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# Portal Vein Resection in Borderline Resectable Pancreatic Cancer: A United Kingdom Multicenter Study

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**BACKGROUND:** Until recently, in the United Kingdom, borderline resectable pancreatic cancer with invasion into the portomesenteric veins often resulted in surgical bypass because of the presumed high risk for complications and the uncertainty of a survival benefit associated with a vascular resection. Portomesenteric vein resection has therefore remained controversial. We present the second largest published cohort of patients undergoing portal vein resection for borderline resectable (T3) adenocarcinoma of the head of the pancreas.

**STUDY DESIGN:** This is a UK multicenter retrospective cohort study comparing pancreaticoduodenectomy with vein resection (PDVR), standard pancreaticoduodenectomy (PD), and surgical bypass (SB). Nine high-volume UK centers contributed. All consecutive patients with T3 (stage IIA to III) adenocarcinoma of the head of the pancreas undergoing surgery between December 1998 and June 2011 were included. The primary outcomes measures are overall survival and in-hospital mortality. Secondary outcomes measure is operative morbidity.

**RESULTS:** One thousand five hundred and eighty-eight patients underwent surgery for borderline resectable pancreatic cancer; 840 PD, 230 PDVR, and 518 SB. Of 230 PDVR patients, 129 had primary closure (56%), 65 had end to end anastomosis (28%), and 36 had interposition grafts (16%). Both resection groups had greater complication rates than the bypass group, but with no difference between PD and PDVR. In-hospital mortality was similar across all 3 surgical groups. Median survival was 18 months for PD, 18.2 months for PDVR, and 8 months for SB ( $p = 0.0001$ ).

**CONCLUSIONS:** This study, the second largest to date on borderline resectable pancreatic cancer, demonstrates no significant difference in perioperative mortality in the 3 groups and a similar overall survival between PD and PDVR; significantly better compared with SB. (*J Am Coll Surg* 2014;218:401–411. © 2014 by the American College of Surgeons)

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Pancreatic cancer is the 13<sup>th</sup> most common cancer worldwide, but the 4<sup>th</sup> most common cause of cancer death in the Western world, with little improvement in survival during the last few decades.<sup>1</sup> Surgical resection remains the only potentially curative option for these patients. However,

<20% of patients who present with pancreatic cancer have resectable tumors.<sup>2</sup> Of the unresectable patients, approximately two thirds present with distant metastases and the rest with locally advanced disease with tumor extension into surrounding vasculature.<sup>3</sup> This has driven

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**Abbreviations and Acronyms**

PD	= pancreaticoduodenectomy
PDVR	= pancreaticoduodenectomy with vascular resection
PV	= portal vein
SB	= surgical bypass
SMV	= superior mesenteric vein

surgeons throughout the years to strive to improve resectability rates. The treatment of borderline resectable pancreatic cancer with aggressive surgery was initially developed by Moore and colleagues, who, in 1951, performed the first superior mesenteric vein (SMV) resection and reconstruction, followed by Asada and colleagues from Japan in 1963.<sup>4,5</sup> Subsequently, Fortner in 1973 first described a “regional pancreatectomy” involving total pancreatectomy, radical lymph node clearance, combined portal vein resection (type 1), and/or combined arterial resection and reconstruction (type 2).<sup>6</sup> These procedures were later abandoned, as they conferred no survival benefit and carried a greater morbidity and mortality than conventional surgery.

During the last decade, with improvements in surgical technique, anesthesia, and critical care support, there has been renewed interest in vascular resection for isolated involvement of the portal vein (PV) and/or SMV in borderline resectable pancreatic cancer. There have been numerous reports on PV resection in borderline resectable pancreatic cancer, but with conflicting results.<sup>7-16</sup> Some studies have reported comparable complication rates between standard pancreaticoduodenectomy (PD) and pancreaticoduodenectomy with vascular resection (PDVR).<sup>11,15-25</sup> In 2004, Tseng and colleagues from the MD Anderson Center, found no survival difference in patients undergoing PD and PDVR.<sup>16</sup> Similarly, Yekebas and colleagues, in 2008, found similar postoperative morbidity and mortality rates between PD and PDVR.<sup>19</sup> Conversely, other studies have reported increased morbidity with no survival benefit with PDVR.<sup>26-29</sup> A systematic review by Siriwardena and Siriwardena in 2006 suggested that PDVR was associated with a high rate of nodal metastases and low survival rates.<sup>27</sup> There is also some evidence of better survival outcomes with PDVR over palliative treatment.<sup>30-33</sup>

This is a multicenter study on PV resection in T3 adenocarcinoma of the head of the pancreas aiming to compare perioperative morbidity and long-term survival in patients surgically explored with the intention to resect.

**METHODS****Patients**

This is a UK multicenter retrospective cohort study comparing PDVR, PD, and surgical bypass (SB) for T3

pancreatic adenocarcinoma of the head of the pancreas. Only patients with pancreatic adenocarcinoma undergoing surgery between December 1998 and June 2011 were included. We included patients with T3 and T4 tumors to capture all patients with venous involvement. The T4 tumors were then reclassified as T3 tumors based on the American Joint Commission on Cancer Staging System for Pancreatic Adenocarcinoma, which, in its 6<sup>th</sup> edition in 2003, reclassified tumors involving venous structures from T4 to T3. The inclusion criteria for the study were resectable disease based on CT or MRI scanning and no evidence of metastatic disease. Patients with any other form of tumor, such as cholangiocarcinoma or neuroendocrine tumors, were excluded to avoid bias. National ethical approval and National Information Governance Board approval were obtained to perform this study as a multicenter study. Nine high-volume UK centers contributed data. Patients were identified from prospectively compiled unit databases or from hospital pathology departments. Data not available from databases were obtained from electronic patient records or patient notes. Patient demographic, perioperative, histologic, and follow-up data were collected. Dates of death were obtained from electronic records, national registries, or the patient’s general practitioner; for patients who were still alive, the last follow-up outpatient visit was considered the last follow-up date.

**Preoperative evaluation**

All patients underwent contrast-enhanced CT as routine preoperative workup. Magnetic resonance imaging, endoscopic ultrasound scan, and laparoscopy were performed on an individual patient basis based on the multidisciplinary team discussion. Magnetic resonance imaging is usually done if there is a suspicion of liver metastases. In the United Kingdom, all cancer cases are discussed at a multidisciplinary team meeting, which comprises hepatobiliary surgeons, oncologists, and radiologists at tertiary referral cancer centers. The multidisciplinary team decides on the best treatment modality for the patient based on all preoperative investigations. However, the final operative decision lies with the surgeon at laparotomy, based on findings. Only patients deemed resectable preoperatively were included. The criteria for en bloc resection where there is no evidence of metastatic disease were the following: tumor not involving the root of the small bowel mesentery; tumor not involving the superior mesenteric artery, coeliac axis, or hepatic artery; and intention of obtaining R0 resection margin status. Patients with PV occlusion were not included. Patients with metastatic disease were excluded.

**Table 1.** Perioperative Patient Characteristics

	Surgical groups				p Value	
	Total	PD	PDVR	SB	PDVR vs PD	PDVR vs SB
n (%)	1,588 (10.0)	840 (52.9)	230 (14.5)	518 (32.6)		
Sex, n (%)						
Male	856 (53.9)	468 (55.7)	115 (50.0)	273 (52.7)	0.14	0.55
Female	732 (46.1)	372 (44.3)	115 (50.0)	245 (47.3)		
Age, y, median (range)	66 (27–89)	66 (27–84)	65 (43–80)	64 (30–89)	0.61	0.12
Endoscopic USS, n (%)	220 (13.9)	122 (14.5)	38 (16.5)	60 (11.6)	0.52	0.08
MRI, n (%)	76 (4.8)	51 (6.1)	8 (3.5)	17 (3.3)	0.17	1.00
Diagnostic laparoscopy, n (%)	195 (12.3)	119 (14.2)	18 (7.8)	58 (11.2)	0.01	0.20
Preoperative biliary drainage, n (%)	953 (60)	515 (61.3)	112 (48.7)	362 (62.9)	0.0008	0.0004
Bilirubin, uM/L, median (range)	47 (3–911)	49 (3–911)	38.5 (4–798)	52 (4–671)	0.05	0.13
Hemoglobin, g/L, median (range)	12.3 (4.7–17.2)	12.7 (6.0–17.2)	12.2 (4.7–17.0)	12.1 (8.0–17.0)	0.16	0.89
Albumin, g/L, median (range)	38 (15–61)	39 (16–61)	38 (15–49)	37 (20–52)	0.02	0.68
Creatinine, mg/dL, median (range)	82 (8–301)	83 (8–301)	75 (41–183)	83 (32–230)	0.002	0.0009
Operation duration, min, median (range)	255 (102–900)	250 (102–720)	300 (108–900)	215 (120–480)	0.0001	0.0001
Hospital stay, d, median (range)	11 (0–130)	13 (0–130)	14 (0–90)	9 (0–96)	0.15	0.0001
ITU stay, d, median (range)	0 (0–40)	0 (0–39)	0 (0–40)	0 (0–14)	0.16	0.0001

ITU, intensive therapy unit; PD, standard pancreaticoduodenectomy; PDVR, pancreaticoduodenectomy with vein resection; SB, surgical bypass; USS, ultrasound scan.

### Perioperative data

Patients deemed resectable underwent a PD with or without vein resection. Pancreaticoduodenectomy performed was a classical Whipple procedure or a pylorus-preserving PD. Vascular resections were carried out as primary closure of the vein, end to end anastomosis, or a segmental resection and reconstruction with interposition graft. The graft was sourced from the patient's jugular vein, long saphenous vein, and renal vein, or from a suitable stored cadaveric donor vessel. Hepaticojejunostomy with or without gastrojejunostomy was performed for patients requiring SB. Major postoperative

complications included in-hospital mortality, pancreatic fistula (drain amylase of >3 times serum amylase after the third postoperative day, as defined by the International Study Group of Pancreatic Surgery),<sup>34</sup> delayed gastric emptying (requirement of nasogastric tube for more than 10 days postoperatively and/or intolerance of food intake for longer than 2 weeks postoperatively),<sup>35</sup> postoperative bleeding (as defined by the International Study Group of Pancreatic Surgery),<sup>36</sup> nonpancreatic anastomotic leak, PV thrombosis, and relaparotomy. Data on neoadjuvant or adjuvant chemoradiation were collected where possible.

**Table 2.** Operative Details for Patients Undergoing Standard Pancreaticoduodenectomy and Pancreaticoduodenectomy with Vein Resection

	Total		PD		PDVR		p Value
	n	%	n	%	n	%	
Type of PD							
Whipple	532	49.7	406	48.3	126	54.8	0.10
PPPD	538	50.3	434	51.7	104	45.2	
Pancreatic anastomosis							
PG	280	26.2	178	21.2	102	44.4	
PJ	790	73.8	662	78.8	128	55.6	0.0001
Vein resection							
Primary closure					129	56.0	NA
End to end anastomosis					65	28.0	
Interposition graft					36	16.0	

NA, not applicable; PD, standard pancreaticoduodenectomy; PDVR, pancreaticoduodenectomy with vein resection; PG, pancreaticogastrostomy; PJ, pancreaticojejunostomy; PPPD, pylorus-preserving pancreaticoduodenectomy.

**Table 3.** Histology Results for Patients Undergoing Standard Pancreaticoduodenectomy and Pancreaticoduodenectomy with Vein Resection

	Surgical groups			p Value
	Total	PD	PDVR	
Tumor size, mm, median (range)	30 (4–96)	30 (4–96)	30 (10–90)	0.03
Lymph node yield, median (range)	17 (0–66)	16 (0–66)	18 (4–50)	0.03
Lymphovascular invasion, n (%)	683 (63.8)	533 (63.5)	150 (65.2)	0.68
Perineural invasion, n (%)	817 (76.4)	637 (75.8)	180 (78.3)	0.50
Resection margin status, n (%)				
R0	482 (46.0)	397 (48.4)	85 (37.1)	0.003
R1	567 (54.1)	423 (51.6)	144 (62.9)	
Resection margin, n (%)				
Anterior	101 (10.0)	61 (7.7)	40 (17.9)	0.0001
Posterior	276 (26.9)	204 (25.5)	72 (31.9)	0.07
SMV, n (%)	173 (17.0)	91 (11.5)	82 (36.1)	0.0001
SMA, n (%)	86 (8.5)	62 (7.9)	24 (10.8)	0.22
Nodal status, n (%)				
N0	199 (18.3)	157 (19.2)	42 (18.3)	0.84
N1	188 (81.2)	663 (80.9)	188 (81.7)	

PD, standard pancreaticoduodenectomy; PDVR, pancreaticoduodenectomy with vein resection; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

### Histologic assessment

Histologic assessment was done at the 9 individual units. Data collected included tumor size, grading, lymphovascular and perineural invasion, and resection margin status. Survival analysis included all patients undergoing a vein resection, regardless of histologic evidence of vascular invasion.

### Statistical analysis

Comparisons of the demographic, pre-, and perioperative characteristics of patients in the 3 groups were performed using chi-square/Fisher's exact tests (for qualitative data) and Kruskal-Wallis tests (for quantitative data), as appropriate. The p values reported from these analyses are global unless otherwise stated. The primary outcomes measures are overall survival and in-hospital mortality. The secondary outcomes measure is operative morbidity. Postoperative complication rates were compared among the 3 groups using chi-square tests, with logistic regression used to quantify the association between mode of surgery and each complication before and after adjustment for potential confounders (age, sex, calendar year, and selected factors that were seen to differ in frequency across the 3 groups). Analyses of in-hospital mortality were performed using chi-square tests and logistic regression as described here. All-cause mortality was described using Kaplan-Meier methods, with multivariable Cox regression models used to quantify associations with surgery type before and after adjustment for confounders. For these analyses, patient follow-up started on the day of surgery and, for patients who remained alive at the

end of the study period, was right-censored on the date of the last outpatient visit.

## RESULTS

### Patient characteristics and preoperative evaluation

A total of 1,588 patients with borderline resectable adenocarcinoma of the head of the pancreas, who fulfilled the inclusion criteria, underwent surgery at the 9 hepatobiliary units included in this study between December 1998 and October 2011. Of these, 230 (14.5%) patients underwent PDVR, 820 (54.9%) underwent PD, and 518 (32.6%) underwent SB. There was a similar distribution of men and women across all 3 groups (Table 1). Median age at surgery was 66 years (range 27 to 89 years), although patients undergoing SB were slightly younger, on average, than the 2 resection groups ( $p = 0.02$ ). Data on operation duration were available for 455 patients; the PDVR group had a significantly longer median operative period (300 minutes) than either the PD (250 minutes) or SB (215 minutes) groups ( $p = 0.0001$ ). Overall median intensive therapy unit stay was 0 days (range 0 to 40 days). Median length of intensive therapy unit stay was the same in all 3 groups. Hospital stay ranged from 0 to 130 days (median 11 days); no difference was observed between the PD and PDVR groups (median 13 days; range 0 to 130 days and median 14 days; range 0 to 90 days, respectively), but hospital stays were shorter, on average, in those undergoing SB (median 9 days; 0 to 96 days;  $p = 0.0001$ ).

All patients had preoperative CT scan. Two hundred and twenty patients (13.9%) had endoscopic ultrasound scan, with similar proportions across the 3 groups. Seventy-six

**Table 4.** Complications for All 3 Surgical Groups

	Surgical groups				p Values	
	Total	PD	PDVR	SB	PDVR vs PD	PDVR vs SB
Pancreatic fistula (%)	101 (9.4)	86 (10.2)	15 (6.5)	n/a	0.09	NA
Delayed gastric emptying (%)	76 (4.8)	39 (4.6)	25 (10.9)	12 (2.3)	0.0007	0.0001
Nonpancreatic anastomotic leak (%)	61 (3.8)	43 (5.1)	10 (4.3)	8 (1.5)	0.76	0.04
Relaparotomy (%)	73 (4.6)	51 (6.1)	17 (7.4)	5 (1.0)	0.57	0.0001
Postoperative bleed (%)	56 (3.5)	40 (4.8)	12 (5.2)	7 (1.3)	0.91	0.0003
Patients transfused, n (%)	290 (19.3)	173 (21.8)	72 (31.9)	45 (9.3)	0.002	0.0001
Median U (range)	0 (0–30)	0 (0–30)	0 (0–9)	0 (0–8)	0.002	0.0001

NA, not applicable; PD, standard pancreaticoduodenectomy; PDVR, pancreaticoduodenectomy with vein resection; SB, surgical bypass.

(4.8%) patients had MRI, with significantly more patients in the PD group (51 patients [6.1%]) having MRI than the other 2 groups (8 [3.5%] and 17 [3.3%] patients in the PDVR and SB groups, respectively;  $p = 0.04$ ). A diagnostic laparoscopy was performed in 195 patients (12.3%), again with similar proportions in the 3 groups. Overall, 953 patients (60%) had preoperative biliary drainage, with significantly fewer patients in the PDVR group ( $n = 112$  [48.7%]) requiring it than in either the PD ( $n = 515$  [61.3%]) or SB ( $n = 326$  [62.9%]) groups ( $p = 0.0006$ ).

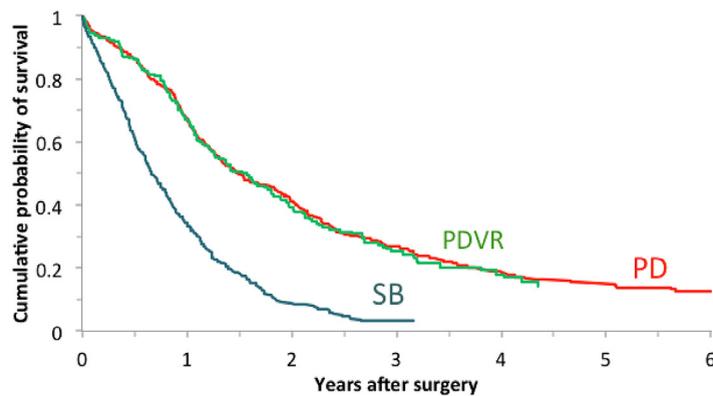
**Operative details**

In both resection groups, a similar proportion of patients underwent a Whipple or pylorus-preserving PD (Table 2). Of the 1,070 patients having a resection, 253 (23.6%) had a pancreaticogastrostomy and 671 (62.7%) had a pancreaticojejunostomy. In the PD group,

a greater proportion of patients underwent a pancreaticojejunostomy (65.1%) than in the PDVR group (53.9%). Of the 230 vein resections performed, the majority were primary closures (129 patients [56%]), with 65 end to end anastomosis (28%) and 36 interposition grafts (16%). Most vein resections were unplanned, but performed with the aim of achieving tumor clearance.

**Histology**

The histology on all resection specimens confirmed pancreatic ductal adenocarcinoma. The median tumor size was 30 mm (range 4 to 96 mm), with the PD group having slightly larger tumors, on average, than the PDVR group (30 mm [range 4 to 96 mm] vs 30 mm [range 10 to 90 mm], respectively;  $p = 0.03$ ). There was no significant difference in tumor grading between the 2 groups. Lymph node yield was greater in the PDVR group than



Years after surgery	0	1	2	3	4	5	6
PD	719	446	226	118	66	41	19
PDVR	218	135	67	34	15		
SB	418	132	28	9			

**Figure 1.** Overall survival between the 3 surgical groups. PD, standard pancreaticoduodenectomy; PDVR, pancreaticoduodenectomy with vein resection; SB, surgical bypass.

the PD group (median values of 18 vs 16, respectively;  $p = 0.03$ ). There were no significant differences observed in lymphovascular invasion, perineural invasion, or nodal status between the 2 groups (Table 3). The PDVR group had more R1 resection margins ( $p = 0.003$ ) and positive anterior and SMV surface margins ( $p = 0.0001$  for each). There were more T4 tumors in the PDVR group than PD group (9.2% vs 2.1% respectively;  $p = 0.0001$ ).

### Complications

Overall, the need for a blood transfusion within 24 hours and pancreatic fistula were the most frequent complications in all patients undergoing a resection (290 patients [19.3%]; 95% CI, 17.3%–21.4%) and 101 [9.4%]; 95% CI, 7.8%–11.4%, respectively). Postoperative bleeding and nonpancreatic anastomotic leak were the least frequent, occurring in 73 (3.5%; 95% CI, 3.6%–5.8%) and 61 (3.8%; 95% CI, 3.0%–4.9%) patients, respectively. Patients in the SB group had the fewest complications. The difference in complication rates between SB and the 2 resection groups persisted when adjusted for age, sex, and year of operation.

When comparing the 2 resection groups, delayed gastric emptying (4.6% vs 10.9%;  $p = 0.0006$ ) and blood transfusion (21.8% vs 31.9%;  $p = 0.02$ ) were more common in the PDVR group. The median number of blood units transfused was the same between the 2 resection groups (Table 4). These differences persisted once corrected for age, sex, and year of surgery.

There were 12 (5.2%) vein resection-related complications. Seven patients had PV thrombosis, 2 of which required a relaparotomy. Six patients had an end to end anastomosis and 1 had an interposition graft. Five patients had bleeding postoperatively, 1 of which had an interposition graft and 5 had primary closures.

### Survival

Overall, 58 patients (4.7%) died in hospital, 26 (4.2%) of the patients in the PD group, 10 (4.6%) of the PDVR group, and 22 (5.4%) of the SB group ( $p = 0.70$ ); adjustment for the potential confounders of age, sex, and calendar year did not reveal any significant differences between the groups. Patients were followed for a median of 1.1 years (interquartile range 0.5 to 1.9 years) after surgery. During this time, 1,058 patients died, with a median survival time of 1.2 years. Median survival was significantly shorter (0.67 years) among patients undergoing SB than in those undergoing either PD (1.50 years) or PDVR (1.52 years;  $p = 0.0001$ , log-rank test). This difference persisted after adjusting for age, sex, and calendar year (adjusted relative hazard for PD vs SB: 0.40 [range, 0.35 to 0.46];  $p = 0.0001$ ; adjusted relative hazard for

PDVR vs SB: 0.41 [range, 0.34 to 0.50];  $p = 0.0001$ ). In pairwise analyses, no significant difference was seen in survival between PD and PDVR ( $p = 0.87$ ) (Fig. 1).

### DISCUSSION

Despite growing evidence, PDVR has not yet secured its place in the surgical management of patients with borderline resectable adenocarcinoma of the head of the pancreas. This is the second largest retrospective series of surgery for borderline resectable pancreatic cancer, as Castleberry and colleagues, in 2012, published a multi-variable analysis that included 281 cases with vascular resection.<sup>37</sup> However, this study did not report on long-term survival and postoperative histology results. Although they demonstrated a greater 30-day mortality and morbidity in the vascular resection group, pancreatic surgery-specific complications, such as pancreatic fistula and gastric emptying delay, were also not recorded.<sup>37</sup> Ours is the only study to specifically compare T3 cancers only between the 3 surgical groups. We included both T3 and T4 tumors before 2003 to capture all the borderline resectable pancreatic cancers, as the American Joint Commission on Cancer Staging System for Pancreatic Adenocarcinoma, in its 6<sup>th</sup> edition in 2003, reclassified tumors involving venous structures from T4 to T3.<sup>38</sup> A comparison with SB was made because the patients in this group were explored surgically with the intention to perform a potentially curative resection. Although it is accepted that some might have had arterial involvement or small-volume metastatic disease precluding resection, a proportion underwent SB instead of a resection because of venous involvement. It is also the closest comparison with inoperable, but not primarily palliative treatment, as also reported by other authors.<sup>13,26,39</sup>

It has been suggested that PDVR might be associated with a higher complication rate when compared with PD.<sup>25,27,40-42</sup> The variation in morbidity rates with PDVR is substantial, varying from 30%<sup>40</sup> to 55%.<sup>28</sup> In our cohort, the morbidity of PDVR was similar to PD. Only delayed gastric emptying and the number of patients requiring a blood transfusion were greater, with PDVR comparable with other published series.<sup>16,25,41,42</sup> However, Yekebas and colleagues in 2008<sup>19</sup> showed no difference in intraoperative blood loss between PD and PDVR, and a meta-analysis by Zhou in 2012<sup>7</sup> found that although there was a trend for higher transfusion requirements in the PDVR group, this did not reach statistical significance. Other studies have similarly reported comparable rates of pancreatic fistula, nonpancreatic anastomotic leaks, relaparotomy, and postoperative bleeding between PD and PDVR.<sup>16,19,43</sup> In our series,

delayed gastric emptying might have occurred more frequently in the PDVR group as a result of more extensive dissection required and potentially greater denervation of the stomach. Complications such as chest and wound infections have not been included in our analyses, as we tried to standardize the reporting of complications where clear definitions were in place.<sup>34-36</sup>

Similar in-hospital mortality between 3 groups was similarly reported by several other groups and a meta-analysis by Zhou and colleagues.<sup>7,11,25,40</sup> In the meta-analysis by Zhou and colleagues, of 19 studies that reported on mortality, no difference was observed between PD and PDVR ( $p = 0.48$ ).<sup>7</sup> All studies reporting perioperative mortality have used different methods from 30-day mortality to 90-day mortality. We chose to record in-hospital mortality, as patients with complications from pancreatic surgery often have a prolonged hospital stay and in-hospital mortality is likely to better capture mortality events that occur later. The primary finding of identical overall survival between PD and PDVR is of particular significance, as this study specifically investigated the use of extensive surgery in locally advanced pancreatic cancers. This has been validated by previous studies, although not exclusively for T3 tumors.<sup>16,18-20,26,44</sup> In contrast, Ouaisi and colleagues, in 2010, reported a significantly lower median survival in the PDVR group compared with PD (17.5 months vs 18.7 months;  $p = 0.0009$ ).<sup>43</sup> Similarly, Siriwardana and Siriwardana, in a systematic review in 2006, found lower rates of 5-year survival in the PDVR group.<sup>27</sup> However, this particular systematic review included reports from the 1960s, reports from small series, and data inaccuracies,<sup>45,46</sup> which might adversely affect estimates of survival. In 2012, Tol and colleagues published a summary of systematic reviews and meta-analyses clearly showing that hospital volume and surgeon volume are the most recognized variables that correlate to mortality.<sup>47</sup>

Besides identical survival in the resection groups, we also showed a considerable advantage when compared with SB. We accept that this might be in part because of more advanced tumors, possibly with arterial involvement being prevalent in the SB group. This has also been noted in other studies.<sup>48,49</sup> In 2009, Boggi and colleagues compared these 3 groups and similarly found no increase in postoperative morbidity and mortality, comparable survival rates between PD and PDVR, and significantly longer survival in PDVR compared with SB.<sup>48</sup> Katz and colleagues investigated the use of neoadjuvant chemotherapy with or without radiotherapy on borderline resectable cases and found that patients who were resected had a significantly better survival than those who had SB.<sup>49</sup> An additional study comparing these 3 groups found better survival in the PDVR group

compared with SB, although not statistically significant, thought to be because of low patient numbers.<sup>26</sup> A randomized controlled trial of en-bloc splenopancreatic and vascular resection vs palliative gastrobiliary bypass was performed by Lygidakis and colleagues in 2004, which showed 2-year survival rates of 81.8% and 0%, respectively.<sup>33</sup> A Japanese randomized controlled trial in 2008 compared PDVR with chemoradiotherapy with or without SB and demonstrated a significantly longer mean overall survival after surgery than after chemoradiotherapy, with a mean difference of 11.8 months.<sup>32</sup> The trial was closed before full recruitment, as an interim analysis showed a clear survival benefit in the surgery arm.<sup>32</sup>

Our results demonstrate a greater proportion of R1 resections in the PDVR group than the PD group (62.9% vs 51.6%). In the United Kingdom, the "Minimum Dataset for the Histopathological Reporting of Pancreatic, Ampulla of Vater and Bile Duct Carcinoma" was published by the Royal College of Pathologists in 2002, which defined the resection margin status (positive if  $<1$  mm from the tumor) and recommended more extensive sampling of the circumferential resection margin.<sup>50</sup> Although these guidelines have established criteria for quality control of pathology reporting, their clinical application can also significantly increase the R1 rate reported for pancreatic cancer and affect survival analysis.<sup>50</sup> As a result, R1 rates vary considerably in the literature, ranging from 37% to 75%.<sup>51</sup> Our PDVR group also had a higher incidence of positive SMV resection margin. As  $>50\%$  of vein resections were tangential, it is possible that the SMV groove was partly exposed with tumor within  $<1$  mm of the resection margin, and in a segmental vein resection, it is the vein itself that occupies this area.

Although some consider resection margin status to be an independent prognostic indicator in determining long-term outcomes,<sup>52-54</sup> others have demonstrated that R1 is associated with better survival than SB,<sup>55-58</sup> and similar to R0 resections.<sup>57-59</sup> We have shown that, despite having significantly greater R1 resections in the PDVR group, this has had no adverse effect on survival. In 2004, Tseng and colleagues at the MD Anderson Cancer Center also reported greater R1 resection in the PDVR group, which did not adversely affect survival.<sup>16</sup> Yekebas and colleagues reported no difference in resection margin status between PD and PDVR in their series.<sup>19</sup> However, their univariate analysis found that R1 status had no adverse influence on survival.<sup>19</sup> The ESPAC (European Study Group for Pancreatic Cancer)-1 trial results suggested that resection margin status was a negative predictor of survival.<sup>60</sup> In contrast, the ESPAC-3 trial subsequently found that resection margin status was not

an independent prognostic indicator of survival on a multivariate analysis.<sup>61</sup> With such discrepancies in the literature with regard to resection margin status, it could be postulated that until histopathologic reporting is more standardized universally, its role as a prognostic indicator remains equivocal.

The opponents of PDVR argue that these tumors are larger with a worse prognosis because of vessel-wall invasion.<sup>28,43,62,63</sup> We found that tumors in the PD group were, on average, slightly larger than PDVR. Perineural and lymphovascular invasion was no different between PD and PDVR. The higher lymph node yield in the PDVR group might be a result of more extensive dissection associated with the procedure. The lack of difference in these prognostic histologic indicators might suggest that PV infiltration might be related to topography rather than a sign of aggressiveness.<sup>15,24,64</sup> Studies have proven that histologic evidence of tumor invasion of venous structures does not impact on survival.<sup>19,43</sup> Often, what appears to be tumor invasion on CT or laparotomy is a result of the inflammatory response from the tumor.<sup>19</sup> If deemed unresectable, these patients would have a bypass procedure with a shorter life expectancy. In addition, the assumption that true histologic vascular invasion is a negative prognostic indicator has been challenged.<sup>23,24</sup> Yekebas and colleagues<sup>19</sup> found no statistical significance of tumor size, resection margin status, and histologic vascular-wall invasion on multivariate analysis.<sup>19</sup> Similarly, Tseng and colleagues from the MD Anderson Cancer Center found no difference in median survival between patients who did and did not have histopathologic evidence of vein invasion.<sup>16</sup>

Before 2004, administration of adjuvant chemotherapy in the resection groups was limited to patients recruited in to the ESPAC-1 trial and was not standard practice. The ESPAC-1 trial revealed a survival benefit for adjuvant chemotherapy (median survival 19.7 months vs 14.0 months;  $p = 0.0005$ ).<sup>65</sup> A subsequent randomized controlled trial, CONKO-001, compared adjuvant chemotherapy with gemcitabine alone vs observation.<sup>66</sup> They reported a greater median disease-free survival period in the gemcitabine group (13.4 months vs 6.9 months;  $p < 0.001$ ).<sup>66</sup> During the last decade, adjuvant chemotherapy has become the routine standard of care in the United Kingdom. In our series, more patients received adjuvant chemotherapy in the resection groups than palliative chemotherapy in the SB group.

Resectional surgery for pancreatic cancer is done with the hope of cure but the expectation that recurrence will develop in many patients. This study has shown that PDVR gives equivalent results to PD where vein resection is not required. Although the PD, PDVR, and

SB groups are not directly comparable, survival was better if the tumor could be removed. Patients who have PV involvement, which is resectable by means of a PD with PV resection and reconstruction, might be better served by this approach than by palliative SB. A definitive study that randomized patients to PDVR or SB at the point of diagnosis of PV involvement would need to be done to definitively prove this point, but is unlikely to ever be done, given the lack of equipoise at this stage.

The main limitation of this study is its retrospective nature. However, it represents, to the best of our knowledge, the largest series of PV resection for adenocarcinoma of the head of the pancreas. In addition, it is the only study to specifically investigate the use of PV resection in T3 tumors, avoiding the bias of including patients who might have more favorable survival results. The comparisons made with surgical bypass might be debatable. We believe this is the best comparison group with the resection group, as the intention in this entire cohort was to resect.

## CONCLUSIONS

This is the only study specifically related to borderline resectable pancreatic adenocarcinoma comparing PD, PDVR, and SB. We have demonstrated PDVR to be as safe as PD with similar morbidity rates. More importantly, we have demonstrated that patients having a vein resection have a prognosis identical to PD, and significantly greater than SB, irrespective of tumor size and resection margin status. We believe that isolated involvement of the portomesenteric axis is not a contraindication to resection with a curative intent and should be routinely offered to patients with borderline resectable pancreatic cancer treated in high-volume specialized centers.

## APPENDIX 1

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