

TITLE PAGE**Portal Vein Resection during Pancreaticoduodenectomy for Pancreatic Neuroendocrine Tumours. An International Multicentre Comparative Study****Authors:**

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24 ARTICLE SUMMARY:

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325 The role of portal vein resection is well established during resection for pancreatic cancer but not for
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526 Pancreatic NeuroEndocrine Neoplasms (PanNENs). The importance of this report is that there is no
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827 significant difference in perioperative risk and a similar overall survival between standard
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1028 pancreaticoduodenectomy and pancreaticoduodenectomy with vascular resection among patients
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1329 with PanNENs.

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45 **ABSTRACT**1
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346 **Background:** The role of portal vein resection is well established during resection for pancreatic
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547 cancer but not for Pancreatic NeuroEndocrine Neoplasms (PanNENs). Evidence from studies
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7 providing information on long term outcome after venous resection in PanNENs patients' is lacking.
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1149 **Methods:** This is a multicenter retrospective cohort study comparing pancreaticoduodenectomy with
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1350 vein resection (PDVR) with standard pancreaticoduodenectomy (PD) in patients with PanNENs. The
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15 primary end-point was to evaluate the long term survival in both groups. Progression Free Survival
1651 (PFS) and Overall Survival (OS) were calculated using the method of Kaplan and Meier but a
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1852 propensity score matched cohort analysis was subsequently performed to remove selection bias and
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20 improve homogeneity. The secondary outcome was Clavien-Dindo ≥ 3 .
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2655 **Results:** 61 (11%) patients underwent PDVR and 480 patients PD. Five (1%) perioperative deaths
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28 were recorded in the PD group and postoperative clinically relevant morbidity rates were similar in
2956 the two groups (PDVR 48% vs PD 33%). In the initial survival analysis PDVR was associated with
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3157 worse 3-year PFS (48% PDVR vs 83% PD; $p < 0.01$) and 5-year OS (67% PDVR vs 91% PD). After
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3358 propensity score matching no significant difference was found in both 3-year PFS (49% PDVR vs
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35 59% PD; $p = 0.14$) and 5-year OS (71% PDVR vs 69% PD; $p = 0.98$).
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43 **Conclusion:** This study demonstrates no significant difference in perioperative risk and a similar
4462 overall survival between PD and PDVR. Tumour involvement of the superior mesenteric/portal vein
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4663 axis should not preclude surgical resection in patients with locally advanced PanNENs.
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68 **Keywords:** pancreatic neuroendocrine tumors; pancreatic surgery; portal vein resection; PanNENs;
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88 INTRODUCTION

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389 Pancreatic Neuroendocrine Neoplasms (PanNENs) are relatively rare accounting for approximately
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590 3% of all pancreatic tumours and for 5% of all pancreatic surgical resections ^{1,2}. In the last two
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891 decades an increase in the diagnosis of incidentally discovered Pan NENs has been observed partly
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1092 but not just as a result of the extensive and liberal use of cross-sectional imaging ^{2,3}. Several small
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1393 low grade PanNENs are diagnosed incidentally and can be observed as recommended by the
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1594 European NeuroEndocrine Tumour Society (ENETS) ⁴. Although incidental PanNENs are more
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1795 commonly associated with lower stages and better prognosis than symptomatic tumors up to 30% of
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2096 these incidental lesions might present with locally advanced or metastatic disease, and this percentage
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2297 is higher in patients with non-functioning PanNENs presenting with mass related symptoms ³. As
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2598 resection remains the only potentially curative option, an aggressive approach has been traditionally
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2799 encouraged in view of the favorable prognosis of PanNENs, even in the presence of metastatic disease
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3100 or extension to surrounding organs and vascular structures ⁵⁻⁷.

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31301 For many years portal vein resection during pancreatectomy for pancreatic cancer has been a
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3502 controversial topic. Whilst some studies showed comparable complication rates between standard
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31803 pancreaticoduodenectomy (PD) and pancreaticoduodenectomy with venous resection (PDVR) ⁸⁻¹²,
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4104 others had reported an increased morbidity with no survival benefit in PDVR ¹³⁻¹⁶. More recently,
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4305 with refinement of surgical techniques and improvement in perioperative care, portal vein resection
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41506 has established its role as isolated venous involvement should no longer be a contraindication to
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4807 proceed to surgery in patients with borderline resectable pancreatic cancer. This principle was ratified
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5108 in a consensus document by the American Hepato-Pancreato-Biliary Association (A-HPBA) in
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5209 2010¹⁷ and by the International Study Group for Pancreatic Surgery (ISGPS) in 2014 ¹⁸, as they
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51510 recommended resection of pancreatic cancers in the presence of reconstructible mesenteric-portal
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5711 axis involvement, based on the updated evidence that overall survival was found to be similar in PD
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61012 and PDVR with no significant difference in the perioperative risk ¹⁹⁻²³.

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

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

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135 METHODS

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1637 The present study was a retrospective cohort study following the STrengthening the Reporting of
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1938 OBservational studies in Epidemiology statement (STROBE) guidelines ³¹. The medical records of
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1139 all patients who underwent radical PD (with or without porto-mesenteric vein resection) for
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1340 pathologically confirmed Pan NENs at the 12 following involved institutions, between January 2007
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11641 and December 2016 were reviewed from a prospectively maintained database: Beaujon Hospital
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1842 France, University of Marburg Germany, University of Verona, University of Pisa and San Raffaele
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2143 Hospital in Italy, Academic Medical Centre Amsterdam in the Netherlands, University of Seoul
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21344 Korea, Karolinska Institute in Sweden, Royal Free Hospital and Southampton Hospital Charity in the
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2645 UK, Memorial Slone Kettering and John Hopkins in the USA. The study was approved by the Ethics
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2846 Committees of participating centers. Inclusion criteria were as follows: age \geq 18 years, sporadic
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3147 forms, macroscopic resection of all the tumor (R0/R1), histologically confirmed PanNEN of the
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3348 pancreatic head. Two patients were excluded because younger than 18 years, 2 patients excluded as
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3549 they had a diagnosis of Multiple Endocrine Neoplasia (MEN 1), 14 patients were excluded as they
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3850 underwent enucleation. A total of 541 patients (61 PDVR and 480 standard PD) were included for
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4051 the analysis.

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4152 Data collection, definition of outcomes and histological assessment

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4753 Demographic variables, radiologic features, perioperative and postoperative variables, and follow-up
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4954 records were retrospectively reviewed from an electronic database. Obesity was dichotomized with
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5155 a cut-off of 30 Kg/m², the segment of vein resected was categorized in the portal vein (PV) and /or
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5456 superior mesenteric vein (SMV), the type of vascular reconstruction was categorized in the following
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5657 categories: primary closure, end to end anastomosis and interposition graft. For the intraoperative
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5958 blood loss, 4 groups were created using used the 400 ml, 700 ml and 1000 ml cut-off. Recurrence
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6159 was defined as a finding on imaging consistent with recurrence and/or pathologic confirmation of
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160 recurrence. Survival was defined as time from surgery to death for disease, recurrence, or censor.
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 1261 Postoperative pancreatic fistula (POPF) was defined according to the latest classification of the
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 1562 International Study Group of Pancreatic Fistula (ISGPF)³². Post-pancreatectomy hemorrhage (PPH)
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 1763 and delayed gastric emptying (DGE) were defined using the classifications stated by International
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 1964 Study Group of Pancreatic Surgery (ISGPS)^{33,34}. Postoperative complications were classified
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 11265 according to the Clavien-Dindo classification (CD) ranging from I (no complications) to V (surgical-
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 1466 related death)³⁵. Minor complications were defined as $CD \leq 2$, a clinically relevant complication was
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 11767 defined as $CD \geq 3$. Postoperative mortality was defined as death occurred within 90 days after surgery
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 1968 or any in-hospital death. Tumor grade was classified according to the latest World Health
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 21269 Organization classification into three categories: PanNET G1, PanNET G2, and PanNEN G3³⁶.
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 21470 Tumor stage was also classified according to UICC TNM 8th Edition 2017³⁷. Venous involvement
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 21771 was defined as the lack of plane between the vessel and the tumour requiring vascular reconstruction
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 21972 regardless of the histologically proven infiltration of the venous wall.

31273 **Statistical analysis**

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 3574 Comparisons, in terms of short and long-terms outcomes, between PD and PDVR groups were
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 31875 evaluated by using Fisher's exact test and Chi-square test for categorical variables or two-tailed
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 41076 Student's t test for continuous and normally distributed data. Disease/Progression free survival (PFS)
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 41377 and Overall survival (OS) curves were calculated using the method of Kaplan and Meier and
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 41578 comparisons by PD and PDVR groups were reported using a log rank test.. Patients without survival
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 41779 or recurrence information were censored at the date of last correspondence or follow-up. In order to
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 51080 eliminate selection bias, a propensity score matched cohort analysis was performed to further explore
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 51281 whether a vascular resection at the time of PD was associated with worst PFS and OS compared
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 51582 standard PD. Propensity scores for all patients were calculated using a logistic regression model based
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 51783 on the following disease prognostic factors: age, gender, pT stage, pN stage, metastatic disease,
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 61084 resection margins, neoadjuvant therapy received, grading and once propensity score was derived, a

185 neighbor-matching algorithm was used to match patients who underwent standard PD with those who
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1²86 had a vascular resection at the time of pancreaticoduodenectomy (PDVR).

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1⁵87 After the propensity score adjustment, 102 patients were selected, 51 patients in each group. Cox
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1888 proportional hazard models were used to evaluate the impact of Vascular resection on the risk for
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1⁰89 disease recurrence/progression and death of disease, before and after the propensity score adjustment.

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11390 A $p < 0.05$ was considered significant. Statistical analysis was performed using the MatchIt R package
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11591 (version 3.0.3, R Foundation for Statistical Computing— www.r-project.org/) and STATA.

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206 RESULTS

2307 Patient characteristics and pre-operative evaluation

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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).

26 Operative details and histology

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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%).

52 Perioperative outcomes

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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

231 relevant postoperative complication ($CD \geq 3$) occurred in 35% of patients, without any statistical
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 2²32 difference within the two groups. Portal or superior mesenteric vein thrombosis was observed in 3
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 2⁵33 patients (5%) in the PDVR group, compared with only 2 (<1%) patients in the standard group (p
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 2⁷34 <0.01). The median length of stay (LoS) was 12 days and the median ICU stay was 1 day. No
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 2⁹35 difference in terms of length of stay and ICU were founded in the two study groups. The
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 12²36 intraoperative, perioperative and histological characteristics of the entire cohort are shown in **Table**
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16 17 18 **Survival**

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 2²1³9 The median follow-up time was 44 months (19.8-67.2 range). The 3-year PFS and 5-year OS was
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 2²3⁴0 83% and 91% in the standard PD group, respectively. Patients who underwent PDVR showed a 3-
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 2⁵41 year PFS of 48% and a 5-year OS of 67%. The differences, for both PFS and OS, were statistically
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 2²8⁴2 significant within the two groups ($p < 0.01$). PFS and OS of the entire cohort are shown in **Figure 1a**
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 3⁰43 and **1b**. On univariate analysis, factors associated with PFS were: liver metastatic disease (HR: 3.1;
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 3²3⁴4 $p < 0.01$) neoadjuvant chemotherapy (HR: 2.2 ; $p < 0.01$); vascular resection (HR: 4.2; $p < 0.01$); G3
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 3⁵45 (HR: 6.5; $p < 0.01$); perineural invasion (HR: 2.1; $p < 0.01$); lymphovascular invasion (HR: 2.8; p
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 3²8⁴6 <0.01); venous involvement at histology (HR:4.1; $p < 0.01$); pT3/4 (HR: 4 ; $p < 0.01$); N1 (HR: 3.6 ;
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 4²0⁴7 $p < 0.01$); R1 (HR: 2.7; $p < 0.01$). On multivariable analysis factors associated with PFS were: G3
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 4²3⁴8 (HR: 3.2; $p < 0.01$), N1 (HR: 2.6 ; $p < 0.01$). On univariate analysis, factors associated with OS were:
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 4²5⁴9 neoadjuvant chemotherapy (HR: 2.5; $p = 0.02$); metastatic disease (HR: 3.0; $p < 0.01$); vascular
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 4⁷2⁵0 resection (HR: 3.7; $p < 0.01$); G3 (HR: 4.9; $p < 0.01$); venous involvement at histology (HR:4.2;
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 5²0⁵1 $p < 0.01$); pT3/4 (HR: 4.0; $p < 0.01$); N+ (HR: 3.2; $p < 0.01$); R1 (HR: 2.6; $p < 0.01$). On multivariable
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 5²2⁵2 analysis factors associated with OS were: G3 (HR: 2.6; $p < 0.01$) and N1 (HR: 2.2; $p = 0.02$) (**Table**
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 5²8⁵4 After propensity score matching, 102 patients were selected for comparison. Fifty-one patients who
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 6⁰2⁵5 underwent standard PD and 51 in the PDVR group. There was no difference in terms of PFS and OS
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256 within the two groups (**Figure 2a** and **2b**). Tumor grading G3 and N1 were the only factors associated
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2²57 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
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2⁵58 <0.02, respectively) (**Table 4**).

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277 **DISCUSSION**

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2378 This is the first study specifically investigating the role of venous reconstruction in patients with
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2579 locally advanced PanNENs. The number of both PD and PDVR was sufficiently large to allow a
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2880 meaningful comparative as well as multivariable analysis and the multicenter design of the study
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12081 contributed to dilute the intrinsic bias associated with its retrospective nature.

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12683 Patients undergoing PDVR were more likely to be symptomatic, to have metastatic disease at
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12884 diagnosis and histologically to exhibit worse pathological features such as higher grade, nodal
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22185 involvement and perineural and lymphovascular involvement. A significantly higher rate of
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22386 microscopically incomplete resections (R1) in the PDVR group was also noticed. All these
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22888 parameters are known to be negative prognostic indicators ^{38,39} and this was reflected in the current
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32390 study as both overall and progression free survival were significantly shorter in the PDVR group
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32692 compared to PD. The marked difference in the clinic-pathological characteristics highlights the lack
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42093 of homogeneity between the two groups as overall PDVR patients had more advanced and aggressive
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42394 tumours. Once this heterogeneity was corrected by performing a propensity score matching, a similar
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42695 OS and PFS was observed in the two groups (3 years PFS 59% with PD vs 49% with PDVR p=0.14;
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42896 5 years OS 69% with PD vs 71% with PDVR p=0.98) suggesting that the need for vascular
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52197 reconstruction *per se* did not affect survival.

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52398 That a larger proportion of patients in the PDVR groups received neo-adjuvant chemotherapy reflects
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53800 the intention to stabilize or downstage a disease with a potentially unfavorable prognosis prior to
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301 synchronous liver metastases at the time of surgery with multivariable analysis confirming its role as
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3²02 a positive prognosticator of poor PFS.
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3⁵03 Histopathological parameters are also robust predicting indicators of survival in pancreatic cancer. In
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3⁸04 a large series of 840 patients with T3 adenocarcinoma of the pancreatic head undergoing PD or
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1³05 PDVR, multivariable logistic and proportional hazards regression analyses identified R1 resection
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1³06 margin status, N1 nodal status, perineural invasion and tumour size >20mm to be independently
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1³07 associated with poorer overall survival ⁴⁰. Similarly in this study on PanNENs, higher grade and
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1⁸08 greater T stage seemed to negatively influence survival in a multivariable analysis of the entire cohort
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2³009 but only grading and nodal status maintained a borderline significance after propensity score
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3¹10 matching.
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2⁵
3¹11 The in-hospital death rate was 1%, with all deaths registered in the standard PD group. Patients with
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2³812 PanNENs are often younger than those with pancreatic cancer, who are more frequently clinically
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3⁰
3¹13 deconditioned presenting with obstructive jaundice and weight loss ⁴¹. The average age in our study
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3³14 was 58 years, similar to the age reported in the literature on extended pancreatic resections for
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3⁵15 PanNENs ²⁵⁻³⁰. In 2012, a summary of systematic reviews and meta-analyses clearly showed that
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3³16 hospital and surgeon volumes were the most important variables correlated with in hospital mortality
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4³017 ^{42,43}. Indeed the postoperative mortality rate was 0.7% in a series of 587 resected patients with
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4³18 PanNENs over 25 years ⁵. Only high volume surgical centers with a specific interest in the
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4³519 management of PanNENs contributed to this study, this being unequivocally one of the main reasons
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3¹20 for this result.
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5¹21 We omitted to record generic complications, such as chest or wound infection, and opted to capture
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5³22 pancreas specific morbidity, like delayed gastric emptying or pancreatic fistula, for which clear
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5⁵
3²23 definitions are in place ³²⁻³⁴. Several studies on vascular resection in pancreatic cancer have used the
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5³24 same standardized definitions to record postoperative morbidity integrated with severity-scoring
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3²25 systems ³⁵, with complication rates after PDVR ranging between 30% ⁴⁴ and 56% ⁴⁵. In our cohort,
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326 the clinically relevant complication rate of PDVR was not significantly different to PD (48% vs 33%
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3²27 p=0.09) but the incidence of pancreatic fistula was significantly greater in the PD group. Tumours in
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3⁵28 the PDVR group were more frequently advanced with a higher rate of T3 and T4 lesions, therefore
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3⁷29 more likely to cause obstruction/dilatation of the pancreatic duct and to increase firmness of the
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3⁹30 parenchyma, both factors well known to be associated with a lower risk of developing postoperative
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13²31 pancreatic fistula ^{46,47}. It has been suggested that patients with PanNENs might have a significantly
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13⁴32 higher risk of postoperative complications than patients with other pancreatic diseases ^{46,48}. In a recent
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13⁷33 article, Partelli et al. ⁴⁹ compared the postoperative course after pancreaticoduodenectomy of 179
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13⁹34 patients with PanNENs to 387 patients with ductal adenocarcinoma and found a significantly higher
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23²35 incidence of surgical specific complications in the PanNENs group. Pancreatic fistula, bile leakage,
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23⁴36 intraabdominal collections and sepsis occurred more frequently in patients with PanNENs whose
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2⁶3⁷37 pancreatic texture was softer and with a significantly smaller pancreatic duct ⁴⁹. With an overall rate
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23⁹38 of 35% of clinically relevant postoperative complications, our experience conforms well to the current
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3¹3⁹39 literature, including a relatively low incidence of vascular thrombosis in patients undergoing PDVR.
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3⁵40 Inevitably this study suffers the limitations of any retrospective project. Only a few reports discuss
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33⁷41 the role of vascular resection/ reconstruction in patients with locally advanced PNET, hence we had
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3⁹3⁴42 to look at the literature on PDVR in pancreatic cancer for comparison, particularly with regard to the
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43²43 rate of postoperative complications. Also, whilst we demonstrated that PD and PDVR for PanNENs
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4⁴4⁴44 carry the same perioperative risk and offer a similar chance of long-term survival, we could not
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43⁷45 compare long-term outcomes with a group of no resected patients with venous involvement as
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43⁹46 surgical palliation is very rarely performed for PanNENs of the pancreatic head. In a large multicenter
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53²47 study from the UK Vascular Resection Group for Pancreatic Cancer, surgical bypass was used a
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53⁴48 surrogate of inoperable but not primarily palliative treatment and compared to both PD and PDVR ²².
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5⁶3⁷49 We could not reproduce the same study design as surgical palliation is very rarely performed for
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53⁵50 PanNENs of the pancreatic head. However, the natural history of unresected PanNENs has been
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6¹3⁵51 documented with a 5 year overall survival between 21% and 45% ^{46,50}. In a retrospective American
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352 study on 728 patients with PanNENs from the Surveillance, Epidemiology, and End Results database,
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3²53 resection of the primary tumor was associated with a significantly improved survival compared with
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3⁵54 those patients who were recommended but did not undergo resection (114 months vs 35 months; P
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3⁷55 <0.0001)⁵⁰. The shorter life expectancy associated with palliation remains therefore a good incentive
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3⁹56 to perform PDVR in patients with venous involvement.
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373 **CONCLUSIONS**

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3374 This is the only study comparing PD with PDVR and represents the largest series of portal vein
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3575 resection for locally advanced PanNENs. We have demonstrated that PDVR gives equivalent results
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3876 to PD where vein resection is not required, with similar morbidity rates and long term prognosis.
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13077 Isolated involvement of the porto-mesenteric axis is not a contraindication to resection with a curative
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13378 intent, which should be routinely offered to patients with locally advanced PanNENs treated in high
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13579 volume specialized centers.

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398 **COI Disclosure, Funding/Financial Disclosure:** The authors have no related conflicts of interest
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3²⁹⁹ to declare and no Funding/Financial support.

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551 **FIGURE LEGENDS**

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5453 **Figure 1: 1a.** PFS for 480 patients who underwent standard PD and 61 patients who underwent

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5654 PDVR; **1b.** OS for 480 patients who underwent standard PD and 61 patients who underwent PDVR;

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5955 **Figure 2: 2a.** PFS after propensity score adjustment for 51 patients who underwent standard PD and

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15256 51 patients who underwent PDVR; **2b.** OS after propensity score adjustment for 51 patients who

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15457 underwent standard PD and 51 patients who underwent PDVR

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558 **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

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

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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
POPF³⁷				

	No	392 (73)	53 (87)	329 (71)	576
1	Yes	149 (27)	8 (13)	141 (29)	<0.01
2	DGE³⁹				577
3	No	182 (34)	24 (39)	158 (33)	578
4	Yes	359 (66)	37 (61)	322 (67)	0.4739
5	Hep- Jej leak				
6	No	516 (95)	58 (95)	458 (95)	580
7	Yes	25 (5)	3 (5)	22 (5)	0.5861
8	Portal/SMV thrombosis				
9	No	536 (99)	58 (95)	478 (100)	582
10	Yes	5 (1)	3 (5)	2 (0)	<0.0031
11	ICU stay, days				
12	≤1 day	308 (56.9)	32 (52.5)	276 (57.5)	584
13	>1 day	233 (43.1)	29 (47.5)	204 (42.5)	0.4855
14	LoS, days				
15	Median (IQR)	12 (9-19)	14 (10-22)	12 (9-18)	586
16	≤12 days	217 (40)	21 (34.4)	196 (40.8)	0.01
17	>12 days	324 (60)	40 (65.6)	284 (59.2)	587
18	90-day mortality				
19	No	536 (99)	61 (100)	475 (99)	589
20	Yes	5 (1)	0	5 (1)	0.5490

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;

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610 **Table 3:** Factors associated with progression-free survival (PFS) and overall survival (OS) for 541
 6111 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		1	
Yes	2.1	<0.01	0.8	0.59	1.5	0.11		
Lymphovascular invasion								
No	1		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
1	DGE				
2	No	1		1	
3	Yes	0.97	0.89	0.9	0.55
4	<hr/>				
5	PFS: progression-free survival; OS: overall survival; BMI: body mass index; PanNET: pancreatic neuroendocrine				
6	tumour; PanNEN: pancreatic neuroendocrine neoplasm; CD: Clavien-Dindo classification; POPF: postoperative				
7	pancreatic fistula; DGE: delayed gastric emptying.				
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641 **Table 4:** Factors associated with progression-free survival (PFS) and overall survival (OS) for 102
 642 patients after propensity score matching.

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Variables	PFS		OS	
	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
POPF³⁷				
No	1		1	
Yes	1.2	0.61	1.1	0.90

56³44
 54 PFS: progression-free survival; OS: overall survival; CD: Clavien-Dindo classification; POPF:
 55 postoperative pancreatic fistula.
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