

ORIGINAL ARTICLE

Results of vascular resections during pancreatotomy from two European centres: an analysis of survival and disease-free survival explicative factors

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Abstract

Objectives. The object of our study was to report on the experience with vascular resections at pancreatotomy in two European specialist hepatopancreatobiliary centres and evaluate outcome and prognostic factors. **Patients and methods.** From 1989 to 2002, 45 patients (21 men, 24 women) underwent pancreatotomy for a pancreatic mass: Whipple's procedure ($n=33$), total pancreatotomy ($n=10$) or left splenopancreatotomy ($n=2$), along with a vascular resection, i.e. venous ($n=39$), arterial ($n=1$) or venous+arterial ($n=5$). **Results.** Operative mortality was nil, postoperative mortality was 2.2% ($n=1$); 34 patients had an uneventful postoperative course. Reoperations were performed for portal vein thrombosis ($n=1$), pancreatic leak ($n=1$), gastric outlet syndrome ($n=1$) and gastrointestinal bleeding ($n=1$). In all, 43 patients had cancer on pathology examination, with retropancreatic invasion in 72% and lymph node extension in 62.8%. Resection was R0 in 21 cases. Vessel wall invasion was present in 13 cases and 19 had perivascular invasion. Disease-free survival (DFS) at 1, 2 and 3 years was 36.0%, 15.0% and 12.0%, respectively. Median DFS length was 8.7 months (95% CI: 7.2; 10.2). Overall survival rates were 56.6%, 28.9% and 19.2%, respectively. Median survival length was 14.2 months (95% CI: 9.8; 18.6). A multivariate analysis of prognostic variables identified tumour location (other than head of pancreas), neoadjuvant chemotherapy and advanced disease stage as adverse factors for DFS. **Conclusion.** Survival and DFS rates of these patients are comparable to those without vascular resection. Tumour localization, tumour stage, neoadjuvant treatment and tumour recurrence are explanatory variables of survival. Tumour localization, tumour stage and neoadjuvant treatment were explanatory variables for DFS. However, the type and extent of vascular resections as well as vessel wall invasion does not affect survival and DFS.

Introduction

Vascular resection during pancreatotomy for pancreatic cancer is still debated. Although the first cases were reported in the early 1970s [1], the reports by Fortner introduced the concept of regional pancreatotomy with vascular resection, describing type I and II where venous or arterial segment were resected, respectively [2–4].

Recent reports from expert centres showed clearly that vascular resection did not increase morbidity and mortality, and can offer these patients the possibility of radical surgery [5–8]. Nonetheless, the presence of vascular invasion on preoperative staging is still

considered by many as a contraindication for surgery. In this study, we report the experience with vascular resection at pancreatotomy in two European specialist hepatopancreatobiliary centres and evaluate outcome and prognostic factors.

Patients and methods

From May 1989 to March 2002, 45 patients (21 men, 24 women; mean age 60 ± 13 years, range 26–82), underwent pancreatotomy for a pancreatic mass, along with a vascular resection. Cases were reviewed from two centres where a total of 756 pancreatotomies were performed. Patients with

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vascular resection represented 16.5% of the pancreatic resections carried out. There was no difference between them regarding main clinical and demographic characteristics. The main clinical presentations were: jaundice in 30 cases, abdominal pain in 25, alteration of general condition and weight loss in 20 and pruritis in 15. Other less frequent manifestations were vomiting in seven patients, diarrhoea in five, diabetes in four, constipation in three, chronic pancreatitis in two, acute pancreatitis in one, cholangitis in one, dysphagia in one, flushing and sweating in one and abdominal mass in one. All patients received radiological and/or endoscopic exploration (US = 29, CT scan = 37, angio-MRI = 2, arteriography = 15, ERCP or percutaneous transhepatic cholangio-pancreatography (PTCP) = 20, US-endoscopy = 4) that revealed the presence of a pancreatic mass. Tumour localization was pancreatic head in 34 patients (2 extending to the uncinate process), pancreatic neck in 1 and body in 5, duodenum in 1, bile duct in 2, ampullary tumour in 1 and right colon tumour extending to the pancreatic head in 1. The mean tumour size on radiological examination \pm SD was obtained in only 21 cases at 2.7 ± 3.1 cm (range 2–13 cm).

In 20 cases, tumour was considered to be limited to the pancreas, in the other 25 cases tumour was invading adjacent structures – vascular invasion in 23 cases (venous invasion was observed in 16, arterial invasion in 1 and combined venous and arterial in 6). These patients presented with venous smooth shift in four cases, unilateral narrowing in three, bilateral narrowing in six and thrombosis with collateral circulation in nine according to the Ishikawa classification [9]. Retropancreatic invasion was seen in five patients, duodenum in two, bile duct in one and colon in one.

Biliary drainage was performed in 20 cases – through an endoscopic stent in 13 patients, percutaneous transhepatic radiological drain in 5, nasobiliary drain in 1 and surgical cholecysto-jejunostomy in 1. None had distant metastasis recognized before surgery.

Preoperative cytological examination of the pancreatic mass was carried out in 16 cases; 8 had adenocarcinoma, 4 had neuroendocrine-type tumour and in 4 no malignancy was identified. Neoadjuvant chemotherapy was administered to five patients with pancreatic adenocarcinoma.

Surgical resections were as follows: Whipple procedure in 33 cases (1 was associated with right colectomy, 15 with pylorus preservation), total pancreatectomy in 10 (8 with associated splenectomy and 2 with pylorus preservation) and left spleno-pancreatectomy in 2. Pancreatic anastomosis was done through pancreatico-jejunostomy in 32 patients and pancreatico-gastrostomy in 1. Gastro-jejunostomy was performed in 28 patients and pylorus preservation

in 17 (37.8%). Hepatico-jejunostomy was performed in 43 patients.

Vascular resections were preoperatively programmed and intentionally performed according to the results of preoperative investigations in 24 cases (1 had associated peroperative vascular injury). In the other 21 cases vascular resection was not preoperatively programmed but was done in 20 cases because of severe adhesions between the pancreatic mass and blood vessels (with associated vascular injury in 4), and in 1 case it was done because of peroperative vascular injury without obvious adhesions between tumour and blood vessels. Venous resections were partial circumference in 17 cases and full circumference in 23, and 3 patients had combined partial and full circumference resection. The mean length of venous resection was 0.98 ± 1.29 cm (range 1–4 cm). Venous reconstruction included 17 direct veno-venous anastomoses, 19 lateral venous repairs and 8 veno-venous homografts.

Arterial resection was carried out in six patients. All were preoperatively programmed arterial vascular resections, confirmed during surgery because of severe adhesions between the tumour mass and the arterial wall; 4 were associated with venous resection and two were isolated arterial resections. All except one arterial resection were full circumferential that included one replaced right hepatic artery (RRHA) + superior mesenteric artery (SMA), one RRHA, one SMA, one proper hepatic artery (PHA) + splenic artery (SA), one common hepatic artery (CHA) and one SA.

Two patients had repair with cryopreserved arterial allograft, one had autologous venous graft, one had lateral suture repair, one had direct anastomosis and one with no repair (SA resection).

Statistical analysis

The statistical unit was the patient. Descriptive statistics were based on percentage for categorical data and on mean \pm SD for continuous variables. The entire population was analysed, then only the subset of cancer patients was considered for clinical, biological and morphological analysis to identify factors affecting prognosis.

Survival and disease-free survival (DFS) analysis was performed according to the Kaplan–Meier technique from the date of surgery to that of death or event (DFS) or to the most recent clinic visit.

Univariate survival analysis was performed to select potential explanatory variables. According to the type of data, comparisons were based on univariate Cox regression model. Multivariate models were built using Cox proportional hazards survival analysis regression model in three ways (i.e. forwards, backwards and manually). Risk factors related to baseline hazards (odds) function for the sample were

examined. The choice of the best explanatory model was made by assessment of the goodness of fit, with an entry level of 0.25 and removal level of 0.15. All analyses were performed with SPSS software (10.0 for Windows; SPSS Inc., Chicago, IL, USA).

Results

There was no operative mortality, one patient died in the postoperative course secondary to acute pancreatitis and fistula, with a 30-day hospital mortality of 2.2%. The postoperative course was uneventful in 34 cases, medical complications were observed in 6 (infection, pleural effusion, diabetes) – all were controlled successfully. All patients were followed for anastomotic leak; pancreatic leak was defined by the presence of leak on radiology control for pancreaticogastric anastomosis or by the presence of raised amylase level in drainage fluid ($5 \times$ serum level) [10]. Surgical complications were observed in five cases: associated pancreatic and biliary leak in one (which was successfully treated conservatively), one pancreatic leak with acute pancreatitis was re-operated for completion pancreatotomy (the patient died postoperatively), one patient had upper gastrointestinal bleeding requiring surgical exploration which revealed haemorrhage secondary to haemobilia that was successfully treated, one patient had gastric outlet syndrome (gastric distention with absence of gastric emptying on postoperative radiology control) requiring gastro-jejunostomy redo with good outcome, and one vascular complication occurred after portal + superior mesenteric vein resection with direct anastomosis; on day one he developed ascites and echo-Doppler examination revealed anastomotic thrombosis. The patient was re-operated and successfully received an autologous venous graft harvested from the superficial femoral vein at mid-thigh.

Pathological examination revealed chronic pancreatitis in 2 cases and malignancy in 43: 36 (75.6%) with pancreatic adenocarcinoma, of which 34 were of ductal type (of which there was 1 microglandular adenocarcinoma, 4 infiltrating and 1 squamous differentiation), the other two cases were mucinous cystadenocarcinoma in 1 and papillary cystic carcinoma in 1. The remaining seven malignancies comprised cholangiocarcinoma in three, neuroendocrine tumour in three (islet cell carcinoma paraganglioma in one), and colonic adenocarcinoma invading the pancreas in one. Tumours were well differentiated in 7 patients, moderately in 13, poorly in 15, undifferentiated in 1 and unknown in 7. Retropancreatic invasion was observed in 31 cases (72%), lymph node invasion in 27 (62.8%), documented peri-neural invasion in 27 (62.8%) and microvascular invasion in 16 (37.2%).

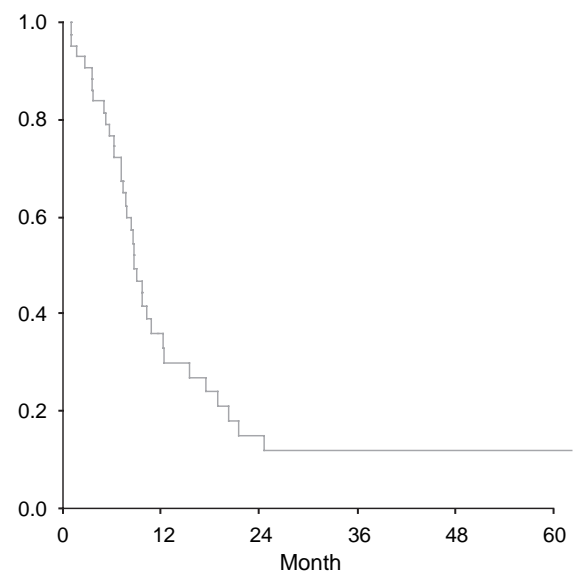
Resection margins were R0 in 21 cases, R1 in 14 because of microscopic invasion of retropancreatic margin in 11 (here retropancreatic free margin <1 mm was considered as R1), pancreatic cut section

in 1 and both in 2, R2 in 1 (macroscopic incomplete retropancreatic clearance) and was not clearly documented Rx in 7.

Pathological examination of resected vessels showed venous wall invasion in 13 cases (30%), 1 of whom had associated arterial wall invasion. Nineteen retropancreatic invasions were considered as perivascular invasion without extension to vessel wall. Information about vascular invasion was not available in three resected specimens.

Adjuvant therapy was given to 10 patients; 8 had combined radiochemotherapy, and 2 had either radiotherapy or chemotherapy alone because of lymph node invasion or non-R0 resection, other patients were not fit for adjuvant treatment.

At the study end point, 44 patients were followed, survival analysis was considered only for patients with malignancies ($n=43$). Two patients operated for pancreatic mass were found to have benign lesions and were thus excluded from survival analysis, the first was lost to follow-up and the second died 8 years after surgery. Of the 43 patients with cancer, 30 (69.8%) had documented tumour recurrence: 11 loco-regional, 14 metastases and 5 had both. Only 14 patients had treatment of their recurrence: 3 received combined radiochemotherapy, 6 had chemotherapy alone, 4 had radiotherapy alone and 1 had percutaneous alcoholization of a liver metastasis. The other 16 patients had symptomatic treatment. DFS at 1, 2 and 3 years was 36.0%, 15.0% and 12.0%, respectively (Figure 1). Median DFS length was 8.7 months (95% CI: 7.2; 10.2). Univariate analysis for overall DFS (Table I) showed that tumour localization, retropancreatic invasion and R0 resection



Disease Free Survival probability

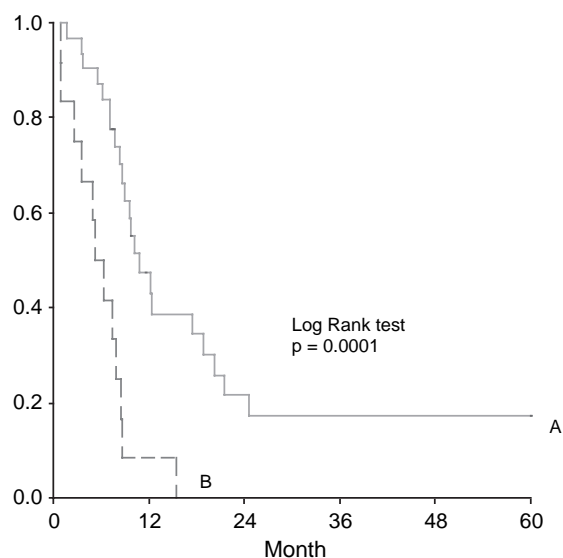
At risk:	43	12	5	4	4	4
Events:	26	7	1	-	-	-

Figure 1. Overall disease-free survival.

Table I. Overall survival and disease-free survival (DFS) explicative variables and at 12 and 36 months follow-up (non-significant at 0.05 level).

Parameter	Overall survival	Overall DFS	12-month survival	12-month DFS	36-month survival	36-month DFS
Institution	NS	NS	NS	NS	NS	NS
Sex	NS	NS	NS	0.024	NS	NS
Tumour localization (HOP/other)	0.005	0.001	0.04	0.001	0.005	0.001
Neoadjuvant treatment	NS	NS	NS	NS	NS	NS
Intervention (PD/other)	NS	NS	NS	NS	NS	NS
Pylorus preservation	NS	NS	NS	NS	NS	NS
PV resection	NS	NS	NS	NS	NS	0.06
SMV resection	NS	NS	NS	NS	NS	NS
SV resection	NS	NS	NS	NS	NS	NS
IVC resection	NS	0.03	NS	NS	NS	0.04
Renal vein resection	NS	0.08	NS	0.08	NS	0.008
Histology (ADK/other)	NS	NS	NS	NS	NS	NS
Tumour size (cm)	NS	NS	NS	NS	NS	NS
Tumour differentiation (good/other)	NS	NS	NS	NS	NS	NS
Node status (+/-)	NS	NS	0.1	NS	NS	NS
Vascular status (+/-)	NS	NS	NS	NS	NS	NS
Retropancreatic invasion	0.1	0.037	NS	0.033	NS	0.057
R0/R1-2	NS	0.048	NS	0.128	NS	0.048
Tumour stage	0.05	NS	0.02	0.02	0.02	0.08
Neoadjuvant treatment	NS	NS	NS	NS	NS	NS
Adjuvant treatment	NS	NS	NS	NS	NS	NS
Recurrence (local and metastatic)	0.01	NS	0.01	NS	0.04	NS
Local recurrence	0.001	NS	0.005	NS	0.03	NS
Metastatic recurrence	NS	NS	NS	NS	NS	NS
Venous resection	NS	NS	NS	0.046	NS	NS
Arterial resection	NS	NS	NS	NS	NS	NS
Arterial and venous resections	NS	NS	NS	NS	NS	NS

NS, not significant; HOP, head of pancreas; PD, pancreatico-duodenectomy; PV, portal vein; SMV, superior mesenteric vein; SV, splenic vein; IVC, inferior vena cava; ADK, adenocarcinoma.



Tumour localisation

A : Head of pancreas

At Risk : 31 11 5 4 4 4
 Events : 15 6 1 - - -

B : Other sites

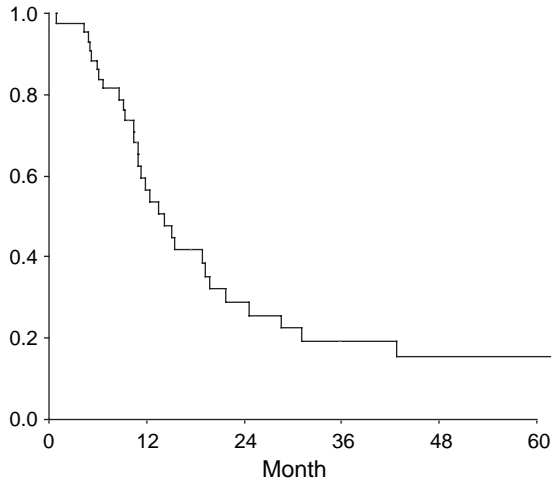
At Risk : 12 1 0
 Events : 11 1

Figure 2. Disease-free survival according to tumour localization: head of pancreas versus other sites.

(p values <0.05) were explanatory variables. Inferior vena cava (IVC) and renal vein (RV) resection, done in one case each, were interesting variables ($p=0.03$ and 0.08 , respectively) but not included in the final model because each were done in only one patient. Multivariate analysis for overall DFS final model included (odds ratio; p value): tumour localization (5.6; <0.0001) (Figure 2), tumour stage (1.4; 0.03), neoadjuvant treatment (3.1; 0.08). These variables were also found at 1 and 3 years (although less significant). None of the other significant variables at the univariate level could remain in the multivariate model.

Of these 43 cancer patients, 12 patients (27.9%) were living and 31 died (1 postoperatively, 27 because of disease recurrence and 3 of intercurrent disease). The overall survival rate at 1, 2 and 3 years was 56.6%, 28.9% and 19.2%, respectively (Figure 3). The median survival was 14.2 months (95% CI: 9.8; 18.6).

Univariate analysis for overall survival (Table I) revealed that tumour localization, tumour stage and recurrence were explanatory variables ($p < 0.05$). Multivariate analysis for the overall survival final model included the following variables (odds ratio; p value): tumour localization (2.7; 0.02) (Figure 4), tumour stage (1.4; 0.02), neoadjuvant treatment



Survival probability

At risk :	43	19	9	5	4	4
Events :	17	9	3	1	-	-

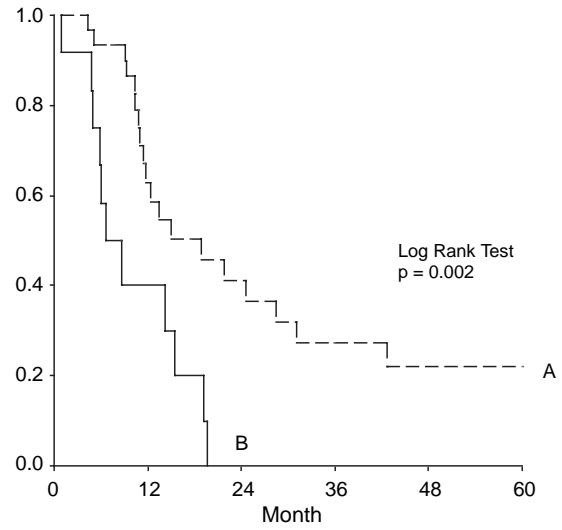
Figure 3. Overall survival probability.

(3.2; 0.09), tumour recurrence (3.3; 0.03). These variables were also found at 1 and 3 years (although less significant) (Table II).

Discussion

The preoperative diagnosis of vascular invasion in the presence of pancreatic carcinoma is difficult to determine and is usually based on imaging. Nowadays, coeliomesenteric angiography [9,11] has been abandoned and replaced by non-invasive imaging procedures such as triphasic helical CT scan, magnetic resonance imaging (MRI), Doppler ultrasound and endosonography explorations [12–14]. Indeed, imaging procedures such as MRI and three-dimensional CT allow the study of perivascular tissues with complete assessment of resectability of pancreatic carcinoma [15–17].

In our strategy, segmental venous resection was adopted systematically in the presence of tight adhesions without concern as to their nature (malignant or not) as long as the resection was considered macroscopically complete. This deliberated strategy was adopted to avoid uncontrollable vascular injuries during dissection. Venous resection was done en monobloc with the pancreas as the final step of resection to shorten the clamping time; associated



Tumour localisation

A : Head of pancreas						
At Risk :	31	15	9	5	4	
Events :	10	5	3	1	-	
B : Other sites						
At Risk :	12	4	0			
Events :	7	4				

Figure 4. Survival according to tumour localization: head of pancreas versus other sites.

SMA clamping was not necessary. A direct end-to-end suture is usually possible and the need for venous graft is rare [18,19] but is usually recommended for resection of >3 cm. This can be done using the long saphenous vein [20] or the internal jugular vein [7] or the superficial femoral vein harvested at mid-thigh level under its confluence with the deep femoral vein, as in one of our cases. The use of cryopreserved vessels is another option for vascular reconstruction, especially for arterial reconstruction when direct anastomosis is not feasible [21].

Our series shows other uncommon types of vascular resections: one patient had a wedge resection of the IVC; 9 years later he is alive and disease-free. Another patient had a ‘necessity’ resection of a RHA arising from the SMA with a transtumoral crossing; 4 years later he is alive and disease-free. As previously reported, arterial resection could be considered when carcinoma-free resection margin is fulfilled in carefully selected cases [22].

Despite progress in imaging techniques, the nature of radiological vascular involvement is still difficult to

Table II. Multivariate analysis for explanatory variables of disease-free survival (DFS) and overall survival.

Parameter	DFS		Overall survival	
	Odds ratio	p value	Odds ratio	p value
Tumour localization (head of pancreas vs other)	5.6	<0.0001	2.7	0.02
Tumour stage	1.4	0.03	1.4	0.02
Neoadjuvant treatment	3.1	0.08	3.2	0.09
Tumour recurrence	-	-	3.3	0.03

Table III. Reported results of pancreatectomy along with vascular resections from different centres.

Authors	Year	No. of cases	VR	AR	Histological vascular invasion (%)	Morbidity rate (%)	Mortality rate (%)	Median survival (months)
Tashiro et al. [38]	1991	27	27	2	25.9		8.4	NA
Ishikawa et al. [9]	1992	31			85.7		5.7	9
Allema et al. [6]	1994	20	20	0	50	63	15	8
Takahashi et al. [25]	1994	79	63	16	61		16.4	14 (curative); 6 (non-curative)
Nakao et al. [11]	1995	89			49.4		8	NA
Fuhrman et al. [7]	1996	23	23	0	77.8			
(7/9 examined specimen)	30	4	NA					
Harrison et al. [18]	1996	58	58	0	NA	Surgical re-intervention = 12	5	13
Roder et al. [30]	1996	31	31	0	61.3	41.9	0	8
Ogata et al. [39]	1997	107	103	21		23.1	5,6	
Leach et al. [40]	1998	31	31	0	72			
(13/18 examined specimen)	NA	0	22					
Shibata et al. [5]	2001	28	28	0	86	32	4	6.8–20.6
Sasson et al. [41]	2002	25	16	9	NA	38	1.7	NA
Kawada et al. [23]	2002	28	28	0	75	46	4	NA
Aramaki et al. [42]	2003	22	22	1	63.6	9.1	4.5	NA
Zhou et al. [28]	2005	32	32	0	62.5	31.25	NA	NA
Present study (43 cancer)	43	6	30 (40/43 examined)	24 (11 surgical complications)	2.2	14.2		

VR, vein resection; AR, artery resection; NA, not available.

Table IV. Survival independent factors according to multivariate analyses.

Variable [refs]	Hazard ratio	<i>p</i> value
Positive lymph node [31–36]	1.51–3.31	0.08–0.0065
Positive surgical margin [34–36]	1.3	0.28
Poor T differentiation [32,35]	1.82	0.0062
Tumour size >2.5 cm [32,36]	2.77	0.0011
Blood vessel invasion [31,33]	1.61–2.19	0.033–0.025
Blood transfusion [32]	2.13	0.015
Intrapancreatic perineural invasion [33]	1.83	0.0018
Radical resection [37]	0.51	0.002
+Adjuvant therapy [34]	0.26	< 0.001

determine. In many instances, a perivascular inflammatory process may have the appearance of true vascular invasion on imaging. Indeed, pathological examination of resected vessels shows that the rate of true vessel wall invasion is variable; according to reported studies it varies from 21% to 86% [6,7,23]. In our series true vessel wall involvement was observed in 30% of cases and only one of six resected arteries was involved (17%). However, 19 other patients had retropancreatic and perivascular invasion which, retrospectively, justified vascular resection as it allowed complete tumour clearance [24]. Nevertheless, the relatively high incidence of R1 resection is explained by the inclusion in this group of all retropancreatic invasion with a free margin of <1 mm. However, this group was not associated with worse prognosis according to multivariate analysis. Another argument for venous resection is the fact that, as shown in our study and other reports, venous resection is done according to the pre- and per-operative evaluation and not according to an objective documented pathology [11,25].

In our series, the survival of patients with and without histologically documented vascular invasion was not statistically different. These observations were similar to the previously reported data [6,7,18], where the survival of patients with or without histologically invaded vessels was not statistically different. For these reasons vascular resectability should be evaluated clinically during operative exploration [26] and venous involvement on preoperative examination should be considered as the reflection of the anatomical barrier for tumour resection but not as an absolute carcinological contraindication (our barrier for resectability is venous involvement of >50% of vascular circumference on angio-CT scan).

The attitude of centres regarding venous involvement varies, but it clearly appears that elective resection of a localized segment of the superior mesenteric vein (SMV) or the portal vein (PV), when all the criteria for carcinological resectability are fulfilled, does not significantly increase the morbidity or mortality, is associated with fair results and

the presence of venous invasion is not associated with poor prognosis [18,25,27–29]. Other authors correlated the depth of vessel wall invasion with survival [6,30]. Our study shows that venous and arterial resections do not increase perioperative mortality and morbidity with a 3-year overall survival rate of 19.2%.

The rationale of venous resection is now admitted in centres of expertise, Table III reports results of pancreatometomies along with vascular resections from different centres, showing a rate of vascular invasion from 25.9% to 77.8% of examined specimens, a morbidity rate of 23.1–63%, a mortality rate ranging from 0 to 16.4% and a median survival range of 8–22 months.

Several studies evaluated the independent risk factors influencing survival after pancreatometomies. According to multivariate analysis (Table IV) lymph node invasion was the most commonly found, followed by surgical margin invasion, then poor tumour differentiation, large tumour size, blood vessel invasion and blood transfusion [31–36], while favourable prognostic factors of good outcome were radical resection and adjuvant radiochemotherapy [34,37]. Our multivariate analysis showed only three explanatory factors that affected DFS: tumour localization outside the pancreatic head, tumour stage and neoadjuvant treatment. These same variables as well as tumour recurrence were found for survival analysis. Vessel wall invasion did not affect either survival or DFS. These analyses also show that neoadjuvant treatment is associated with worse prognosis and does not seem beneficial in this retrospective analysis where neoadjuvant treatments were done in different heterogeneous situations that do not allow definite conclusions and the *p* value was not statistically significant in the multivariate model. Because of worse prognosis for tumour located in the body and tail of the pancreas, these patients might benefit from systematic adjuvant therapy.

Conclusion

Vascular resections associated with pancreatometomies do not increase perioperative mortality and morbidity and should be considered as part of the surgical strategy. These resections should be planned and decided as soon as possible during the preoperative evaluation. During surgery, if it is difficult to determine whether the tight adhesions with the vessel wall are only due to inflammation or secondary to tumour extension, in these situations we perform a controlled segmental venous resection to avoid uncontrollable vascular injuries. Nevertheless, in all cases vascular resections are only performed when all oncological criteria for resectability are fulfilled and to obtain cancer-free surgical margins.

Our results showed that tumour localization, tumour stage, neoadjuvant treatment and tumour recurrence are explanatory variables of survival.

Tumour localization, tumour stage and neoadjuvant treatment were explanatory variables for DFS, whereas the type and extent of vascular resection as well as vessel wall invasion do not affect survival and DFS.

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