TITLE PAGE

Portal Vein Resection during Pancreaticoduodenectomy for Pancreatic Neuroendocrine Tumours. An International Multicentre Comparative Study

Authors:

Giuseppe K. Fusai, Prof[1], Domenico Tamburrino, MD, PhD[2], Stefano Partelli, PhD[2], Panagis Lykoudis, PhD[1], Peter Pipan, MBBS[1], Francesca Di Salvo, PhD[2], Nassiba Beghdadi, MD[3], Safi Dokmak, PhD[3], Dominik Wiese, MD[4], Luca Landoni, MD[5], Chiara Nessi, MD[5], O.R.C Busch, Prof [6], Niccolò Napoli, MD[7], Jin-Young Jang, Prof[8], Wooil Kwon, PhD[8], Marco Del Chiaro, Prof, FACS[9,10], Chiara Scandavini MD[10], Mahmoud Abu-Awwad, MD[11], Thomas Armstrong, PhD[11], Mohamed Abu Hilal, Prof[11,12], Peter J Allen, Prof, FACS[13,14], Ammar Javed, MD[15], ,Magnus Kjellman, PhD[16] , Alain Sauvanet, Prof[3], Detlef K. Bartsch, Prof[4], Claudio Bassi, Prof, FACS[5], E.J.M. Nieveen van Dijkum[6], M.G. Besselink, Prof[6], Ugo Boggi, Prof[7], Sun-Whe Kim, Prof[8], Jin He, Prof, FACS[15], Christofer L. Wolfgang, Prof, FACS[15], Massimo Falconi, Prof[2]

Affiliations:

[1] Department of HPB and Liver Transplant Surgery, Royal Free Hospital, London, United Kingdom

[2] Pancreatic Surgery Unit, Vita-Salute University, San Raffaele Hospital, Milan, Italy

[3] Department of Hepato-Pancreato-Biliary Surgery, Pôle des Maladies de l'Appareil Digestif, Université de Paris-Paris Diderot, Beaujon Hospital, 92110 Clichy, France.

[4] Department of Visceral, Thoracic, and Vascular Surgery, Philipps University, Marburg, Germany

[5] Unit of General and Pancreatic Surgery, University and Hospital Trust of Verona, Italy

[6] Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Netherlands

[7] Division of General and Transplant Surgery, University of Pisa, Pisa, Italy

[8] Department of Surgery, Seoul National University College of Medicine, South Korea

[9] Division of Surgical Oncology, Department of Surgery, University of Colorado Anschutz Medical Campus, Denver, USA

[10] Department of Clinical Science, Intervention, and Technology (CLINTEC), Karolinska Institute; Department of Upper Gastrointestinal Diseases, Karolinska University Hospital, Stockholm, Sweden.

[11] Department of Surgery, University Hospital Southampton, Southampton, United Kingdom

[12] Department of Surgery, Istituto Fondazione Poliambulanza, Brescia, Italy

[13] Department of Surgery, Hepatopancreatobiliary Service,Memorial Sloan Kettering Cancer Center, New York, NY, USA.

[14] Department of Surgical Oncology, Duke University, Durham, USA.

[15] Division of Surgical Oncology, Surgical Oncology, Pathology and Oncology, Johns Hopkins Medical Institution, Baltimore, MD, USA.

[16] Department of Molecular Medicine and Surgery, Division of Endocrine Surgery, Karolinska Institutet, Stockholm, Sweden

Corresponding Author:

Domenico Tamburrino, MD, PhD

Pancreatic Surgery Unit

San Raffaele Hospital

Via Olgettina 60

20132 Milano

tamburrino.domenico@hsr.it

Tel: +39 02 26432324

Fax: +39 02 26437807

ARTICLE SUMMARY:

The role of portal vein resection is well established during resection for pancreatic cancer but not for Pancreatic NeuroEndocrine Neoplasms (PanNENs). The importance of this report is that there is no significant difference in perioperative risk and a similar overall survival between standard pancreaticoduodenectomy and pancreaticoduodenectomy with vascular resection among patients with PanNENs.

ABSTRACT

Background: The role of portal vein resection is well established during resection for pancreatic cancer but not for Pancreatic NeuroEndocrine Neoplasms (PanNENs). Evidence from studies providing information on long term outcome after venous resection in PanNENs patients' is lacking.

Methods: This is a multicenter retrospective cohort study comparing pancreaticoduodenectomy with vein resection (PDVR) with standard pancreaticoduodenectomy (PD) in patients with PanNENs. The primary end-point was to evaluate the long term survival in both groups. Progression Free Survival (PFS) and Overall Survival (OS) were calculated using the method of Kaplan and Meier but a propensity score matched cohort analysis was subsequently performed to remove selection bias and improve homogeneity. The secondary outcome was Clavien-Dindo ≥ 3.

Results: 61 (11%) patients underwent PDVR and 480 patients PD. Five (1%) perioperative deaths were recorded in the PD group and postoperative clinically relevant morbidity rates were similar in the two groups (PDVR 48% vs PD 33%). In the initial survival analysis PDVR was associated with worse 3-year PFS (48% PDVR vs 83% PD; p <0.01) and 5-year OS (67% PDVR vs 91% PD). After propensity score matching no significant difference was found in both 3-year PFS (49% PDVR vs 59% PD; p= 0.14) and 5-year OS (71% PDVR vs 69% PD; p= 0.98).

Conclusion: This study demonstrates no significant difference in perioperative risk and a similar overall survival between PD and PDVR. Tumour involvement of the superior mesenteric/portal vein axis should not preclude surgical resection in patients with locally advanced PanNENs.

Keywords: pancreatic neuroendocrine tumors; pancreatic surgery; portal vein resection; PanNENs; pancreatic neoplasms

INTRODUCTION

Pancreatic Neuroendocrine Neoplasms (PanNENs) are relatively rare accounting for approximately 3% of all pancreatic tumours and for 5% of all pancreatic surgical resections [1,2]. In the last two decades an increase in the diagnosis of incidentally discovered Pan NENs has been observed partly but not just as a result of the extensive and liberal use of cross-sectional imaging [2,3]. Several small low grade PanNENs are diagnosed incidentally and can be observed as recommended by the European NeuroEndocrine Tumour Society (ENETS) [4]. Although incidental PanNENs are more commonly associated with lower stages and better prognosis than symptomatic tumors up to 30% of these incidental lesions might present with locally advanced or metastatic disease, and this percentage is higher in patients with non-functioning PanNENs presenting with mass related symptoms [3]. As resection remains the only potentially curative option, an aggressive approach has been traditionally encouraged in view of the favorable prognosis of PanNENs, even in the presence of metastatic disease or extension to surrounding organs and vascular structures [5-7].

For many years portal vein resection during pancreatectomy for pancreatic cancer has been a controversial topic. Whilst some studies showed comparable complication rates between standard pancreaticoduodenectomy (PD) and pancreaticoduodenectomy with venous resection (PDVR) [8-12], others had reported an increased morbidity with no survival benefit in PDVR [13-16]. More recently, with refinement of surgical techniques and improvement in perioperative care, portal vein resection has established its role as isolated venous involvement should no longer be a contraindication to proceed to surgery in patients with borderline resectable pancreatic cancer. This principle was ratified in a consensus document by the American Hepato-Pancreato-Biliary Association (A-HPBA) in 2010[17] and by the International Study Group for Pancreatic Surgery (ISGPS) in 2014 [18], as they recommended resection of pancreatic cancers in the presence of reconstructible mesenteric-portal axis involvement, based on the updated evidence that overall survival was found to be similar in PD and PDVR with no significant difference in the perioperative risk [19-23].

On the contrary, this evidence is lacking for locally advanced PanNENs requiring vascular reconstruction. Several studies have highlighted the potential benefit of liver resection to remove metastatic disease from primary PanNENs, but there are only few case reports and small single digit series of venous resection included in surgical cohort studies recommending extensive resections for advanced and metastatic PanNENs [7, 24-30].

The aim of this international multicenter study is therefore to specifically compare perioperative morbidity and long-term survival in patients undergoing pancreaticoduodenectomy for Pan NENs of the pancreatic head with or without portal vein resection (PDVR vs PD).

METHODS

Patients

The present study was a retrospective cohort study following the STrengthening the Reporting of OBservational studies in Epidemiology statement (STROBE) guidelines [31]. The medical records of all patients who underwent radical PD (with or without porto-mesenteric vein resection) for pathologically confirmed Pan NENs at the 12 following involved institutions, between January 2007 and December 2016 were reviewed from a prospectively maintained database: Beaujon Hospital France, University of Marburg Germany, University of Verona, University of Pisa and San Raffaele Hospital in Italy, Academic Medical Centre Amsterdam in the Netherlands, University of Seoul Korea, Karolinska Institute in Sweden, Royal Free Hospital and Southampton Hospital Charity in the UK, Memorial Slone Kettering and John Hopkins in the USA. The study was approved by the Ethics Committees of participating centers. Inclusion criteria were as follows: age ≥ 18 years, sporadic forms, macroscopic resection of all the tumor (R0/R1), histologically confirmed PanNEN of the pancreatic head. Two patients were excluded because younger than 18 years, 2 patients excluded as they had a diagnosis of Multiple Endocrine Neoplasia (MEN 1), 14 patients were excluded as they underwent enucleation. A total of 541 patients (61 PDVR and 480 standard PD) were included for the analysis.

Data collection, definition of outcomes and histological assessment

Demographic variables, radiologic features, perioperative and postoperative variables, and follow-up records were retrospectively reviewed from an electronic database. Obesity was dichotomized with a cut-off of 30 Kg/m^2, the segment of vein resected was categorized in the portal vein (PV) and /or superior mesenteric vein (SMV), the type of vascular reconstruction was categorized in the following categories: primary closure, end to end anastomosis and interposition graft. For the intraoperative blood loss, 4 groups were created using used the 400 ml, 700 ml and 1000 ml cut-off. Recurrence was defined as a finding on imaging consistent with recurrence and/or pathologic confirmation of

recurrence. Survival was defined as time from surgery to death for disease, recurrence, or censor. Postoperative pancreatic fistula (POPF) was defined according to the latest classification of the International Study Group of Pancreatic Fistula (ISGPF) [32]. Post-pancreatectomy hemorrhage (PPH) and delayed gastric emptying (DGE) were defined using the classifications stated by International Study Group of Pancreatic Surgery (ISGPS) [33,34]. Postoperative complications were classified according to the Clavien-Dindo classification (CD) ranging from I (no complications) to V (surgical-related death) [35]. Minor complications were defined as CD ≤2, a clinically relevant complication was defined as CD ≥3. Postoperative mortality was defined as death occurred within 90 days after surgery or any in-hospital death. Tumor grade was classified according to the latest World Health Organization classification into three categories: PanNET G1 , PanNET G2, and PanNEN G3 [36]. Tumor stage was also classified according to UICC TNM 8th Edition 2017 [37]. Venous involvement was defined as the lack of plane between the vessel and the tumour requiring vascular reconstruction regardless of the histologically proven infiltration of the venous wall.

Statistical analysis

Comparisons, in terms of short and long-terms outcomes, between PD and PDVR groups were evaluated by using Fisher's exact test and Chi-square test for categorical variables or two-tailed Student's t test for continuous and normally distributed data. Disease/Progression free survival (PFS) and Overall survival (OS) curves were calculated using the method of Kaplan and Meier and comparisons by PD and PDVR groups were reported using a log rank test.. Patients without survival or recurrence information were censored at the date of last correspondence or follow-up. In order to eliminate selection bias, a propensity score matched cohort analysis was performed to further explore whether a vascular resection at the time of PD was associated with worst PFS and OS compared standard PD. Propensity scores for all patients were calculated using a logistic regression model based on the following disease prognostic factors: age, gender, pT stage, pN stage, metastatic disease, resection margins, neoadjuvant therapy received, grading and once propensity score was derived, a

neighbor-matching algorithm was used to match patients who underwent standard PD with those who had a vascular resection at the time of pancreaticoduodenectomy (PDVR).

After the propensity score adjustment, 102 patients were selected, 51 patients in each group. Cox proportional hazard models were used to evaluate the impact of Vascular resection on the risk for disease recurrence/progression and death of disease, before and after the propensity score adjustment. A $p < 0.05$ was considered significant. Statistical analysis was performed using the MatchIt R package (version 3.0.3, R Foundation for Statistical Computing— www.r-project.org/) and STATA.

RESULTS

Patient characteristics and pre-operative evaluation

Between January 2007 and December 2016, 541 patients underwent PD for PanNEN. Among these 61 (11%) required PV/SMV resection and reconstruction. The clinical features and preoperative characteristics of the entire population are shown in **Table 1.** Patients who underwent PDVR were older with a median age of 63 years (range 26-82) compared to 58 (range 20, 85) in those who underwent standard PD (P 0.07). Neoadjuvant chemotherapy was administered to 25% of patients who underwent PDVR (n= 15) compared with 4% (n= 19) of patients in the PD standard group (P <0.01). Metastatic disease was present, at preoperative staging, in 31% of patients (n= 19) in the PDVR resection as opposed to 9% (n= 41) in the PD group (p <0.01).

Operative details and histology

In both groups a similar proportion of patients underwent a Whipple or PPPD (**Table 2**). The median intraoperative blood loss was significantly higher in the PDVR group (575 ml vs 300 ml; p <0.01), as well as the median operative time (425 vs 330 min; p<0.01). Perineural and lymphovascular invasion, the T stage and N stage were significantly higher in the PDVR group. An R0 resection was achieved in 90% of patients (n= 434) in the PD group compared with 57% of patients (n= 35) in the PDVR group (p <0.01). Among patients who underwent vascular resection, reconstruction was by primary closure in 30 of them (49%), an end-to-end anastomosis was required in 20 patients (33%), while an interposition graft in 11 patients (18%). In the PDVR group, postoperative histology confirmed tumour infiltration of the portal or superior mesenteric vein in 40 patients (7.4%).

Perioperative outcomes

Overall, 90-day mortality after surgery was 1% (n= 5), with no mortality in PDVR group. The overall rate of postoperative complication was 76% (n= 410). POPF occurred in 27% (n= 149) of the entire population and it was significantly higher in the PD group (29% vs 13%; p <0.01). A clinically

relevant postoperative complication (CD ≥ 3) occurred in 35% of patients, without any statistical difference within the two groups. Portal or superior mesenteric vein thrombosis was observed in 3 patients (5%) in the PDVR group, compared whit only 2 (<1%) patients in the standard group (p <0.01). The median length of stay (LoS) was 12 days and the median ICU stay was 1 day. No difference in terms of length of stay and ICU were founded in the two study groups. The intraoperative, perioperative and histological characteristics of the entire cohort are shown in **Table 2**.

Survival

The median follow-up time was 44 months (19.8-67.2 range). The 3-year PFS and 5-year OS was 83% and 91% in the standard PD group, respectively. Patients who underwent PDVR showed a 3-year PFS of 48% and a 5-year OS of 67%. The differences, for both PFS and OS, were statistically significant within the two groups (p <0.01). PFS and OS of the entire cohort are shown in **Figure 1a** and **1b.** On univariate analysis, factors associated with PFS were: liver metastatic disease (HR: 3.1; p <0.01) neoadjuvant chemotherapy (HR: 2.2 ; p <0.01); vascular resection (HR: 4.2; p <0.01); G3 (HR: 6.5; p <0.01); perineural invasion (HR: 2.1; p <0.01); lymphovascular invasion (HR: 2.8; p <0.01); venous involvement at histology (HR:4.1; p <0.01); pT3/4 (HR: 4 ; p <0.01); N1 (HR: 3.6 ; p <0.01); R1 (HR: 2.7; p <0.01). On multivariable analysis factors associated with PFS were: G3 (HR: 3.2; p <0.01), N1 (HR: 2.6 ; p <0.01). On univariate analysis, factors associated with OS were: neoadjuvant chemotherapy (HR: 2.5; p = 0.02); metastatic disease (HR: 3.0; p <0.01); vascular resection (HR: 3.7; p <0.01); G3 (HR: 4.9; p <0.01); venous involvement at histology (HR:4.2; p<0.01); pT3/4 (HR: 4.0; p <0.01); N+ (HR: 3.2; p <0.01); R1 (HR: 2.6; p <0.01). On multivariable analysis factors associated with OS were: G3 (HR: 2.6; p <0.01) and N1 (HR: 2.2; p= 0.02) (**Table 3**).

After propensity score matching, 102 patients were selected for comparison. Fifty-one patients who underwent standard PD and 51 in the PDVR group. There was no difference in terms of PFS and OS

within the two groups (**Figure 2a** and **2b**). Tumor grading G3 and N1 were the only factors associated with PFS (HR: 4.0; p<0.01 – HR: 3.2; p <0.01 respectively) and OS (HR: 4.5; p <0.01- HR: 2.1; p <0.02, respectively) (**Table 4**).

DISCUSSION

This is the first study specifically investigating the role of venous reconstruction in patients with locally advanced PanNENs. The number of both PD and PDVR was sufficiently large to allow a meaningful comparative as well as multivariable analysis and the multicenter design of the study contributed to dilute the intrinsic bias associated with its retrospective nature.

Patients undergoing PDVR were more likely to be symptomatic, to have metastatic disease at diagnosis and histologically to exhibit worse pathological features such as higher grade, nodal involvement and perineural and lymphovascular involvement. A significantly higher rate of microscopically incomplete resections (R1) in the PDVR group was also noticed. All these parameters are known to be negative prognostic indicators [38,39] and this was reflected in the current study as both overall and progression free survival were significantly shorter in the PDVR group compared to PD. The marked difference in the clinic-pathological characteristics highlights the lack of homogeneity between the two groups as overall PDVR patients had more advanced and aggressive tumours. Once this heterogeneity was corrected by performing a propensity score matching, a similar OS and PFS was observed in the two groups (3 years PFS 59% with PD vs 49% with PDVR p=0.14; 5 years OS 69% with PD vs 71% with PDVR p=0.98) suggesting that the need for vascular reconstruction *per se* did not affect survival.

That a larger proportion of patients in the PDVR groups received neo-adjuvant chemotherapy reflects the intention to stabilize or downstage a disease with a potentially unfavorable prognosis prior to complex surgery. Whilst some authors consider the presence of liver metastases as the only prognostic factor associated with poor survival, others have reported a worse prognosis after extended pancreatectomy when compared with conventional resection for PanNENs. In 2015, a report from an International Multicenter Study suggested that only patients presenting with both locally advanced and metastatic disease had a worse survival [7]. In our experience, overall 11% of patients had

synchronous liver metastases at the time of surgery with multivariable analysis confirming its role as a positive prognosticator of poor PFS.

Histopathological parameters are also robust predicting indicators of survival in pancreatic cancer. In a large series of 840 patients with T3 adenocarcinoma of the pancreatic head undergoing PD or PDVR, multivariable logistic and proportional hazards regression analyses identified R1 resection margin status, N1 nodal status, perineural invasion and tumour size >20mm to be independently associated with poorer overall survival [40]. Similarly in this study on PanNENs, higher grade and greater T stage seemed to negatively influence survival in a multivariable analysis of the entire cohort but only grading and nodal status maintained a borderline significance after propensity score matching.

The in-hospital death rate was 1%, with all deaths registered in the standard PD group. Patients with PanNENs are often younger than those with pancreatic cancer, who are more frequently clinically deconditioned presenting with obstructive jaundice and weight loss [41]. The average age in our study was 58 years, similar to the age reported in the literature on extended pancreatic resections for PanNENs [25-30]. In 2012, a summary of systematic reviews and meta-analyses clearly showed that hospital and surgeon volumes were the most important variables correlated with in hospital mortality [42,43]. Indeed the postoperative mortality rate was 0.7% in a series of 587 resected patients with PanNENs over 25 years [5]. Only high volume surgical centers with a specific interest in the management of PanNENs contributed to this study, this being unequivocally one of the main reasons for this result.

We omitted to record generic complications, such as chest or wound infection, and opted to capture pancreas specific morbidity, like delayed gastric emptying or pancreatic fistula, for which clear definitions are in place [32-34]. Several studies on vascular resection in pancreatic cancer have used the same standardized definitions to record postoperative morbidity integrated with severity-scoring systems [35], with complication rates after PDVR ranging between 30% [44] and 56% [45]. In our cohort,

the clinically relevant complication rate of PDVR was not significantly different to PD (48% vs 33% p=0.09) but the incidence of pancreatic fistula was significantly greater in the PD group. Tumours in the PDVR group were more frequently advanced with a higher rate of T3 and T4 lesions, therefore more likely to cause obstruction/dilatation of the pancreatic duct and to increase firmness of the parenchyma, both factors well known to be associated with a lower risk of developing postoperative pancreatic fistula [46,47]. It has been suggested that patients with PanNENs might have a significantly higher risk of postoperative complications than patients with other pancreatic diseases [46,48]. In a recent article, Partelli et al. [49] compared the postoperative course after pancreaticoduodenectomy of 179 patients with PanNENs to 387 patients with ductal adenocarcinoma and found a significantly higher incidence of surgical specific complications in the PanNENs group. Pancreatic fistula, bile leakage, intraabdominal collections and sepsis occurred more frequently in patients with PanNENs whose pancreatic texture was softer and with a significantly smaller pancreatic duct [49]. With an overall rate of 35% of clinically relevant postoperative complications, our experience conforms well to the current literature, including a relatively low incidence of vascular thrombosis in patients undergoing PDVR.

Inevitably this study suffers the limitations of any retrospective project. Only a few reports discuss the role of vascular resection/ reconstruction in patients with locally advanced PNET, hence we had to look at the literature on PDVR in pancreatic cancer for comparison, particularly with regard to the rate of postoperative complications. Also, whilst we demonstrated that PD and PDVR for PanNENs carry the same perioperative risk and offer a similar chance of long-term survival, we could not compare long-term outcomes with a group of no resected patients with venous involvement as surgical palliation is very rarely performed for PanNENs of the pancreatic head. In a large multicenter study from the UK Vascular Resection Group for Pancreatic Cancer, surgical bypass was used a surrogate of inoperable but not primarily palliative treatment and compared to both PD and PDVR [22]. We could not reproduce the same study design as surgical palliation is very rarely performed for PanNENs of the pancreatic head. However, the natural history of unresected PanNENs has been documented with a 5 year overall survival between 21% and 45% [46,50]. In a retrospective American

study on 728 patients with PanNENs from the Surveillance, Epidemiology, and End Results database, resection of the primary tumor was associated with a significantly improved survival compared with those patients who were recommended but did not undergo resection (114 months vs 35 months; P <0.0001) [50]. The shorter life expectancy associated with palliation remains therefore a good incentive to perform PDVR in patients with venous involvement.

CONCLUSIONS

This is the only study comparing PD with PDVR and represents the largest series of portal vein resection for locally advanced PanNENs. We have demonstrated that PDVR gives equivalent results to PD where vein resection is not required, with similar morbidity rates and long term prognosis. Isolated involvement of the porto-mesenteric axis is not a contraindication to resection with a curative intent, which should be routinely offered to patients with locally advanced PanNENs treated in high volume specialized centers.

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FIGURE LEGENDS

Figure 1: 1a. PFS for 480 patients who underwent standard PD and 61 patients who underwent PDVR; **1b.** OS for 480 patients who underwent standard PD and 61 patients who underwent PDVR;

Figure 2: 2a. PFS after propensity score adjustment for 51 patients who underwent standard PD and 51 patients who underwent PDVR; **2b**. OS after propensity score adjustment for 51 patients who underwent standard PD and 51 patients who underwent PDVR

Table 1. Demographic and preoperative patients' characteristics.

Variables	All (*n*=541) n (%)	PDVR (*n*=61) n (%)	Standard PD (*n*=480) n (%)	p
Gender				
Female	280 (52)	21 (34)	259 (54)	
Male	261 (48)	40 (66)	221 (46)	<0.01
Age, years				
Median (IQR)	58 (20-85)	63 (27-83)	58 (20-85)	0.07
≤58 years	276 (51)	27 (44)	249 (48)	
>58 years	265 (49)	34 (56)	231 (52)	0.26
ASA score				
I	63 (12)	9 (15)	54 (11)	
II	147 (27)	21 (34)	126 (26)	
III	208 (38)	19 (31)	189 (40)	
IV	123 (23)	12 (20)	111 (23)	0.42
Obesity				
BMI ≤30 Kg/m^2	364 (67)	39 (64)	325 (68)	
BMI >30 Kg/m^2	177 (33)	22 (36)	155 (32)	0.55
Symptomatic				
No	290 (54)	17 (28)	290 (54)	
Yes	251 (46)	44 (72)	207 (43)	<0.01
Functioning				
No	502 (93)	58 (95)	444 (93)	
Yes	39 (7)	3 (5)	36 (7)	0.46
Neoadjuvant therapy				
No	507 (94)	46 (75)	461 (96)	
Yes	34 (6)	15 (25)	19 (4)	<0.01
Liver Metastatic disease				
No	481 (89)	42 (69)	439 (91)	
Yes	60 (11)	19 (31)	41 (9)	<0.01

PDVR: Pancreaticoduodenectomy with vein resection, PD: Pancreaticoduodenectomy, BMI: Body mass index

Table 2. Intraoperative, perioperative and histological characteristics of the entire cohort.

Variables	All (*n*=541) n (%)	PDVR (*n*=61) n (%)	Standard PD (*n*=480) n (%)	p
Surgery type				
PPPD	258 (48)	28 (46)	230 (48)	
Whipple	283 (52)	33 (54)	250 (52)	0.78
Segment resected				
PV and SMV	15 (25)	15 (25)	-	
PV	24 (39)	24 (39)	-	
SMV	22 (36)	22 (36)	-	-
Vein reconstruction				
Primary closure	30 (49)	30 (49)	-	
End to end anastomosis	20 (33)	20 (33)	-	
Interposition graft	11 (18)	11 (18)	-	-
Intraoperative blood loss, mL				
Median (IQR)	350 (200-700)	575 (350-1000)	300 (200-600)	
<400 mL	282 (52)	17 (28)	265 (56)	
400-700 mL	134 (25)	22 (36)	112 (23)	
700-1000 mL	76 (14)	12 (20)	64 (13)	
>1000 mL	49 (9)	10 (16)	39 (8)	<0.01
Operative time, minutes				
Median (IQR)	340 (259-425)	425 (315-530)	330 (255-420)	<0.01
Grade				
PanNET-G1	380 (70)	28 (46)	352 (74)	
PanNET-G2	110 (20)	16 (26)	94 (19)	
PanNEN-G3	51 (10)	17 (28)	34 (7)	<0.01
Perineural Invasion				
No	352 (65)	24 (40)	328 (68)	
Yes	189 (35)	37 (60)	152 (32)	<0.01
Lymphovascular invasion				
No	326 (60)	12 (20)	314 (66)	
Yes	215 (40)	49 (80)	166 (34)	<0.01
Venous involvement on Histology				
No	501 (93)	21 (34)	480 (100)	
Yes	40 (7)	40 (66)	0 (0)	<0.01
pT stage				
pT0/pT1	175 (32)	1 (2)	174 (36)	
pT2	163 (30)	10 (16)	153 (32)	
pT3/pT4	203 (38)	50 (82)	153 (32)	<0.01
pN stage				
N0	310 (57)	17 (28)	293 (61)	
N1	231 (43)	44 (73)	187 (39)	<0.01
Resection margin				
R0	469 (87)	35 (57)	434 (90)	
R1	72 (13)	26 (43)	46 (10)	<0.01
Postoperative complications				
No complications	131 (24)	13 (21)	118 (25)	
CD ≤2	220 (41)	19 (31)	201 (42)	
CD >3	190 (35)	29 (48)	161 (33)	0.09
POPF[37]				

No	392 (73)	53 (87)	329 (71)	576
Yes	149 (27)	8 (13)	141 (29)	<0.01
DGE[39]				577
No	182 (34)	24 (39)	158 (33)	578
Yes	359 (66)	37 (61)	322 (67)	0.543
Hep- Jej leak				
No	516 (95)	58 (95)	458 (95)	580
Yes	25 (5)	3 (5)	22 (5)	0.586
Portal/SMV thrombosis				582
No	536 (99)	58 (95)	478 (100)	
Yes	5 (1)	3 (5)	2 (0)	<0.001
ICU stay, days				584
≤1 day	308 (56.9)	32 (52.5)	276 (57.5)	
>1 day	233 (43.1)	29 (47.5)	204 (42.5)	0.485
LoS, days				586
Median (IQR)	12 (9-19)	14 (10-22)	12 (9-18)	0.01
≤12 days	217 (40)	21 (34.4)	196 (40.8)	587
>12 days	324 (60)	40 (65.6)	284 (59.2)	0.383
90-day mortality				589
No	536 (99)	61 (100)	475 (99)	
Yes	5 (1)	0	5 (1)	0.490

PPPD: Pylorus-preserving pancreaticoduodenectomy; PDVR: pancreaticoduodenectomy with vein resection; PD: pancreaticoduodenectomy; PV: portal vein; SMV: superior mesenteric vein; IQR: interquartile range; CD: Clavien-Dindo classification; POPF: Postoperative pancreatic fistula; DGE: Delayed gastric emptying; Hep-Jej leak: Hepatico-jejunostomy leak; SMV: Superior mesenteric vein; ICU: Intensive care unit; LoS: Length of stay;

Table 3: Factors associated with progression-free survival (PFS) and overall survival (OS) for 541 patients who underwent pancreaticoduodenectomy (PD) (with or without venous resection).

Variables	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR	p	HR	p	HR	p	HR	p
Gender								
Female	1				1			
Male	1.3	0.18			1.0	0.99		
Obesity								
BMI ≤30 Kg/m^2	1				1			
BMI >30 Kg/m^2	1.0	0.98			0.8	0.42		
Neoadjuvant therapy								
No	1		1		1		1	
Yes	2.2	<0.01	1.1	0.88	2.5	0.02	1.3	0.58
Liver Metastatic disease								
No	1		1		1		1	
Yes	3.1	<0.01	1.7	0.06	3.0	<0.01	1.4	0.38
Vascular resection								
No	1		1		1		1	
Yes	4.2	<0.01	1.5	0.43	3.7	<0.01	1.4	0.70
Grade								
PanNET-G1	1		1		1		1	
PanNET-G2	1.9	<0.01	1.6	0.10	0.6	0.29	0.5	0.23
PanNEN-G3	6.5	<0.01	3.2	**<0.01**	4.9	<0.01	2.6	**<0.01**
Perineural Invasion								
No	1		1		1			
Yes	2.1	<0.01	0.8	0.59	1.5	0.11		
Lymphovascular invasion								
No	1		1		1			
Yes	2.8	<0.01	1.3	0.34	1.7	0.06		
Venous involvement								
No	1		1		1		1	
Yes	4.1	<0.01	1.1	0.86	4.2	0.01	1.5	0.63
pT stage								
pT0/pT1	1		1		1		1	
pT2	1.7	0.08	1.3	0.41	1.7	0.23	1.2	0.70
pT3/pT4	4.0	<0.01	1.4	0.43	4.0	<0.01	1.8	0.15
pN stage								
N0	1		1		1		1	
N1	3.6	<0.01	2.6	**<0.01**	3.2	<0.01	2.2	**0.01**
Resection margin								
R0	1		1		1		1	
R1	2.7	<0.01	1.1	0.71	2.6	<0.01	0.8	0.58
Postoperative complications								
No complications	1				1		1	
CD ≤2	0.8	0.28			1.1	0.74	1.3	0.47
CD ≥3	1.3	0.27			2.0	0.05	1.9	0.10
POPF								
No	1				1			

Yes	0.8	0.19	1.1	0.63
DGE				
No	1		1	
Yes	0.97	0.89	0.9	0.55

PFS: progression-free survival; OS: overall survival; BMI: body mass index; PanNET: pancreatic neuroendocrine tumour; PanNEN: pancreatic neuroendocrine neoplasm; CD: Clavien-Dindo classification; POPF: postoperative pancreatic fistula; DGE: delayed gastric emptying.

Table 4: Factors associated with progression-free survival (PFS) and overall survival (OS) for 102 patients after propensity score matching.

	PFS		OS	
Variables	**Univariate analysis**		**Univariate analysis**	
	HR	p	HR	p
Gender				
Female	1		1	
Male	0.8	0.41	1.2	0.71
Neoadjuvant therapy				
No	1		1	
Yes	0.8	0.53	1.6	0.31
Metastatic disease				
No	1		1	
Yes	1.4	0.33	1.8	0.19
Vascular resection				
No	1		1	
Yes	1.6	0.14	1.1	0.98
Grade				
PanNET-G1	1		1	
PanNET-G2	0.7	0.29	0.7	0.60
PanNEN-G3	4.0	**<0.01**	4.5	**<0.01**
Perineural Invasion				
No	1		1	
Yes	1.3	0.41	1.9	0.17
Lymphovascular invasion				
No	1		1	
Yes	1.9	0.07	1.7	0.28
pT stage				
pT0/pT1/pT2	1		1	
pT3/pT4	0.8	0.61	1.7	0.29
pN stage				
N0	1		1	
N1	1.8	0.08	2.0	0.17
Resection margin				
R0	1		1	
R1	1.4	0.33	1.1	0.60
Postoperative complications				
No complications	1		1	
CD ≤2	0.7	0.39	0.9	0.87
CD ≥3	0.9	0.82	1.4	0.51
POPF[37]				
No	1		1	
Yes	1.2	0.61	1.1	0.90

PFS: progression-free survival; OS: overall survival; CD: Clavien-Dindo classification; POPF: postoperative pancreatic fistula.

Figure 1

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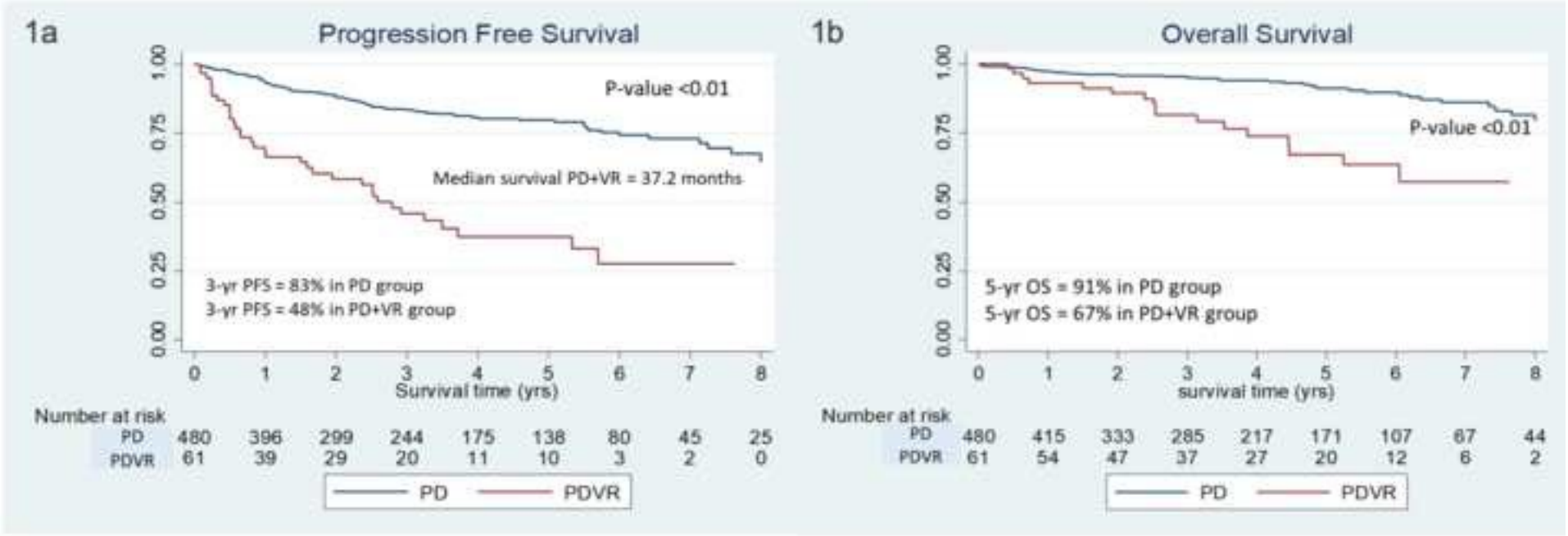

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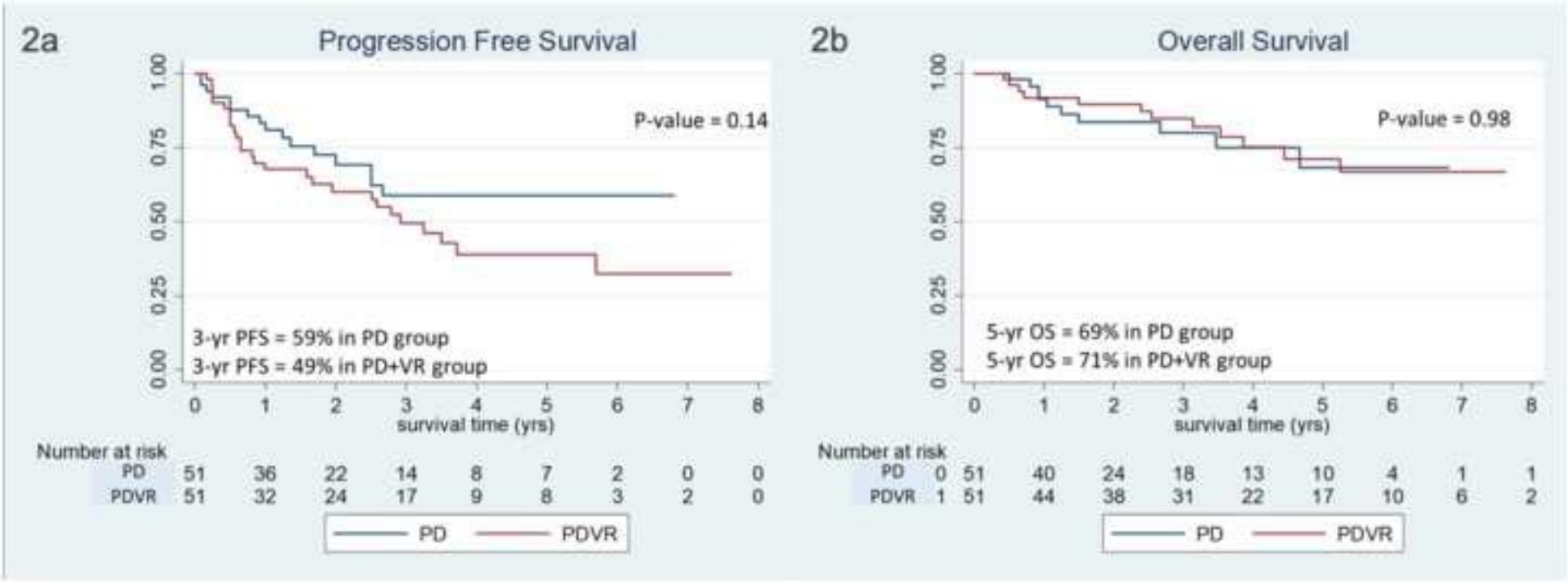
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