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ORIGINAL ARTICLE

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The retroperitoneal resection margin and vessel involvement are important factors determining survival after pancreaticoduodenectomy for ductal adenocarcinoma of the head of the pancreas

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Abstract The prognosis of ductal adenocarcinoma of the pancreas is still poor. We analysed the factors that have a major influence on the survival of patients. Surgical specimens from 51 patients with ductal adenocarcinoma of the head of the pancreas were examined for tumour size, histological type, grade and local extension. In 7 patients the retroperitoneal resection margin was involved either macroscopically or histologically. Their mean survival was 10.6 months (1–17 months), compared with 22.7 months for the 44 patients with curative R0 resection. In 10 patients large vessels (portal and/or mesenteric vein) had to be resected; they survived for only 2-11 months, with a mean of 5 months ($P<0.05$). Non-R0-resected patients and patients in whom tumour-invaded vessels had to be resected constitute a high-risk group with a significantly shorter mean survival of 8.8 months, compared with 24.3 months for R0 resected patients without vessel invasion ($P<0.05$). Lymph node metastases were seen in 35 of 51 patients. Survival analysis based on nodal status revealed a mean survival of 33 months for patients staged as N0, 21.4 for N1a patients and 14 month for N1b patients. The differences were not statistically significant, however. Our data suggest that tumour invasion of the retroperitoneal resection margin and large vessel involvement are the major factors determining survival in patients with pancreatic cancer.

Key words Pancreatic carcinoma · Duodenopancreatectomy · Resection margin involvement

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Introduction

Ductal adenocarcinoma is the most common malignant tumour of the pancreas and accounts for more than 80% of the cases. Among 60 common cancers it is still the one with the least favourable prognosis and the lowest 5-year survival rate. A major reason for the poor outcome is the generally advanced tumour stage at the time of diagnosis, which leaves only limited therapeutic options open. Because chemotherapy and radiotherapy have had no clear impact on survival, surgery remains the only curative strategy. Surgical treatment has changed to a more radical approach, in some studies with extensive node dissection and even vessel resection [4, 6, 8]. The results are contradictory, with some studies showing improved survival rates [13, 18, 22] while others fail to support such findings [4].

In a companion paper [7] we analysed the influence of extended versus regional lymphadenectomy on the survival of patients who underwent a curative partial duodenopancreatectomy for carcinoma of the head of the pancreas. We found that these patients derived no significant benefit from extended lymphadenectomy. This suggests that tumours that have already involved juxtaregional lymph nodes are too advanced (have led to distant metastases) to be controlled by radical surgery. An alternative interpretation is that tumour recurrence in resected patients is primarily due to incomplete removal at the site of the resection rather than to metastatic disease [10] because of microscopic tumour spread into the retroperitoneal tissue behind the pancreas. The retroperitoneal resection margin is therefore particularly important, because this area is not well defined and is hence difficult to examine. In this study we analysed the influence of tumour-free resection on patient survival. We defined the resection margins and worked out a proposal for processing of the pathological specimens. In addition, we studied how survival relates to other prognostic indicators, such as tumour type and grade and lymph node metastases. The basis of this work is a series of 53 patients who were treated for pancreatic cancer by the same team of surgeons.

Materials and methods

From 1988 to 1996, 53 patients with cancer of the head of the pancreas underwent partial pancreaticoduodenectomy in the Departments of Surgery of the Universities of Hamburg (1988–1991) and Kiel (1992–1996).

The patients were 20 men and 33 women. Their mean age was 59.8 (45–75). In 20 patients (group A, RLA=regional lymphadenectomy) partial duodenopancreatectomy was combined with "regional" lymph node dissection, including the node compartments within the hepatoduodenal ligament, along the common hepatic artery, the coeliac trunk and the right side of the mesenteric artery, as well as the ventral surface of the vena cava (compartments 1–4). In the other 33 patients (group B, ELA=extended lymphadenectomy) partial duodenopancreatectomy was combined with "extended" lymphadenectomy. In addition to the regional lymph nodes (see group A), this included the distant node compartments from the left side of the superior mesenteric artery, the aorta below and between the inferior mesenteric artery and the coeliac trunk (compartments 5–7). These compartments were completely freed not only from lymph node tissue but also from perivascular soft tissue, including all lymphatic vessels and ganglia. Because of gross tumour involvement of the mesenteric vessels a partial resection of the mesenteric vein and/or of the portal vein was performed in 10 patients (9 with extended lymphadenectomy and 1 with regional lymphadenectomy). In 7 of these patients vessel reconstruction was achieved by direct anastomosis; in the other 3 interposition of a Gore-Tex graft was needed.

Gross examination of the pancreaticoduodenectomy specimens was performed in most cases on unfixed specimens. The bile duct and the main pancreatic duct were probed, and the whole specimen was cut horizontally along the probes (Fig. 1). The gross tumour size and the distance between the tumour and the ampulla of Vater and the pancreatic resection margin (cut surface) were measured. An average of three (range 2–6) blocks of tumour tissue and one additional block from the ampulla/papilla were obtained.

Further tissue was obtained from the resection margin of the pancreas and the common bile duct and from the retroperitoneal transsection site. The latter area was defined as the peripancreatic fatty tissue behind the pancreatic head and lateral to the mesenteric vessels. This margin was inked or marked with OPTI-fluid (CITIUS, Gersthofen, Germany) and sectioned perpendicular to the pancreatic duct (Fig. 2). If and only if the macroscopically estimated distance of the carcinoma from the retroperitoneal margin was at least 1 cm, the dorsal adipose tissue was "shaved" from the specimen. In cases in which vessels were resected, the complete segment was embedded and both ends were examined separately as additional resection margins. Where required serial sections were performed.

The local lymph nodes attached to the superior and the inferior aspects of the head of the pancreas and to the anterior or posterior duodenopancreatic grooves were dissected away from the main specimen and investigated separately. The lymph nodes from compartments 5–7 (see above) were received as separate specimens and numbered according to their anatomic site. All tissues were routinely fixed in 10% buffered formalin and paraffin embedded. Sections 5 µm thick were stained with H&E and PAS and, in the case of vessel segments, with elastica van Gieson.

The tumours were staged according to the recently updated TNM system [20]. In addition, we classified the lymph node metastases into locoregional (involvement of lymph nodes attached to the head of the pancreas and from those compartments 1–4) and distant (involvement of compartments 5–7). The tumours were typed histologically and graded according to defined criteria [11]. Intrapancreatic tumour spread and peripancreatic fatty tissue, lymphatic, vascular and perineural invasion were evaluated.

The cumulative survival rate after surgery was calculated by the Kaplan-Meier method, and the data were compared with the log-rank test. The significance of mean differences was evaluated with Student's *t*-test [2]. Two patients who died of postoperative complications (one each in groups A and B) were excluded from the survival analysis.

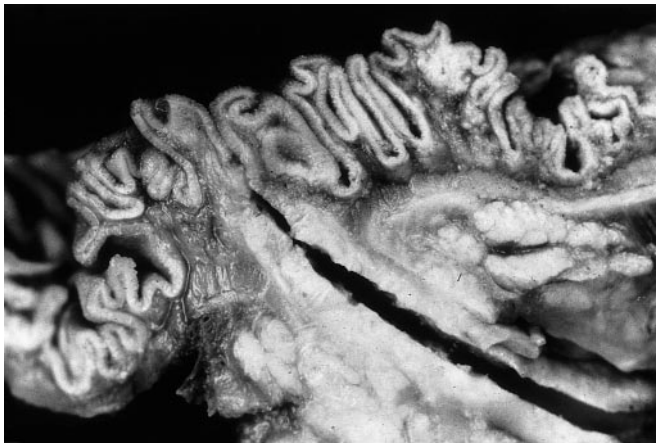

Fig. 1 Gross pathology. Cut surface of a carcinoma of the head of the pancreas causing narrowing of the pancreatic duct

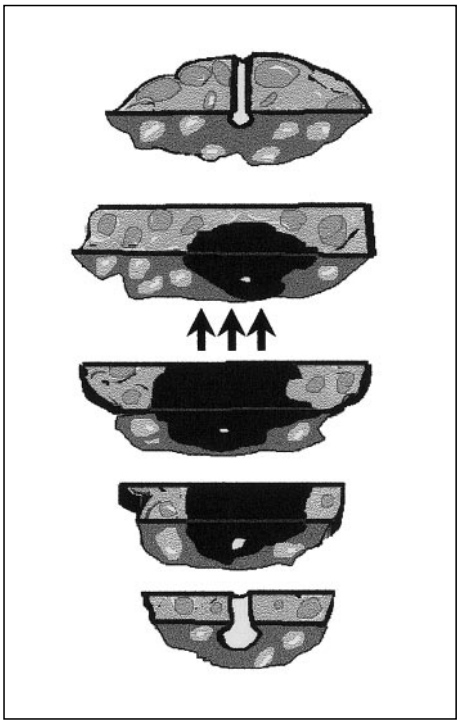

Fig. 2 Sketch of the retroperitoneal side of the pancreas, with dissection lines for cases of dorsal tumour extension. *Arrows* indicate the retroperitoneal resection margin with tumour invasion

Results

The pancreatic resection margin of the paraffin-embedded tissue showed papillary hyperplasia of the ductal epithelium with moderate dysplasia (n=2), mildly dysplastic mucinous hypertrophy (n=6), or ductal papillary hyperplasia without atypia (n=2). Severely dysplastic duct epithelium and frankly invasive carcinoma were not found. The resection margin of the common bile duct was tumour free in all patients.

The retroperitoneal resection margin was involved in 7 patients. In 3 this was grossly obvious (R2 resection),

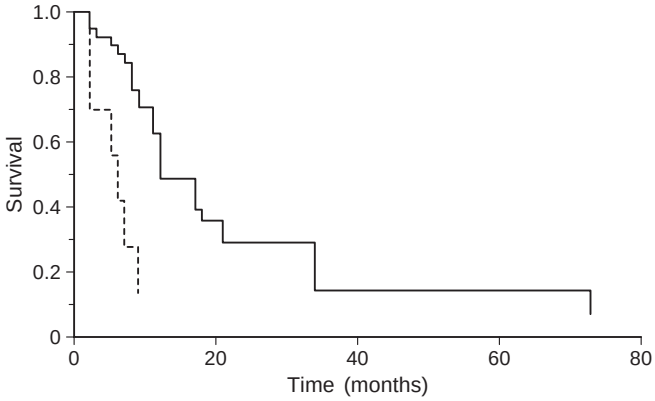

Fig. 3 Kaplan-Meier curves for patients with (------, *n*=10) and without (——, *n*=41) vessel resection. Mean survival was 5 months after vessel resection and 23.8 month without

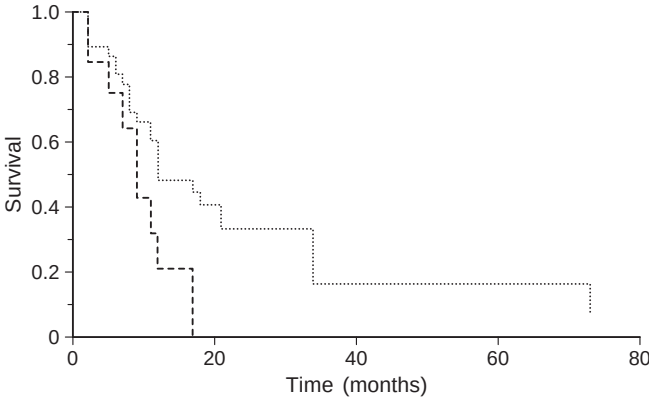

Fig. 5 Kaplan-Meier curve of patients with non-R0 resection and/or vessel invasion (------, 14/51) and without (·····37/51). Mean survival was 24.3 months with R0 and 8.82 months with non-R0 resection and/or vessel invasion, a difference significant for survival ($P<0.05$)

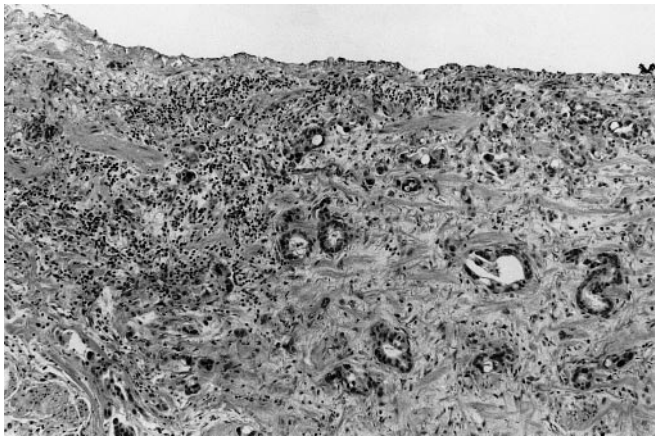

Fig. 4 Microscopy of a vessel segment. All layers are invaded by disseminated tumour cells. H&E, ×400

and in 4, microscopically. One patient was thought on macroscopic examination to have had an R2 resection. Since histologically he showed only chronic inflammatory changes, he was reclassified as having had an R0 resection. The mean survival of the 7 R1/R2 patients was 10.6 months (range 1–17), compared with 22.7 months for the 44 R0 patients (range 2–75). The difference was not statistically significant, however, probably because of the small sample size (see below).

The 10 patients in whom the portal and/or mesenteric vein was resected had a mean survival of 5 months (2–11), which is comparable to that for the patients who had undergone non-R0 resection and significantly shorter ($P<0.012$) than the 23.7 months for the 41 patients without vessel resection (Fig. 3). The vessel wall showed tumour invasion in 7 cases (Fig. 4). These patients had a mean survival of 4.42 months (range 2–9), compared with 6.3 months (range 1–17) for the other 3. When these patients with vessel involvement were added to the patients with R1/R2 resections (Fig. 5), there was a group of patients (*n*=14) who had a significantly shorter mean survival (8.8 months) than those with R0 resection (*n*=37) or without vessel resection (24.3 months). Because of the similarly short survival of patients with vessel resection and those with non-R0 status, the available blocks from the vessel specimens were serially cut (up to

Table 1 Patients with resected vessels and their R stage (*N1** local lymph nodes involved, *N2** distant lymph nodes involved, *ELA* extended lymphadenectomy, *RLA* regional lymphadenectomy)

Vessel status	Vessel status after serial sectioning	N stage	Tumour diameter (cm)	Survival (months)	R stage
Media	Inner 1/3	1b(N2*) (ELA)	2.0	5 (dead)	0
Intima	Intima + vessel margin	1b (N2*) (ELA)	3.2.	2 (dead)	R1 retrop. R vessel[a]
Intima	Intima + vessel margin	1a (N1*) (RLA)	2.5	2 (dead)	0 R1 vessel[a]
Media	Media	N0 (ELA)	4.5	3 (alive)	R1 retrop.
Media	Media	N0 (ELA)	3.5	7 (alive)	0
No invasion	No invasion	1b (N1*) (ELA)	2.0	6 (alive)	0
No invasion	Adventitial soft tisssue	N0 (ELA)	3.0	11 mo (alive)	0
			2.5	3 (alive)	0
Media	Inner media + vessel margin	N0 (ELA)			R1 vessel[a]
No invasion	No invasion	1b (N2*) (ELA)	2.0	2 (dead)	0
Advent. Soft tissue	Outer media	N0 (ELA)	3.0	9 mo (dead)	0

[a] After serial sectioning R1 in the vessel margin

Table 2 Pathomorphologic characteristics of the pancreatic ductal adenocarcinomas and nodal status (*n.s.* not significant for survival, *s.f.* significant)

	Cases (*n*=51)		Nodal status (*n*=51)
Tumour size (cm)	2.9 (0.9–6.0)	Mean number of nodes (per case)	16 (3–51)
Peripancreatic adipose tissue invasion	45 (90%) n.s.	Cases with positive nodes	35 (68%)
T stage (TNM 97)	51	N stage (TNM 97)	51
1	1	N0	16
2	3	N1a	15
3	33	N1b	20
4	14		
Tumour grade		R0 cases	44
1	7 (13.7%) s.f. p<0.05	Node negative	14 (32%) (4 v +)
2	32 (32%) s.f. p>0.05	Node positive	30 (68%)
3	12 (23.5%) s.f. p<0.05		
Capillary invasion	16 (31%) n.s.	Perineural invasion	40 (76%) n.s.

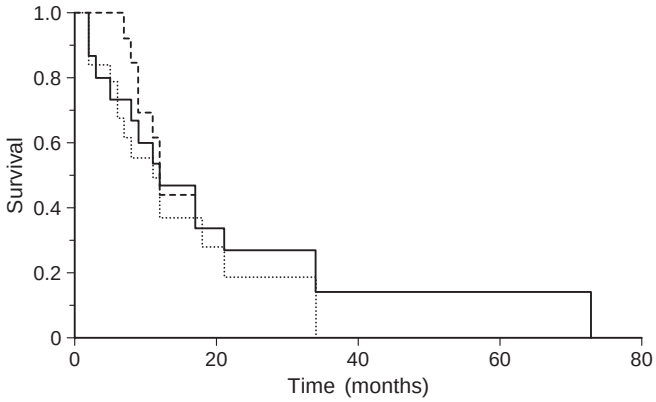

Fig. 6 Kaplan-Meier curve of patients (*n*=51) according to their nodal stage. Mean survival was 32.9 months for N0 patients (——, *n*=16), 21,4 month for N1a patients (------, local lymph nodes involved, *n*=15) and 14.2 months for N1b patients (·····,distant lymph nodes involved, *n*=20). The differences were not significant for survival (*P*>0.05)

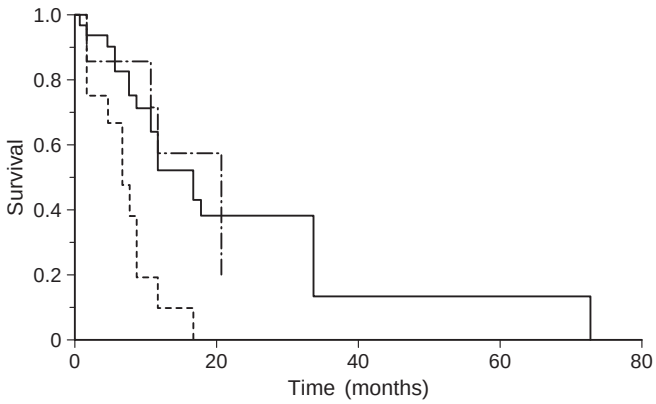

Fig. 7 Kaplan-Meier curves for the groups differentiated according to tumour grade. Mean survival was 21 months with grade 1 tumour (–·–·–, *n*=7). 17 months with grade 2 (——, *n*=32) and 7 months with grade 3 tumour (-----, *n*=12). Differences were significant for survival (*P*<0.008; *P*<0.001)

40 sections per case). The resection margins of two vessel segments showed tumour involvement. In 1 further case invasion of the the perivascular adipose tissue was detected, and in 3 other cases, more advanced invasion of the vessel wall to the inner layer (Table 1).

On average 16 lymph nodes were dissected (range 3–51), with a mean of 13 nodes for regional lymphadenectomy and 19 nodes for extended lymphadenectomy. The difference of 6 nodes between the dissection techniques was statistically significant (*P*<0.05) and showed that the extended dissection was effective. The 51 patients included 35 (68%) who had lymph node metastases, with a range of 1–8 positive nodes (Table 2).

One patient had an involved paracoeliac node, which was classified as M1 (distant organ metastasis).

The updated TNM classification [20] was used to classify the 51 patients according to their lymph node metastases: 16 patients fell in the category N0, 15 into the category N1a and 20 into N1b. Their mean survival times of 33, 21.4 and 14 months, respectively, differed considerably, but the differences were not statistically significant (*P*<0.02; Fig. 6). This was due in part to a rather short follow-up period and to 4 cases with N0 stage but with vessel involvement. For the comparison of survival in group A (RLA) and group B (ELA) only patients with R0 resection were considered (for a detailed analysis and data see [7]). Irrespective of their N stage, the patients in group A (14/44) survived longer on average (28.2 months) than those in group B (30/44, 19 months). However, this difference also failed to reach statistical significance (*P*<0.02). Reasons for this difference could be the large number of patients (9/30) in group B with additional vessel resection, which had a major influence on survival, and also the too-small sample size.

The diameter of the tumours (*n*=51) ranged from 0.6 to 6 cm (mean 2.9 cm; Table 2). The colon or stomach was invaded in 3 patients, the duodenal wall in 14 patients, the bile duct in 11 patients and the peripancreatic tissue in 45 patients (90%). Extensive vessel invasion was found in 10 patients, lymphatic vessel invasion in 45 (80%) and perineural invasion in 39 (76%) (Table 2).

None of these features showed a statistically significant relationship to survival.

The tumours were classified (TNM 1997) as T1 in 1 patient, T2 in 3 patients, T3 in 33 and T4 in 14 (Table 2). Twelve patients were staged as stage 1, 2 as stage 2, 33 as stage 3 and 3 as stage 4. Stage 4 patients had a significantly shorter survival (4.6 months) than patients in the other stages ($P<0.05$).

Histological examination revealed 45 cases of ductal adenocarcinoma and 6 variants (3 mucinous noncystic carcinomas and 3 adenosquamous carcinomas). Seven tumours were well differentiated (grade 1), 32 moderately differentiated (grade 2) and 12 poorly differentiated (grade 3). Grade 1 tumours proved to have a significantly better prognosis ($P<0.05$; Fig. 7) than did grade 2 and 3 tumours, regardless of the surgical procedure.

Discussion

In a previous study we found that extended lymph node resection in patients with ductal adenocarcinoma does not result in significantly survival [7]. This result was surprising, because approximately 10% of patients treated by the radical approach were found to have involved lymph nodes in the juxtaregional groups, suggesting that in a reasonable number of patients lymph node metastases will be left behind when they are treated by the classic Whipple resection. One possible explanation for the fact that patients with regional resection have the same survival probability as patients with an extended resection is that advanced lymph node involvement is an indication that the disease is already generalized. Alternatively, we may assume that local tumour spread into soft tissues, especially the retroperitoneum, and vascular structures (the portal vein and/or mesenteric vessels) is more important for patient survival than metastatic spread. However, local tumour spread seems to be difficult to estimate. Our results in 51 patients appear to favour the second possibility, because we found that survival correlated best with involvement of the retroperitoneal resection margin and, especially, the large blood vessels. However, we also recognize that the retroperitoneal resection margin is difficult to evaluate and that it is difficult to be certain whether it is involved.

A number of studies have already emphasized the importance of tumour-free vessels and retroperitoneal tissue for patient survival after the resection of ductal adenocarcinoma of the head of the pancreas. In a series of 79 patients with vessel resection Takahashi et al. [17] found a correlation between depth of invasion and length of survival. No patient in whom the tumour had invaded the vessel lumen survived for more than 1 year. They also described 4 long-term survivors living for more than 6 years, with 3 of these patients in stage 1 and 1 in stage 2. Moreover, 1 of these patients survived despite tunica media invasion, a condition that led to death within 2.5 years at the latest in all other patients. Takahashi et al. did not specify the R state for any of these patients, however. In the series of Harrison et al. [6] three long-term survivors after vessel resection/ invasion were reported, but no details concerning the depth of vessel invasion or the R state were provided and specific histological data were lacking. Hence, it is not possible to deduce the reasons for the different survival times. This is an important point, since the grounds given for vessel resection were isolated clinical involvement of the portal vein.

Kayahara et al. [10], who analysed the site of tumour recurrence, found that 80% of retroperitoneal recurrences occurred via neural and lymphatic invasion. In a retrospective analysis Willett et al. [21] found that no patient with involved margins survived beyond 41 months. They did not, however, specify their method or the extent of their histopathological investigation. In a study of carcinomas of the pancreatic head region Allema et al. [1] reported a 4% 5-year survival for patients with tumour involvement of the resection margin, as opposed to 49% for patients without. They also did not explain how the R state was assessed.

In our study we paid particular attention to the retroperitoneal tissue and resected vessel segments and their margins. Initially 7 of the 51 patients were diagnosed as having an incomplete tumour resection (R1/R2 resection) with the retroperitoneum as the site of tumour residue. The resection margins of the common bile duct and the duodenum were always tumour free. In 2 cases the pancreatic margin showed atypical papillary ductal hyperplasia, which revealed K-*ras* mutation (data not shown), but did not lead to tumour recurrence. In 7 further patients the tumour invaded the mesenteric or portal vein. The involvement of the vessel margins in 2 of them was only detected after up to 40 additional slides had been prepared. This reinvestigation was done retrospectively, because patients with vessel resection were found to have an average survival of only 5 months. In 5 of these cases it could not be proven that the margins were invaded, but it is likely that the short survival of these patients was also caused by residual tumour at the resection margins.

In a series of 113 patients Sperti et al. [15] found local tumour recurrence in 56 patients (71.8%) after duodenopancreatectomy or total pancreatectomy, although the resection margins had been tumour free histologically. The authors did not specify their methods of examining the resection specimen, however. Once the adipose or perivascular tissue along large vessels is infiltrated to a certain extent, it is difficult to ascertain the R0 state reliably. This is especially true in this diffuse type of tumour invasion, which is comparable to Laurén's diffuse type in gastric cancer [12]. We therefore assume that there may be more R1 cases than are diagnosed at present.

To improve this situation, Staley et al. [16] reported a detailed protocol for the preparation of Whipple specimens. However, this protocol lacks instructions for the preparation of the retroperitoneal margin and vessel specimens. For routine processing we suggest inking the adipose tissue at the retroperitoneal surface. Shaving of the dorsal tissue is only appropriate if the tumour ex-

tends predominantly towards the ventral surface with a macroscopically estimated distance of at least 1 cm from the retroperitoneal adipose tissue. In cases of dorsal extension, where it is expected that the distance from the margin will be small, we recommend sagittal macrodissection into 0.5-cm-thick slices. Resected vessel segments should also be inked, macrodissected into 0.5-cm-thick segments and completely embedded. Two or three histological sections or serial sections should be prepared on demand.

We did not find any predictive factors for margin or vessel involvement. In our patients vessel invasion or non-R0 resection did not correlate with any of the tumour features (grade, histological type, lymphatic invasion). Tumour size was not predictive of vessel or margin invasion; our study group consisted mainly of patients with tumours less than 5 cm in diameter. Beyond this size a significant increase in vessel invasion has been reported [14]. Node involvement has been shown to be a prognostically significant factor [8, 10]. In our study it did not correlate with tumour size, R state or vessel involvement and was similar to the group of small carcinomas reported by Furukawa et al. [5] and Tsuchiya et al. [19]. We did not find a significant difference in the survival of patients, whether their disease was staged as N0 or N1a or N1b, although the mean survival time differed considerably. This was true for the overall comparison, irrespective of the extent of node resection. An explanation for this surprising outcome may be the relatively large number of patients with N0 stage but vessel involvement (n=4) and therefore short survival. Moreover, the follow-up period of some patients was rather short. Nevertheless, nodal stage is of minor prognostic importance compared with margin or large vessel involvement. In a prospective study Johnstone and Sindelaar [11] found that local tumour recurrence was independent of nodal involvement. They confirmed, as we did, that local tumour extension to the retroperitoneum and vessels is the main reason for the poor survival rates in pancreatic cancer. To improve the prognosis in pancreatic cancer therapeutic strategies mainly must take accont of this fact, perhaps by additional application of local radiotherapy and/or chemotherapy.

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