

Pancreaticoduodenectomy With Vascular Resection: Margin Status and Survival Duration

Jennifer F. Tseng, M.D., Chandrajit P. Raut, M.D., Jeffrey E. Lee, M.D., Peter W.T. Pisters, M.D., Jean-Nicolas Vauthey, M.D., Eddie K. Abdalla, M.D., Henry F. Gomez, M.D., Charlotte C. Sun, Dr.P.H., Christopher H. Crane, M.D., Robert A. Wolff, M.D., Douglas B. Evans, M.D.

Major vascular resection performed at the time of pancreaticoduodenectomy (PD) for adenocarcinoma remains controversial. We analyzed all patients who underwent vascular resection (VR) at the time of PD for any histology at a single institution between 1990 and 2002. Preoperative imaging criteria for PD included the absence of tumor extension to the celiac axis or superior mesenteric artery (SMA). Tangential or segmental resection of the superior mesenteric or portal veins was performed when the tumor could not be separated from the vein. As a separate analysis, all patients who underwent PD with VR for pancreatic adenocarcinoma were compared to all patients who underwent standard PD for pancreatic adenocarcinoma. A total of 141 patients underwent VR with PD. Superior mesenteric-portal vein resections included tangential resection with vein patch (n = 36), segmental resection with primary anastomosis (n = 35), and segmental resection with autologous interposition graft (n = 55). Hepatic arterial resections were performed in 10 patients, and resections of the anterior surface of the inferior vena cava were performed in 5 patients. PD was performed for pancreatic adenocarcinoma in 291 patients; standard PD was performed in 181 and VR in 110. Median survival was 23.4 months in the group that required VR and 26.5 months in the group that underwent standard PD ($P = 0.177$). A Cox proportional hazards model was constructed to analyze the effects of potential prognostic factors (VR, tumor size, T stage, N status, margin status) on survival. The need for VR had no impact on survival duration. In conclusion, properly selected patients with adenocarcinoma of the pancreatic head who require VR have a median survival of approximately 2 years, which does not differ from those who undergo standard PD and is superior to historical patients believed to have locally advanced disease treated nonoperatively. (J GASTROINTEST SURG 2004;8:935-950) © 2004 The Society for Surgery of the Alimentary Tract

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The first resection and reconstruction of the superior mesenteric vein (SMV) as part of pancreaticoduodenectomy (PD) was reported by Moore et al. from the University of Minnesota in 1951.¹ Subsequent reports described various techniques to reconstruct the SMV and/or portal vein (PV),² with Symbas et al.³

concluding that autologous vein grafts remained patent, while synthetic prostheses had a high rate of occlusion. PV resection at the time of PD was reported by surgeons from Japan in an attempt to improve survival duration by performing an en bloc resection of the pancreas and surrounding structures.⁴

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From the Departments of Surgical Oncology (J.F.T., C.P.R., J.E.L., P.W.T.P., J.-N.V., E.K.A., H.F.G., D.B.E.), Gynecologic Oncology (C.C.S.), Radiation Oncology (C.H.C.), and Gastrointestinal Medical Oncology (R.A.W.), The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

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Reprint requests: Douglas B. Evans, M.D., Department of Surgical Oncology, Unit 444, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. e-mail: devans@mdanderson.org

This concept was also supported in the United States in 1973 when Fortner⁵ proposed “regional pancreatectomy,” which involved the systematic resection of major peripancreatic vascular structures together with wide soft tissue clearance. Contrary to the beliefs of Fortner and others, radical or extended PD has not been demonstrated to confer a survival benefit.⁶

A more contemporary debate continues regarding the use of vascular resection (VR) for isolated invasion of the SMV, PV, or superior mesenteric–portal vein (SMPV) confluence. It is important to emphasize the distinction between this procedure and regional pancreatectomy. The first operation incorporates venous resection during PD only when, in the opinion of the operating surgeon, the involved segment of SMV or SMPV confluence cannot be separated from the pancreatic tumor. PD with segmental resection of the SMV, PV, or SMPV confluence is not performed in an effort to achieve a greater extent of lymphatic clearance. However, similar to regional pancreatectomy, isolated resection of the SMV or SMPV confluence is technically challenging, and therefore consensus has not been reached on whether the risk of operation may outweigh the potential oncologic benefit of tumor resection. In 1946, Waugh and Clagett⁷ modified the Whipple operation to its current form and, most important, outlined the goals of surgical therapy for pancreatic cancer: (1) there should be reasonable opportunity for cure, (2) the risk of death should not outweigh the prospects for cure, and (3) the patient should be left in as normal a condition as possible. The debate over whether major vascular resection should be performed at the time of PD can be framed in the context of these goals. Ongoing questions regarding VR at the time of PD include the following: Is the survival of patients who require VR different than that of patients who undergo standard PD? Can VR and reconstruction be accomplished with acceptable morbidity and mortality?

We address these important issues in this article, which represents the largest reported experience with VR and reconstruction at the time of PD in the Western literature.

METHODS

Patients

Data on all patients who underwent PD at The University of Texas M. D. Anderson Cancer Center between July 1, 1990, and July 31, 2002, were retrieved from a prospective pancreatic tumor database. Patients who underwent pancreatic operations other than PD (e.g., distal pancreatectomy or total

pancreatectomy) were excluded. All patients who underwent major VR at the time of PD for any histologic diagnosis were identified, and data on patient demographics, treatment, histopathology, and follow-up were recorded. This retrospective study was approved by the institutional review board. Venous resection involving the SMV, PV, or SMPV confluence included tangential resection with a saphenous vein patch (V1), segmental resection with splenic vein ligation and either primary anastomosis (V2) or interposition grafting (V3), or segmental resection without splenic vein ligation and either primary anastomosis (V4) or interposition grafting (V5) (Fig. 1). For purposes of this analysis, the occasional patient who underwent minor tangential resection of the SMV or PV, which did not require at least a patch, was considered not to have undergone venous resection as there was no way to determine the extent of the tangential resection, which usually was insignificant. Other VRs and reconstructions performed at the time of PD included resection of the hepatic artery (usually at the origin of the gastroduodenal artery or a replaced right hepatic artery) or the anterior surface of the inferior vena cava (IVC). As a separate analysis, all patients who underwent PD for pancreatic adenocarcinoma were identified to allow comparison of those who did and did not undergo VR.

Preoperative Evaluation

Preoperative evaluations included physical examination, routine laboratory testing, chest radiography, and contrast-enhanced computed tomography (CT). To be considered for PD, patients had to fulfill objective radiographic criteria for resectability, which included (1) the absence of extrapancreatic metastatic disease; (2) no evidence of tumor extension to the superior mesenteric artery (SMA) or celiac axis, as defined by the presence of a fat plane between the tumor and these arteries; and (3) a patent SMPV confluence with a suitable segment of SMV and PV to allow venous resection and reconstruction if necessary. The extent of venous involvement by the primary tumor was not a contraindication for operation as long as there was no CT evidence of tumor extension to the celiac axis or SMA and there was a suitable SMV (below) and PV (above) the site of venous involvement.

Pancreaticoduodenectomy

PD was performed in a standard fashion, with six clearly defined steps, as previously described.⁸ The most oncologically important and difficult part of the operation was the sixth and final step, which involved division of the pancreas and completion of the

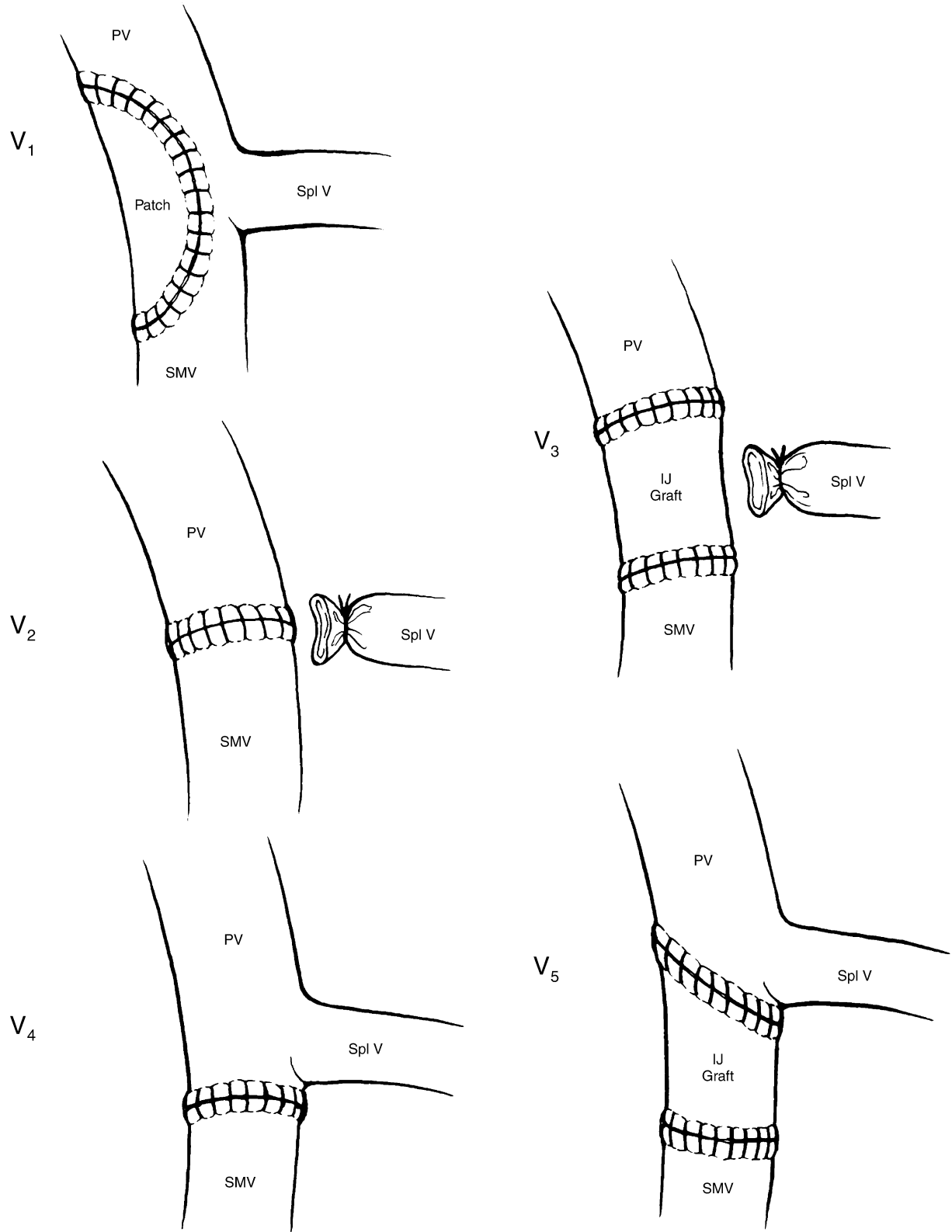


Fig. 1. Illustration of the five forms of venous resection and reconstruction.

retroperitoneal (RP) dissection. In standard PD that did not require venous resection, the surgeon was able to separate the pancreas from the SMPV confluence by reflecting the specimen laterally and dividing the small venous tributaries to the uncinate process and pancreatic head. The uncinate process was completely removed from the SMV and its first jejunal branch to ensure full mobilization of the SMPV confluence and subsequent identification of the SMA. The first jejunal branch of the SMV originates from the posteromedial aspect of the SMV (at the level of the uncinate process), travels posterior to the SMA, and enters the proximal aspect of the jejunal mesentery. This first jejunal branch usually gives off one or two venous tributaries to the uncinate process that require division. If tumor involvement of the SMV (at the level of the first jejunal branch) prevented dissection of the uncinate process from the SMV, the first jejunal branch was divided. Division of the first jejunal branch of the SMV was not considered venous resection for the purposes of this study. After full mobilization of the SMPV confluence and retraction of it medially (to the patient's left), the SMA was then exposed. In more complicated situations, such as those that typically required venous resection, the SMA was identified medial to the SMV. The specimen was then removed from the right lateral border of the SMA in a distal-to-proximal direction up to the celiac ganglion. All soft tissue to the right of the adventitia of the SMA was removed with the PD specimen. The soft tissue adjacent to the right lateral border of the proximal 3–4 cm of the SMA represented the RP margin, also known as the mesenteric or uncinate margin⁹ (Fig. 2).

Venous Resection

Tangential or segmental resection of the SMV, PV, or SMPV confluence was performed when, in the opinion of the operating surgeon, the pancreatic head and/or uncinate process could not be dissected free of the SMPV confluence without either leaving gross tumor on the vein or creating a venotomy. Elective venous resections in the absence of tumor adherence were not performed. The standard technique for segmental venous resection has historically involved transection of the splenic vein. Division of the splenic vein allowed complete exposure of the SMA medial to the SMV and provided increased SMV and PV length (as these structures were no longer tethered by the splenic vein) for a primary venous anastomosis following segmental vein resection. With the splenic vein divided, the RP dissection was then completed by sharply dividing the mesentery and RP tissues anterior to the aorta and to the right

of the exposed SMA; the specimen was then attached only by the SMPV confluence. Vascular clamps were placed 2–3 cm proximal (on the PV) and distal (on the SMV) to the involved venous segment, and the vein was transected, allowing tumor removal. A generous 2- to 3-cm segment of SMPV confluence could be resected without the need for interposition grafting if the splenic vein was divided. Venous resection was always performed with inflow occlusion of the SMA to prevent small bowel edema, which makes pancreatic and biliary reconstruction more difficult. Systemic heparinization (2500–5000 units) was used before occluding the SMA. The free ends of the vein were reapproximated using interrupted sutures of 6-0 Prolene.

Splenic vein preservation was possible only when tumor invasion of the SMV or PV did not involve the splenic vein confluence. Preservation of the splenic vein–SMV–PV confluence significantly limits mobilization of the PV and prevents primary anastomosis of the SMV following segmental SMV resection unless segmental resection is limited to 2 cm or less. Therefore, in most patients who underwent SMV resection with splenic vein preservation, an interposition graft was required. Our preferred conduit for interposition grafting was the internal jugular vein.¹⁰ Preservation of the splenic vein adds significant complexity to venous resection because it prevents direct access to the most proximal 3–4 cm of the SMA (medial to the SMV). In such cases, therefore, venous resection and reconstruction were performed either before the specimen was separated from the right lateral wall of the SMA or after complete mesenteric dissection by separating the specimen first from the SMA.^{8,11}

Five types of venous resection were performed, as illustrated in Fig. 1. A tangential resection of the SMPV confluence (V1) was performed for tumor adherence that was limited to a small aspect of the lateral or posterior wall of the SMPV confluence and repaired using a patch from the greater saphenous vein. When tumor involved the SMV–splenic vein–PV confluence, splenic vein ligation was necessary. If the SMPV confluence could be reapproximated without tension, an end-to-end primary anastomosis was performed (V2); if the SMPV confluence could not be reapproximated without tension, autologous internal jugular vein was used for an interposition graft (V3). When tumor involvement was limited to the SMV or PV such that the splenic vein could be preserved, a primary end-to-end anastomosis of the SMV or PV was occasionally possible (V4). However, with preservation of the splenic vein, an interposition graft (V5) was usually necessary because of the

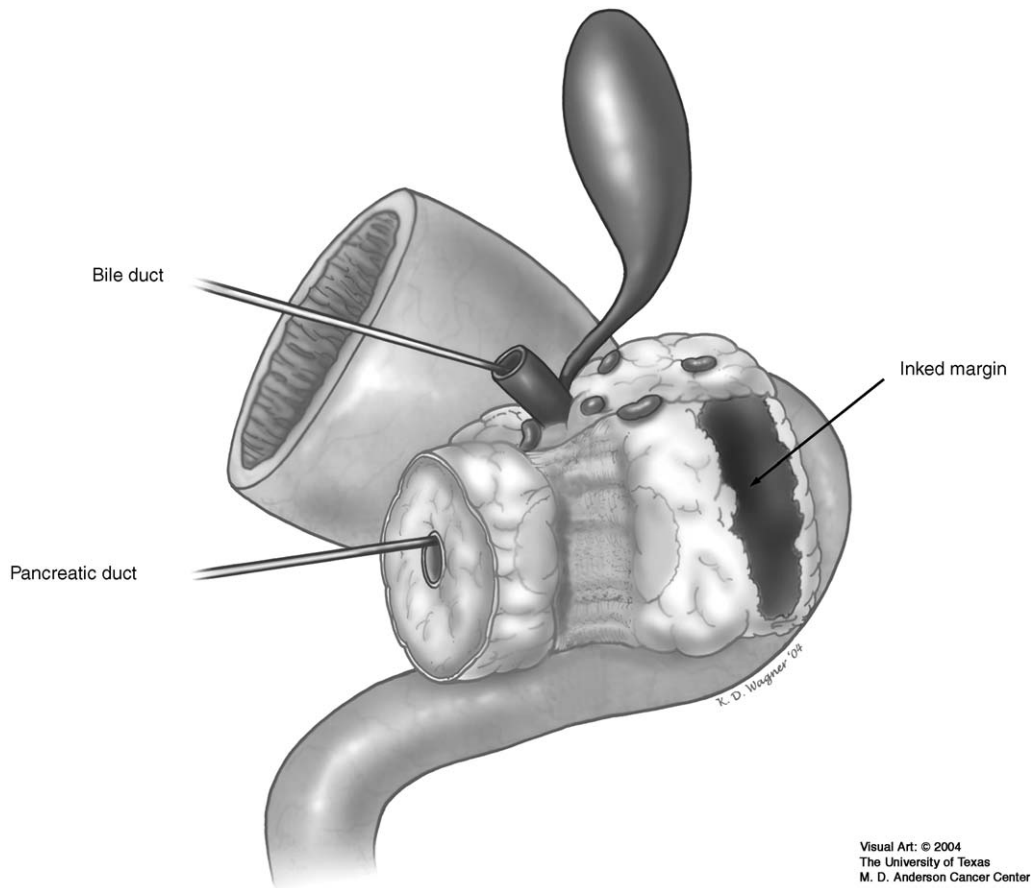


Fig. 2. Illustration of a pancreaticoduodenectomy specimen demonstrating how the retroperitoneal margin (tissue adjacent to the superior mesenteric artery) should be inked at the time of permanent section pathologic examination. This is the only way to determine the status of this important margin of excision; this margin cannot be retrospectively evaluated if the margin was not inked for identification at the time of gross inspection. A small probe is in both the bile duct and the pancreatic duct.

limited mobility of the PV caused by an intact PV-splenic vein confluence.

Other Vascular Resections

Other than resection and reconstruction of the SMPV confluence, VRs were rarely performed. Hepatic artery resection and reconstruction were performed at the time of PD when limited tumor involvement of the origin of the gastroduodenal artery necessitated resection of a short segment of the common and/or proper hepatic arteries. A primary anastomosis or a reversed saphenous vein graft was used to repair the hepatic artery. If a replaced right hepatic artery (arising from the SMA) was inseparable from the primary tumor, it was resected. The need for revascularization was based on the underlying hepatic arterial anatomy and the extent of back-bleeding in the distal artery. Resection of the anterior wall of the

IVC was performed when, at the time of Kocher maneuver, the surgeon could not separate the posterior aspect of the tumor from the IVC.

Pathologic Analysis

Since July 1990, a standardized system for the pathologic evaluation of PD specimens has been used at our institution.¹² Tumor size (maximal transverse diameter) was recorded at the time of pathologic evaluation of the PD specimen. This measurement was difficult or impossible to make in some cases due to preoperative treatment if gross tumor could not be distinguished from uninvolved adjacent pancreatic parenchyma. Evaluation of the status of the RP margin of resection was performed prospectively in all surgical specimens. The RP margin was defined as the soft-tissue margin directly adjacent to the proximal 3–4 cm of the SMA. Early in our experience, the

RP margin was evaluated by microscopic examination of an en face section measuring approximately 2 mm in thickness; the margin was recorded as positive (R1, microscopically positive following a gross complete resection) or negative (R0, microscopically negative) for carcinoma. For the past 5 years, the RP margin was evaluated according to the sixth edition of the *AJCC Cancer Staging Manual*⁹ and illustrated in Fig. 2. The RP margin was recorded as positive (R1) or negative (R0) for tumor; if negative, the distance in millimeters from the tumor to the inked margin was recorded. Margins interpreted as suspicious for carcinoma (n = 2) were considered positive (R1) for the purposes of this analysis. Histologic evidence of tumor cell invasion of the segment of resected vein was defined as tumor cell infiltration of the tunica adventitia and/or tunica media of the vein wall. Tumor cell abutment without histologic evidence of invasion of at least the tunica adventitia was not considered vein invasion.

Operative Details and Perioperative Complications

Surgical time was recorded from the anesthesia record and defined as the time from incision to application of the final wound dressing. Intraoperative blood loss and intraoperative transfusions of red blood cells were also recorded from the anesthesia record, not the operative report. Major postoperative complications were defined as previously described and included perioperative death (within the first 30 days after surgery or during the original hospital stay if longer than 30 days); need for reoperation; clinically evident pancreaticojejunal anastomotic leak (as defined by drain amylase >2.5 times the upper limit of normal and clinical symptoms including fever, leukocytosis, fistula, or abscess); intra-abdominal hemorrhage; intra-abdominal fluid collection (sterile collection or abscess); myocardial infarction or sudden cardiac death; pulmonary complications including pneumonia; gastrointestinal bleeding; and sepsis syndrome.¹³ Regarding the incidence of clinical pancreatic anastomotic leaks, it is important to note that the pancreatic anastomosis was rarely drained in our more contemporary experience. Therefore, a pancreatic anastomotic leak would not be clinically evident in the absence of the need for percutaneous drainage or reoperation. Hospital stay was calculated by considering the day of surgery as day 1, and the day of discharge was not counted as a hospital day.

Adjuvant Therapy

Preoperative and/or postoperative chemoradiation included either protocol-based or off-protocol treatment. Radiation therapy was delivered using either a

standard-fractionation (50.4 Gy in 28 fractions) or a rapid-fractionation (30 Gy in 10 fractions) regimen. Concomitant chemotherapy included 5-fluorouracil, paclitaxel, or gemcitabine.¹⁴⁻¹⁶

Statistical Analysis

All data analyses were performed with SPSS version 11.5 software (SPSS, Inc., Chicago, IL). The χ^2 test was used to compare categorical variables. Independent *t* tests and Mann Whitney μ tests were used to evaluate continuous variables. Survival and follow-up were calculated from the time of initial cytologic or histologic diagnosis to date of death or last follow-up. All deaths from any cause, including perioperative deaths, were included in our survival analysis and subsequent multivariate analysis. Overall survival was estimated using the method of Kaplan and Meier.¹⁷ The log-rank test was used to evaluate differences between survival curves. A value of *P* < 0.05 was considered statistically significant.

Univariate and multivariate analyses of the effects of potential prognostic factors on survival were done using a Cox proportional hazards regression. Covariates included age, gender, tumor size, T and N status, need for reoperative PD, presence of a major complication, operative blood loss, RP margin status, use of adjuvant therapy (preoperative and/or postoperative), need for major VR and histologic evidence of venous invasion.

To evaluate the unconfounded effect of VR on RP margin status, a logistic regression was performed to examine the impact of age, gender, performance of VR, tumor size, N status, and use of preoperative therapy on RP margin status.

RESULTS

During the study period, 572 patients underwent PD for all histologic diagnoses, and 141 (25%) required major VR (Table 1). Resection of the SMV, PV, or SMPV confluence was performed in 126 (89%) of the 141 patients. These venous resections included V1 in 36, V2 in 24, V3 in 15, V4 in 11, and V5 in 40. Segmental resection of the hepatic artery, with or without interposition grafting, was performed in 17 (12%) of the 141 patients; 7 of these also underwent concomitant venous resection and reconstruction. Resection of the anterior wall of a portion of the IVC was performed in six patients (4%), of whom one also underwent concomitant venous resection and reconstruction.

Operative characteristics and perioperative complications for the 141 patients who required VR are listed in Table 2. There were three perioperative

Table 1. Demographics, tumor histology, and type of vascular resection in the 141 patients who underwent pancreaticoduodenectomy with vascular resection

Variable	No. of patients (%)
Gender	
Male	89 (63)
Female	52 (37)
Age (yr)	
Median	62.4
Range	23–81
Histology	
Adenocarcinoma	
Pancreas	111 (79)
Bile duct	3 (2)
Duodenum	3 (2)
Neuroendocrine carcinoma	9 (6)
Other carcinoma	5 (3.5)
Sarcoma	4 (3)
Lymphoma	1 (1)
Benign disease	5 (3.5)
Type of vascular resection	
V1	36 (26)
V2	24 (17)
V3	15 (11)
V4	11 (8)
V5	40 (28)
Hepatic artery	17 (12)*
Inferior vena cava	6 (4)*

*Concomitant venous resection and reconstruction was performed in 7 patients who underwent hepatic arterial resection and 1 patient who underwent inferior vena cava resection. See text for explanation of V1–V5.

deaths, for a mortality rate of 2.1%. Major perioperative complications occurred in 29 patients (21%). Reoperation was necessary in four patients; three of them had intra-abdominal hemorrhage. In the other patient, the biliopancreatic and gastrointestinal reconstruction was delayed for approximately 36 hours (necessitating a second laparotomy) because of bowel edema caused by a prolonged period of venous occlusion at the time of venous resection and reconstruction. At reoperation, there was no evidence of intestinal ischemia, and the patient had an uneventful recovery. A clinically evident pancreatic anastomotic leak occurred in 2 (1.4%) of 141 patients. This low number is clearly influenced by the infrequent placement of an abdominal drain in proximity to the pancreatic anastomosis (and therefore the inability to measure drain fluid amylase) in our more recent experience. The median hospital stay was 13 days.

PD was performed for adenocarcinoma of pancreatic origin in 291 (51%) of the 572 patients: 181 (62%) of the 291 patients underwent standard PD, and 110 (38%) required VR and reconstruction. A

Table 2. Operative characteristics and perioperative complications in 141 patients who underwent pancreaticoduodenectomy with vascular resection

Variable	No. of patients (%)
Median estimated blood loss (range)	1675 ml (250–14,200)
Median operative time (range)	603 min (244–1340)
Median hospital stay (range)	13 days (2–108)
Perioperative death	3 (2)
Major perioperative complication*	29 (21)
Reoperation	4 (3)
Pancreaticojejunal anastomotic leak	2 (1)
Intra-abdominal hemorrhage	3 (2)
Intra-abdominal fluid collection: sterile	3 (2)
Intra-abdominal fluid collection: abscess	5 (2)
Myocardial infarction	3 (2)
Pulmonary complications	14 (10)
Gastrointestinal bleeding	6 (4)
Sepsis syndrome	1 (1)

*Some patients had more than one complication.

comparison of the two groups appears in Table 3. The median age in both groups was 63.9 years (range, 30.0–83 years for the two groups). Among the 110 patients who required VR, venous resection was performed in 100 patients and consisted of V1 in 29, V2 in 21, V3 in 10, V4 in 10, and V5 in 30. Of these 100 patients, 3 required concomitant resection of the hepatic artery, and 1 required concomitant resection of the anterior surface of the IVC. In the remaining 10 patients, 8 required isolated hepatic artery resection and reconstruction, and 2 required isolated resection of the anterior surface of the IVC. The performance of VR and reconstruction was associated with a greater likelihood of the surgery being a reoperative PD after an unsuccessful attempt at PD before referral, increased intraoperative blood loss, larger tumor size, and a greater likelihood of having a microscopically positive RP margin (R1 resection). Not shown in Table 3 is that T3 tumors were more common in the VR group (82% versus 64%, $P = 0.001$), consistent with the larger tumor diameter in the patients who required VR.

A multivariate logistic regression was used to examine the impact of the following variables on the outcome of RP margin status: age, sex, reoperative status, estimated blood loss, performance of VR,

Table 3. Univariate analysis of demographic, operative, pathologic, and treatment characteristics for 291 patients who underwent pancreaticoduodenectomy (PD) for pancreatic adenocarcinoma

	Vascular resection	Standard PD	<i>P</i> value
Total No. of patients	110	181	
Gender, n (%)			
Male	69 (63)	106 (59)	0.48
Female	41 (37)	75 (41)	
Median (mean) age (yr)*	63.9 (62.1)	63.9 (63.4)	0.23
Range	41–81	30–83	
Reoperative PD, n (%)	27 (25)	25 (14)	0.02
Operative blood loss (ml) *†			
Median (mean)	1600 (1829)	800 (923)	<0.001
Range	250–6000	100–2900	
Tumor size (cm)*‡			
Median (mean)	3.0 (3.2)	2.8 (2.8)	<0.001
Range	1.0–6.0	0.2–6.0	
Positive retroperitoneal margin (R1), n (%)	24 (22)	21 (12)	0.02
Positive lymph nodes (N1), n (%)	50 (45)	95 (52)	0.25
Major perioperative complication, n (%)	20 (18)	39 (22)	0.43
Perioperative death	1 (1)	2 (1)	0.86
Hospital stay (days)*§			
Median (mean)	13.5 (15.5)	12.0 (13.9)	0.01
Range	7–108	5–70	
Intraoperative radiation therapy, n (%)	31 (28)	73 (40)	0.04
Adjuvant therapy (preoperative or postoperative), n (%)	97 (88)	165 (91)	
Preoperative chemoradiation	82 (75)	127 (70)	0.51
Postoperative chemoradiation	25 (23)	50 (28)	0.34

*Mann-Whitney U test used.

†Estimated blood loss was not recorded in the anesthesia record for 8 patients.

‡Tumor size could not be accurately assessed at the time of pathologic evaluation of the pancreaticoduodenectomy specimen in 27 patients due to the effect of neoadjuvant therapy.

§*P* > 0.05 if the 10% of patients with the lowest and highest lengths of hospital stay are excluded from analysis.

tumor size, N stage, and use of neoadjuvant therapy. After adjusting for these variables, only tumor size and the use of neoadjuvant therapy, not the performance of VR, had significant effects on RP margin status. Tumor size was associated with a significantly increased risk of a microscopically positive RP margin (odds ratio [OR] = 1.5, 95% confidence interval [CI] = 1.1–2.0), and neoadjuvant treatment was associated with a significantly decreased risk of a microscopically positive RP margin (OR = 0.47; 95% CI = 0.23–0.96).

Log-rank tests were used to compare Kaplan-Meier survival curves for each prognostic factor of interest among the 291 patients with pancreatic adenocarcinoma (Table 4). The median overall survival for the 291 patients was 24.9 months. On univariate analysis, the only significant predictor of decreased survival was the presence of lymph node metastases, with a median survival of 21.1 months for patients with N1 disease compared with 31.9 months for patients with N0 disease (*P* = 0.005). The median survival

was 23.4 months for the group who required VR and 26.5 months for the group who underwent standard PD (*P* = 0.18). Kaplan-Meier survival curves for patients who underwent VR and who underwent standard PD are displayed in Fig. 3.

Histopathologic evaluation of the resected segment of SMV, PV, or SMPV confluence was performed in 62 of the 100 patients who underwent venous resection. In the remaining 38 patients, the surgeon did not identify the specimen as containing a portion of the SMPV confluence and so an evaluation was not done, or the pathologist did not include information about this evaluation in the final pathology report. Such information cannot be retrieved retrospectively. Among the 62 patients who had histopathologic evaluation of the resected venous segment, tumor cell invasion of the vein wall was present in 38 patients (61%) and absent in 24 (39%). The median survival did not differ between patients who did and did not have histopathologic evidence of vein invasion (Table 4).

Table 4. Univariate analysis of factors influencing median survival in 291 patients who underwent pancreaticoduodenectomy (PD) for pancreatic adenocarcinoma

Prognostic variable	No. of patients	Median survival (mo)	95% Confidence interval	P value
Overall	291	24.93	21.40–28.46	—
Gender				
Male	175	23.10	19.05–27.15	0.47
Female	116	26.97	22.43–31.50	
Extent of PD				
Standard PD	181	26.50	21.11–31.89	0.18
PD with vascular resection	110	23.43	19.50–27.37	
Reoperative PD*				
No	238	24.93	20.68–29.18	0.23
Yes	52	25.13	17.88–32.39	
T status				
Tis [†]	4	—	—	0.22
T1	25	30.77	16.61–44.92	
T2	56	25.87	20.27–31.46	
T3	206	23.70	19.94–27.46	
N status				
N0	146	31.93	24.57–39.30	0.005
N1	145	21.07	17.40–24.73	
Retroperitoneal margin				
R0	246	26.50	22.29–30.71	0.14
R1	45	21.37	17.05–25.68	
Histopathologic evidence of vein invasion [‡]				
No	24	19.67	10.30–29.03	0.66
Yes	38	19.83	13.34–26.33	
Major complication*				
No	228	26.50	20.18–32.82	0.11
Yes	59	24.40	18.51–30.29	
IORT				
No	187	24.93	20.60–29.27	0.85
Yes	104	24.47	16.78–32.16	
Adjuvant therapy*				
No	29	18.50	9.48–27.52	0.92
Yes (preoperative or postoperative)	261	25.13	21.42–28.85	
Preoperative (neoadjuvant) therapy				
No	80	25.37	19.56–31.18	0.46
Yes	209	24.93	20.44–29.43	
Postoperative therapy				
No	215	24.47	20.39–28.54	0.42
Yes	75	26.50	13.30–39.70	

*Missing data were secondary to transition from paper to electronic medical record when the prospective database was being developed and included reoperative PD (1 patient), major complication (4 patients), preoperative therapy (2 patients), and postoperative therapy (1 patient).

[†]For Tis, 3 of 4 patients censored (1 patient died at 39 months), so a median survival was not calculated. All 4 patients received preoperative (neoadjuvant) therapy; 2 of the 4 had a complete pathologic response and 2 had only in situ carcinoma at the time of permanent pathologic evaluation of the surgical specimens. All 4 patients had biopsy proved invasive adenocarcinoma before neoadjuvant therapy. If Tis (n = 4) is excluded, $P = 0.52$ for remaining T1–T3 stages.

[‡]Of 100 patients, 62 had information available.

IORT = intraoperative radiation therapy.

We performed a multivariate analysis of the effect of all potential prognostic factors on survival in patients undergoing PD for pancreatic adenocarcinoma. To assess the impact of prognostic variables such as VR, all variables except histopathologic evidence of vein invasion were included in the Cox pro-

portional hazards model for the first analysis (Table 5). Evidence of vein invasion was excluded from the multivariate analysis because results were available for only 62 patients. Thus, inclusion of vein invasion in the multivariate analysis would have dramatically decreased its power to assess the effects of other

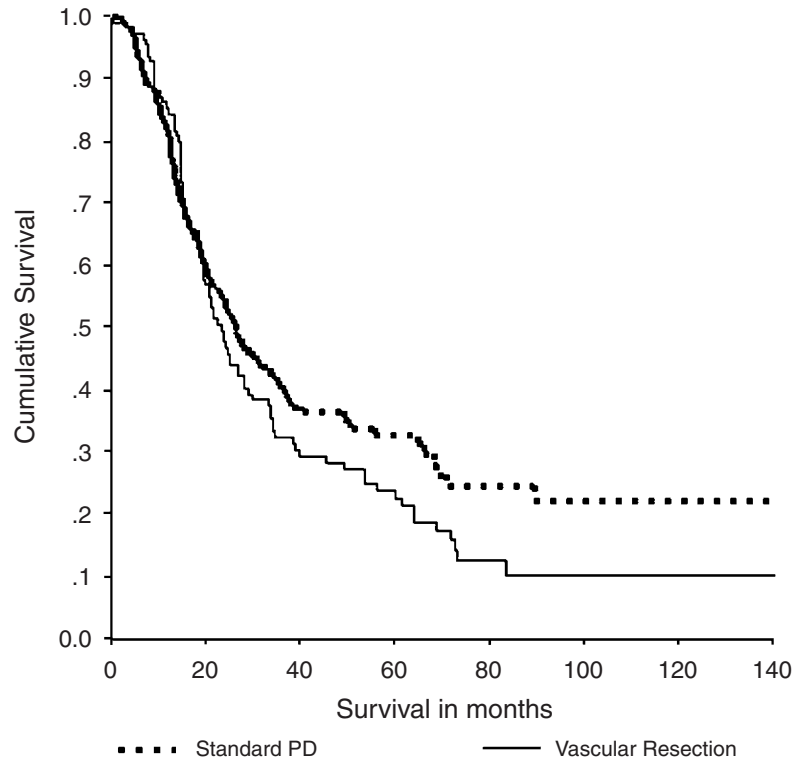


Fig. 3. Kaplan-Meier survival curves in patients with pancreatic adenocarcinoma who underwent standard pancreaticoduodenectomy (PD) or PD with vascular resection and reconstruction. Median survival for standard PD was 26.50 months. Median survival for PD with vascular resection was 23.43 months. Log-rank test: $P = 0.18$.

covariates. In the first multivariate analysis performed ($n = 291$), the presence of N1 disease was identified as a significant predictor of decreased survival (hazard ratio [HR] = 1.50, $P = 0.01$). The only other prognostic factor of significance was the occurrence of one or more major perioperative complication(s) (including perioperative deaths), which was associated with a significantly decreased survival (HR = 1.52, $P = 0.024$). These results were consistent when the multivariate analysis was repeated for the 229 patients for whom vein invasion data were not available; presence of lymph node metastases (HR = 1.6, $P = 0.012$) and major perioperative complication(s) (HR = 1.8, $P = 0.007$) were the only statistically significant covariates. VR was not associated with decreased survival in either multivariate analysis (for $n = 291$ analysis, HR = 1.1, $P = 0.499$; for $n = 299$ analysis, HR = 0.759, $P = 0.276$). Finally, a third multivariate analysis was performed including only the 62 patients who had histologic vein invasion data available. The results were also similar. However, in this small subgroup, any preoperative or postoperative adjuvant treatment proved protective (HR = 0.049, $P = 0.007$), and nodal metastases lost

significance (HR = 0.90, $P = 0.78$). Because all 62 patients who had histologic vein invasion data available had VRs, the effect of VR could not be assessed in this smaller group.

Finally, all postoperative CT scan reports within the first year of operation were reviewed to detect the presence of early occlusion of the SMV, PV, or SMPV confluence. Of the 126 patients who underwent SMV-PV reconstruction, at least one postoperative CT scan, transabdominal ultrasound, or vascular radiographic study was available for 116 (92%); 8 patients (6.9%) were noted to have venous occlusion.

DISCUSSION

VR and reconstruction at the time of PD remains controversial because of the complexity and magnitude of the operative procedure combined with the aggressive biologic behavior of pancreatic adenocarcinoma, which results in a short survival duration for most patients, even those who undergo a potentially curative PD. Therefore, physicians are appropriately hesitant to accept an operative approach

Table 5. Multivariate analysis of factors that may influence survival in 291 patients who underwent pancreaticoduodenectomy (PD) for pancreatic adenocarcinoma

Covariate	No. of patients	No. of deaths	Hazards ratio	95% Confidence interval	P value
Gender					
Male	175	126	1.00		
Female	116	84	0.93	0.67–1.29	0.64
Age of surgery (yr)	—	—	1.01	0.99–1.03	0.35
Reoperative PD					
No	238	166	1.00		
Yes	52	43	1.09	0.72–1.66	0.67
Vascular resection					
No	181	120	1.00		
Yes	110	90	1.13	0.79–1.63	0.50
Blood loss (ml)	—	—	1.0	1.00–1.00	0.45
Tumor size (cm)	—	—	0.95	0.82–1.11	0.54
T stage (AJCC)*					
Tis	4	1	1.00		
T1	25	15	0.77	0.10–6.12	0.81
T2	56	43	1.12	0.15–8.34	0.92
T3	206	151	1.13	0.15–8.35	0.90
Nodal metastasis					
No	146	97	1.00		
Yes	145	113	1.50	1.10–2.05	0.01
Retroperitoneal margin					
No	246	173	1.00		
Yes	45	37	1.16	0.77–1.76	0.47
Major perioperative complication					
No	228	159	1.00		
Yes	59	47	1.52	1.06–2.19	0.02
Any adjuvant treatment					
No	29	21	1.00		
Yes	261	188	0.96	0.41–2.24	0.93
Preoperative treatment					
No	80	60	1.00		
Yes	209	149	1.18	0.62–2.25	0.62
IORT					
No	187	126	1.00		
Yes	104	84	1.00	0.72–1.38	0.98
Postoperative treatment					
No	215	154	1.00		
Yes	75	55	0.95	0.54–1.66	0.85

*Hazards ratios not significantly changed when Tis category is excluded (n = 4) and T1 category is used as reference.
IORT = intraoperative radiation therapy.

that may be associated with increased patient morbidity and mortality. In addition, confusion remains over the indications for vascular resection of the SMV or SMPV confluence. Venous resection was initially performed as part of a regional pancreatectomy in an effort to maximize lymphatic and soft tissue resection.⁵ Subsequent clinical investigation demonstrated that a wider or more extensive lymphadenectomy at the time of PD for pancreatic adenocarcinoma has little impact on survival duration.^{6,18} Therefore, many physicians simply classify patients with suspected isolated tumor involvement of the SMV, PV, or SMPV

confluence (on CT or at the time of laparotomy) as having locally advanced disease. Such patients have a median survival of 10–12 months,¹⁹ far inferior to the survival duration of almost 2 years reported herein.

Our experience with resection and reconstruction of the SMV, PV, or SMPV confluence has been restricted to those patients in whom tumor adherence to these venous structures prevented the surgeon from mobilizing the SMPV confluence from the pancreatic head and uncinate process, as is necessary for standard PD. The assessment of tumor adherence to the

SMPV confluence is a judgment made at the time of surgery, and final pathologic evaluation of the surgical specimen will not demonstrate tumor infiltration of the vein wall in all cases (61% in this series). If dissection along the periadventitial plane of the SMV or PV is unable to separate the vein from the tumor, venous resection and reconstruction is the only way to accomplish a complete resection. To what degree peritumoral inflammation is enhanced secondary to the neoplastic process or endoscopic intervention is not known. Similarly, little is known about the effect of chemoradiation on the tumor–vessel interface. Importantly, venous resection was not performed in an effort to achieve a greater degree of lymphatic clearance. In addition, the pancreatic tumors in all patients in this series fulfilled a CT-based definition of resectability that includes the absence of tumor extension to the celiac axis and SMA. Our series is unique in incorporating strict preoperative radiographic criteria for local tumor resectability; patients whose primary tumors did not meet this definition did not undergo PD. Such criteria are necessary to avoid the inclusion of patients with grossly incomplete resections (gross residual disease; R2 resection). Survival duration in this group will be affected more by the failure to remove all gross tumor than by other potential prognostic variables.

VR and reconstruction were required in 141 (25%) of 572 patients who underwent PD during a 12-year period. Although the proportion of patients who required VR might seem high, patients were not refused operation based on the presence of tumor-induced narrowing of the SMV, PV, or SMPV confluence as long as there was no evidence of tumor extension to

the celiac axis or SMA. Previous studies from our institution have demonstrated that approximately 80% of patients taken to surgery for planned PD are able to undergo PD, even those with pancreatic adenocarcinoma; this finding attests to the high accuracy of radiographic imaging studies and the value of strict objective anatomic criteria in predicting resectability.²⁰ If objective criteria for resectability, as used in this and other studies from our institution, become more widely adopted, especially in the conduct of future clinical trials, it should not be unexpected that 20–25% of patients with otherwise resectable pancreatic cancer will be found to have isolated venous involvement. As demonstrated in this report, such patients have a survival duration similar to those without venous involvement if treated with PD as part of a multimodality approach to their disease.

Perioperative death occurred in 3 (2%) of 141 patients who underwent VR and reconstruction. Although 21% of VR patients experienced a major perioperative complication, only 3% required reoperation and only 1.4% experienced a clinically significant pancreaticojejunal anastomotic leak. Importantly, this report represents our entire institutional experience with such complicated pancreatic surgeries. As can be seen in Figs. 4 and 5, perioperative blood loss and operative time have declined over the past decade as we have gained experience and refined various technical aspects of the operative procedure. PD with VR and reconstruction is clearly more complicated than standard PD and should be undertaken only by surgeons and at institutions experienced with this operation.

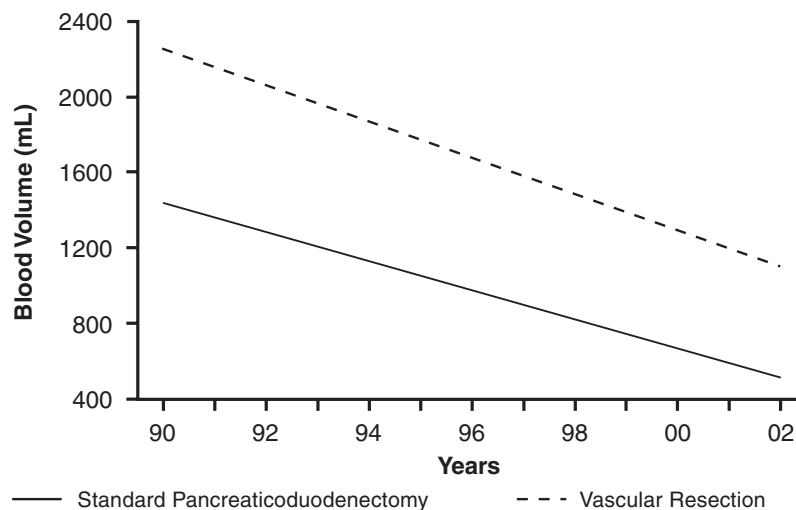


Fig. 4. Median estimated blood loss per year for standard pancreaticoduodenectomy and pancreaticoduodenectomy with vascular resection during the time of this report.

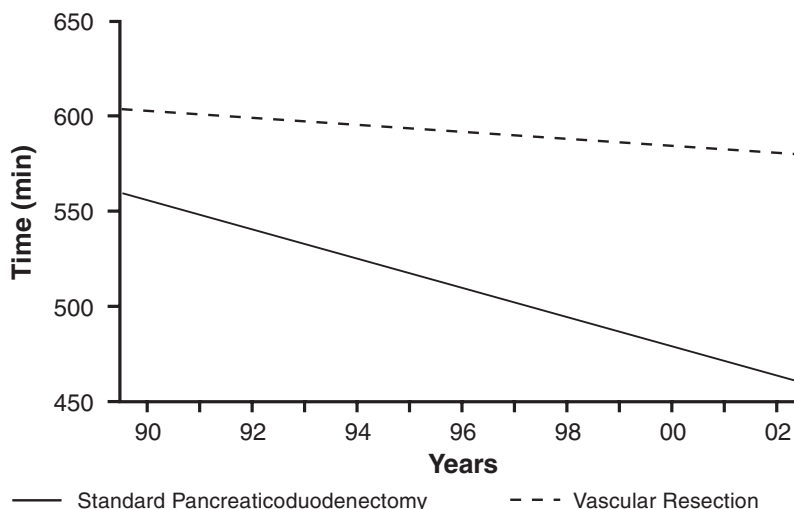


Fig. 5. Median operative time per year for standard pancreaticoduodenectomy and pancreaticoduodenectomy with vascular resection during the time of this report.

In the analysis of 291 patients who underwent PD for adenocarcinoma of pancreatic origin, we found no difference in survival duration between those who did and those who did not require VR and reconstruction (see Fig. 3). This finding is particularly striking given the fact that patients who underwent VR and reconstruction were more likely to have undergone a previous unsuccessful attempt at PD before referral and had larger tumors (see Table 3). In contrast to our previous report, reflective of our early experience, the larger sample size presented in this report revealed that R1 resections were more common in patients who required VR (22%) compared to standard PD (12%).²¹ However, after adjustment for tumor size, no significant difference in R1 resections remained, suggesting that the finding of a positive RP margin was a function of tumor size. Importantly,

the increased frequency of R1 resections in those who required VR did not translate into a significant survival difference compared to patients who underwent standard PD.

Unique to this series was the absence of grossly incomplete (R2) resections (attributable to accurate preoperative determination of resectability) and the prospective evaluation of the RP margin to allow accurate determination of R status. Such data are not available in many other reports of venous resection at the time of PD²²⁻³¹ (Table 6). In the absence of prospective evaluation of the RP margin, reports of venous resection during PD are impossible to interpret. When venous involvement is an unexpected finding at the time of PD, surgeons will often attempt to separate the SMPV confluence from the pancreatic

Table 6. Report of pancreaticoduodenectomy with venous resection in the Western literature

First author (year)	No. of patients	Operative mortality (%)	Median survival (mo)	No. with positive margin (%)
Capussotti ²² (2003)	22	0	NA	5/6 (83)*
Howard ²³ (2003)	13	8	13	3 (23)
van Geenen ²⁴ (2001)	34	0	14	20 (59)
Bachellier ²⁵ (2001)	21	3.2	12	8 (38)
Roder ²⁶ (1996)	22	0	8	15 (68)
Harrison ²⁷ (1996)	42	2	13	10 (24)
Yeo ²⁸ (1995)	10	NA	NA	NA
Launois ²⁹ (1993)	9	0	6.1†	NA
Trede ³⁰ (1990)	12	0	NA	NA
Sindelar ³¹ (1989)	20	20	12	NA

NA = not available/not reported.

*Retroperitoneal margin assessed in 6 of 22 patients.

†Value is given as mean.

head. When this maneuver is unsuccessful, the surgeon is left with either a grossly positive margin or an inadvertent venotomy. Venous injury often results in uncontrolled hemorrhage and the necessity for rapid removal of the tumor without proper attention to the SMA dissection; such cases often also result in an R2 resection. Therefore, studies that retrospectively examine the presence or absence of VR as a prognostic factor for survival should include only those patients who have undergone a complete gross resection (R0 or R1). Patients who have undergone an R2 resection have a predictable course: local and eventually distant recurrence will limit survival duration. It is inappropriate, therefore, to include such patients in an analysis of prognostic factors predictive of survival duration under the assumption that they have undergone complete tumor removal. The current edition of the *AJCC Cancer Staging Manual*⁹ emphasizes the importance of the R designation in all pathology reports. The surgeon should document the presence or absence of a complete gross resection at the time of PD, and if the RP margin is microscopically positive, the histopathology report should not be finalized until the pathologist has reviewed the operative note and can accurately apply an R1 or R2 designation.

In interpreting the RP margin results in this series, it must also be noted that multimodality therapy was delivered to almost all patients with adenocarcinoma (88% of the VR group and 91% of the standard PD group). The extent to which chemotherapy and/or chemoradiation may abrogate the negative biologic effect of an R1 resection is unknown at the present.

Multivariate analysis demonstrated that only positive regional lymph nodes and major perioperative complications were associated with a significant decrease in survival duration. All potential prognostic factors were included in this analysis except for the presence or absence of histologic evidence of invasion of the vein wall, which was available for only 62 patients. To confirm that excluding vein invasion did not change the results of the multivariable analysis, two additional analyses were performed: the multivariate analysis was repeated excluding the 62 patients for whom vein invasion data were available and again for these 62 patients. In all applicable multivariate analyses performed, the need for VR and the status of the RP margin did not have a significant effect on survival.

In summary, VR and reconstruction at the time of PD add significant complexity to an already lengthy operation associated with significant morbidity and occasional mortality. However, our data suggest that with proper patient selection and surgeon experience, VR and reconstruction can be performed safely. In

patients with adenocarcinoma of pancreatic origin, the need for VR does not significantly impact survival duration. The median survival of patients who underwent VR was 23 months, approximately 1 year longer than the survival of patients believed to have locally advanced, surgically unresectable pancreatic cancer and treated nonsurgically.

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Discussion

Dr. John Hoffman (Philadelphia, PA): Jennifer, you did a marvelous presentation of a very difficult set of data. I thank you for giving me the manuscript early. You have shown these data representing, to my knowledge, the largest series of major vascular resections for pancreatic cancer in the world. We have certainly come a long way since the 1970s, when any kind of tumor encroachment upon the vein indicated unresectability. I have a few questions.

For patient selection, you have not totally defined what would make a tumor unresectable with respect to venous involvement. What about the small segmental occlusion with collaterals? What about severe bilateral vein narrowing? How many cases of advanced venous involvement such as this were included in your series? The outstanding results probably mean that this is a group with less advanced cancer than most other series of vein resection. Second, what was the accuracy of CT prediction of venous involvement and the need for resection? How many with resection had normal CT scans? You had patients with histologic venous invasion and those without. Was the CT able to predict histologic involvement? You have shown in a subset of patients with histologic investigations that there is no survival

difference between those with actual microscopic invasion and those without. Are the numbers really large enough to give you enough statistical power to determine that?

Did you look at depth or extent of venous invasion as a risk factor? Were any of the veins involved at the cut margin of the vein? You have shown that those with vein resection have a statistically significant increase in positive retroperitoneal or SMA margins, at least in the univariate analysis. Could you tell us if the correlation was any stronger between those with histologic vein involvement and retroperitoneal (RP) margin involvement positivity? In other words, did those veins that were actually involved have a higher incidence of SMA margin involvement?

Are any of the other RP surgical margins examined at M. D. Anderson such as the portal, SMV, and posterior RP margins, and do they make a difference if you have looked at them? Most series of vein resections show them to comprise maybe 10% or 15% of the total resectional experience. You have major venous resections in 38% of your operations, plus other operations where you are actually resewing the vein where you have resected some of it, and you counted those as nonvenous resections. So it is a

higher likelihood to have a vein resected at M. D. Anderson than I believe at other hospitals.

Last question. This may be unfair to ask of you, but Dr. Evans has preached for years that a positive RP margin means stage IV disease in which the resection shouldn't have been done, yet you have shown no difference in survival between those with positive and negative margins. Has this finding changed his thinking and advice?

Dr. Tseng: Thank you, Dr. Hoffman. Regarding short segment vein occlusion, it is uncommon to see occlusion of the SMV or SMV–portal vein confluence in the absence of SMA involvement due to the close proximity of the SMV to the SMA. In addition, it is very rare to see short segment occlusion of the SMV with an adequate venous segment above (portal vein) and below (SMV) to allow successful venous interposition grafting. Therefore, because patients with isolated short segment SMV occlusion, and no extension to the SMA and suitable anatomy for interposition grafting, are so rare, the majority of patients with an occluded SMV or SMV–portal vein confluence have a locally advanced, surgically unresectable primary tumor.

The second question referred to CT prediction of vein invasion. In our previous publication by Bold et al. that was also presented to this society, CT predicted the need for venous resection in 84% of patients. Pathologic analysis revealed tumor invasion of the vein wall in 71% of resected specimens. In the current report, of the 62 patients who had histopathologic evaluation of the resected venous segment, tumor cell invasion of the vein wall was present in 38 patients (61%) and absent in 24. Median survival did not differ between patients who had histopathologic evidence of vein invasion and those who did not. This is not surprising considering that the tumor has access to the systemic circulation long before the patient is diagnosed. We did not look at the depth of the vein invasion.

Third, regarding the RP margin analysis, after adjusting for age, gender, reoperative status, estimated blood loss, performance of vascular resection, tumor size, N stage, and use of neoadjuvant therapy, only tumor size, with an odds ratio of 1.5, and the use of neoadjuvant therapy, with an odds ratio of 0.47, were associated with a positive RP margin (neoadjuvant therapy protective), but not the performance of vascular resection.

Regarding our pathologic evaluation of pancreaticoduodenectomy specimens, we follow the sixth edition of the *AJCC Cancer Staging Manual*, and prospectively evaluate the RP margin as outlined by the AJCC and the UICC. While I agree that it is reasonable to also focus on other margins such as the

soft tissue margin posterior to the pancreatic head and anterior to the IVC, the RP margin (you will agree) is the margin most likely to be positive when an R1 or R2 resection is performed.

With respect to your question that vein resections are more commonly performed at M. D. Anderson, as you know, we use an objective CT-based definition of “resectable.” We do not refuse patients who have significant venous involvement if their primary tumor is resectable based on the absence of metastatic disease and the absence of arterial involvement (as discussed in detail in the manuscript). I suspect these patients would not be offered an operation at many other institutions. The substantial number of reoperative pancreaticoduodenectomies performed at our institution supports this hypothesis.

You are correct that we defined venous resection as the need for a patch or a segmental resection. Nonsegmental resections repaired without a patch were not considered venous resections. This thereby removed subjective analysis from the definition of venous resection.

Last, you asked about the significance of a positive RP margin. Our data on R1 resections, as discussed in detail by Dr. Raut yesterday at the meeting of the Pancreas Club, are unique, due to the prospective evaluation of the RP margin. We are not aware of any other large series, which has such rigorous margin analysis. Our data do suggest that multimodality therapy and careful attention to surgical technique may abrogate the negative biologic effect of an R1 resection. However (and this is an emphatic however), this does not mean that R2 resections with gross tumor left at the RP margin would achieve the same result.

Thank you very much.

Dr. Sukamal Saba (Flint, MI): If I am not mistaken 70% of your patients in both groups had neoadjuvant treatment?

Dr. Tseng: Yes.

Dr. Saba: So at this point, what is your criteria for not giving somebody neoadjuvant, and from your historical control, is it because your data are better because neoadjuvant treatment has been given to 70% of the patients or because of your surgical techniques?

Dr. Tseng: Our goal at M. D. Anderson is to treat all patients with pancreatic cancer on a clinical trial. We always have an open neoadjuvant and adjuvant trial; if a patient with resectable pancreatic cancer has tissue confirmation of adenocarcinoma, they are encouraged to enroll in the current neoadjuvant protocol.

Dr. Saba: But 30% of patients you did not.

Dr. Tseng: If we do not have a positive diagnosis of pancreatic adenocarcinoma, then we proceed with surgery first.