival of some patients with positive lymph nodes.

MATERIALS AND METHODS

The records of all patients undergoing a regional pancreatectomy from January 1, 1979, through December 31, 1991, at Memorial Sloan-Kettering Cancer Center were reviewed. In this retrospective study, patients undergoing a curative type 0 or type I regional pancreatec-

Table 1. REGIONAL PANCREATECTOMY: 1979–1992

No. of patients	97
Operative procedure	
Type 0 and type 1	81
Total pancreatectomy	40
Adenocarcinoma head of pancreas	30*
Other cancers	7
Pancreatitis	3
Subtotal pancreatectomy	41
Adenocarcinoma head of pancreas	26
Other cancers	11
Benign tumor	1
Pancreatitis	3
Palliative resection	11
Type 2 operation	5

* One patient had only a periaortic, porta hepatic, and partial celiac axis lymph node dissection.

tomy were separated for study. A type 0 operation refers to a total or subtotal pancreatectomy with a regional lymph node dissection without resection of the portal vein. A type I procedure adds resection and reconstruction of the pancreatic segment of portal vein. A type I operation with the addition of resection and reconstruction of a major artery is called a type II procedure.[2,7–10]

A histologic review was done in all cases. Only ductal adenocarcinomas of the head of the pancreas are included in the current review. Tumor was classified by type, and pathologic staging criteria were assessed (size, extrapancreatic extension, invasion of adjacent structures, and nodal metastases). Tumor size in the current report refers to pathologic measurement of the specimen.

Statistical procedures for univariate analysis of the data included the chi square test applied to categorized data, the Student's t test for continuous variables, and nonparametric analysis for variables not distributed normally. Survival rates were calculated by the method of Kaplan and Meier.[11] The equality of the distribution was tested by the Mantel–Cox procedure.[12] Multivariate analysis was done with the Cox proportional hazards model.[13] The BMDP statistical package (BMDP Statistical Software, Los Angeles, California) was used.

RESULTS

A regional pancreatectomy was performed for 97 patients during the study period. The type of regional pancreatectomy performed is classified in Table 1. Fifty-six patients underwent a type 0 or type I regional pancreatectomy for cure of a ductal-type adenocarcinoma of the head of the pancreas. These patients are the focus of the current analysis. Seven other patients (7%) un-

derwent the operation for benign disease. Of these patients, one had a benign cystadenoma; one had positive results on frozen-section biopsy, but the final diagnosis was pancreatitis; two patients had negative results on frozen-section biopsies, but resection was done on clinical grounds with a final diagnosis of pancreatitis; and three patients underwent resection on the basis of clinical findings without a biopsy and were found to have pancreatitis only.

Of note in Table 1 are the 11 patients who underwent noncurative procedures. These procedures were classified as palliative because the peripancreatic soft tissue margins of resection were positive, microscopically, in seven patients; liver metastases had been present at surgery but were undetected until later review in three patients, and all gross disease could not be removed in one patient.

The mean age of the 56 patients who had a curative-type regional pancreatectomy for ductal adenocarcinoma of the head of the pancreas was 58.8 years (SD, 7.4 years). Age did not differ significantly by sex: the mean age of the 21 female patients was 57.9 years (SD, 6.9 years), and that of the 35 male patients was 59.2 years (SD, 7.7 years). Sixty-six percent of the patients were diagnosed between the ages of 51 and 64 years; 21% were 65 years or older.

The mean number of days between first symptoms and definitive surgery reported by 48 (91%) of the 53 patients who survived 30 days or longer after the operation was 76.8 days (SD, 57 days). The duration of preoperative symptoms was not noted for the remaining 5 patients. Among female patients, 12 of 14 who reported symptoms had a lapse of 65 days or more between their first symptom and definitive surgery. However, for 33 of the 34 male patients who reported symptoms, the interval from first symptom to surgery was less than 65 days. This difference in duration of symptomatology by sex was statistically significant (p < 0.01). The duration of symptoms was not associated with the risk of dying of pancreatic cancer. Thirty patients reported weight loss of between 5 and 72 lb before surgery.

Eighteen (32%) patients had undergone an earlier operation on the pancreatic tumor, but a resection had not been done. Just before undergoing definitive surgery, 41 (77%) of the 53 patients with recorded preoperative bilirubin levels had median values of 5.9 mg/dL (range, 1.1 to 24.4 mg/dL). Twenty-six patients had undergone a biliary decompression procedure before undergoing pancreatectomy. At time of pancreatectomy, routine bacteriologic examination results of bile obtained immediately after transection of the common hepatic duct revealed that 17 of 56 patients (30.3%) had infected bile. Five others had experienced recent septic episodes of intra-abdominal origin. Two others had had bile peritonitis recently.

For 30 patients, the operation included a total pancreatectomy. Twenty-six (46%) had a subtotal pancreatectomy, which included the head of the pancreas. Twenty-nine patients received a type I total pancreatectomy and 22 received a type I subtotal pancreatectomy. One type 0 patient had a modified operation in that only periaortic, porta hepatic, and partial celiac node dissections were done. The pancreas was usually transected in line with the site where the splenic artery approaches the pancreas from its origin at the celiac axis. A pancreatic duct anastomosis was done for 18 patients.[8-10] An open-end-to-side pancreaticojejunostomy without duct anastomosis was done for 8 patients. A stent was not used in any instance.

The common hepatic duct was transected routinely just below the hepatic duct bifurcation. An end-to-side anastomosis to a loop of proximal jejunum was done as described previously.[8-10] Neither a T tube nor other stent was used. Reconstruction of the subtotal gastric resection involved a Polya or Hofmeister repair, which was a sutured anastomosis for 47 patients and a stapled anastomosis for 7. An earlier subtotal gastrectomy had been done for 2 patients.

The median operating time for the subtotal operation was 8 hours 53 minutes (range, 6.25–13.5 hours). The total regional procedure had a median operating time of 8.5 hours (range, 6–11 hours). Median portal venous occlusion time for the 36 patients for whom it was recorded was 17 minutes (range, 14–60 minutes).

The 30-day operative mortality rate was 5.3% (3 of 56); subtotal resection, 3.8% (1 of 26); total resection, 6.6% (2 of 30). The patient with the fatal subtotal resection died of gram-negative sepsis with cardiac arrest on postoperative day 5. One patient died 20 days after a total pancreatic resection of sepsis and respiratory failure, and another died on postoperative day 25 of adult respiratory distress syndrome. There were two in-hospital deaths after 30 days (Table 2).

The complication rate was high (Table 3). Sepsis, gastrointestinal bleeding, and delayed gastric emptying were the most common complications. Nasogastric tube drainage was present after 5 days in 29 (52%) patients. Only one patient had a pancreatic fistula, which was treated conservatively without untoward outcome. Fifty-one patients were discharged from the hospital a median of 27 days (range, 15–123 days) after their operation. The extensive nature of disease in patients treated in this series is shown in Table 4. Excluding the 3 patients dying within 30 days of operation, 45 (85%) had peripancreatic extension of their primary cancer. Eleven of 12 patients with primary tumor 2.5 cm or less in diameter had peripancreatric soft tissue invasion microscopically. Five of the 12 (42%) had lymph node metastasis. Overall, 31 (58%) had spread to regional lymph nodes. Thirteen of the 31 patients (42%) had more than one

Table 2. DEATHS FROM CAUSES OTHER THAN RECURRENT CANCER

Patient No.	Survival	Cause of Death
1	35 days	Hypoglycemia
2	42 days	Ruptured superior mesenteric artery and intraabdominal bleeding presumed secondary to infection
3	49 days	In-hospital death from accidental bolus of KCl
4	2 mos	Stroke
5	4 mos	In-hospital death from prolonged sepsis and multiple organ failure
6	7 mos	Ruptured liver abscess with peritonitis
7	50 mos	Portal vein thrombosis, liver failure (type 0 procedure)
8	93 mos	Oat cell carcinoma of lung
9	122 mos	Stroke
10	125 mos	Unknown but with no known pancreatic cancer recurrence

lymph node group involved, and 2 patients had three or more lymph nodes involved in one group. One patient with negative lymph nodes had metastatic cancer in the adventitia of the superior mesenteric vein; one patient with positive lymph nodes also had metastatic cancer in the wall of the gallbladder.

Tumor size was recorded for 51 patients; the mean size was 3.9 cm (SD, 1.5 cm). The sizes ranged from 1 cm to 7 cm. Thirty-nine patients (76%) had tumors larger than 2.5 cm. Mean tumor size was not significantly associated with nodal status. The mean tumor size of 22 patients with negative lymph nodes was 3.6 cm (SD, 1.7 cm). This was similar to the mean size of 4.1 cm (SD, 1.3 cm) of the 29 patients with positive lymph nodes. Although more female patients (53%) were diagnosed with stage I disease than male patients (29%), the percentages of males (76.5%) and females (74%) dying of pancreatic cancer did not differ significantly.

Months of survival of the 38 patients who had died of pancreatic cancer by 5 years after their operation were compared with that of the 15 patients who were alive or had died of other causes by 5 years (Table 5). Analysis of variance indicated statistically significant differences in survival (p < 0.01).

Mean survival time differed significantly by categorized tumor size; mean length of survival (48 months) was significantly greater when the tumor was 2.5 cm or smaller compared with larger tumors (22 months). Kaplan–Meier[11] survival curve (Fig. 1) indicated 33% survival at 5 years for patients with tumor measuring 2.5 cm or less. This is a significantly greater proportion than the 12% who survived 5 years after surgery for tumors larger than 2.5 cm (p < 0.01). No patient with a tumor larger than 5 cm in diameter survived 5 years. In contrast, nodal status was not statistically associated with 5-

year survival (p = 0.3). Twenty-four percent of patients with negative lymph nodes and 14% with positive lymph nodes survived 5 years after surgery, but the difference did not reach statistical significance (p = 0.3). Similarly, 5-year survival of patients with stage I disease was 25%, which was not statistically different from the 13% with stage III disease who survived. The apparent failure of lymph node metastases as a prognostic indicator is likely a reflection of sample size and would have become statistically significant if the sample were larger.

Eight patients have lived 5 or more years after surgery. One patient had a modified type 0 pancreatectomy, in that only the periaortic, porta hepatic, and limited celiac axis dissections were done. All others had the standard procedure. Six survivors had peripancreatic soft tissue extension of their cancer, and one also had extensive duodenal invasion. In three patients, disease had spread to regional lymph nodes. Two patients died of recurrent disease after 5 years. In one of these patients, who died 63 months after surgery, cancer cells may have spread when a positive incisional biopsy was obtained from tissue between the common bile duct and the portal vein at an operation done before referral for definitive surgery.

Certain features of some of the patients who died merit comment. One patient died of chronic sepsis 4 months after surgery. Another patient experienced a rupture of undiagnosed multiple liver abscesses that had been treated with 5-fluorouracil for metastatic disease. A third patient died 4 months after surgery, apparently from implanted cancer cells that tracked and spread along the percutaneous biopsy tract. Recurrent cancer in one patient was histologically distinct from the original primary pancreatic cancer and may have been from a different primary cancer.
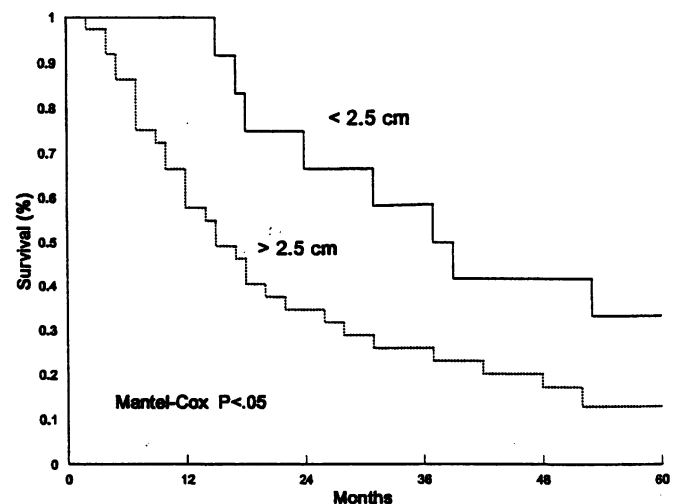
Figure 1. Kaplan-Meier Survival curves for 12 cases with tumors ≤2.5 cm (solid line) and 39 cases with tumors >2.5 cm. Survival differed significantly by tumor size category (Mantel-Cox <0.05).

Table 3. POSTOPERATIVE COMPLICATIONS OF REGIONAL PANCREATECTOMY*

	Type of Pancreatectomy	
	Subtotal	Total
None	3/25 (12%)	4/28 (14%)
Infection		
Intra-abdominal abscess with wound infection	1	2
Wound infection	4	6
With dehiscence	1	0
Sepsis	4	10
Infected drain site	1	0
Urinary tract	0	1
Nonfatal ARDS	1	0
FUO	3	1
Leg infection	0	1
Multiple organ failure	0	1
Bleeding		
Anastomotic site	2	0
Intra-abdominal	1	1
Abdominal wall drain site	0	1
Mild upper GI of undetermined source	4	5
Bile gastritis	1	0
Pulmonary		
Pneumonia	2	5
Atelectasis	8	5
Pleural effusion	4	8
Cardiac		
Arrhythmias	2	5
Congestive heart failure	0	2
Other		
Allergy to FFP	1	0
Anxiety-depression	3	4
Bile leak	2	0
Bile stasis	0	1
Brittle diabetes	0	4
Broken drain on attempted removal	1	0
Central line air embolus	0	1
Central line pulled accidentally	1	0
Chemical thrombophlebitis	0	1
Cholangitis (presumed)	0	1
Cholestatic jaundice	0	1
Chylous ascites	1	0
Decubitus ulcer	0	1
Delay >5 days in removal of nasogastric tube	16	13
Drug rash	0	1
Encephalopathy	0	1
Failure to thrive	0	1
Fatal cardiac arrest secondary to accidental bolus KCl	0	1
Fluid overload	1	2
Gastritis	2	1
Hypovolemia	0	1
Ileus	5	1
Pancreatic fistula	1	—
Peroneal nerve palsy	1	2
Phlebothrombosis	2	1
Profuse diarrhea	1	0
Small bowel obstruction	0	1
Temporary malnutrition	0	3
Transient hyperbilirubinemia	2	0
Wound seroma or separation	1	1
Overall	80 in 22 patients	98 in 24 patients

ARDS = adult respiratory distress syndrome; FUO = fever of undetermined origin; GI = gastrointestinal; FFP = fresh frozen plasma.
* Excludes three 30-day operative deaths.

Table 4.   AJCC STAGE OF DISEASE

Stage	No. of Patients	30-Day POD*	5-Year Survival
I			
T1 N0 M0	5		
T2 N0 M0	15		5
II			
T3 N0 M0	2	1	
III			
T1b N1 M0	2	1	
T2 N1 M0	27		
T3 N1 M0	3		3
IV			
T2 N0 M1	1		
T2 N1 M1	1	1	

* POD = 30-day operative death.

DISCUSSION

The most important prognostic factor for adenocarcinoma of the head of the pancreas after regional pancreatectomy was size of the primary cancer. Mean tumor diameter was 3.9 cm, with a range of 1 to 7 cm, but no patient survived more than 5 years with a tumor larger than 5 cm. A mean of 48 months' survival for patients with primary cancer 2.5 cm or less in diameter was significantly greater than the mean of 22 months for patients with larger tumors. Kaplan–Meier survival curves indicated a 33% survival at 5 years for patients who had 2.5 cm or smaller primary tumor and 12% 5-year survival for patients with larger tumors. Mulitvariate analysis with the Cox proportional hazards model[13] confirmed that tumor size significantly influenced survival after controlling for nodal status. The hazard ratio was 2.1 (confidence interval, 1.1–4.3) for each centimeter increase in size.

The inverse relationship of tumor size and prognosis has been noted by others but does not seem to have been as powerful a prognosticator as was evident in the current series. The data appear to provide a basis for an improved ability to select patients who might benefit from surgical resection. If other studies are confirmatory, then noninvasive technologies, such as spiral computed tomography scanning, could be used to determine tumor size before surgery. With rare exception, any cancer larger than 5 cm appears unlikely to be curable by surgical means. Such patients could be spared the risks, time, discomfort, and expense of curative-type cancer surgery.

Peripancreatic soft tissue invasion was present microscopically in 85% of patients. This was not a statistically significant prognostic factor, but removal of the primary tumor by a wide margin is obviously a necessity for cure. Six of the 5-year survivors had this finding, thus regional pancreatectomy can be effective in controlling locally extensive disease.

The presence or absence of lymph node metastasis was not related statistically to tumor size. The mean tumor size of 22 patients without lymph node metastasis was 3.6 cm (SD, 1.7 cm) and 4.1 cm (SD, 1.3 cm) for 29 patients with lymph node metastasis. Surprisingly, the presence of lymph node metastasis did not significantly influence survival. Instead, the size of the primary tumor was the most powerful determinant and prognosticator.

The relative importance of tumor size and lymph node metastases in the prognosis of pancreatic cancer had not been evident previously. The commonly used pancreaticoduodenectomy does not involve a regional lymph node dissection, thus, generally, the incidence and prognostic significance of lymph node metastases at the time of surgery has not been evident. Lymph node metastasis among patients in the current series were not apparent at surgery, because grossly positive lymph nodes were considered a sign of incurability. Some lymph nodes might have become evident if the peripancreatic region had been explored. Such exploration was not done, but an extensive extraregional search was made for metastatic disease. Sampling of lymph nodes in the region to be resected was not done, and no attempt was made to determine involvement of the portal vein in order to preserve the integrity of the region to be resected.

Microscopically, lymph node metastases were present in 58% (31) of the patients. Thirteen patients had more than one lymph node group involved, and two patients had involvement of three or more lymph nodes in one group. Forty-two percent of patients with tumors 2.5 cm or less in diameter had lymph node metastases. This finding supports the need for a regional lymph node dissection. That it can be effective in controlling disease is indicated by the finding that three of the eight patients surviving 5 or more years after surgery had lymph node metastases. However, the adverse effects of tumor size larger than 5 cm in diameter appear to negate any beneficial effects of regional lymph node dissection for such tumors.

There was no apparent curative advantage to doing a total *versus* a subtotal pancreatectomy. The physiologic

Table 5.   MEAN SURVIVAL IN 53 PATIENTS*

Status at 5 years	No. of Cases	Mean Survival (mos)	SD (mos)
NED	6	89.3	31.2
AWC	2	64.0	1.4
DOD	38	19.7	14.0
DOC	7	9.4	18.0

SD = standard deviation; NED = no evidence of disease; AWC = alive with cancer; DOD = died of disease; DOC = died of cause other than cancer.
* Excludes three 30-day operative deaths.

consequences of a total pancreatectomy can be severe, thus it should be avoided except in unusual cases.

Complications and postoperative deaths were related predominantly to infection. This is not surprising, because 22 patients (39%) had recent or current intra-abdominal sepsis, 2 others (4%) had bile peritonitis on referral, and 18 (32%) had undergone exploration for cancer before referral. No patient died as a result of operative maladventure or technical fault.

The only pancreatic leak that occurred was of no clinical significance. It was detected only by a rise in amylase level of peritoneal fluid drainage, which was one of the tests done routinely after surgery for patients who had had a partial pancreatectomy. On first visit to a physician, there had been a long interval between first symptoms and definitive surgery in the current series. The mean number of days was 76.8, with a statistically significant longer interval for women than for men. However, the duration of symptoms was not statistically associated with the risk of dying of pancreatic cancer. This finding may indicate that the cancer was already advanced when symptoms first appeared.

The data in the current study support the use of regional pancreatectomy for the treatment of pancreatic cancer, possibly no larger than 5 cm. There appears to be no benefit of resection for more advanced lesions. Only a randomized prospective study can establish whether this procedure is superior to others.

Quality control is necessary, particularly regarding the extent of the dissection and the way in which it is done, including the avoidance of tearing or intraoperative biopsy of regional lymph nodes. Future studies should include only noninfected, previously unoperated cases to help avoid the high infectious rate and many of the other complications and deaths seen in the current series.

References

1. Fortner JG. Regional resection of cancer of the pancreas: a new surgical approach. Surgery 1973; 73:307–320.
2. Fortner JG, Kim DK, Cubilla A, et al. Regional pancreatectomy: en bloc pancreatic, portal vein and lymph node resection. Ann Surg 1977; 186:42–50.
3. Nagakawa T, Konishi I, Ueno K, et al. Surgical treatment of pancreatic cancer. The Japanese experience. Int J Pancreatol 1991; 9: 135–143.
4. Fortner JG. "Radical" abdominal cancer surgery: current state and future course. Jpn J Surg 1989; 19:503–509.
5. Trede M, Schwall G, Saeger HS. Survival after pancreatoduodenectomy: 118 consecutive resections without an operative mortality. Ann Surg 1990; 211:447–458.
6. Cameron J, Christ DW, Sitzmann JV, et al. Factors influencing survival after pancreaticoduodenectomy for pancreatic cancer. Am J Surg 1991; 161:120–125.
7. Fortner JG. Surgical principles for pancreatic cancer: regional total and subtotal pancreatectomy. Cancer 1981; 47:1712–1718.
8. Fortner JG. Technique of regional subtotal and total pancreatectomy. Am J Surg 1985; 150:593–600.
9. Fortner JG. The rationale, technique and results of treating pancreatic and peripancreatic cancer by regional pancreatectomy. Acta Gastro Enterologica Belgica 1987; 40:121–127.
10. Fortner JG. Regional subtotal and total pancreatectomy. In Daly JM, Cady B, eds. Atlas of Surgical Oncology. St. Louis, MO: Mosby-Yearbook Inc; 1993:307–315.
11. Kaplan EL, Meier P. Nonparametric estimations from uncomplete observations. J Am Stat Assoc 1958; 53:457–481.
12. Montel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966; 50:163–170.
13. Cox DR. Regression models and life tables. J R Stat Soc (B) 1972; 34:187–220.