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ORIGINAL

Influence of portal vein/superior mesenteric vein resection on morbility, mortality and survival of patients with pancreatic ductal adenocarcinoma in the Balearic Islands

Influencia de la resección de vena porta/vena mesentérica superior en la morbilidad, mortalidad y supervivencia de los pacientes con adenocarcinoma ductal de páncreas en las Islas Baleares

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Summary

Introduction: Recent developments have enabled associate to standard pancreaticoduodenectomy (DPC), vascular resections to increase resectability in pancreatic cancer.
Objectives: Analyze morbidity, mortality and survival of a consecutive series of patients with pancreatic cancer, in which a DPC with portal vein resection was performed, and compared it with a group of patients with standard DPC without venous resection.
Methodology: Consecutive series of 67 patients who underwent a DPC ought to pancreatic ductal adenocarcinoma, between January 2005 and January 2015.
Results: Standard resection (RV-) was performed in 49 cases, and a venous resection in another 18 patients (RV+). There were no significant differences in age (65 vs 68.9 years), ASA, or intraoperative transfusion. Duration of intervention was significantly lower in the RV- group (6.1 vs 6.7; p = 0.05). Morbidity grade III -IV was 14.2 % Clavien in the RV- group and 16.6 % in the RV + group (p = 0.87). There were no differences in hospital mortality (0 % vs 5.5%), or hospital stay (14.4 vs 15.2 days). The surgical margin involvement was more frequent in the RV+ group (18 % vs 50 % ; p = 0.003). One, 3 and 5 years survival was 77, 34 and 11% in the RV- group and 92, 23 and 8% in the group with venous resection.
Conclusions: DPC with venous resection can be performed with morbidity and mortality rates similar to standard DPC1. Survival shows no significant difference between the two groups.Venous resection may increase resectability in a selected group of patients with pancreatic adenocarcinoma.

Keywords: Pancreatic ductal adenocarcinoma, morbidity, mortality, pancreaticoduodenectomy

Resumen

Introducción: Los progresos recientes han permitido asociar a la duodenopancreatectomía cefálica estándar (DPC), resecciones vasculares para incrementar la resecabilidad en el cáncer de páncreas.
Objetivos: Analizar la morbi-mortalidad y supervivencia de una serie consecutiva de pacientes con cáncer de páncreas, en los que se realizó una DPC con resección de vena porta y compararla con un grupo de pacientes con DPC estándar sin resección venosa.
Material y métodos: Serie consecutiva de 67 pacientes intervenidos con adenocarcinoma ductal de páncreas, entre enero 2005 y enero 2015.
Resultados: En 49 casos se realizó una resección estándar (RV-) y en 18 pacientes, una resección venosa (RV+). No hubo diferencias significativas en la edad (65 vs 68,9 años), ASA, ni en la transfusión intraoperatoria. La duración de la intervención fue significativamente menor en el grupo RV- (6,1 vs 6,7; p= 0,05). La morbilidad grado III-IV de Clavien fue del 14,2% en el grupo RV- y del 16,6% en el grupo RV+ (p=0,87). No hubo diferencias en la mortalidad hospitalaria (0% vs 5,5%), ni en la estancia hospitalaria (14,4 vs 15,2 días). La afectación del margen quirúrgico fue más frecuente en el grupo RV+ (18% vs 50%; p=0,003). La supervivencia al año, 3 y 5 años fue del 77, 34 y 11% en el grupo RV-,y del 92, 23 y 8% en el grupo con resección venosa.
Conclusiones: La DPC con resección venosa puede realizarse con tasas de morbi-mortalidad similares a la DPC estándar. La supervivencia no muestra diferencias significativas entre los dos grupos. La resección venosa puede aumentar la resecabilidad en un grupo seleccionado de pacientes con adenocarcinoma de páncreas.

Palabras clave: Adenocarcinoma ductal de páncreas, morbilidad, mortalidad, duodenopancreatectomía

Introduction

Pancreatic cancer is the fourth leading cause of cancer deaths in the world, with more than 100,000 deaths in Europe in 2012 and an increasing incidence over the last years due to unknown reasons.[1-5] Although curative resection followed by adjuvant chemotherapy is the therapeutic scheme offering the highest survival results, little progress has been made in terms of survival in the last decades. Distant metastases (hepatic, pulmonary or peritoneal) at diagnosis appear in 50% of patients, with an estimated survival of 6 8 months. Furthermore, only 20 25% of patients are eligible for surgical resection, whereas venous infiltration by contiguity (portal vein, superior mesenteric vein, superior mesenteric artery, hepatic artery or celiac trunk) appears in approximately 30% of the diagnosed cases and this situation is considered a contraindication to surgical resection, with a median survival of 4 11 months despite de use of new cytostatic agents.[1,6,7,8,9] On the other hand, the median survival of patients undergoing surgical resection is of 20 25 months, with a survival at 5 years of around 20% and a local recurrence rate of 60 70% in the first 18 months after resection.[7,10,11] These figures show the aggressive biological behaviour of pancreatic cancer and its great capacity both for distant dissemination and for loco regional invasion with lymphovascular and perineural infiltration.

For many years, the low surgical resection indexes have motivated continuous efforts to perform resection of locally advanced tumours with vascular resection techniques. The first attempts were done by Moore[12] (USA) in 1951 and Asada[13] (Japan) in 1963, who performed a cephalic pancreaticoduodenectomy (CPD) with resection and reconstruction of the superior mesenteric vein. Later, in 1973, Fortner[14] (USA) used the term "regional pancreatectomy" to describe a surgical resection including a total pancreatectomy, a radical regional lymphadenectomy, and a resection with reconstruction of the portal vein (type I resection) and/or the superior mesenteric artery (type II resection). These radical procedures were abandoned during decades due to their lack of impact on survival and their high morbi mortality, arguing that tumours affecting the venous wall were bigger, more aggressive and presented a worse prognostic.

However, in the last years, progress in surgical technique and in perioperative care has been able to reduce perioperative mortality to less than 5%, allowing for a more radical approach of locally advanced pancreatic tumours with invasion of the portal vein (PV) and/or the superior mesenteric vein (SMV).[4,15,16,17,18] As a result, a group of selected patients considered until recently as unresectable are now eligible for CPD with vascular resection, thus obtaining a higher survival as if treated only with chemoradiotherapy.[17,19] Tumours of this group of patients have been defined as "borderline", that is, tumours halfway between clearly resectable tumours without vascular invasion and locally advanced, technically unresectable tumours with massive mesenteric portal venous and/or arterial infiltration.[1] The meta analysis published by Siriwardana in 2006 revealed a median survival of 13 months and a survival at 5 years of 5% of the patients with vascular resection.[20] Two following meta analyses showed greater operative time and transfusion requirements for patients with vascular resection, but did not find any differences in postoperative morbility and mortality between patients undergoing a CPD with and without vascular resection.[2,3] As for long term survival, recent studies showed that medium and long term survival of patients after vascular resection is similar to that of patients who did not undergo vascular resection and, more important, survival in this patients is significantly higher to that of patients who have not undergone any kind of surgical resection or who had a palliative enterobiliary bypass done.[2,3,4]

Because of these reasons, the American Joint Commission on Cancer (AJCC) modified its classification in 2002, staging the infiltration of the mesenteric portal vein confluence as T3 instead of T4, and the National Commission on Cancer (NCCN) included venous resection in its recommendations for cases of localized vascular infiltration if clear resection margins and an appropriate vascular reconstruction was possible.[21]

There is total unanimity with respect to considering that this kind of interventions are most profitable when performed in hospitals with a high volume of patients. The coordinated multidisciplinary approach required to perform this surgery allows to modify the management of at least 25% of the patients with pancreatic cancer and to rescue many patients who were considered as unresectable until today.[22]

Despite all these promising results and recent recommendations, and probably due to its greater technical complexity, venous resection in pancreatic cancer has not been widely included in all hospitals. The two main reasons that explain why tumours with infiltration of the mesenteric portal vein confluence are still being considered as unresectable are, first, that venous resection is considered to have a significantly higher surgical morbility and mortality and, second, that this kind of tumours are assumed to have a more aggressive biology both locally and systemically, thus having a worse prognosis and a lower short and medium term survival which result in considering these patients at prohibitive surgical risk and low survival. Luckily, recent studies prove the contrary, and it is therefore necessary to introduce these surgical techniques in the management of patients with pancreatic cancer.

The present study formulates two hypotheses:
First hypothesis. Pancreaticoduodenectomy with

vascular resection of the mesenteric portal vein confluence can be performed with a rate of postoperative complications and mortality similar to that of standard pancreaticoduodenectomy without vascular resection.

Second hypothesis. Patients who underwent a cephalic pancreaticoduodenectomy with venous resection present a medium and long term survival comparable to that of patients who underwent a standard pancreaticoduodenectomy without vascular resection.

The main objectives of the study were:

1. To analyse postoperative mortality and morbility of patients with pancreatic cancer with infiltration of the portal vein and/or the superior mesenteric vein who underwent a pancreaticoduodenectomy with venous resection, and compare it with the morbi mortality of patients who underwent a CPD without vascular resection to evaluate if venous resection implies a greater surgical risk.

2. To determine medium and long term survival in patients who underwent vascular resection and compare it with that of patients who undergo a standard pancreaticoduodenectomy without venous resection to determine if venous resection can increase long term survival in patients with pancreatic cancer with portal vein invasion.

Material and methodology

Tumour extension and resectability

Between January 2005 and January 2015, a total of 125 consecutive pancreaticoduodenectomies were performed and their data was prospectively entered in a data base. A final diagnosis of pancreatic ductal adenocarcinoma was established in 67 patients, who constitute the object of the present study. All patients were studied following a pre established diagnostic therapeutic protocol and evaluated by a multidisciplinary committee of pancreatic tumours made up by oncologists, gastroenterologists, radiologists, pathologists, radiotherapists and surgeons.

The preoperative diagnostic therapeutic management scheme consisted of:

- Analytical study with tumour markers (CEA; CA 19.9).
- Radiologic evaluation: ultrasonography, three phase computerized axial tomography (CAT) of the pancreas, and magnetic resonance imaging.
- Endoscopic evaluation: upper endoscopy, endosonography, fine needle aspiration biopsy (FNAB), endoscopic retrograde cholangiopancreatography (ERCP).
- Endoscopic or transhepatic biliary drainage in cases of surgical delay >10 days.
- Cytological study.
- Assessment of resectability.

Inclusion and exclusion criteria

Inclusion criteria: Patients diagnosed with pancreatic ductal adenocarcinoma in the pancreatic head, with/without extension to the rest of the pancreas, who underwent a total resection with curative intention.

Exclusion criteria:

1. Systemic dissemination (hepatic or pulmonary).
2. Peritoneal dissemination.
3. Arterial vascular infiltration (celiac trunk, common hepatic artery or superior mesenteric artery).

Surgical technique

All interventions were performed by the same group of surgeons. Pancreaticoduodenectomy included antrectomy (Whipple). In those cases of diffuse tumours or a positive intraoperative biopsy of the surgical margin, a total pancreaticoduodenectomy with splenectomy was performed. Routine included a lymphadenectomy of the hepatoduodenal ligament, the hepatic artery, the celiac trunk, the interaortocaval space and the right lateral side of the superior mesenteric artery.[23] In both groups, reconstruction was performed with a double loop Roux en Y and an end to side pancreaticojejunal anastomosis in two layers with or without a silicone stent depending on the diameter of the pancreatic duct. The bile duct was reconstructed with an end to side hepaticojejunostomy. Gastrojejunal anastomosis was antecolic as described by Hartel.[24] All patients remained in the postoperative care unit for at least 24 hours. Octreotide was only administered to patients with a great risk of pancreatic fistula (pancreatic duct ≤1 mm or soft pancreas). Two abdominal drainages were used: a subhepatic drainage and one close to the pancreatic anastomosis.

Three types of vascular reconstruction were performed:

1. Lateral suture of SMV or PV in cases of infiltration ≤25% of vein circumference (**Figures 1A** and **1B**).
2. Segmental resection with end to end anastomosis with autologous vein in cases with infiltration >50% of vein circumference (**Figures 2A** and **2B**).
3. Replacement by a polytetrafluoroethylene (PTFE) prosthesis in a case with PV infiltration of 3 cm of length.

In those cases of venous segmental resection, the superior mesenteric artery (SMA) was clamped before the venous resection and during the vascular resection, in order to avoid swelling of the small intestine. Once the resection pieces had been extracted, the retroperitoneal margin of the SMA was painted with ink and the cutting area of the vein was marked to facilitate its identification by the pathologist.

Patients with lateral venous resection were given the usual dose of low molecular weight heparin. In those cases of venous segmental resection and replacement by a PTFE prosthesis, patients were given a dose of intravenous

Figure 1A: Illustration of the lateral resection of the portal veinables.

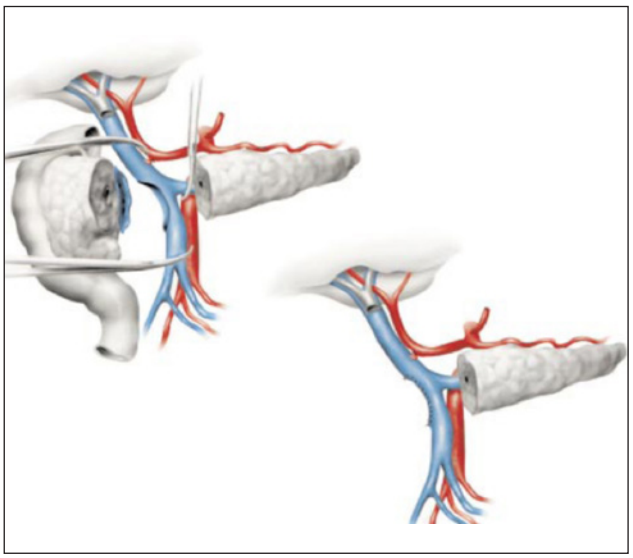


Figure 1B: Surgical image of the lateral resection of the portal vein. 1. Portal vein with lateral resection and vascular suture; 2. Cava vein; 3. Common hepatic artery.

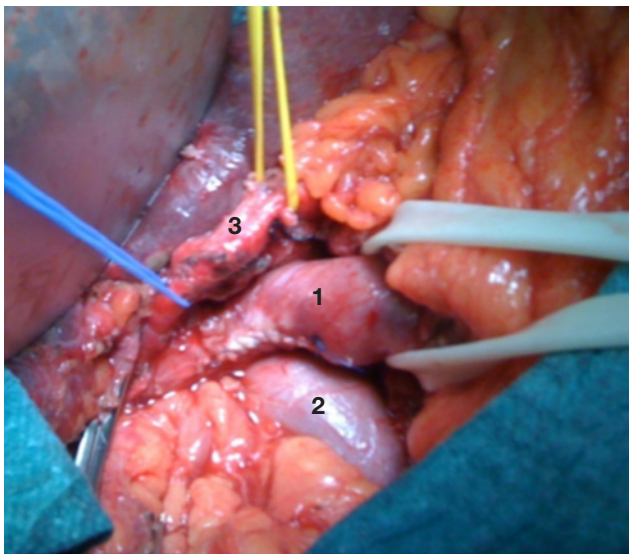


Figure 2A: Illustration of the segmental resection of 2 cm of portal vein with end to end vascular anastomosis.

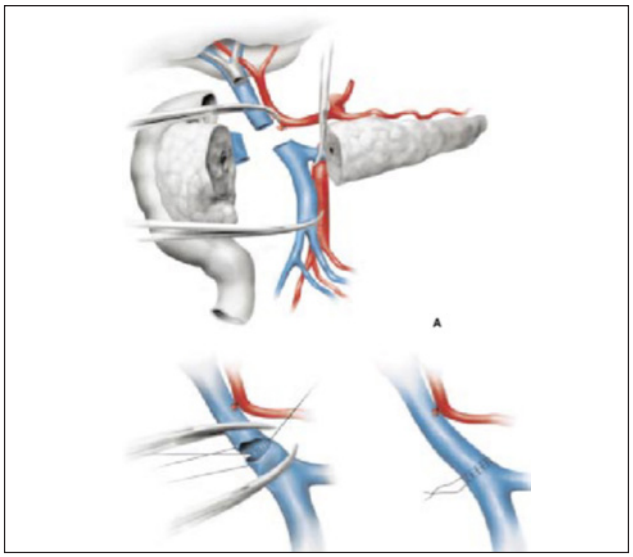
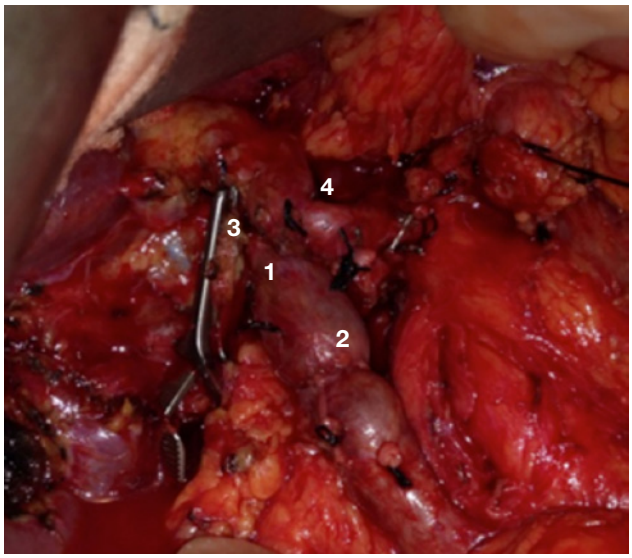


Figure 2B: Surgical image of the segmental resection of 2 cm of portal vein with end to end vascular anastomosis. 1. Portal vein; 2. End to end anastomosis; 3. Cut and clamped bile duct; 4. Common hepatic artery.



sodium heparin at the moment of clamping the SMA. All patients with venous resection were monitored with hepatoportal Doppler 24 hours after surgery.

Drainages in the portal mesenteric resection group were removed according to the amylase determination in the drainage liquid after the third postoperative day. Prokinetic drugs were only administered to patients with delayed gastric emptying (DGE).

Definitions

Pancreatic fistula. Drain output on or after postoperative day 3, with an amylase content greater than 3 times the upper limit of normal serum amylase level. The type of pancreatic fistula was categorized according to the grades and criteria of the International Study Group on Pancreatic Surgery (ISGPS).[25]

Delayed gastric emptying (DGE). Need of a nasogastric tube during more than 3 days or its insertion after postoperative day 3, as well as the lack of oral tolerance after the first postoperative week.[26]

Biliary fistula. Drain output on or after postoperative day 5, with a bilirubin content greater than 3 times the upper limit of normal serum bilirubin level.

Perioperative variables

The study population consisted of consecutively operated patients, and their data were prospectively

Table I: Clavien Dindo classification

Grade	Type of complication
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed regimens are drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Complication requiring pharmacological treatment with drugs other than such allowed for Grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III a	Complication requiring surgical, endoscopic or radiological intervention with local anaesthesia.
Grade III b	Complications requiring surgical, endoscopic or radiological intervention with general anaesthesia.
Grade IV	Life threatening complication requiring IC/ICU management (including central nervous system complications).
IV a	Single organ dysfunction (including dialysis).
IV b	Multi organ dysfunction.
Grade V	Death of patient.

entered in a pancreatic resection data base. Studied demographical variables included age, sex, operation time, intra and postoperative transfusion, intensive care unit (ICU) stay, mortality, morbility and hospital stay. Mortality and complications were followed up until hospital discharge or death of the patient. Postoperative complications were registered using the Clavien Dindo classification (**Table I**).[28] Readmissions were registered up to the 30th day after hospital discharge.

Postoperative follow up and survival

All patients were evaluated by the Oncology Department and received the corresponding adjuvant treatment and oncologic follow up. During the first two years after surgery, patients attended the oncology consultation every 6 months for evaluation by means of abdominal CAT scans, analyses, and tumour markers. After the second year, controls took place yearly. The follow up included visits to the oncology and surgery consultation, retrieval of their medical history through the Balearic Department of Health, and phone calls.

The median survival was calculated on the basis of patients' median follow up. The control group in terms of survival consisted of a group of patients with a pancreatic head tumour with infiltration of the mesenteric portal vein confluence who did not undergo vascular resection because they were diagnosed before the introduction of the CPD vascular resection program.

Histopathological examination

An intraoperative biopsy of the pancreatic and biliary margin was performed routinely. In those cases in which the intraoperative margin was positive, the solution was either to increase this margin or to conduct a total pancreatectomy. The pathological study included the analysis of histological type, degree of cell differentiation, tumour size, lymph node infiltration, perineural infiltration and lymphovascular invasion. Resection margins involvement was defined following the classification by the American Joint Committee on Cancer definitions 2010 (AJCC) until 2014. The following margins were studied and painted with different colours for their histological examination: stomach, bile duct, pancreatic trasnsection, portal vein and superior mesenteric artery. (**Figure 3**).

After 2014, the Verbeke guidelines were applied, which consider resection as R0 if there is a minimum clearance of 1 mm (**Figure 4**).[29]

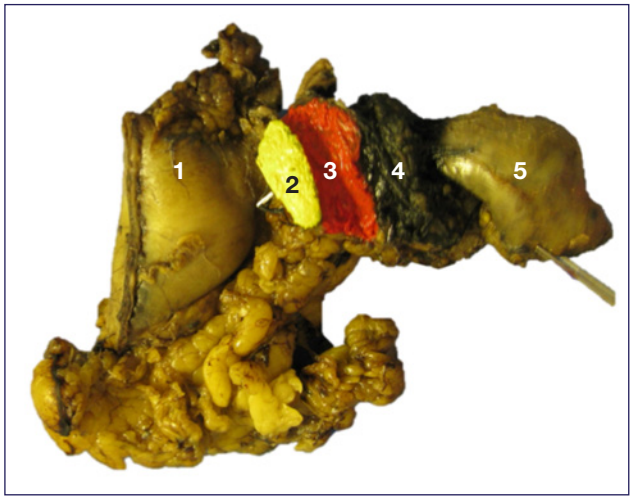
Statistical analysis

Results are presented as the median ± SE (CI 95%), range or percentage (%). The Kolmogorov Smirnov test was applied to guarantee a Gaussian distribution of results. Comparisons among groups were performed by using the independent samples t test, the analysis of variance (ANOVA) or the Mann Whitney test for continuous variables, and the chi square test or the Fisher's exact test for categorical variables. Survival estimates were calculated with the Kaplan Meier method and comparisons among curves were analysed with the log rank test. Finally, to analyse the impact of some variables on survival, odds ratio were calculated adjusted with 95% confidence intervals (CI) by means of logistic regression. For all calculations, a value of $p<0.05$ was considered statistically significant. Statistical analysis were done using the software package SPSS® 16.0 for Windows (SPSS® Inc., Chicago, IL, USA).

Ethical considerations and confidential treatment of data

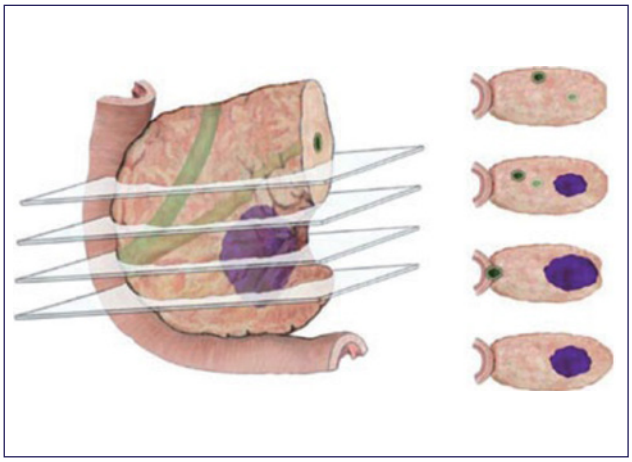
The management, communication and transfer of personal data of all participants took place according to the provisions of the corresponding Spanish legislation (Organic Law 15/1999, of 13th December, on the Protection of Data of a Personal Nature). Handling of data

Figure 3: Painted surgical resection margins.



1. Stomach; 2. Pancreas section; 3. Portal vein margin; 4. Sup. mesenteric artery margin; 5. Duodenum Jejunum

Figure 4: Axial slicing of pancreatoduodenectomy specimens. Image from Verbeke CS. Redefining resection margin status in pancreatic cancer. HBP 2009; 11: 282 289.[29]



was totally confidential, and only the main researcher had access to codified information. All participants were informed of the study and signed, before joining it, an informed consent with detailed explanations of the interventions, the surgical technique and the possibility of postoperative complications. All doubts and questions arisen were answered by the surgeon responsible for the study. Patients were also informed that their decision would not affect the medical care received and that they could abandon the study at any point.

Results

The population of the study consisted of all patients diagnosed with pancreatic ductal adenocarcinoma who consecutively underwent a CPD with curative intention between January of 2005 and January of 2015.

Demographical data

The study group consists of 67 patients, from whom 49 (73.1%) underwent a CPD without venous resection (VR- group) and 18 patients (26,9%) a CPD with venous resection due to infiltration of the wall of the mesenteric portal vein confluence (VR+ group). Distribution by sex, age, histology and preoperative risk measured by ASA was homogeneous in both groups. Median age of the VR- group was 65 ± 1.6 years (range 53 80) and that of the VR+ group, of 68.9 ± 2.4 years (range 47 80) (p=0.184) (**Table II**). A CPD was performed total on 65 patients and in two cases a total pancreatoduodenectomy was required due to a tumour with diffuse invasion of the pancreas.

Table II: Demographical data.

Demographical data	VR (-)	VR (+)	p
Age	65	68.9	0.184
Women	18/49 (36.8%)	9/18 (50%)	0.403
Men	31/49 (63.2%)	9/18 (50%)	
ASA I	13/49 (26.5%)	1/18 (5.6%)	0.090
ASA II	36/49 (73.59%)	17/18 (94.4%)	

Intraoperative results

Global median operation time was of 6.2 hours in the VR- group and of 6.9 hours in the VR+ group (non significant difference). The intraoperative and postoperative transfusion median was greater in the VR+ group (0.8 1.2 packed red blood cells) than in the VR- group (0.47 1 packed red blood cells), but the difference was non significant (p=0.26). Operation time was significantly greater in the VR+ group (7.3 hours) than in the VR- group (6.1 hours) (p=0.05).

Type of venous resection

In 15 patients (83.5%), infiltration of the venous wall was smaller than 50% of the circumference, so it was possible to perform a lateral resection with primary reparation using 6/0 polypropylene without a vein patch. Two patients presented infiltration greater than 50% of the circumference, requiring a resection of a PV/SMV segment of 1.5 2 cm of length. In these cases, reconstruction was performed by end to end anastomosis with 5/0 polypropylene. One patient presented tumour infiltration of approximately 3.5 cm of length, requiring the interposition of an expanded PTFE graft and a double anastomosis (proximally and distally) (**Table III**).

Postoperative complications; reinterventions

Global mortality of the series was 1.5%. The VR- group presented less complications than the VR+ group, but without significant differences (44.8% vs. 55.5%) (p=0.582). The Clavien Dindo classification makes it possible to group complications according to its severity

Table III: Type of venous resection of the mesenteric portal confluence (PV/SMV).

Type of venous resection	N (%)
Lateral resection	15/18 (83.5%)
Segmental resection with end to end anastomosis	2/18 (11%)
Segmental resection with end to end anastomosis with a PTFE graft	1/18 (5.5%)

(see **Table I**). The VR+ group presented a slightly greater incidence of severe complications (groups III and IV of Clavien's classification), but again without significant differences (VR- group: 14.2%; VR+ group: 16.6%) (p=0.582). Most frequent complications were pancreatic fistula (7 cases, 10.4%), followed by delayed gastric emptying (6 cases, 8.9%), biliary fistula (4 cases, 5.9%), abdominal abscess (3 cases, 4.5%) and central catheter infection (3 cases, 4.5%). Complications of both groups are detailed in **tables IV** and **V**.

Table IV: General mortality and morbility.

COMPLICATIONS	VR (-) N: 49	VR (+) N: 18	P
Global Morbidity	33/67 (49.2%)		
Morbility	22/49 (44.8%)	10/18 (55.5%)	0.582
III IV Clavien	7/49 (14.2%)	3/18 (16.6%)	1.000
Global mortality	1/67 (1.5%)		
Mortality	0/49	1/18 (5.5%)	0.258

Table V: Specific complications.

COMPLICATIONS	VR (-) N: 49	VR (+) N: 18
Pancreatic fistula	5	2
DGE	4	2
Biliary fistula	2	2
Central catheter infection	3	1
Wound infection	3	0
Abdominal abscess	3	0
Intestinal obstruction	1	0
Hepatic abscess	1	0
Respiratory distress	1	0
Subclavian thrombosis	1	0
Upper gastrointestinal bleeding	1	0
Extravasation of jejunostomy	1	0
Urinary infection	1	1
Chylous ascites	0	1
Yeyunal dehiscence	0	1
Pulmonary thromboembolism	0	1
Portal vein thrombosis	0	1

The VR+ group also presented a greater incidence of reinterventions (11.1%) than the VR- group (8.2%), although without significant differences (p=0.666). **Table VI** describes the etiology of surgical reinterventions.

Table VI: Etiology of surgical reinterventions.

Reinterventions	VR (-) N: 49	VR (+) N: 18	
Reinterventions	**4/49 (8.2%)**	**2/18 (11.1%)**	**p=0.666**
Loop dehiscence	0	1	
H J dehiscence	0	1	
Intestinal obstruction	1	0	
Abdominal abscess	1	0	
Pancreatic fistula	1	0	
Extravasation of jejunostomy	1	0	
Total	**4**	**2**	

In hospital mortality

Global mortality of the series was 1.5%. No death was registered in the VR- group, whereas one death occurred in the VR+ group, thus resulting in a 5.5% mortality rate. However, the difference when comparing both groups (p=0.258) remains non significant. The deceased patient was a 76 year old woman with a tumour presenting a large infiltration of the mesenteric portal confluence which required a venous resection of 3.5 cm of length. An expanded PTFE prosthesis was needed for its reconstruction. The patient presented an early thrombosis in the graft with shock and rapidly progressive multiorgan failure during the immediate postoperative period (24 hours).

Hospital stay

Global median hospital stay was 16.1 days, in line with most of the series consulted. Paradoxically, the VR- group presented a slightly greater median stay as the VR+ group (15.2 vs. 16.4 days), although without statistical signification (p=0.977).

Readmissions

The VR+ group presented a higher incidence of readmissions after hospital discharge than the VR- group (11.1% vs. 6.1%) (p=0.590). Reasons for readmissions were dehydration, delayed gastric emptying, pneumonia and hepatic abscess, and are presented in **table VII**.

Table VII: Reasons for readmission after hospital discharge

Urgent readmissions	VR (-) N: 49	VR (+) N: 18	
Readmissions	**3/49 (6.1%)**	**2/18 (11.1%)**	**p= 0.590**
Delayed gastric emptying	0	1	
Dehydration	1	1	
Pneumonia	1	0	
Hepatic abscess	1	0	
Total	**3**	**2**	

Histopathological results

Of the 18 patients who underwent venous resection, 72.2% (13 patients) presented histological demonstration of vascular infiltration (true venous infiltration) and the

Table VIII: Histological results

HISTOLOGY	VR (-) N: 49	VR (+) N: 18	True venous infiltration N: 13	P
Tumour size	2.9 ± 0.1	3.1 ± 0.2	3,2 ± 0,39	0.465
G1	8/49 (16.3%)	6/18 (33.3%)	3/13 (23.1%)	
G2	32/49 (65.3%)	7/18 (38.9%)	7/13 (53.8%)	0.403
G3	9/49 (18.4%)	5/18 (27.8%)	3/13 (23.1%)	
Surgically removed lymph nodes (median)	18.2	17.6	19.7	0.857
N0	11/49 (22.4%)	6/18 (33.3%)	3/13 (23.1%)	0.424
N1	38/49 (77.6%)	12/18 (66.6%)	10/13 (72.2%)	
Perineural infiltration	47/49 (95.9%)	18/18 (100%)	13/13 (100%)	0.523
Lymphatic vessel infiltration	44/49 (89.8%)	16/18 (88.9%)	11/13 (84.6%)	0.871
R0 margin	40/49 (81.6%)	9/18 (50%)	5/13 (38.5%)	0.003
R1 margin	9/49 (18.4%)	9/18 (50%)	8/13 (61.5%)	

resting 27.8% (5 patients) presented a non tumoural inflammatory desmoplastic reaction on the venous wall. As for the histological study, this subgroup of 13 patients was compared with the other two groups in order to avoid bias when comparing patients with venous resection but without true venous infiltration. The tumour size was similar in the three groups (2.9 vs. 3.1 vs. 3.2 cm) (p=0.465). As shown in **table VIII**, there are no significant differences when studying the degree of cell differentiation among the different groups (p=0.403), with very similar percentages of undefined tumours in all three groups. Unlike other series consulted, in the present study lymph node infiltration was more common in the VR- group (77.5 vs. 66.6%), obtaining the same result when separately analysing tumours with true venous infiltration (76.9 vs. 77.5%), although without a significant difference (p=0.424). No differences were found either in the number of lymph nodes surgically removed (p=0.857) nor in the percentage of tumours with perineural infiltration (100 vs. 95.9%) (p=0.523).

As for the resection margin involvement, patients with venous resection and with tumours with a true venous infiltration presented a higher incidence of positive surgical margins (18.4 vs. 50 vs. 61.5%) (p=0.003).

Survival results

The median follow up of all patients was 25.3 months (range 4 104). Median survival was similar in both VR- and VR+ groups (25.6 and 24.6 months) and no significant differences were detected. The survival study was completed comparing the two groups of study (VR- and VR+) with a third group of patients considered unresectable due to infiltration of the mesenteric portal confluence who were diagnosed before the introduction of the vascular resection program. Median survival of these two groups was significantly higher than that of unresectable patients. Survival of the VR- group was significantly higher than that of the group of unresectable patients (25.6 ± 3.6 vs. 10.6 ± 2.3) (p=0.000). Likewise, survival of the VR+ group was significantly higher than that of the group of unresectable patients (22.1 ± 4.2 vs. 10.6 ± 2.3) (p=0.007). An analysis of medium and long term survival reveals that these are similar in patients who underwent a CPD with and without vascular resection, and that this similarity is maintained at 5 years of follow up. These figures support the second hypothesis, that is, that patients with venous infiltration that allow for a vascular resection have a similar survival to those without vascular infiltration (**Table IX**) (**Figure 5**).

Table IX: Median medium and long term survival

SURVIVAL	VR (-)	VR (+)	Unresectable patients
Follow up in months (range)	4-104	6-42	2-36
Median survival	25.6 ± 3.6	22.1 ± 4.2	10.6 ± 2.3**,***
1 year	34/44 (77.3%)	12/13 (92.3%)	5/22 (22.7%)
2 years	15/44 (34.1%)	6/13 (46.2%)	5/22 (22.7%)
3 years	7/44 (15.9%)	3/13 (23.1%)	2/22 (9.1%)
4 years	5/44 (11.4%)	1/13 (7.7%)	0/23 (0%)
5 years	5/44 (11.4%)	1/13 (7.7%)	0/23 (0%)

One way ANOVA, VR+/palliative, p=0.007; VR-/palliative, p=0.000

Figure 5: Actuarial survival of patients with and without venous resection.

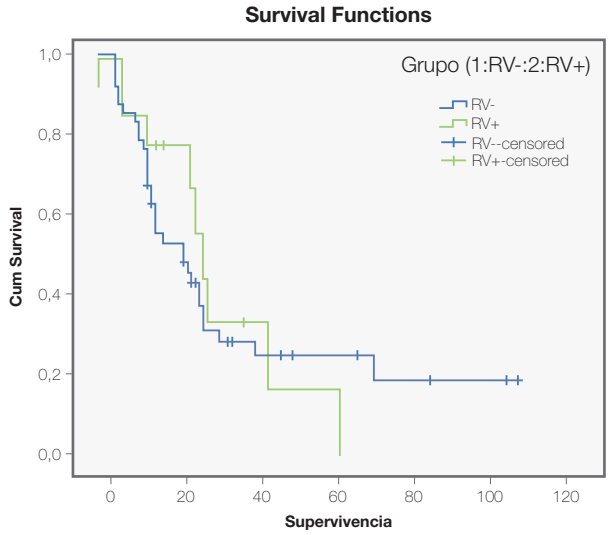
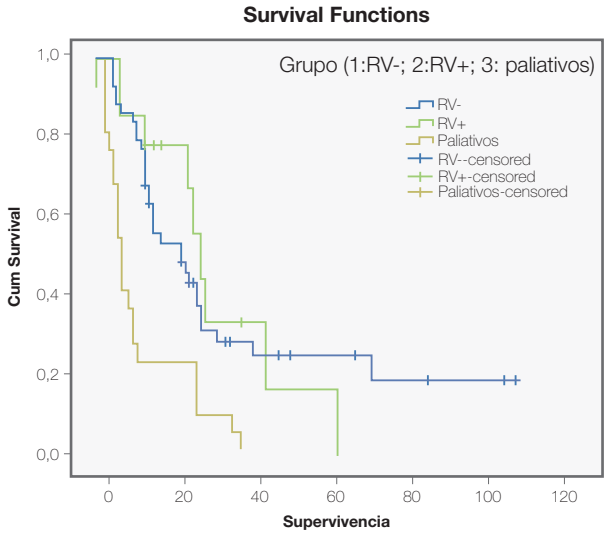


Figure 6: Actuarial survival of patients with and without venous resection, compared to patients who did not undergo surgery due to venous infiltration.



However, survival of those patients who did not undergo a surgery due to venous infiltration was of 21.7% at 1 year, 17.4% at 2 years and 4.3% at 3 years. In this group of patients, the median survival was significantly smaller (10.6 months) with no survivors registered at 4 and 5 years. The statistical contrast log rank (with a value of 19.918 and a degree of freedom 2) gives a p value associated to the contrast of 0.000, thus denoting statistically significant differences in survival for these groups (**Figure 6**).

Discussion

Pancreatic cancer is actually the fourth leading cause of cancer deaths in western countries, with an increasing incidence over the last two decades due to unknown reasons.[2,3,30] Despite the development of diagnostic imaging, most patients with pancreatic cancer are diagnosed when the tumour has already reached an advanced stage. At the moment of diagnosis, 50% of patients present hepatic, pulmonary or peritoneal dissemination, and 25-30% of them have locally advanced infiltration of the mesenteric vessels or the celiac trunk. As for the prognosis, pancreatic cancer is still the digestive cancer with worst prognosis, with a global survival at 5 years of 5% and a life expectancy for patients with successfully removed tumours of 15-22 months.[31,32] Patients whose pancreatic cancer is presented with hepatic, pulmonary or peritoneal metastases have a survival of 3-6 months, whereas those patients with locally advanced tumours with infiltration of the mesenteric portal confluence who do not undergo vascular resection have an estimated survival of 3-12 months.[1,33] Despite its poor prognosis, resectable patients have the highest life expectancy with a survival at 5 years of 25%, explaining the great efforts made to increase resectability and survival both from the oncological and the surgical point of view.[15,31,34]

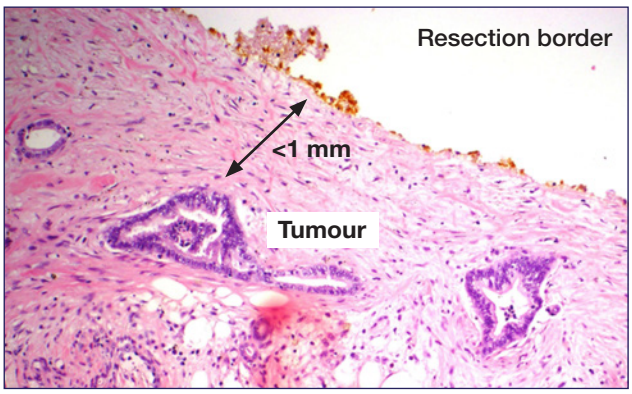
Prognostic factor

The most important independent factors described in long term prognosis for pancreatic cancer are the degree of cell differentiation, lymph node affectation, resection margin involvement and infiltration of peripancreatic nerve plexus.[6,31,32,35,36,37] Patients without lymph node infiltration have a survival at 1 and 3 years of 85 and 45%, respectively, whereas this decreases to 70 and 24% in cases of microscopic lymph node infiltration.[6,31]

Resection margins

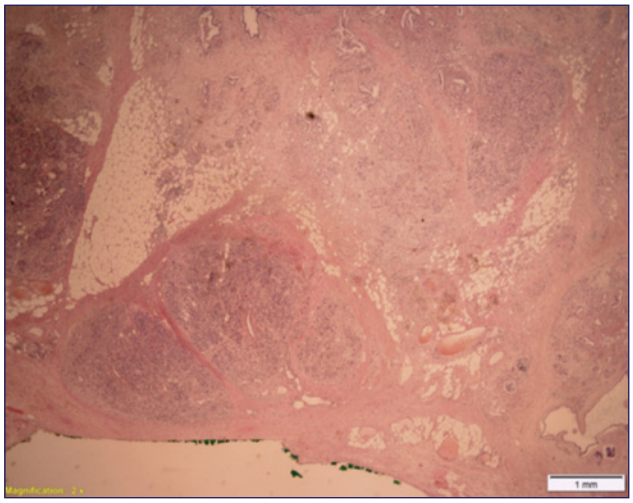
Due to the existing variety in the definitions of tumoural infiltration, there is a great divergence in published involvement indexes of margin resection.[1,2] Until recently, criterion by the *American Joint Commission on Cancer (AJCC)* was the most commonly used, staging microscopic margin involvement as R1 if the tumour cells are present at the line of resection (0 mm). Therefore, according to this criterion, tumour resections with a margin involvement of 0 1 mm were considered as clear margins (**Figure 7**).

Figure 7: Surgical resection margin at <1 mm of the tumour.



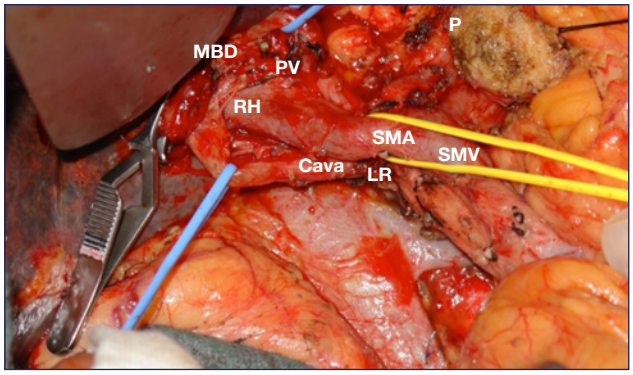
However, in an attempt to decrease the local recurrence rate, most reference centres are actually following Verbeke's criteria[29], who considers margins as infiltrated if tumour cells are at ≤1 mm of the line of resection (**Figure 8**). This shift has very important implications, as the application of the ≤1 mm criteria has increased the incidence of positive resection margins (R1), with the resulting increase in the indication of postoperative radiotherapy.

Figure 8: Surgical resection margin at >1 mm of the tumour.



In Zhang's study,[2] the median survival of patients without margin involvement (R0) was 28.7 months, whereas that of patients with margin involvement (R1) was 17 months. Likewise, survival at 1 and 3 years for R0 patients was of 91 and 37%, respectively, whereas these figures decreased to 37 and 18%, respectively, for R1 patients. When surgical resection margins are macroscopically involved (R2), survival is practically similar to that of patients who do not undergo surgical resection.[38] Among the variety of resection margins obtained in CPD, the SMA margin plays the main role, as this is the most commonly involved margin and that most directly related with survival, so it is therefore necessary to make an effort to obtain surgical margins without tumoral involvement.[1,2,29,35,39] Current surgical protocols insist on the need of performing a CPD with lymphadenectomy and resection of the perineural tissue until reaching the right lateral wall of the SMA in order to obtain a clear retroperitoneal margin (**Figure 9**).[37,40]

Figure 9: Dissection field after removal of the piece; superior mesenteric artery exposed.



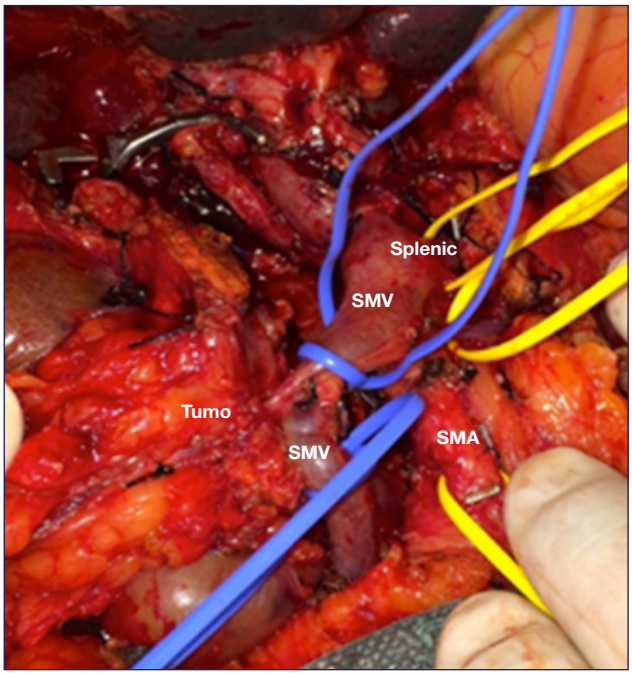
Right hepatic artery originating from the superior mesenteric artery (anatomical variant). LRV: left renal vein; SMA: superior mesenteric artery; RHA: right hepatic artery originating from the superior mesenteric artery; PV: portal vein; P: Cut pancreas; MBD: Main biliary duct, cut and clamped.

In the series of the present study, degree of cell differentiation, lymph node affectation and perineural infiltration was similar in both groups. However, patients requiring a venous resection and patients with true venous infiltration presented a significantly greater involvement of resection margins. Even though the size of our series is still limited, this suggests a greater local aggressivity in this group of tumours.

Infiltration of the mesenteric portal confluence

Due to the close contact between the mesenteric vessels and the pancreatic head, and particularly the uncinate process, pancreatic cancer frequently infiltrates the mesenteric portal confluence (**Figure 10**). Very often, this vascular infiltration takes place on the postero lateral side of the vein and can be only evidenced once the surgeon has cut the pancreatic neck, thus raising the dilemma of whether to perform a vascular resection to obtain a clear margin (R0) or to leave a macroscopically positive margin (R2), with the consequent survival reduction.[2]

Figure 10: Uncinate process tumour with infiltration of the superior mesenteric vein larger than 1 cm of cranio caudal length.



This fact, combined with the frequent systemic dissemination at the moment of diagnosis, explains why surgical resectability of pancreatic cancer has been performed in less than 20% of patients in the last decades.[6,33]

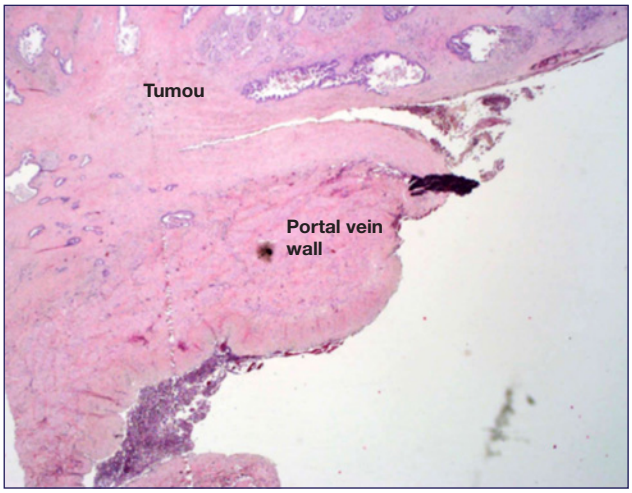
Traditionally, tumoural infiltration of the mesenteric portal confluence has been considered as a contraindication for surgical resection of pancreatic tumours. Authors such as Moore (1953)[12], Asada (1963)[13] and Fortner (1973)[14] considered the possibility of performing mesenteric vascular resections with the aim of increasing resectability and survival of patients with locally advanced pancreatic cancer, but had to abandon these radical resections due to the high morbility and mortality registered.

The advances in surgical technique and perioperative care and the concentration of this type of complex surgery in high volume centres have succeed in reducing postoperative mortality below 5% and in improving short and long term results in CPD patients.[27,33,41] Furthermore, this improvement in the results has made it possible to approach more complex resections with equal morbility and mortality rates.[11,19,32,42] Currently, numerous groups are publishing results that show that patients undergoing a VR+ CPD have a similar survival as patients with pancreatic head tumours without venous infiltration, as well as a clearly greater survival than patients considered as unresectable due to venous infiltration.[1,3,6,15,19,35,43,44] According to these results, clinical guidelines have been modified (including those by the National Comprehensive Cancer Network, NCCN)[1,21,41], thus creating a group of patients defined as "borderline" that comprises cases of PV/SMV confluence infiltration which allow for a vascular resection and reconstruction in order to obtain a clear surgical margin (R0), and which make it possible to turn a clinical stage with an indication of palliative chemotherapy and a survival of 10 12 months to a case of resected tumour with greater life expectancy. The possibility of performing a pancreaticoduodenectomy with resection of the mesenteric portal confluence followed by a vascular reconstruction constitutes the difference between "borderline" tumours and locally advanced tumors with massive infiltration of the mesenteric vessels that do not allow for surgical resection.[39,41]

Currently, there is an ongoing dispute with respect to the infiltration of the mesenteric portal confluence by pancreatic tumours: on the one hand, it seems a sign of its more aggressive biology[32,45] whereas, on the other hand, it could be a mere result of the tumour location and would therefore not imply a worse prognosis once the tumour has been resected.[35,42] There is though unanimity in finding that tumours with venous infiltration larger than 3 cm of length or of the entire vein circumference and those causing thrombosis or complete venous occlusion are associated with a worse tumoral stage and an increased index of resection margin involvement, and therefore venous resection does not seem to present a clear benefit in terms of survival.[11,32,33,38] Likewise, vascular resection is not recommended in tumours of the uncinate process with infiltration of the SMV and its tributary branches due to the great difficulty of obtaining a secure vascular reconstruction.[44,46]

Nowadays, preoperative radiological evaluation makes it possible to reliably determine a suspected vascular infiltration, and vascular resection is supposed to be considered before starting the operation. However, and despite the development of diagnostic imaging, radiological differentiation between vascular infiltration and the inflammatory desmoplastic reaction that characterises pancreatic tumours makes it difficult to differentiate them even during surgery. In fact, histologically determined vascular infiltration widely varies among the different series, ranging from 40 to 85% of tumoral infiltration in the final histological examination.[2,6,35,42,44] In the present study, true histological infiltration of the PV wall was demonstrated in 72.2% of VR+ patients (**Figure 11**).

Figure 11: Histological preparation showing the infiltration of the tumour on the portal vein wall.



The "non touch" principle of oncological surgery aims to achieve an *en bloc* resection of the tumour with clear resection margins and the minimum handling of tumour during dissection. This concept includes the dissection of the right SMA wall and the resection of the infiltrated vein segment.[6,39,47,48] The type of venous resection varies depending on the degree of vascular infiltration and determines several surgical aspects. It requires a correct exposition of the PV/SMV confluence, of the splenic vein and of the SMV branches. In addition, the entire root of the mesentery and the right colon must be widely mobilized. In cases in which a vein segment is removed, it is recommended to clamp the SMA during venous reconstruction to avoid congestion and edema of the small intestine.[34,43] It is always recommendable to preserve the splenic vein, but its ligation greatly facilitates vascular reconstruction and splenic drainage is then maintained through the short vessels. In cases where this drainage is not suitable, it is necessary to replace the splenic vein in the reconstructed mesenteric portal confluence by performing an end to side anastomosis.[6,19,34] Most of the consulted series show longer interventions and higher transfusion indexes in VR+ patients. In the present

study, venous resection supposed a higher interoperative transfusion index but without statistical signification. However, median operation time was significantly greater in the VR+ group.

Morbility and mortality

Most studies agree that this type of larger vascular resections involve a complications rate ranging from 35 to 60%.[4,6,19,36,43] However, when comparing patients who underwent a standard CPD, the differences observed are non significant. Other studies do describe a higher complications rate in the VR+ group.[17,49] The last two meta analyses, published by Zhou and Yu in 2012 and 2014, did not find significant morbility and mortality differences either.[3,16] In the present study, global mortality was 49%. The VR+ group presented more complications than the VR- group (55.5% vs. 44.8%), but without significant differences. Furthermore, the incidence of severe complications (groups III and IV of Clavien Dindo classification requiring surgical/radiological reintervention) is in a low range in relation to the series consulted and shows no differences among the two groups studied (14.2% for VR- and 16.6% for VR+). No significant differences could be found either in the incidence of specific postoperative complications. Likewise, the VR+ group had a greater index of reinterventions than the VR- group, but without statistical significance (11.1% vs. 8.1%) (p=0,666).

In order to increase the accuracy of the present study, operative mortality was defined as that occurring during the hospital stay and not only during the first 30 days, as complications arising from pancreatic surgery frequently extends the hospital stay beyond 30 days. Global mortality of the present study was 1.5% (1 patient). The only death of this series occurred in the VR+ group and it was due to an acute venous thrombosis in the PTFE graft. This mortality did not show a significant difference with the VR- group, and is comparable to that of other series consulted.[19,32,33] These results confirm the first hypothesis by considering that, with a precise surgical technique and increased perioperative care, it is possible to perform a pancreaticoduodenectomy with venous resection in properly selected patients with a similar morbi mortality to that of standard pancreaticoduodenectomy. However, the authors are conscious that the sample size of the VR+ group is still limited, so results must therefore be analysed with caution.

Like in other studies,[4,35,42] patients of the present study with venous infiltration presented a lymph node affectation and a degree of cell differentiation similar to that of the group without venous infiltration. Although resection margin involvement was greater in the VR+ group, the lymph node affectation of the group with true venous infiltration did not show significant differences, what leads us to think that venous infiltration is mainly due to anatomical factors and not a more aggressive biological behaviour.

Survival

A first meta analysis published by Siriwarna in 2006[20] did not reflect a survival increase of VR+ patients. However, two recent meta analysis (Zhou in 2012 and Yu in 2014), describe a survival at 2 years similar to that obtained in VR- patients, with a survival of 50 65% at 1 year, of 20 30% at 3 years, and of 13 17% at 5 years.[3,16] These figures have been confirmed by monocentric studies with a high volume of patients.[19,33,35,36] Other works such as those by Kelly, Zhang and Castleberry,[2,35,49] describe a smaller survival for VR+ patients. In the present study, survival of both groups was similar and comparable to the above mentioned series. In addition, the study of short and medium term survival (at 1 and at 5 years) did not show significant differences. Most authors agree that VR+ patients have a significantly greater survival than patients who did not undergo surgery due to infiltration of the mesenteric portal confluence or than those undergoing a palliative bilioenteric bypass.[6,11] In the present study, VR+ patients presented a median survival of 22.1 months, whereas survival of non operated patients due to venous infiltration was 10.6 months.

These results confirm the second hypothesis of the study and show that patients with local infiltration of the mesenteric portal confluence can benefit of vascular resection and reconstruction, thus obtaining a similar survival as patients undergoing a standard pancreaticoduodenectomy without vascular resection. In fact, the survival obtained doubles that of patients considered as unresectable due to venous infiltration. Likewise to postoperative morbi mortality, these figures must be analysed with caution, and further work and research is needed in this direction with a greater number of patients.

Limitations of the study

The first limitation is its retrospective nature, even though the analysed data was obtained from a prospective registry of consecutive patients.

The second limitation is the relatively limited sample size of the VR+ patients, a problem which seems to occur in most of the monocentric studies consulted.

The third limitation is the long duration of the data collection period, which has supposed that techniques that were not applied at the start (such as extended lymphadenectomy, initial dissection of the SMA and enlargement of resection margins) were being progressively included. However, this reflects the logical evolution of surgery to obtain a greater radicality and resectability.

Conclusions

The results of the present study allow us to obtain several conclusions which, in any case, should be analysed with caution.

1. Mesenteric portal venous resection in patients with pancreatic cancer can be performed in tumours that locally infiltrate the mesenteric portal confluence and that allow for a proper vascular reconstruction in order to obtain an R0 resection margin.

2. Patients with local resection of the mesenteric portal confluence present a postoperative morbility and mortality similar to that of patients undergoing a CPD without vascular resection.

3. Vascular resection combined with CPD makes it possible to surgically rescue a group of patients considered as unresectable until now. These patients present a median and long term survival similar to that of VR- patients and significantly greater to that of patients who did not undergo surgery. Therefore, tumoral infiltration of the mesenteric portal confluence must not be considered as a formal contraindication for surgery.

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