

## One Hundred Pancreatectomies with Venous Resection for Pancreatic Adenocarcinoma

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### Rezumat

#### *O sută de rezecții pancreatice asociate cu rezecții venoase pentru carcinom ductal pancreatic*

**Introducere:** Invazia de venă portă (PV)/ mezenterică superioară (SMV) nu mai reprezintă astăzi o contraindicație de rezecție în carcinomul ductal pancreatic (PDAC) dacă reconstrucția venoasă este tehnic posibilă. Totuși, datele din literatură prezintă concluzii contradictorii în ceea ce privește rezultatele imediate și la distanță după rezecțiile venoase asociate rezecțiilor pancreatice pentru PDAC. Studiul are drept scop prezentarea rezultatelor unei serii largi de pacienți cu pancreatectomie și rezecții venoase asociate pentru PDAC, din experiența unui singur centru chirurgical.

**Pacienți & Metodă:** Datele a 100 de pacienți cu rezecții pancreatice asociate cu rezecție de PV și/ sau SMV operați în perioada 2002 - 2016 (1 februarie) au fost analizate retrospectiv dintr-o bază de date prospectiv întocmită, care a inclus 474 de pancreatectomii pentru PDAC. Doar pacienții cu diagnosticul de carcinom ductal pancreatic au fost incluși în studiu.

**Rezultate:** Un procent de 21,1% dintre pacienții cu pancreatectomie pentru PDAC au necesitat rezecție venoasă asociată (100 de pacienți din 474). Rezecție segmentară venoasă s-a realizat la 77 de pacienți (77%) (din 100 de pacienți cu rezecție venoasă), în timp ce la 23 de pacienți (23%) s-a realizat rezecție venoasă tangențială. În grupul pacienților cu rezecție venoasă segmentară, reconstrucția s-a realizat prin anastomoză directă termino-terminală la 53 de pacienți (din 77 de pacienți – 68,8%), în timp ce 24 de pacienți (din

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77 de pacienți – 31,2%) au necesitat interpoziția unui graft. Margini de rezecție negative s-au obținut la 63 de pacienți (63%). Un număr de 64 de pacienți (64%) au avut documentată invazia tumorală a segmentului venos rezecat. Complicații postoperatorii s-au observat la 47 de pacienți (47%), severe (grad III-V Dindo-Clavien) fiind notate la 19 pacienți (19%). Rata fistulei pancreatice, parezei gastrice și sângerării postoperatorii a fost de 9%, 20% și respectiv 15%. Tromboza PV/ SMV a apărut la 5 pacienți (5%). Mortalitatea evaluată la 90 de zile în cazul pacienților doar cu rezecție venoasă asociată a fost de 8%. Chimioterapie adjuvantă s-a realizat la 63 de pacienți (63%) și neoadjuvantă la doar 2 pacienți (2%). Valoarea mediană a timpului de urmărire postoperator a fost de 105 luni (3 – 186 luni), iar supraviețuirea globală a fost de 13 luni (3 – 186 luni). În grupul pacienților cu margini de rezecție negative, valoarea mediană a timpului de supraviețuire globală a fost de 16 luni (3 – 186 luni).

**Concluzii:** Rezecția de PV/ SMV asociată rezecțiilor pancreatice pentru PDAC este posibilă tehnic iar grafturile sunt rareori necesare pentru reconstrucția venoasă. Totuși, rezecțiile venoase se asociază cu o rată mare de complicații postoperatorii iar mortalitatea nu este deloc de neglijat. Principalul scop al acestor proceduri chirurgicale complexe este obținerea de margini de rezecție negative, situație asociată cu șanse de supraviețuire la distanță încurajatoare.

**Cuvinte cheie:** carcinom ductal pancreatic; vena portă; vena mezenterică superioară; complicații; supraviețuire

## Abstract

**Introduction:** Invasion of portal vein (PV)/ superior mesenteric vein (SMV) in pancreatic ductal adenocarcinoma (PDAC) is no longer a contraindication for resection when reconstruction is technically feasible. However, the literature data reached conflicting conclusions regarding the early and long-term outcomes of patients with venous resection and pancreatectomies for PDAC. The study aims to present the outcomes in a large series of patients with pancreatectomies and associated PV/ SMV resection for PDAC, in a single center experience.

**Patients & Methods:** The data of 100 patients with pancreatectomies and PV and/ or SMV resection performed between 2002 and 2016 (February, 1st) were retrospectively analyzed from a prospectively maintained electronic database, which included 474 pancreatectomies for PDAC. Only patients with a final pathological diagnosis of PDAC were included in the present study.

**Results:** Overall, 21.1% of patients with pancreatectomies for PDAC required a venous resection (100 patients out of 474 patients). Segmental resection was performed in 77 patients (out of 100 patients with pancreatectomies and venous resection – 77%), while 23 patients (23%) have had tangential venous resection. In the group of patients with segmental venous resection, reconstruction was made by end-to-end anastomosis in 53 patients (out of 77 patients – 68.8%), while in 24 patients (out of 77 patients – 31.2%) a graft interposition was necessary. Negative resections margins were obtained in 63 patients (63%). Histological tumor invasion of the resected vein was confirmed in 64 patients (64%). Postoperative complications occurred in 47 patients (47%), with severe complications (i.e., Dindo-Clavien grade III-V) in 19 patients (19%). Postoperative pancreatic fistulae, delayed gastric emptying and post-pancreatectomy hemorrhage rates were 9%, 20% and 15%, respectively. PV/ SMV thrombosis occurred in 5 patients (5%). The 90-day mortality rate in the group of patients with venous only resection, without any associated procedures, was 8%. Adjuvant treatment was performed in 63 patients (63%), while only 2 patients (2%) underwent neoadjuvant chemotherapy. Median follow-up time was 105 months (range, 3 – 186 months), with a median overall survival time of 13 months (range, 3 – 186 months). In the group of patients with negative resection margins, the median overall survival time was 16 months (range, 3 – 186 months).

**Conclusions:** PV/ SMV resection during pancreatectomies for PDAC is technically feasible, and

grafts are rarely required for venous reconstruction. However, venous resection is associated with high postoperative complications rates, and the mortality rate is not neglectable. The main goal of such complex procedure is to obtain negative resection margins, a situation associated with encouraging survival rates.

**Key words:** pancreatic ductal adenocarcinoma, portal vein, superior mesenteric vein, complications, survival

## Introduction

Pancreatic ductal adenocarcinoma (PDAC) represents the main malignant pathology in which pancreatectomy is indicated (1). Pancreatectomies represent the single hope for long-term survival in patients diagnosed with PDAC, and a negative resection margins surgery represents the most important determinant of survival (2).

PDAC frequently extends directly to the retroperitoneal space, where there are major vessels such as portal vein (PV), superior mesenteric vein (SMV) and superior mesenteric artery. Invasion of PV/ SMV in PDAC is no longer a contraindication for resection when reconstruction is technically feasible (1). However, the literature data reached conflicting conclusions regarding the early and long-term outcomes of patients with venous resection and pancreatectomies for PDAC (3,4).

The study aims to present the outcomes in a large series of patients with pancreatectomies and associated PV/ SMV resection for PDAC, in a single center experience.

## Patients and Methods

The data of 100 patients with pancreatectomies and PV and/ or SMV resection performed between 2002 and 2016 (February, 1st) at Fundeni Clinical Institute, “Dan Setlacec” Center of General Surgery and Liver Transplant, Bucharest were retrospectively analyzed from a prospectively maintained electronic database. Only patients with a final pathological diagnosis of PDAC were included in the present study.

Patients were selected from a total number

of 474 pancreatectomies for PDAC performed during the same period at our Department of Surgery: 344 pancreatico-duodenectomies, 102 distal pancreatectomies, and 28 total pancreatectomies.

PV/SMV resection was considered only when the preoperative imaging or intraoperative exploration suspected the venous invasion by the tumor.

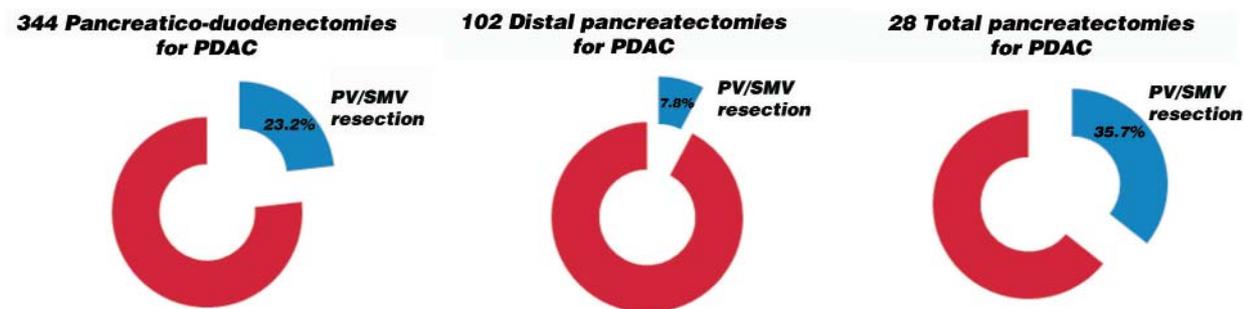
Postoperative morbidity was assessed as in-hospital complications. Postoperative mortality was considered at 90 days. Severity of postoperative complications was graded according to Dindo-Clavien classification (5). Furthermore, for specific complications such as postoperative pancreatic fistula (6), delayed gastric emptying (7) and postoperative hemorrhage (8) the International Study Group of Pancreatic Surgery definitions and grading system were used.

Data are expressed as median (range) or as number (percentage). The Kaplan-Meier curves were used to estimate survival. Overall survival time was considered the time from resection to death occurrence or last follow-up (April 1st, 2018).

## Results

The overall percent of PV/ SMV resection was 21.1% during the analyzed period of time (i.e., 100 patients out of 474 pancreatectomies for PDAC). The percentages of venous resection according to the type of pancreatectomy are shown in *Fig. 1*.

Median age of the cohort was 62 years (range, 35 – 78 years), with equal gender distribution.



**Figure 1.** Percentages of venous resection according to the type of pancreatectomy in 100 patients with pancreatectomies and portal vein (PV)/ superior mesenteric vein (SMV) resection for PDAC.

Cardiovascular co-morbidities were observed in 31 patients (31%), while diabetes mellitus was present in 30 patients (30%).

The main symptoms and signs were: jaundice (62 patients – 62%), upper abdominal pain (58 patients – 58%), weight loss (39 patients – 39%), upper digestive stenosis (8 patients – 8%), and cholangitis (4 patients – 4%).

Median preoperative CA 19-9 serum level was 274 UI/ ml (range, 1 – 2083 UI/ ml).

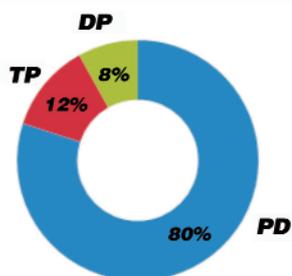
Preoperative biliary drainage was performed in 12 patients (12%).

The types of pancreatectomies performed in the present cohort are shown in *Fig. 2*. The type of venous resection and reconstruction methods are shown in *Fig. 3*, 4 and 5. In the group of patients with tangential venous resection, reconstruction was made by direct suture in 21 patients (out of 23 patients – 91.3%), while a venous patch was used in 2 patients (out of 23 patients – 8.7%). In the group of patients with segmental venous resection, reconstruction was made by end-to-end anastomosis in 53 patients (out of 77 patients – 68.8%), while in 24 patients (out of 77 patients – 31.2%) a graft interposition was necessary. In the group of patients with graft interposition reconstruction, 19 patients (out of 24 patients – 79.2%) received a synthetic graft, while 5 patients (out of 24 patients – 20.8%) received a cadaveric venous graft.

Associated procedures were performed in 11 patients (11%), as shown in *Table 1*.

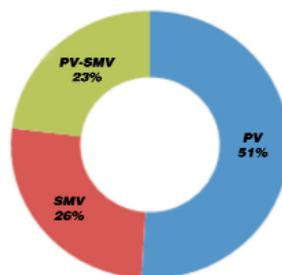
Median operative time and estimated blood loss were 320 min (range, 180 – 600 min) and

**Types of pancreatectomies in 100 patients with PV/SMV resection for PDAC**



**Figure 2.** Types of pancreatectomies in 100 patients with portal vein (PV)/ superior mesenteric vein (SMV) resection for PDAC (PD – pancreatico-duodenectomy; DP – distal pancreatectomy; TP – total pancreatectomy)

**Type of venous resection in 100 pancreatectomies for PDAC**

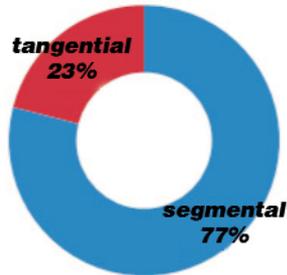


**Figure 3.** Types of venous resection in 100 patients with pancreatectomies and portal vein (PV)/ superior mesenteric vein (SMV) resection for PDAC

800 ml (range, 300 – 4000 ml), respectively.

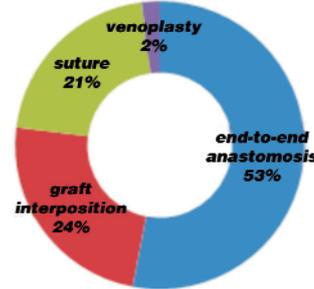
Final pathology examination of the operative specimen revealed ductal adenocarcinoma

**Type of venous resection in 100 pancreatectomies for PDAC**



**Figure 4.** Types of venous resection in 100 patients with pancreatectomies and portal vein/ superior mesenteric vein resection for PDAC.

**Type of venous reconstruction in 100 pancreatectomies for PDAC**



**Figure 5.** Types of venous reconstruction in 100 patients with pancreatectomies and portal vein/ superior mesenteric vein resection for PDAC.

**Table 1.** Associated procedures in 100 patients with pancreatectomies and PV/ SMV resection for PDAC

Procedure	Number of patients (%)
Right colectomy	3 patients (3%)
Superior mesenteric artery resection	2 patients (2%)
Common hepatic artery resection	1 patient (1%)
Spleno-renal shunt for left portal hypertension	1 patient (1%)
Right hemi-hepatectomy	1 patient (1%)
Gastrectomy	1 patient (1%)
Enterectomy	1 patient (1%)
Cholecystectomy	1 patient (1%)

**Table 2.** TNM stages in 100 patients with pancreatectomies and PV/ SMV resection for PDAC (7th Edition)

TNM stage	Number of patients (%)
Stage Ia	-
Stage Ib	5 patients (5%)
Stage IIa	44 patients (44%)
Stage IIb	44 patients (44%)
Stage III	3 patients (3%)
Stage IV	4 patients (4%)

in 95 patients (95%) and cystadenocarcinoma in 5 patients (5%). Median tumor diameter was 3 cm (range, 0.5 – 12 cm). According to tumor grade differentiation, 47 patients (47%) were assessed as G1, 38 patients (38%) as G2, and 15 patients (15%) as G3. A number of 48 patients (48%) presented lymph nodes metastases. Tumor staging in the cohort is presented in *Table 2*.

The type of resection was assessed as negative resection margins (i.e., R0) in 63 patients (63%), as microscopic positive resection margins (i.e., R1) in 30 patients (30%), and as macroscopic positive resection margins (i.e., R2) in 7 patients (7%). Histological tumor invasion of the resected vein was confirmed in 64 patients (64 %).

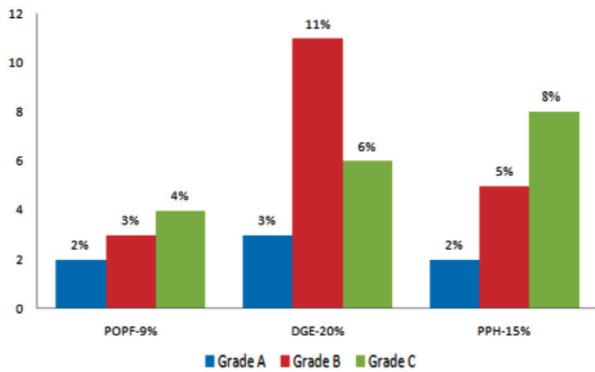
Postoperative complications occurred in 47 patients (47%), as shown in *Table 3*.

**Table 3.** Postoperative complications classified according to Dindo-Clavien in 100 patients with pancreatectomies and PV/ SMV resection for PDAC

Dindo-Clavien grade of complication	Number of patients (%)
Grade I	6 patients (6%)
Grade II	22 patients (22%)
Grade IIIa	1 patient (1%)
Grade IIIb	4 patients (4%)
Grade IVa	3 patients (3%)
Grade IVb	-
Grade V	11 patients (11%)

Postoperative pancreatic fistulae, delayed gastric emptying and post-pancreatectomy hemorrhage rates were 9%, 20% and 15%, respectively, as shown in *Fig. 6*. Other complications are shown in *Table 4*.

PV/ SMV thrombosis occurred in 5 patients (5%), out of what 3 patients underwent venous reconstruction with prosthetic graft interposition.



**Figure 6.** Postoperative pancreatic fistulae (POPF), delayed gastric emptying (DGE) and post-pancreatectomy hemorrhage (PPH) rates in 100 patients with pancreatectomies and portal vein/ superior mesenteric vein resection for PDAC

Re-laparotomy for postoperative complications was performed in 13 patients (13%).

Median postoperative hospital stay was 14 days (range, 1 – 60 days).

Death within 90 postoperative days occurred in 11 patients (11%), and the main causes were multiple organ failure in 4 patients (4%), acute liver failure in 3 patients (3%), pulmonary embolism, acute myocardial infarction and hemorrhagic shock (one patient each). However, postoperative mortality rate in the group of patients with venous only resection, without any associated procedures, was 8%.

Adjuvant treatment was performed in 63 patients (63%): chemotherapy only (58 patients – 58%) or chemo-radiotherapy (5 patients – 5%). Only 2 patients (2%) underwent neoadjuvant chemotherapy.

Median follow-up time in the present cohort was 105 months (range, 3 – 186 months), with a median overall survival time of 13 months (range, 3 – 186 months) (Fig. 7). The 1-, 2-, 3-, 5-, and 10-year overall survival rates were 52%, 25%, 18%, 8%, and 4%, respectively. It is worth mentioning that in the group of patients with negative resection margins the median overall survival time was 16 months (range, 3 – 186 months) (Fig. 8), with 1-, 2-, 3-, 5-, and 10-year overall survival rates of 57%, 30%, 23%, 9%, and 7%, respectively. From the survival analyses were

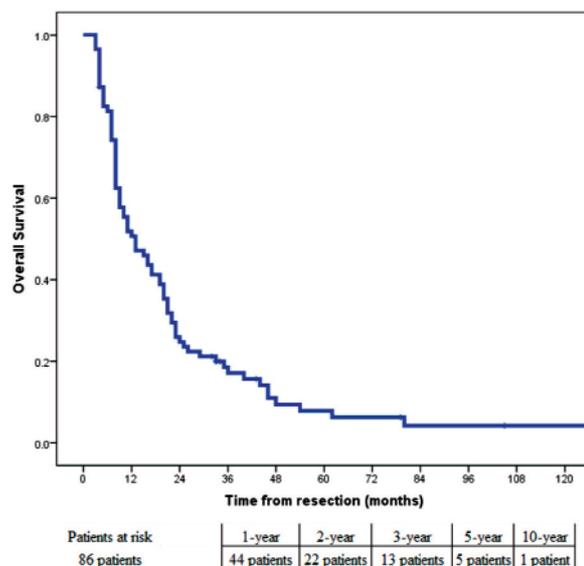
**Table 4.** Table 4. Other complications in 100 patients with pancreatectomies and PV/ SMV resection for PDAC

Complication	Number of patients (%)
Ascites	11 patients (11%)
Wound infection	8 patients (8%)
Chyle leak	4 patients (4%)
Bile leak	3 patient (3%)
Acute myocardial infarction	2 patient (2%)
Pulmonary embolism	1 patient (1%)
Pneumonia	1 patient (1%)
Paroxysmic atrial fibrillation	1 patient (1%)
Mesenteric artery infarction	1 patient (1%)
Hepatic artery infarction	1 patient (1%)
Celiac trunk infarction	1 patient (1%)

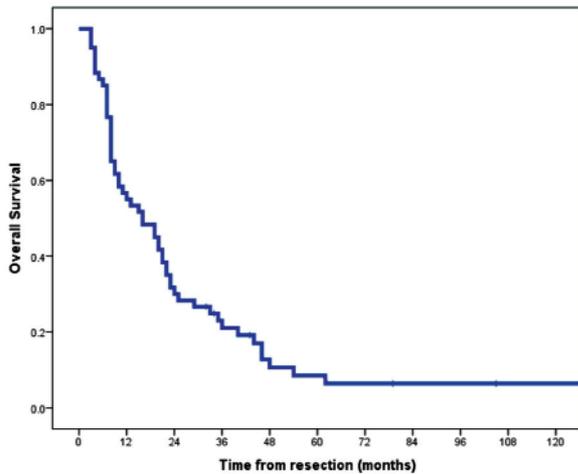
excluded the 90-day deaths and 3 patients without follow-up data.

## Discussion

The management of a patient diagnosed with PDAC should be discussed in a multidisciplinary team, and the aim is to reach the best decision that fits the patient’ profile of disease (9), particularly for patients planned for



**Figure 7.** Overall survival Kaplan-Meier curve in 86 patients with pancreatectomies and portal vein/ superior mesenteric vein resection for PDAC.



**Figure 8.** Overall survival Kaplan-Meier curve in 60 patients with pancreatectomies and portal vein/ superior mesenteric vein resection for PDAC and negative resection margins

venous resection who have a high risk of post-operative complications (10).

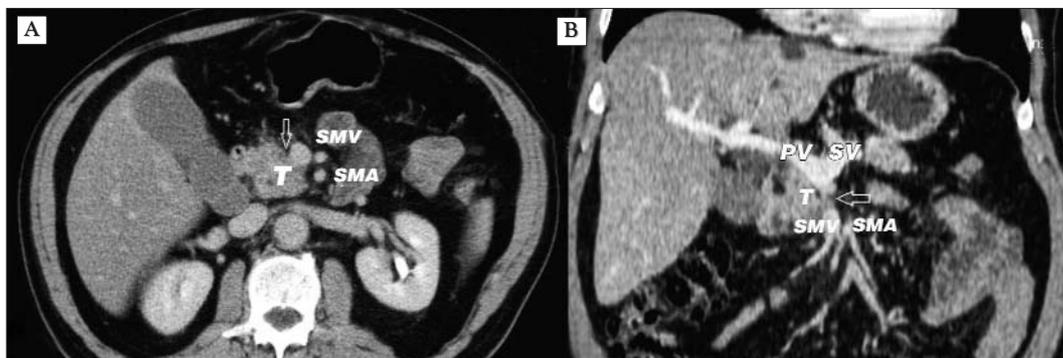
Patients with PDAC and PV/ SMV invasion represent the largest part of patients with so-called borderline resectable disease (9). A borderline resectable PDAC is defined as tumor without distant metastases, with PV/ SMV invasion that allows safe resection and reconstruction, and/ or gastro-duodenal artery encasement up to the hepatic artery, without extension to the celiac trunk, and/ or tumor abutment of the superior mesenteric artery less than 180 degrees of the circumference (11).

Preoperative computed tomography (*Fig. 9*) or magnetic resonance is the most widely used method to detect venous invasion by the tumor in PDAC (12), albeit these methods tend to under-report venous invasion (3).

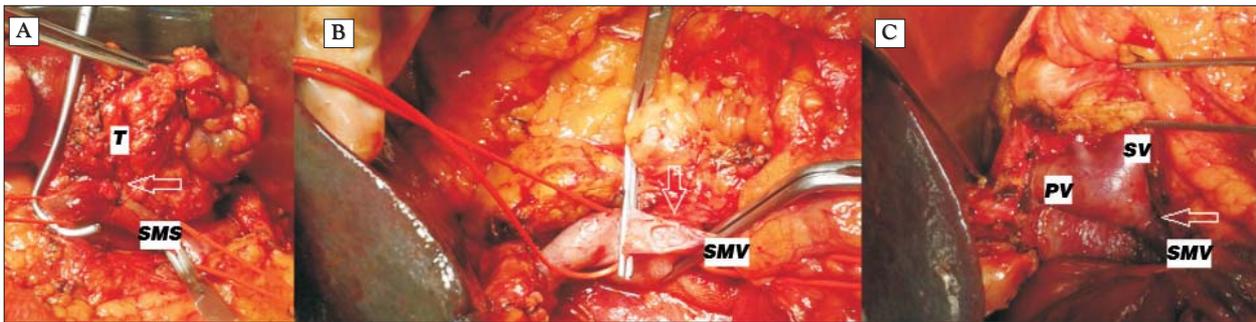
Nowadays, there were proposed two onco-surgical strategies for a patient with PDAC and suspected PV/ SMV invasion: upfront surgery or neoadjuvant therapy followed by pancreatectomy (9). Some studies favor upfront surgery (4,11), while others showed improved survivals after neoadjuvant therapy (13). In the present study, only 2% of patients underwent neoadjuvant chemotherapy followed by pancreatectomy.

The reported incidence of venous resection during pancreatectomies for PDAC recognizes large variability (2% - 77%)(14), mainly depending on surgical team perspective on the need to achieve negative resection margins (15). Thus, high venous resection rates are reported in surgical centers from East Asia, while in Western series around 20% venous resection rates were observed in patients with pancreatectomies for PDAC (15). In the present series the percentage of venous resection during pancreatectomies for PDAC was 21.1%, quite similar to the reported rates in Western surgical centers (15).

Routine venous resection during pancreatectomy for PDAC was first proposed by Fortner and co-workers to resect better PDAC, aiming to increase negative resection margins rates (16). Further studies have shown no survival



**Figure 9.** Preoperative contrast enhanced computed tomography (portal phase) (A) transverse plane and (B) coronal plane showing a pancreatic head ductal adenocarcinoma (T) with tumor encasement of the superior mesenteric vein (SMV) less than 180 degrees (arrow) (SMA – superior mesenteric artery; PV – portal vein; SV – splenic vein)



**Figure 10.** Intraoperative aspects showing (a) a pancreatic head ductal adenocarcinoma (T) invading the superior mesenteric vein (SMV) (arrow); (b) running suture end-to-end anastomosis (arrow) after segmental resection of the superior mesenteric vein (SMV); (c) completed end-to-end venous anastomosis (arrow) (PV – portal vein; SV – splenic vein)

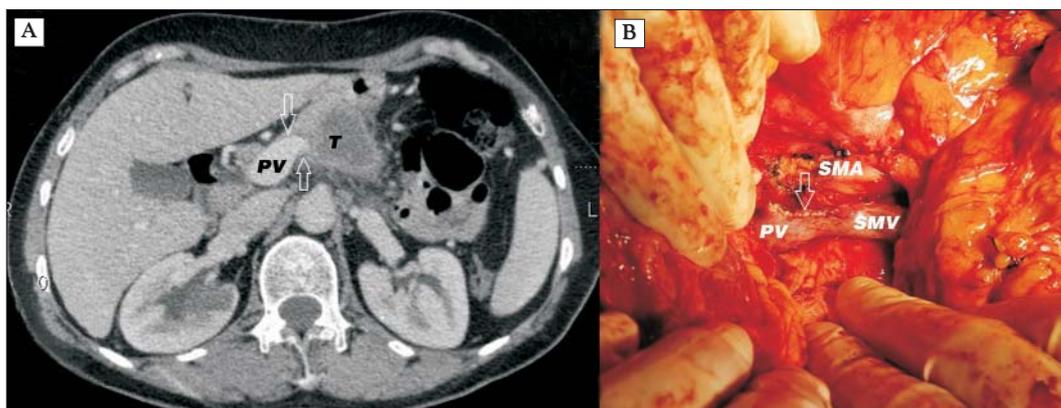
benefits for routine PV resection during pancreatectomies for PDAC (17). Thus, nowadays it is widely accepted that venous resection during pancreatectomy for PDAC should be done only selectively, when the preoperative imaging or intraoperative exploration raise the suspicion of venous invasion by the tumor, as it was the case in the present series (14).

The most common techniques of venous reconstruction reported in the literature are end-to-end anastomosis (46.5%) (*Fig. 10*), direct suture (*Fig. 11*) or patch (34.3%), and graft interposition (19.2%)(18). It is recommended to do the venous resection at a late stage of pancreatectomy to reduce the time of venous reconstruction (19). Thus, a posterior approach

pancreatico-duodenectomy facilitates en bloc resection in patients with PDAC and PV/ SMV invasion (19-21). In the present series, the venous reconstruction was made by end-to-end anastomosis in 53% of patients, direct suture in 21% of patients, and with graft interposition in 24% of patients.

Several multicentre studies(13;22;23) and meta-analyses(18) have shown that venous resection is associated with increased operative time and blood loss, compared with pancreatectomies without venous resection.

Initially, some studies did not show any significant differences in morbidity and mortality rates between patients with pancreatectomies with and without venous resection (3,13).



**Figure 11.** (A) Preoperative contrast enhanced computed tomography (portal phase, transverse plane) showing a pancreatic body ductal adenocarcinoma (T) with tumor encasement of the superior mesenteric vein (SMV) – portal vein (PV) confluence less than 180 degrees (arrow); (B) Intraoperative aspects showing direct suture (arrow) after tangential resection of the superior mesenteric vein (SMV) – portal vein (PV) confluence (SMA – superior mesenteric artery)

However, more recent data including meta-analyses have shown increased mortality rates (18,24,25) and morbidity rates (18,25) when a venous resection is performed with pancreatectomy. The reported mortality rates after pancreatectomies with venous resection vary between 0% and 14% (12). Mortality rates appear to be higher when grafts are used for venous reconstruction (23). Morbidity rates after pancreatectomies with venous resection vary between 9% and 78% (14,26). In the present cohort, the morbidity rate was 47%.

Our previous studies have associated venous resections during pancreatectomies for PDAC with increased operative time and blood loss, along with trends toward increased 90-day mortality and severe morbidity rates (15).

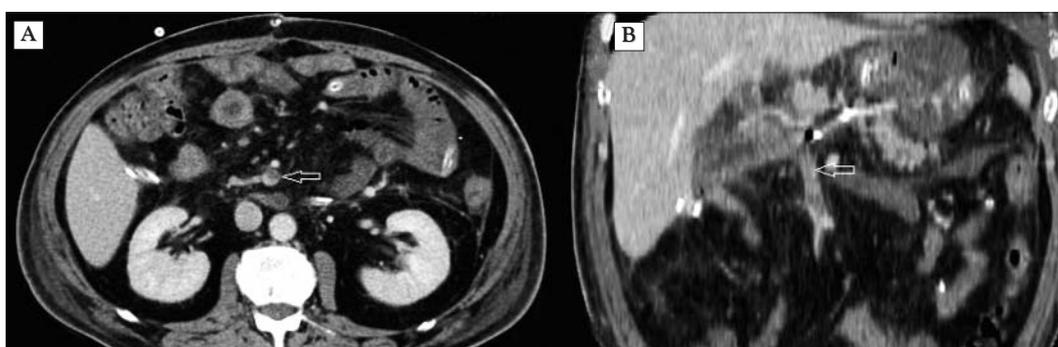
PV/ SMV thrombosis (*Fig. 12*) is widely considered a rare complication after pancreatectomy (less than 7% of patients), but sometimes can lead to severe morbidity, and was associated with high mortality rates (27). The benefit of anticoagulation therapy in patients with pancreatectomies with venous resection remains unclear. Thus, a systematic review published in 2014 did not show any significant differences of early PV thrombosis rates in patients with pancreatectomies and vascular resection with or without anticoagulation therapy (27). However, it seems that a portal venous thrombosis is more likely to appear when prosthetic grafts are used (27, 28). In the present cohort, early portal venous thrombosis occurred in 5% of patients, out of what 3 patients underwent venous reconstruction

with prosthetic graft interposition.

The survival benefit of a venous resection during pancreatectomies for PDAC remains controversial. Recent meta-analyses have shown that venous resection is associated with higher R1 rates and lower survivals (18, 24, 25). The reported negative resection margins rates vary between 14% and 100% (12). The reported median survival times for pancreatectomies with venous resection for PDAC vary between 5 months and 23 months (12, 18), with a median survival time of 13 months (14). The survival benefits of venous resection during pancreatectomies for PDAC appear to be relevant when negative resection margins can be obtained (29). In the present cohort, the negative resection margins rate was 63%, and the median overall survival time was 13 months for the entire cohort, and 16 months for patients with negative resection margins.

Presence of tumor invasion of the resected vein during pancreatectomies for PDAC was reported in the literature in 21% - 100% of cases (12, 24), and it was associated with decreased survival rates (29), as our previous studies have shown (15). In our series, the percent of histological tumor invasion of the resected vein was 64%.

Arterial resections during pancreatectomies were proven to be technically feasible (30-33), but the rate of postoperative complications including postoperative mortality is high (34, 35), with highly controversial oncological benefits for patients with PDAC (33, 34). Resection of combined PV/ SMV resection with



**Figure 12.** Postoperative contrast enhanced computed tomography (portal phase) (A) transverse plane and (B) coronal plane showing a superior mesenteric – portal vein confluence thrombosis (arrow)

superior mesenteric artery resection during pancreatectomies for PDAC were associated with up to 91% morbidity rates and 20% mortality rates, as a recent systematic review has shown (34). Furthermore, the long-term survival after such complex procedures is very poor – median survival times between 7.5 months and 11.5 months (33, 34). Nevertheless, extended pancreatectomies including gastrectomy, colectomies, etc are also associated with increased morbidity and mortality rates (25). In the present cohort, 11% of patients have had associated procedures including gastrectomy, colectomies and arterial resections and might explain the relatively high mortality rate in the entire cohort. However, in the group of patients with venous only resection the 90-day mortality was 8%.

## Conclusions

PV/ SMV resection during pancreatectomies for PDAC is technically feasible, and grafts are rarely required for venous reconstruction. However, venous resection is associated with high postoperative complications rates, and the mortality rate is not neglectable. The main goal of such complex procedure is to obtain negative resection margins, a situation associated with encouraging survival rates.

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