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Results of Pancreaticoduodenectomy in Patients With Periampullary Adenocarcinoma

Perineural Growth More Important Prognostic Factor Than Tumor Localization

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Objective: To study the impact of perineural growth as a prognostic factor in periampullary adenocarcinoma (pancreatic head, ampulla of Vater, distal bile duct, and duodenal carcinoma).

Summary Background Data: Pancreatic head carcinoma is considered to have the worst prognosis of the periampullary carcinomas. Several other prognostic factors for periampullary tumors have been identified, eg, lymph node status, free resection margins, tumor size and differentiation, and vascular invasion. The impact of perineural growth as a prognostic factor in relation to the site of origin of periampullary carcinomas is unknown.

Methods: Data of 205 patients with periampullary carcinomas were retrieved from our prospective database. Pancreaticoduodenectomy was performed in 121 patients. Their clinicopathological data were reviewed and analyzed in a multivariate analysis.

Results: Perineural growth was present in 49% of the cases (37 of the 51 patients with pancreatic head carcinoma; 7 of the 30 patients with ampulla of Vater carcinoma; 7 of the 19 with distal bile duct carcinoma; and 8 of the 21 with duodenal carcinoma). Overall 5-year survival was 32.6% with a median survival of 20.7 months. Median survival in tumors with perineural growth was 13.1 months compared with 36.0 months in tumors without perineural growth ($P < 0.0001$) Using multivariate analysis, the following unfavorable prognostic factors were identified: perineural growth (RR = 2.90, 95% CI 1.62–5.22), nonradical resection (RR = 2.28, 95% CI 1.19–4.36), positive lymph nodes (RR = 1.96, 95% CI 1.11–3.45), and angioinvasion (RR = 1.79, 95% CI 1.05–3.06). Portal or superior mesenteric vein reconstruction and tumor localization were not of statistical significance.

Conclusion: Perineural growth is a more important risk factor for survival than the primary site of periampullary carcinomas.

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Periampullary tumors encompass carcinomas of the pancreatic head, distal bile duct, duodenum, and ampulla of Vater.[1] In general, pancreatic head carcinoma is considered to have the worst prognosis among these tumor types.[2–9] Especially ampullary carcinomas seem to have a better prognosis, which might be related to the fact that jaundice is an early symptom. The factors that could negatively influence the survival of patients with periampullary cancer are positive resection margins,[2,7,10–14] lymph node metastases,[6,7,11,12,14–18] tumor size,[12,14,19] blood vessel invasion,[12,15] and poor tumor differentiation.[7,11,20] Perineural growth is an important prognostic factor in several other types of cancer, eg, prostate,[21] salivary gland,[22] gastric,[23] lung,[24] and breast.[25] Only a limited number of studies analyzed perineural growth as a prognostic factor in periampullary tumors.[12,20,26–38] However, to our knowledge, no studies could be found that concurrently analyzed perineural growth and tumor localization as prognostic variables in a multivariate analysis. This is relevant because in the preoperative workup patients are informed about their prognosis based on tumor localization. For instance, patients with an ampullary carcinoma are told that they have a better prognosis than patients with carcinoma of the pancreatic head. Additionally, studies in which the effect of any (neo)adjuvant treatment is analyzed should stratify patients based on important prognostic or predictive variables.

In this study we tested the hypothesis that, analogous to other types of cancer, perineural invasion is an important prognostic variable in periampullary carcinomas. To this end, we analyzed various clinicopathological variables, including, but not limited to, the site of origin of the

tumor, lymph node status, resection margin, angioinvasion, and perineural growth.

PATIENTS AND METHODS

Between January 1989 and December 2006, 270 patients with a tumor of the periampullary region underwent surgical treatment at our center. Patient data were entered in a prospectively collected database. Preoperative workup consisted of computed tomography scan of the abdomen and thorax, and endoscopic retrograde cholangiopancreatography with stent placement in jaundiced patients. Detection of liver metastases or encasement of the superior mesenteric artery or celiac axis was considered as a contraindication for pancreaticoduodenectomy. Visible tumors of the ampulla and duodenum were routinely biopsied during ERCP. Biopsy of pancreatic head masses was not routinely performed because a negative result of the biopsy does not preclude a surgical procedure. Since 1995 diagnostic laparoscopy has been performed in patients with pancreatic head tumors. This has only been done in patients in whom a single or double bypass was not indicated on clinical grounds in case tumors were not resectable. Patients were scheduled for resection if during laparoscopy no liver or peritoneal metastases were found.

During laparotomy, lymph nodes around the celiac trunk and below the left renal vein between the aorta and caval vein (numbers 9, 16, and 14, 15, respectively[39]) were sent for frozen section, and if any of these were positive, the patient was considered incurable and a double bypass consisting of hepaticojejunostomy and gastrojejunostomy was performed. Invasion of the portal or superior mesenteric vein was not regarded as a contraindication for resection. In those cases a venous reconstruction was performed using either saphenous vein or umbilical vein.[40] All patients who underwent a resection received octreotide 3 times daily 0.1 mg subcutaneously (Sandostatine, Novartis, Arnhem, The Netherlands) from the day of operation until 2 weeks thereafter.

Several peri- and postoperative variables of the patients were recorded: American Society of Anesthesiologists (ASA) score,[41] venous reconstruction, total blood loss, number of blood transfusions needed intraoperatively or within the first 48 hours postoperatively, postoperative complications, length of hospital stay, length of stay in the intensive care unit, number of reoperations, number of percutaneous reinterventions, and 30-day mortality. Postoperative complications were classified as general complications (pulmonary or urinary tract infection necessitating antibiotic treatment, drainage of wound abscess, deep vein thrombosis or pulmonary embolism) or procedure-related complications such as leakage of biliary, pancreatic or enteric anastomoses, intra-abdominal abscess or infected ascites (necessitating drainage), or bleeding for which a reoperation was performed.

For this study all pathology specimens were reviewed by one pathologist (ASHG) to confirm the diagnosis, lymph node status, resection margins, the presence of perineural growth, and angioinvasion. Tumors were reclassified according to the most recent Tumor Node Metastasis (TNM) classification.[42]

All patients had a regular follow-up schedule consisting of 3-monthly visits during the first 2 years after surgery and 6-monthly thereafter. Routine radiologic examinations were not performed. Investigations like ultrasound, pulmonary x-rays, or computed tomography scans were performed whenever local recurrence or metastases were suspected. In patients with recurrences palliative treatment, which could include gemcitabin, was started. Depending on patients' preference, follow-up could be stopped 5 years after surgery. In those patients, general practitioners were contacted for definite long-term follow-up.

Survival analysis was performed using the Kaplan-Meier method with the log rank test for comparisons. To perform a more reliable analysis on the effect of the clinicopathological characteristics, patients who died within 30 days after the operation were excluded from the long-term survival analysis. Variables with a significant ($P \leq 0.1$) effect in the univariate analysis were included in the multivariate analysis, using the Cox proportional hazard model.

RESULTS

Surgery for a periampullary tumor was performed in 270 patients; 163 (60%) patients were male and 107 patients (40%) were female. The median age at the time of operation was 60 years (range 11–80). A diagnostic laparoscopy was performed in 116 patients (43%). An exploratory laparotomy was then performed in 251 patients (92%). The total resectability rate was 176 of 270 (65%) patients, of whom 155 (57%) underwent a pylorus-preserving and 21 (8%) a classic pancreaticoduodenectomy (Whipple procedure). If the tumor was not resectable during laparotomy, palliative bypass surgery was performed. In 32 patients (12%) a double bypass (hepaticojejunostomy and gastroenterostomy) was performed, and 38 patients (14%) underwent a single bypass (hepaticojejunostomy or gastroenterostomy).

The 30-day mortality rate was 4% (n = 7) in the 176 patients who underwent a resection. The median intensive care unit stay was 1 day (range 0–73) and median total hospital stay was 24 days (range 9–131). Sixty-eight percent of the 176 patients (n = 119) did not require a blood transfusion during or in the first 2 postoperative days. Nine patients (5.1%) received 1 blood transfusion, 19 patients (10.8%) received 2 blood transfusions, and the remaining 29 patients (16.5%) received >2 blood transfusions. In 26 patients (14.8%) a second laparotomy was necessary. In 16 patients (9.1%) a postoperative complication had to be solved with a percutaneous intervention. In the patients who underwent a resection, 29.5% (n = 52) had one or more general complications, and 34.1% (n = 60) had a procedure-related complication.

In 55 of the 176 patients who underwent pancreaticoduodenectomy, various diagnoses other than periampullary carcinoma were found on histologic examination; dysplasia in 6% (n = 11), neuroendocrine tumors in 6% (n = 10), rare malignant tumors in 4% (n = 7), and benign disorders in 15% (n = 27). The diagnosis in the 121 patients (69%) who had a periampullary carcinoma was pancreatic head carcinoma (n = 51, 42%), ampulla of Vater carcinoma (n = 30, 25%),

duodenum carcinoma (n = 21, 17%), or distal bile duct carcinoma (n = 19, 16%).

Further analysis was done on the data from the 121 patients who underwent a resection for periampullary cancer (pancreatic head, ampulla of Vater, distal bile duct, or duodenal carcinoma). Patient characteristics and more detailed pathologic findings of this patient group are listed in Table 1. Angioinvasion was found in 29% (n = 35) of the patients and perineural growth (Fig. 1) in 49% (n = 59) of the cases. Perineural growth was more frequently encountered in carcinomas of the pancreatic head (73%) than in carcinomas of the ampulla of Vater (23%), distal bile duct (37%), and duodenum (38%).

The median survival of all patients who underwent pancreaticoduodenectomy for periampullary cancer was 29.1 months with an overall 5-year survival of 31.8%. In patients with nonresectable tumors the median survival was 4.6 months, with no survivors after 24 months. If a microscopic free resection margin (R0) could be obtained, the 5-year overall survival was 38.5% and the median survival was 38.9 months. The median time of survival was 17.5 months, with hardly any survivors beyond 36 months in patients with a R1 resection (Fig. 2). Survival in patients with R2 resections was not different from patients who did not undergo pancreaticoduodenectomy.

TABLE 1. Clinicopathological Characteristics of the 4 Types of Periampullary Carcinoma

Variables	Pancreatic Head (n = 51)	Ampulla of Vater (n = 30)	Distal Bile Duct (n = 19)	Duodenum (n = 21)	Total (n = 121)
Age (median)	63.3	65.6	61.9	57.5	63.1
Range	(11–80)	(46–76)	(38–75)	(18–80)	(11–80)
Sex					
Male	26	13	14	17	70
Female	25	17	5	4	51
T stage					
1	5	10	5	2	22
2	20	14	3	6	43
3	26	5	11	8	50
4	0	1	0	5	6
N stage					
0	16	16	15	9	56
1	35	14	4	12	65
Angioinvasion					
Yes	20	7	2	6	35
No	31	23	17	15	86
Perineural growth					
Yes	37	7	7	8	59
No	14	23	12	13	62
SMV/PV invasion					
Yes	15	0	1	3	19
No	36	30	18	18	102
Resection margin					
R0	30	29	18	17	94
R1	14	0	1	3	18
R2	7	1	0	1	9

SMV indicates superior mesenteric vein; PV, portal vein.

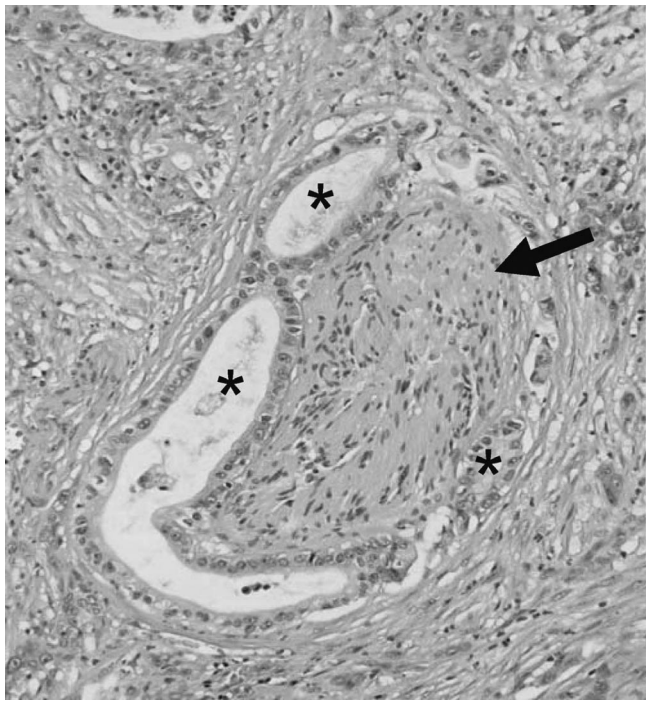

FIGURE 1. Perineural growth: glandular structures of the adenocarcinoma (asterisks) are present within the perineurium of a nerve (arrow).

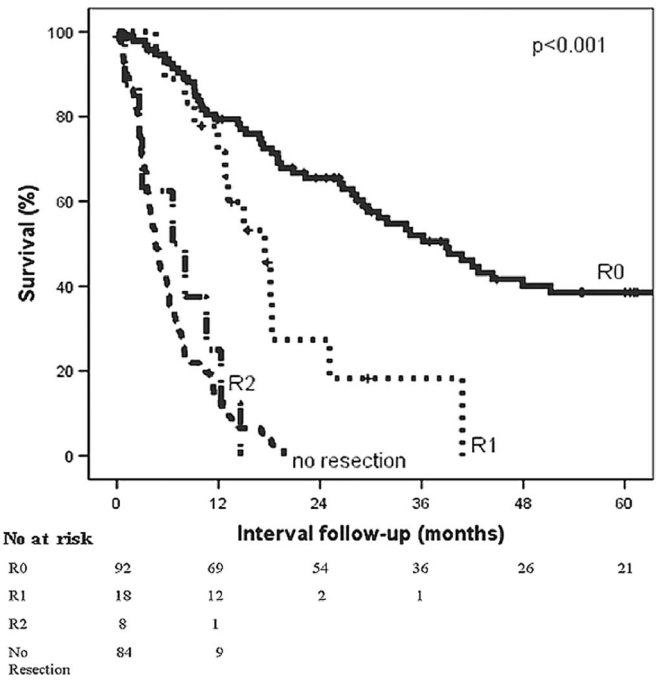

FIGURE 2. Survival rate for patients with periampullary carcinoma and R0, R1, R2 resection, or no resection.

Overall 3- and 5-year survival rates of patients stratified according to the site of origin of the 4 tumor types in the periampullary region are 26.1% and 17.9% (pancreatic head), 43.6% and 35.2% (ampulla of Vater), 73.7% and 53.6% (distal bile duct), and 71.1% and 44.4% in duodenal carcinoma, respectively. The corresponding median survival times are 15.0 months (pancreatic head), 31.9 months (ampulla of Vater), 102.0 months (distal bile duct), and 44.4 months (duodenum).

In the combined group of patients with periampullary cancer the presence of perineural growth was a significant adverse risk factor. Patients having tumors with perineural growth had a median survival of 17.3 months compared with 64.4 months in the group without perineural growth ($P < 0.002$). In the patients with perineural growth there were no 5-year survivors, which is in contrast to the 50.3% 5-year survival in the patients without perineural growth (Fig. 3). In Figure 4 it can be seen that a 5-years survival of more than 50% can be obtained in patients with nonpancreatic head carcinomas without perineural invasion. In contrast, patients with nonpancreatic head carcinomas, in whom the tumors show perineural invasion, have a comparable low survival as patients with pancreatic head carcinoma with or without perineural growth.

In the univariate analysis the following variables were analyzed: T-status (T1 and T2 versus T3 and T4), N-status (node positive versus node negative), tumor localization, number of blood transfusions given (no transfusions versus one or more transfusions), perineural growth (present versus absent), angioinvasion (present versus absent), portal or superior mesenteric vein reconstruction (yes versus no) and resection margin (radical versus nonradical resection). Only N status, perineural growth, angioinvasion, and resection margin were significant prognostic variables in the univariate analysis. Of note, median survival of patients with a venous reconstruction because of tumor adherence to the portal or superior mesenteric vein (18.1 months) was not significantly different from those without this procedure (34.1 months, $P = 0.14$).

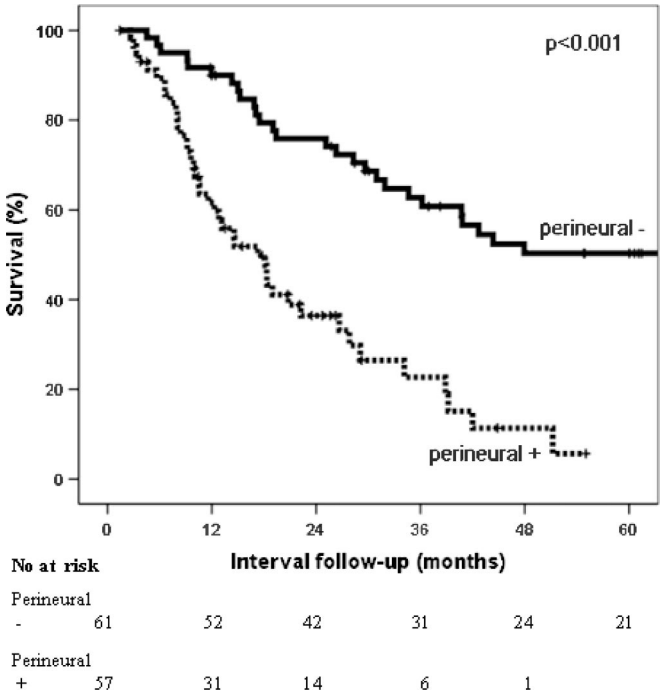

FIGURE 3. Survival rate after resection in patients with periampullary carcinoma with (perineural +) or without (perineural −) perineural growth.

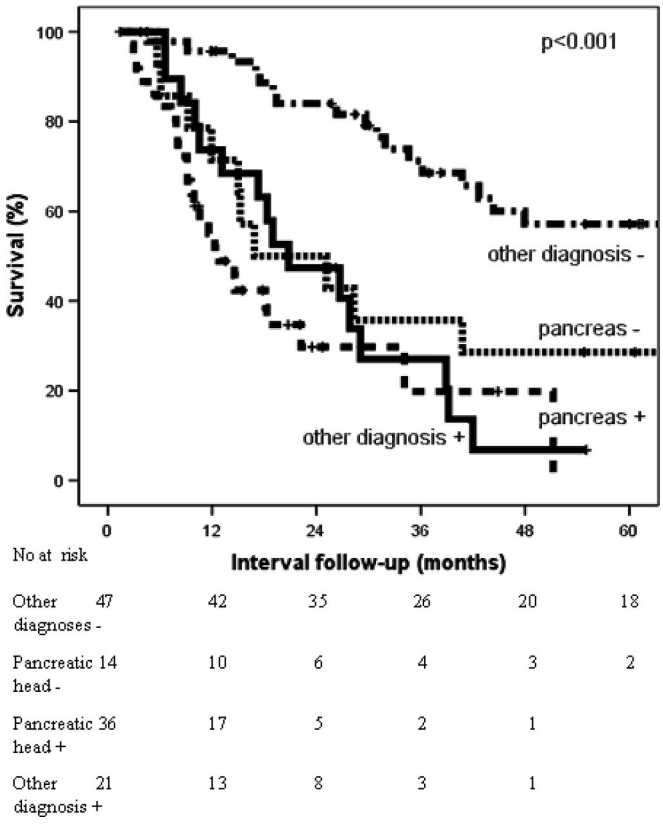

FIGURE 4. Survival rates in patients with resected periampullary carcinoma. Other diagnosis − = ampulla of Vater, distal bile duct or duodenum carcinoma without perineural invasion. Pancreas − = pancreatic head carcinoma without perineural invasion. Pancreas + = pancreatic head carcinoma with perineural invasion. Other diagnoses + = ampulla of Vater, distale bile duct, or duodenal carcinoma with perineural invasion.

The multivariate analysis (Table 2) shows that perineural growth is the most important independent risk factor for survival (RR = 2.90). Other independent risk factors were the resection margin, lymph node status, and the presence of angioinvasion. Tumor localization proved not to be a significant risk factor ($P = 0.095$); the P values of the individual tumor localizations were not corrected for multiple comparisons and thus the P value of 0.02 (ampulla) should be ignored.

DISCUSSION

In the present study we found that perineural invasion is a more important prognostic factor than the primary site of

the periampullary carcinomas. Generally, pancreatic head carcinoma is considered to have a worse prognosis compared with the other periampullary carcinomas.[2–4,7–9] However, it might very well be that information, based on averages obtained from a specific population (eg, patients with ampulla of Vater cancer versus patients with pancreatic head cancer) does not apply to the individual patient. Our data showed that perineural growth is of paramount importance for the prognosis of the individual patient. For instance, patients with a pancreatic head carcinoma without perineural growth could obtain a 5-year survival of around 30%, which is in contrast to a 5-year survival of only 10% in patients with carcinomas of the other periampullary sites, presumed to have a better prognosis, with perineural growth. This difference is important in the "personalized medicine" approach because a patient is more interested in his particular prognosis than in an average prognosis of a patient group. Our data, however, are not in contrast to several other series reporting on prognosis of patients with periampullary carcinomas. We also confirmed the generally worse prognosis in the patient group with pancreatic head carcinoma compared with patient groups with the other periampullary carcinomas. This is probably associated with the fact that perineural invasion is as high as 73% in pancreatic head carcinomas and only 23% to 38% in the other periampullary carcinomas.

TABLE 2. Results of Multivariate Analysis Using Cox Regression, Showing the Relative Risk and 95% Confidence Interval (CI) Compared To the Reference Standard (1.00).

Factor	Relative Risk (95% CI)	*P*
Perineural growth		<0.001
Absent	1.00	
Present	2.91 (1.62-5.22)	
Resection margin		0.013
Free margin (R0)	1.00	
Not-free margin (R1,2)	2.28 (1.19-4.36)	
Lymph node status		0.020
Negative	1.00	
Positive	1.96 (1.11-3.45)	
Angioinvasion		0.034
Absent	1.00	
Present	1.79 (1.05-3.06)	
Localization of carcinoma		0.095
Duodenum	1.00	
Distal bile duct	1.44 (0.52-3.94)	0.481
Ampulla of Vater	2.60 (1.16-5.80)	0.020
Pancreatic head	2.03 (0.92-4.45)	0.079

Table 3 shows the studies in which perineural growth was included as a risk factor in periampullary tumors. These studies, however, either restricted their analysis to pancreatic head cancer or analyzed only a limited number of patients. To the best of our knowledge no published study that addressed perineural growth as an independent risk factor in patients with all 4 types of periampullary cancer treated with a pancreaticoduodenectomy is available. The current study shows that perineural growth is an important clinicopathological factor in a relatively large group of 121 patients with resected periampullary tumors.

Perineural growth is a phenomenon in which cancer cells grow in close apposition to nerves. It can be encountered in various tumor types, including head and neck cancer,[22] prostate[21] and pancreas carcinoma, and is, in general, associated with a worse prognosis compared with tumors without perineural growth. Originally, the idea was that lymphatics in nerves harbor cancer cells, but later on it was suggested that nerves are the routes of lowest resistance and thereby form a

TABLE 3. Overview of Literature With Analysis of Perineural Growth as a Prognostic Factor for Survival in Patients With Periampullary Carcinoma

	Pancreatic Head Carcinoma			Ampulla of Vater Carcinoma			Distal Bile Duct Carcinoma			Periampullary Carcinoma		
Author, Year	**N**	**UV**	**MV**	**N**	**UV**	**MV**	**N**	**UV**	**MV**	**N**	**UV**	**MV**
Nagakawa, 1993[26]	21	−		15	−							
Griffanti-Bartoli,1994[27]	14	−	−	22	+	+						
Sperti, 1995[28]	113	+	−									
Chan, 1995[29]	20	−	−	29	+	+						
Nakao, 1996[30]	129	−										
Takahashi, 1997[31]	90	+	+									
Zerbi, 1998[32]							27	−	−			
Bouvet, 2000[20]										129	+	−
Schwartz, 2001[34]										49	+	−
Okusaka, 2001[35]	95	−										
Hirai, 2002[36]	24	+	+									
Duffy, 2003[37]				55	+	+						
Shimada, 2006[38]	80	+	−									
Garcea, 2007[12]	33	+	+	20	+	+						

No literature was found on the impact of perineural growth in patients with duodenal carcinoma.

N indicates the number of patients; MV, multivariate analysis; UV, univariate analysis; +, significant impact on prognosis of the patient; −, no significant impact on prognosis.

paved way for dissemination and spread of tumor cells.[43] More recent studies revealed that the interaction of nerves and tumor cells is more complex. In prostate cancer it was shown that nerves provide a prosperous environment for tumor growth by up-regulation of antiapoptotic pathways in cancer cells.[44] In this study it was found that prostate cancer cells in the perineural space had a higher proliferation index and a lower apoptotic index than tumor cells located distant from nerves. In cocultures of dorsal root ganglia and pancreatic cancer cells the neuroepithelial interaction had beneficial effects on the growth of both nerves and cancer cells.[45] It was suggested that the production of growth factors by the nerves contributes to tumor progression. Overexpression of transforming growth factor α in nerves combined with the presence of its receptor, epidermal growth factor receptor, in pancreatic cancer cells provides a plausible explanation for cancer progression by paracrine stimulation.[46]

More recently another mechanism was described; it was found that the neurotrophic growth factor artemin and its receptors are up-regulated in human pancreatic cancer specimens.[47] In vitro experiments revealed that artemin enhances the invasive potential of pancreatic cancer cells but not their proliferation rate.[47] Other evidence of the possible reciprocal stimulation of nerves and pancreatic cancer was obtained from experiments that revealed that vascular endothelial growth factor (VEGF) stimulates proliferation of pancreatic cancers and cancer cell lines, despite the absence of VEGF receptors.[48] The authors supplied compelling evidence that VEGF is able to exert this action by binding to neuropilins, which are (co)receptors for VEGF and also stimulators of axonal outgrowth and survivals.[48,49] Up-regulation of neuropilin-1 was associated with an increase in invasiveness and metastatic behavior in various other gastrointestinal cancers.[50]

Taken together, nerves and pancreatic cancer cells interact by reciprocal stimulation via paracrine and autocrine mechanisms and thereby contribute to cancer progression, more aggressive behavior and its associated poor prognosis.

Another important finding in our study is that a venous reconstruction of the portal or superior mesenteric vein (performed in 16% of the patients) did not adversely affect the prognosis. This finding is in agreement with the results published by other authors.[51–53] In one study real tumor invasion into the portal or superior mesenteric vein was associated with a significantly worse prognosis compared with patients in whom the tumor was adherent to the vein but the resection margin was negative.[54]

Our finding of a difference of the 5-year survival between patients with R0 and R1 resections concurred with the results of Raut et al.[18] In their study 92% of the patients with R1 resections had either preoperative or postoperative (chemo)radiotherapy. This probably explains the comparable survival in patients with R0 and R1 resection in their series as compared with ours in which no prior postoperative (chemo)-radiotherapy was given.

Recently Oettle et al described that gemcitabine given postoperatively significantly delayed the development of recurrent disease after complete resection of pancreatic cancer compared with observation only.[55] However, this randomized study used a randomization procedure with stratification for resection status, T status (according to TNM classification[42]) and nodal status, without mentioning perineural growth. In our study we found perineural growth the most important prognostic factor. We therefore recommend using perineural growth as a stratification marker in future studies on promising chemotherapeutics. In conclusion, the results of this study show that perineural growth is an important prognostic factor in patients with periampullary adenocarcinomas.

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