



Recurrence after Resection for Ductal Adenocarcinoma of the Pancreas

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Abstract. We analyzed the pattern of failure and clinicopathologic factors influencing the disease-free survival of 78 patients who died after macroscopic curative resection for pancreatic cancer. Local recurrence was a component of failure in 56 patients (71.8%) and hepatic recurrence in 48 (61.5%), both accounting for 97% of the total recurrence rate. About 95% of recurrences occurred by 24 months after operation. Median disease-free survival time was 8 months, and cumulative 1-, 3-, and 5-year actuarial disease-free survival rates were 66%, 7%, and 3%, respectively. Multivariate analysis showed that tumor grade ($p = 0.04$), microscopic radicality of resection ($p = 0.04$), lymph node status ($p = 0.01$), and size of the tumor ($p = 0.005$) were independent predictors of disease-free survival. Patterns of failure and disease-free survival were not statistically influenced by the type of surgical procedure performed. Median survival time from the detection of recurrence until death was 7 months for local recurrence versus 3 months for hepatic or local plus hepatic recurrence ($p < 0.05$). From our experience and the data collected from the literature, it appears that surgery alone is an inadequate treatment for cure in patients with pancreatic carcinoma. Effective adjuvant therapies are needed to improve locoregional control of pancreatic cancer after surgical resection.

Long-term survival for patients with carcinoma of the pancreas is poor, even after resection [1, 2]. Most patients who undergo curative resection develop recurrence [3–5] usually at the same site of resection or in the liver, but there are only a few reports on the incidence and pattern of tumor relapse [3, 5–8]. Detailed knowledge of the sites of recurrence of carcinoma of the pancreas and the study of the factors influencing disease-free survival are important when developing surgical and adjuvant treatment. In this study we analyzed the patterns of failure and the clinicopathologic factors influencing disease-free survival in patients who died from tumor recurrence after resection of pancreatic cancer.

Materials and Methods

From 1970 to 1992 a total of 113 (21%) patients underwent pancreatic resection among 549 patients with histologically proved pancreatic adenocarcinoma. Cystadenocarcinomas, islet cell tumors, and cancer of the bile duct, duodenum, or ampulla of Vater were excluded from the study. Surgical resection was performed whenever technically possible and when no distant

metastases were identified. Limited invasion of the hepatic portal or mesenteric vein was not considered a contraindication to pancreatic resection. At the time of surgery the cancer was staged according to the pTNM (UICC) system [9]. During the period 1970–1981 a standard Whipple's operation was performed for cancer of the head of the pancreas. From 1982 a subtotal pancreatoduodenectomy was performed, dividing the pancreas 2 cm to the left of the origin of the splenic artery and leaving approximately 4 to 5 cm length of the pancreas. No patient was treated with adjuvant radiotherapy or chemotherapy. Clinical and pathologic records of each patient were reviewed, and the following features were analyzed: age, sex, diabetes, type of resection, microscopic complete excision, perioperative blood transfusion, size and grading of the tumor, nodal status, vascular invasion, microscopic involvement of perineural spaces, and lymphatic and blood vessels. Follow-up of the patients included clinical evaluation, routine laboratory tests after 1 month of operation, and then abdominal ultrasonography (US), computed tomography (CT) (when available), or both, as well as a chest radiograph, every 3 months. Causes of death and sites of failure were recorded on the basis of death certification, medical interview, radiologic findings, surgical exploration, and autopsy. In this study recurrence was recorded as the first site of detectable failure. Local recurrence was defined as tumor recurrence in the pancreatic bed, regional nodes, or immediately adjacent structures.

Statistical analysis was performed using the chi-square test. Survival curves were prepared using the Kaplan-Meier method, and statistical comparisons were made by the Mantel-Cox (generalized Savage) test. A Cox proportional-hazards analysis was used to determine the independent variables that influenced disease-free survival. Significance was considered as $p < 0.05$.

Results

Patients

Of the 113 patients who underwent resection, one was lost at follow-up, 17 died after operation (hospital mortality), 7 are still alive and disease-free (range 84–216 months), and 3 died after 7, 26, and 34 months, respectively, from causes unrelated to pancreatic cancer. Of the remaining 85 patients, 7 had a macroscopically incomplete resection and were excluded from the study. The

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Table 1. Characteristics of patients who developed recurrence ($n = 78$) after resection for adenocarcinoma of the pancreas.

Characteristic	Whipple	SPD	PT	DP
Age (years), mean	55.1	60.4	54.5	63.4
Sex				
Men	15	20	5	7
Women	8	16	3	4
Stage (UICC)				
I	11	12	1	4
II	0	3	3	4
III	12	21	4	3
Grade (differentiation)				
Well	11	13	6	4
Moderately	10	14	2	5
Poorly	2	9	0	2
Venous resection				
Yes	0	6	5	1
No	23	30	3	10
Radicality				
Yes	22	28	8	7
No	1	8	0	4

SPD: subtotal pancreateoduodenectomy; PT: total pancreatectomy; DP: distal pancreatectomy.

remaining 78 patients who had macroscopically complete resection and who died of tumor recurrence were entered in this study (Table 1). There were 47 men and 31 women, with a mean age of 58.8 years (range 27–81 years). Twelve patients (15%) were older than 70 years of age, and 47 patients (60%) had preoperative diabetes mellitus.

Operative Procedures

Twenty-three patients underwent a standard Whipple's resection, 36 had a subtotal pancreateoduodenectomy, 8 had a total pancreatectomy, and 11 had a distal pancreatectomy. Twelve patients had a segmental hepatic portal or mesenteric vein resection (or both) (6 after subtotal, 5 after total, and 1 after distal pancreatectomy); a pylorus-preserving pancreatectomy was performed in 13 patients (11 after subtotal and 1 after total pancreatectomy). In 13 patients (17%) the resection was not considered radical because of microscopic involvement of the hepatic portal vein ($n = 4$), line of resection ($n = 3$), peripancreatic tissue ($n = 3$), or adjacent organs ($n = 3$). Nine of these patients had undergone a pancreateoduodenectomy, and the other 4 had a distal pancreatectomy.

Tumor and Staging

The tumor was located in the head of the gland in 64 cases and in the body and tail in 12; it was diffuse in 2 cases. The mean tumor diameter was 3.4 cm (range 1.5–10.0 cm); in 10 patients the tumor was ≤ 2.0 cm, in 51 it was 2.1 to 4.0 cm, and in 17 it was > 4.0 cm. There were 34 well differentiated, 31 moderately differentiated, and 13 poorly differentiated tumors. Of the 78 patients, 40 (51%) had lymph node metastases; 28 patients had stage I, 10 had stage II, and 40 had stage III disease (Table 1).

Patterns of Failure

The site of first recurrence was local in 26 cases (33%), the liver in 19 (24%), local and liver in 28 (36%), local and lung in 2 (3%), lung in 2 (3%), and liver and lung in 1 (1%) (Table 2). Local recurrence was a component of failure in 56 patients (72%) and hepatic recurrence in 48 patients (62%); they accounted for 97% of the recurrences. Extraabdominal recurrence was a component of failure in five patients (6%), but it was the only site of relapse in just two patients. Abdominal carcinomatosis was the initial presenting feature of recurrence in eight cases but was present in most patients at the time of death. The pattern of failure did not differ statistically between the types of operative procedure. About 44% of recurrences occurred by 6 months after operation, 71% by 12 months, and 95% by 4 months; two patients experienced tumor relapse after 5 years. The median time for local recurrence was 9.5 months, 9.0 months for hepatic failure and 6.0 months for local and hepatic failure. About 19% of hepatic recurrences occurred within 3 months after operation and 48% within 6 months.

Survival

The cumulative 1-, 3-, and 5-year actuarial disease-free survival rates were 66%, 7%, and 3%, respectively (Fig. 1); and the median disease-free survival time was 8 months. The disease-free survival was significantly influenced by the number of units of blood transfused ($p = 0.01$), tumor grade ($p = 0.04$), lymph node metastases ($p = 0.02$), radicality of resection ($p = 0.04$), tumor size ($p = 0.02$), tumor stage ($p = 0.03$), and perineural infiltration ($p = 0.02$) (Table 3). Actuarial survival curves according to lymph node status and tumor grade and size are reported in Figures 2, 3, and 4, respectively. Multivariate analysis showed that tumor grade ($p = 0.04$), radicality of resection ($p = 0.04$), lymph node status ($p = 0.01$), and tumor size ($p = 0.005$) were independent predictors of disease-free survival. The median survival time from the detection of recurrence until death was 7 months for patients who experienced local recurrence alone versus 3 months for patients with hepatic or local and hepatic recurrence ($p < 0.05$).

Discussion

Complete resection of the primary tumor offers the only chance of cure for patients with pancreatic cancer. The crude 5-year survival rate is less than 5%, however [1], and most of the patients die from recurrent disease. In the current series, 78 (89%) of 88 patients who underwent a macroscopically radical resection and survived after operation experienced tumor recurrence. Ninety-five percent of tumor relapses occurred within 2 years of operation. The most common sites of failure (97%) were intraabdominal and included the locoregional area (tumor bed), the liver, and the peritoneal cavity. Local and hepatic failure accounted for 72% and 62%, respectively, as a component of the total failure rate. The pattern of failure was similar in the 65 patients (83%) who underwent a microscopically radical operation. The present results are in accordance with those collected from recently published series [6–8, 10–16] (Table 4). Among 549 evaluable patients who underwent resection for pancreatic carcinoma using different surgical procedures, 393 (72%) developed disease recurrence. Local and hepatic failure occurred in 34% and 35%,

Table 2. Type of resection and patterns of failure.

Site of recurrence	Whipple (<i>n</i> = 23)	SPD (<i>n</i> = 36)	PT (<i>n</i> = 8)	DP (<i>n</i> = 11)	Total (<i>n</i> = 78)	%
Local	5	12	2	7	26	33
Liver	8	9	1	1	19	24
Local + liver	9	13	4	2	28	36
Local + lung	0	1	0	1	2	3
Liver + lung	0	1	0	0	1	1
Lung	1	0	1	0	2	3
Peritoneal	2 ^a	1 ^a	0	5 ^a	8 ^a	10 ^a

SPD: subtotal pancreatectomy; PT: total pancreatectomy; DP: distal pancreatectomy.

^aAs a component of initial failure.

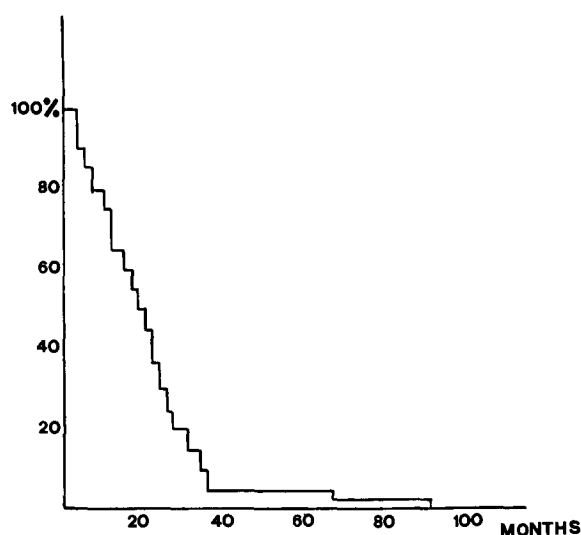


Fig. 1. Cumulative actuarial disease-free survival for 78 patients who had recurrence after resection for pancreatic adenocarcinoma.

respectively. Most of the patients (96%) experienced intraabdominal recurrence, and 23% had extraabdominal disease. Tepper et al. [3] reported a 50% local recurrence rate after resection for pancreatic cancer. Westerdahl et al. [7] reported that 64 (86%) of 74 patients had local recurrence in the pancreatic bed as a component of total failure and found no significant difference between the number of patients with or without local recurrence after total compared to subtotal pancreatectomy. Similarly, there was no statistical difference in the pattern of failure according to the extent of resection in the present series.

To improve local control of the disease, various surgical procedures, such as total pancreatectomy [17], regional pancreatectomy [18], and extended lymphadenectomy [11, 19], have been suggested. Intraoperative (IORT) and postoperative radiotherapy have also been advocated as adjuvant treatment to reduce local recurrence [13, 20, 21]. Total pancreatectomy, however, does not substantially improve long-term survival [22] or local control of the disease [5, 7]; and regional pancreatectomy does not show any significant advantage over standard resection [12].

Although radical pancreatic resection with extended lymph node dissection and soft tissue clearance was claimed to reduce the rate of death from local recurrence in retrospective studies [11], Kayahara et al. [8], reported a local retroperitoneal failure rate of more than 80%. Whether the extended lymphadenectomy

can improve local control of the disease is at present unproved and requires prospective validation. IORT showed better local tumor control than surgery alone in uncontrolled studies [20, 23], but these findings were not confirmed by another report [24], and long-term survival is not substantially influenced by resection plus IORT [24].

The aim of resection is to maintain the patients free of disease for as long as possible, but in most patients it is for only a short time [6, 7]. In the present series, the median time before recurrence was 8 months, and the disease-free survival was not influenced by the extent of the pancreatic resection. Disease-free survival was mainly influenced by the pathologic features of the tumor as in other series [14, 25–27]. Liver metastases as the initial site of failure in resected cases is frequently reported [6, 8, 15]. The early development of liver metastases after pancreatic resection (15 of 78 patients within 3 months in our series, of whom 10 had had a radical operation) supports the hypothesis that occult microscopic liver metastases are frequently present at the time of resection [15]. Then disease control after resection must include prevention of liver failure.

Conclusions

Despite pancreatic resection being undertaken with curative intent, the disease-free survival is short (8 months in our experience). Life expectancy after detection of the recurrence is only 3 months in patients with liver metastases and 7 months in patients with local relapse. Based on the high rate of local and hepatic recurrence, surgery alone is seen to be inadequate treatment for cure in most patients with pancreatic carcinoma. Improvement of locoregional control of pancreatic cancer after surgical resection may be improved with adjuvant treatment but must be validated by randomized controlled trials.

Résumé

Les échecs thérapeutiques et les facteurs clinico-pathologiques jouant un rôle sur la survie sans maladie ont été analysés chez 78 patients décédés après une résection pancréatique à visée macroscopiquement curatrice. La récurrence locale a été constatée chez 56 patients (71.8%), la récurrence sous forme de localisation hépatique chez 48 (61.5%), l'ensemble des deux représentant 97% des récurrences globales. Quatre-vingt quinze pour-cent des récurrences se sont produites moins de 24 mois après l'intervention. La durée médiane de survie sans maladie a été de 8 mois et les survies cumulatives actuarielles à 1, 3 et à 5 ans ont été respectivement de

Table 3. Disease-free survival according to risk factor.

Risk factor	Patients (no.)	Survival (%)				Median (mo)	p*
		1 Year	3 Years	5 Years			
Age (years)							
< 60	35	71	13	6	10		
60-69	31	57	0	0	8		0.12
≥ 70	12	78	7	0	5.5		
Sex							
Male	47	65	5	0	7		0.18
Female	31	68	8	5	10		
Operation							
PD	59	68	8	3	8		
PT	8	71	0	0	4		0.09
DP	11	50	0	0	5.5		
Vascular resection							
Yes	12	67	0	0	6.5		0.05
No	66	67	7	3	9		
Pancreatectomy (extension to right)							
Antrectomy	54	73	8	4	7		0.49
PPPD	13	58	0	0	11		
Pancreatectomy (extension to left)							
Whipple	23	72	12	6	10		0.18
Subtotal	36	64	4	0	8		
Radical resection							
Yes	65	71	9	3	10		0.04
No	13	55	0	0	6		
Blood transfusion (units)							
≤ 2	23	79	16	8	12		
3-5	32	53	0	0	7		0.01
> 5	12	66	0	0	3.5		
Grade							
Well	34	83	8	3	12.5		
Moderate	31	57	6	3	6		0.04
Poor	13	40	0	0	5		
Lymph nodes							
Positive	38	58	3	0	6		0.02
Negative	40	75	10	5	12		
Lymphatic invasion							
Yes	54	67	5	2	7		0.46
No	24	65	9	4	10		
Vessel invasion							
Yes	41	66	8	5	7		0.77
No	37	67	5	0	10		
Neural invasion							
Yes	49	62	2	2	6		0.02
No	29	75	14	4	12		
Peripancreatic invasion							
Yes	60	65	5	3	7		0.37
No	18	72	11	0	10		
Tumor size (cm)							
≤ 2	10	80	20	10	11		
2.1-4.0	51	72	6	2	8		0.002
> 4.0	17	47	0	0	6		
Diabetes							
Yes	47	69	6	2	6		0.08
No	31	63	6	3	8.5		
Stage (UICC)							
I	28	72	16	8	13.5		
II	10	76	0	0	10		0.03
III	40	60	2	0	6		

PD: pancreatoduodenectomy; PT: total pancreatectomy; DP: distal pancreatectomy; PPPD: pylorus-preserving pancreatoduodenectomy.

*By Kaplan-Meier analysis. Curves compared using generalized Wilcoxon's test. Significant at $p < 0.05$.

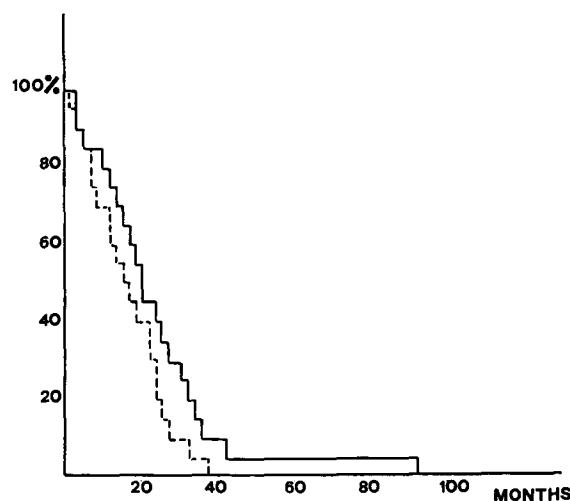


Fig. 2. Actuarial disease-free survival with (---) or without (—) lymph node involvement ($p = 0.02$).

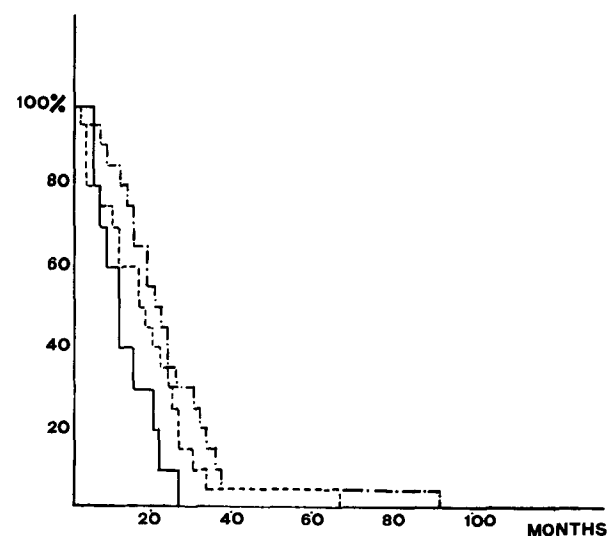


Fig. 3. Actuarial disease-free survival according to degree of tumor grade in well (—), moderately (---), and poorly (···) differentiated tumors ($P = 0.04$).

66%, 7% et 3%. L'analyse multifactorielle a montré que le stade tumoral ($p = 0.04$), la radicalité de la résection ($p = 0.04$), l'état ganglionnaire ($p = 0.01$) et la taille de la tumeur ($p = 0.005$) étaient des facteurs indépendants de prédiction de survie sans maladie. Ni les échecs ni la survie n'ont été statistiquement influencés par le type de chirurgie effectuée. La durée médiane entre la détection de la récurrence et le décès a été de 7 mois pour la récurrence locale contre trois mois pour la récurrence hépatique ou combinée, hépatique et locale ($p < 0.05$). A partir de notre expérience et l'information recueillie dans la littérature, il apparaît que la chirurgie seule ne suffit pas pour traiter le cancer pancréatique. On a besoin de thérapies adjuvantes pour améliorer le contrôle locorégional du cancer du pancréas après résection.

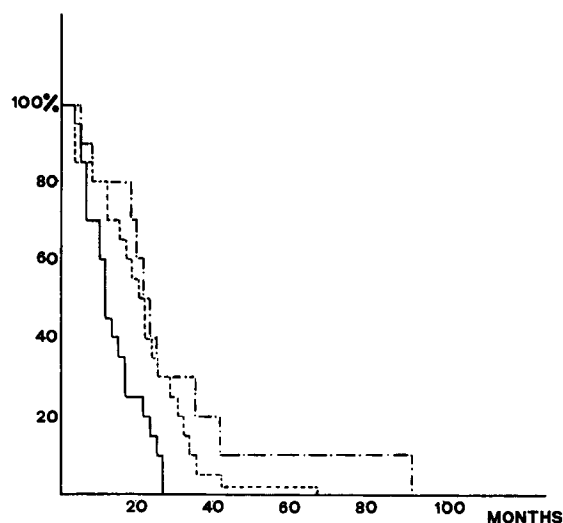
Resumen

Analizamos el patrón de falla y los factores clínico-patológicos que tienen influencia sobre la supervivencia libre de enfermedad de

Table 4. Patterns of failure after pancreatic resection for cancer in published series.

First author	Year	Follow-up (no. pts.)	Recurrences		Local		Hepatic		Abdominal		Extraabdominal	
			No.	%	No.	%	No.	%	No.	%	No.	%
Tsuchiya [10]	1986	45	13	29	NR	—	NR	—	NR	—	NR	—
Ishikawa [11]	1988	53	40	75	NR	—	NR	—	NR	—	NR	—
Sindelar [12]	1989	17	14	82	13	76	NR	—	NR	—	NR	—
Griffin [6]	1990	36	26	72	7	27	4	15	26	100	6	23
Hiraoka [13]	1990	51	43	84	NR	—	NR	—	NR	—	NR	—
Westerdahl [7]	1993	86	74	86	6	8	10	13.5	74	100	NR	—
Kayahara [8]	1993	45	30	67	10	33	3	10	30	100	13	43
Nitecki [14]	1995	169	112	66	38	25	42	37.5	101	90	11	10
Amikura [15]	1995	47	41	87	11	27	30	73	41	100	NR	—
Takahashi [16]	1995	25 ^a	25	NV	25	100	20	80	25	100	14	56
Total evaluable cases		574	393	71.6	110	34.2	109	35.3	297	96.1	44	22.7
			549		322		308		308		193	
Present series		88	78	88.6	26	33.3	19	24.3	76	97.4	5	6.4

NR: not reported; NV: not evaluable.

^aSelected autopsies cases.**Fig. 4.** Actuarial disease-free survival according to tumor size: ≤ 2 cm (—); 2.1–4.0 cm (---); > 4.0 cm (···) ($p = 0.02$).

78 pacientes que murieron luego de resección macroscópicamente curativa de cáncer pancreático. La recurrencia local fue el componente de falla en 56 pacientes (71.8%), la recurrencia hepática en 48 (61.5%), con ambos factores representando el 97% de la tasa total de recurrencia. Noventa y cinco por ciento de las recurrencias ocurrieron en los primeros 24 meses luego de la operación. El intervalo libre de enfermedad promedio fue de 8 meses y las tasas actuariales de sobrevida libre de enfermedad acumulativas a 1, 3 y 5 años fueron 66%, 7% y 3% respectivamente. El análisis multivariado demostró que el grado tumoral ($P = 0.04$), el estado de los ganglios linfáticos ($P = 0.01$) y el tamaño del tumor ($P = 0.005$) son predictores independientes de la sobrevida libre de enfermedad. Los patrones de falla y de sobrevida libre de enfermedad no aparecieron estadísticamente afectados por el tipo de cirugía realizada. El tiempo medio de sobrevida a partir de la detección de la recurrencia hasta la muerte fue de 7 meses para la recurrencia local versus 3 meses para la recurrencia hepática o la recurrencia local más hepática ($P < 0.05$). Según nuestra experiencia y los datos recolectados de

la literatura, parece que la cirugía sola es un tratamiento inadecuado para la curación de pacientes con carcinoma pancreático. Se requieren terapias coadyuvantes eficaces para mejorar el control local-regional del cáncer pancreático luego de la resección quirúrgica.

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Invited Commentary

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Long-term survival after surgical removal of pancreatic adenocarcinoma continues to be dismal. Most patients develop recurrent disease. In the thorough study by Sperti and coworkers, special emphasis was placed on the incidence of local and other abdominal recurrences. The authors also defined the factors that were independent predictors of disease-free intervals in their patient series.

Knowledge of the frequency and reasons for recurrence help to identify and develop new treatment options. Sperti and coworkers found isolated local recurrence in 33% of their patients, which is clearly a higher figure than the 8% of our study with a similar design [1]. When local and hepatic recurrence were grouped together, the incidence was 69% in their study and 78% in our study. Differences in the reported results may reflect dissimilarities in study design. From this point of view it would have been advantageous if Sperti and coworkers had included data on how the recurrence was diagnosed in the individual patients—be it by imaging, surgery, autopsy, or histology. Interestingly, they did not find any influence of the surgical method used (Whipple or subtotal pancreatectomy) on the incidence of recurrence. Similarly, we found the same local or hepatic recurrence rate after total as after subtotal pancreatectomy [1]. These data again accentuate the inability of current surgical treatment to offer cure. Although the initial expectations on extended pancreatectomy [2] and intraoperative radiotherapy (IORT) [3] still have not been met, it seems logical to continue along this line and try to “sterilize” the pancreatic bed in one way or the other after resection. Presently for this purpose we are evaluating laser treatment in addition to IORT.

Sperti et al. included tumors in the pancreatic body and tail as

well in their analysis. This point must be kept in mind when assessing their data. In addition, the proportion of patients with this tumor location who underwent resection was surprisingly high (12 of 78). Despite this inconsistency between their and our [1] reports, patients of both studies with local recurrence only survived significantly longer than those suffering recurrence at other locations as well.

At multivariate analysis the authors found histologic tumor differentiation, radicality of resection, lymph node metastases, and tumor size to be independent prognostic factors. These findings are in accordance with previous investigations using the Cox proportional hazards model except that tumor size rarely has turned out to be an independent factor for long-term survival [4, 5].

This worthwhile study by Sperti and coworkers contributes to our understanding of the “natural course” following resection of pancreatic cancer and points to the need for a continuing search for adjunctive pre-, per-, and postoperative treatment modalities to be used in these patients with the aim of cure or prolonged disease-free interval.

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