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REVIEW ARTICLE

Extended Pancreaticoduodenectomy with Vascular Resection for Pancreatic Cancer: A Systematic Review

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Abstract
Objectives This systematic review objectively evaluates the safety and outcomes of extended pancreaticoduodenectomy with vascular resection for pancreatic cancer involving critical adjacent vessels namely the superior mesenteric-portal veins, hepatic artery, superior mesenteric artery, and celiac axis.
Methods Electronic searches were performed on two databases from January 1995 to August 2009. The end points were: firstly, to evaluate the safety through reporting the mortality rate and associated complications and, secondly, the outcome by reporting the survival after surgery. This was synthesized through a narrative review with full tabulation of results of all included studies.
Results Twenty-eight retrospective studies comprising of 1,458 patients were reviewed. Vein thrombosis and arterial involvement were reported as contraindications to surgery in 62% and 71% of studies, respectively. The median mortality rate was 4% (range, 0% to 17%). The median R0 and R1 rates were 75% (range, 14% to 100%) and 25% (range, 0% to 86%), respectively. In high volume centers, the median survival was 15 months (range, 9 to 23 months). Nine of 10 (90%) studies comparing the survival after extended pancreaticoduodenectomy with vascular resection versus standard pancreaticoduodenectomy reported statistically similar ($p>0.05$) survival outcomes. Undertaking vascular resection was not associated with a poorer survival.
Conclusions The morbidity, mortality, and survival outcome after undertaking extended pancreaticoduodenectomy with vascular resection for pancreatic cancer with venous involvement and/or limited arterial involvement is acceptable in the setting of an expert referral center and should not be a contraindication to a curative surgery.

Keywords Morbidity · Mortality · Postoperative complication · Pancreatic cancer · Pancreaticoduodenectomy · Whipple's operation · Roux-en-Y anastomosis · Vascular procedures

Introduction

The current curative treatment paradigm for pancreatic cancer entails a strategy of complete surgical resection combined with adjuvant chemotherapy or chemoradiotherapy. Randomized clinical trials have reported a median survival of approximately 22 months compared to 18 months in patients undergoing adjuvant therapy with gemcitabine chemotherapy after surgery compared to observation alone.[1,2] When chemotherapy is combined with radiation therapy as a radio-sensitizer, the survival benefit appeared to be more pronounced with the chemo-radiation group having a median survival of about 25 months compared to 19 months in patients undergoing observation alone.[3] Although these strategies have not shown a significant difference in overall survival, they may delay the time to recurrence and may, therefore, be useful in treating patients with a microscopically positive margin (R1). In patients with unresectable tumors otherwise termed locally advanced pancreatic cancer, gemcitabine in combination with oxaliplatin evaluated in the GERCOR and GISCAD phase-III trial yielded a median

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survival of 9 months.[4] When treated with chemoradiation, the median survival may increase to about 13 months as reported in the 2001-01 FFCD/SFRO study.[5] The survival disparity in nonresectable tumors as compared to resectable tumors in these trials emphasizes the positive impact of a complete surgical resection (R0) and a rationale towards undertaking aggressive curative surgery where possible.

A common contraindication for resection in the current clinical practice for patients with locally advanced tumors (T3/T4 tumors) is the presence of vascular involvement of the critical adjacent vessels. However, there is a recognized arbitrary state of borderline resectable pancreatic cancer where tumors involve the superior mesenteric-portal veins but may remain relatively resectable with additional vascular surgical procedure. Hence, the definition of resectability may vary between different treatment centers with varying level of expertise and willingness to undertake extended pancreaticoduodenectomy. The concept of a regional pancreatectomy as first described by Fortner[6] was an attempt to improve results of surgical resection of pancreatic cancer by performing a subtotal or total pancreatic resection which usually involves resection and reconstruction of the pancreatic segment of the portal vein, en bloc regional lymphadenectomy, and in highly selected cases resection and reconstruction of a major artery. Such extended pancreatectomy may facilitate resection in patients with tumors that are classified as T3/T4 and total clearance of the peripancreatic, hepatoduodenal, mesenteric, and celiac lymph nodes. The clinical benefit of extended pancreatic resections must, however, be balanced with the risk of the procedure. With regard to extended lymphadenectomy, its role as a routine procedure is no longer proven following evidence from randomized trials that showed no survival advantage and increased morbidity.[7,8] It has been shown that the prognosis in patients with lymph node involvement is related more so to the number of nodes involved than just the nodal status itself.[9] Therefore, lymphadenectomy may still have a role in the management of patients with nodal disease. Observations from a multicenter study of patients following R0/R1 pancreatectomy showed that patients with node positive disease are likely to benefit from adjuvant chemoradiation treatment.[10] With regard to vascular resection as part of an extended pancreatectomy procedure, it continues to remain controversial due to the procedural complexity, the safety and consequential morbidity imposed on the patient in a disease that portends a poor survival, and the lack of randomized evidence to demonstrate its efficacy.

A previous systematic review by Siriwardana and colleague failed to recognize the heterogeneity in survival outcomes that reflected the expertise of the treatment center, hence, leading to an overstated conclusion that did not reflect the current consensus of expert pancreatic surgeons.[11] More recently, a collective review of recent publications of pancreatectomy combined with superior mesenteric-portal vein resection concluded that the procedure was safe, feasible, and provides important survival benefits.[12] The objective of the current review serves to provide a systematic review with full tabulation of published studies with stratification of vessel (vein or artery) involvement and level of expertise (high- or low-volume centers) and to compare the extended pancreaticoduodenectomy with vascular procedure to a standard pancreaticoduodenectomy alone to thoroughly supplement and establish the current evidence in this field.

Methods

Literature Search Strategy

Original published studies on pancreaticoduodenectomy with vascular resection of both veins and arteries for pancreatic cancer were identified by searching the MEDLINE database (1995 to August 2009) and PubMed (January 1995 to August 2009) using the keywords: "pancreatectomy, pancreaticoduodenectomy, pancreatic cancer, vascular resection, portal vein, superior mesenteric vein, hepatic artery, celiac axis, and superior mesenteric artery." The search was limited to human articles published in the English language. The reference lists of all retrieved articles were manually reviewed to further identify potentially relevant studies. All relevant articles identified were assessed with application of a predetermined selection criterion.

Selection Criteria

Studies which specifically addressed pancreaticoduodenectomy with vascular resection and reported the complications, mortality, and survival outcomes were evaluated. Studies which reported vascular resection as a subset analysis in pancreatectomy without evaluating the mentioned endpoints of review or not comprehensively reported were excluded. To ensure that the sample size would not bias the reporting of the morbidity and mortality outcomes, only studies reporting more than 10 patients were included. For institutions reporting updated experiences, only the most recent or complete paper was selected for review. Studies were selected for evaluation if they were level I evidence: randomized controlled trials; level II evidence: nonrandomized controlled clinical trials or well-designed cohort studies; level III evidence: observational studies, as described by the US Preventive Services Task Force.

Data Extraction and Critical Appraisal

Two reviewers (T.C.C. and A.S.) independently critically appraised each article using a standard protocol. Data extracted include the methodology, quality criteria, perioperative variables, morbidity and mortality outcomes, and survival data. All data were extracted and tabulated from the relevant articles' texts, tables, and figures. Discrepancies were resolved by discussion and consensus. Following tabulation of the results, the morbidity, mortality, and survival outcomes were synthesized. Stratification was made based on whether the institution was considered as a high- or low-volume center by searching the literature for publications on pancreatectomy for pancreatic cancer. High-volume centers were assigned if prospective case series from the institution reported at least 20 pancreatic resection cases per year irrespective of the number of pancreatic surgeons in the institution. Meta-analysis was inappropriate because of the heterogeneous nature of the included studies and the lack of a controlled comparative arm.

Results

Quantity and Quality of Evidence

Literature search using the above-described search strategy through both MEDLINE and PubMed databases identified 182 articles. Through reviewing of the abstracts and references lists, 58 relevant articles were identified. The specific selection criteria were applied, and serial publications of papers reporting accumulating number of participants or increased length of follow-up were excluded with only the most recent and definitive update from each institution or the paper that fulfilled the specified endpoints of this review being included for appraisal and data extraction. In total, 28 articles were critically evaluated and tabulated (Table 1). The level of evidence from these studies was low (all level III). They comprised of retrospective observational studies. The 28 articles arose from institutions in the USA (n=7), Europe (n=11), and Asia (n=10). In total, 1,458 patients were evaluated.

Treatment Criteria

In selecting patients for treatment, 21 studies[13–33] reported the mode of investigations performed. This include computed tomography scans in all 21 institutions (100%), magnetic resonance imaging or magnetic resonance cholangiopancreatography in 12 institutions (57%), and angiography in nine institutions (43%). After treatment investigations, all studies (n=28) reported patients with pancreatic head tumors (100%), 12 studies (43%) included patients with pancreatic body tumors, and seven studies (25%) included patients with pancreatic tail tumors.

The priori basis of selecting patients for extended pancreaticoduodenectomy with vascular resection and reconstruction was reported in 21 studies (75%).[13–22,24,26–29,31,32,34–37] Among which, vein thrombosis was a reported contraindication to surgery in 13 of 21 studies (62%), and arterial involvement was a reported contraindication to surgery in 15 of 21 studies (71%) (Table 1).

Procedure of Extended Pancreaticoduodenectomy with Vascular Resection and Reconstruction

All 28 studies undertook resection of superior mesenteric-portal vein. Five of 28 studies (18%)[21,22,30,35,37] undertook resection of the celiac axis, six studies (21%)[21,22,30,31,35,37] undertook resection of the hepatic artery, and five studies (18%)[21,22,30,31,35] undertook resection of the superior mesenteric artery. One thousand, one hundred thirty-six patients (78%) underwent pancreaticoduodenectomy. In undertaking vascular resection, 23 of 28 studies (82%)[13–15,17–27,29–32,34–36,38,39] examined the resected vessel histologically. The histopathological analysis of the resected vessel indentified true neoplastic invasion in between 21% and 100% of cases with a median of 63%. The most common techniques of reconstruction after vascular resection include end–end anastomosis and graft reconstruction (using either an autologous vein graft or synthetic graft). The surgical procedure resulted in estimated blood loss that was reported in 18 of 28 studies (64%)[15–20,22–24,26–29,32,33,37,40] ranging between 700 and 3,083 mL with a median of 1,494 mL (Table 2).

Postoperative Complications and Mortality Outcome

The mortality rate was reported in 27 of 28 studies (96%)[14–40] and ranged from 0% to 17% with a median of 4%. The median rate of bleeding was 4% (range, 0% to 16%), rate of collection or abscess was 5% (range, 0% to 29%), rates of vascular thrombosis was 0% (range, 0% to 4%), rate of pancreatic fistula was 6% (range, 0% to 18%), rate of biliary leak was 0% (range, 0% to 16%), rate of pancreatic duct leak was 1% (range, 0% to 17%), and the reoperation rate was 9% (range, 0% to 25%). The median average length of hospital stay was 17 days (range, 11 to 69 days; Table 3).

Treatment Efficacy

Twenty-one of 28 studies (75%)[13–19,22–25,27–29,31–34,36–40] reported margin status after extended pancreaticoduodenectomy with vascular resection. Microscopically clear margin

Table 1 Characteristics of the Studies from the Various Institutions

First author	Institution city/ country	Year published	Patients (*n*)	Preoperative imaging			Tumor location	Contraindications	
				Computed tomography	Magnetic resonance imaging	Angiography		Vein thrombosis (Y/N)	Arterial involvement (Y/N)
Kaneoka [19]	Ogaki, Japan	2009	42	Y	Y	Y	Head	N	Y
Martin [22]	Louisville & Atlanta, USA	2009	36	Y	Y	N	Head	N	N
Muller [23]	Heidelberg, Germany	2009	110	Y	Y	N	Head	NR	NR
Yekebas [31]	Hamburg, Germany	2009	136	Y	N	N	Head, Body, Tail	Y	Y
Illuminati [18]	Rome, Italy	2008	29	Y	N	N	Head, Body, Tail	Y	Y
Stitzenberg [37]	Philadelphia, USA	2008	12	NR	NR	NR	Head, Body, Tail	N	N
Wang [30]	Wuhan, China	2008	80	Y	Y	Y	Head	NR	NR
Al-Hadad [13]	Jacksonville, USA	2007	22	Y	Y	Y	Head, Body, Tail	N	Y
Riediger [25]	Freiburg, Germany	2006	53	Y	Y	Y	Head	NR	NR
Nakao [35]	Nagoya, Japan	2006	200	NR	NR	NR	Head, Body, Tail	N	N
Carrere [16]	Cedex, France	2006	45	Y	Y	Y	Head	Y	Y
Shimada [27]	Tokyo, Japan	2006	86	Y	Y	Y	Head, Body	N	Y
Jain [33]	Athens, Greece	2005	48	Y	Y	Y	Head	NR	NR
Zhou [32]	Shanghai, China	2005	32	Y	Y	N	Head, Body	Y	Y
Koniaris [20]	Various, USA	2005	11	Y	N	N	Head	N	NR
Li [21]	Xiamen, China	2004	79	Y	Y	N	Head	N	N
Poon [24]	Hong Kong, China	2004	12	Y	N	N	Head	Y	Y
Tseng [28]	Houston, USA	2004	141	Y	N	N	Head	Y	Y
Nakagohri [39]	Kashiwa, Japan	2003	33	NR	NR	NR	Head, Body, Tail	NR	NR
Capussotti [15]	Torino, Italy	2003	24	Y	N	N	Head	Y	Y
Howard [17]	Indianapolis, USA	2003	13	Y	N	N	Head	Y	Y
Kawada [34]	Sapporo, Japan	2002	28	NR	NR	NR	Head	Y	NR
Bachellier [14]	Strasbourg Cedex, France	2001	31	Y	Y	Y	Head	Y	Y
Shibata [26]	Sendai, Japan	2001	28	Y	N	Y	Head, Body	Y	Y
Van Geenen [29]	Amsterdam, Netherlands	2001	34	Y	N	N	Head	Y	Y
Launois [38]	Saint Gregoire, France	1999	14	NR	NR	NR	Head	NR	NR
Harrison [40]	New York, USA	1996	58	NR	NR	NR	Head, Body, Tail	NR	NR
Roder [36]	Hamburg, Germany	1996	21	NR	NR	NR	Head, Body	Y	Y

(R0) rates ranged from 14% to 100% with a median of 75%. The rate of margins that were grossly clear but microscopically involved (R1) ranged from 0% to 86% with a median of 25%. The median survival in studies reporting vein resection was 13 months (range, 5 to 23 months), with a median 1-year survival rate of 56% (range, 23% to 88%), median 3-year survival rate of 18% (range, 0% to 49%), and median 5-year survival rate of 12% (range, 0% to 25%). The median survival in studies reporting both vein and artery resection was 18 months (range, 3 to 20 months), with a median 1-year survival rate of 65% (range, 26% to 83%), median 3-year survival rate of 13% (range, 0% to 35%), and median 5-year survival rate of 0% (range, 0% to 20%; Table 4).

Outcomes in High-Volume Centers

Sixteen high-volume centers each reporting more than 20 pancreatectomy procedures per annum were identified, and their outcomes were reported separately in Table 5.[14,16,18,22,23,25,27–33,36,37,40] In these centers, 10 of 16 studies (63%)[14,16,18,22,25,27,28,31,36,40] reported a com-

Table 2 Vascular Surgical Procedures

First author	Vascular involvement					Patients with true vessel Invasion (%)	Type of pancreatic resection			Reconstruction techniques	Estimated blood loss (ml)
	Portal vein	Superior mesenteric vein	Celiac axis	Hepatic artery	Superior mesenteric artery		PD (*n*, %)	TP (*n*, %)	DP (*n*, %)		
Kaneoka [19]	Y	Y	N	N	N	60	42 (100)	0	0	End–end Graft reconstruction	1,280
Martin [22]	Y	Y	Y	Y	Y	67	36 (100)	0	0	End–end Patch Interposition Venorrhaphy	700
Muller [23]	Y	Y	N	N	N	78	110 (100)	0	0	Venorrhaphy Patch End–end Interposition	1,182
Yekebas [31]	Y	Y	N	Y	Y	57	92 (68)	34 (25)	10 (7)	Primary closure Patch End–end Interposition	NR
Illuminati [18]	Y	Y	N	N	N	76	17 (59)	2 (7)	7 (24)	Primary closure Patch End–end Interposition	700
Stitzenberg [37]	Y	Y	Y	Y	N	NR	6 (50)	4 (33)	2 (17)	End–end Graft reconstruction	1,250
Wang [30]	Y	Y	Y	Y	Y	71	80 (100)	0	0	NR	NR
Al-Hadad [13]	Y	Y	N	N	N	64	19 (86)	2 (9)	1 (5)	End–end Graft reconstruction	NR
Riediger [25]	Y	Y	N	N	N	60	49 (92)	4 (8)	0	Primary closure Patch End–end	NR
Nakao [35]	Y	Y	Y	Y	Y	57	NR	NR	NR	End–end Graft reconstruction	NR
Carrere [16]	Y	Y	N	N	N	NR	45 (100)	0	0	End–end Graft reconstruction	812
Shimada [27]	Y	Y	N	N	N	67	81 (94)	5 (6)	0	NR	1,686
Jain [33]	Y	Y	N	N	N	NR	48 (100)	0	0	Venorrhaphy End–end	700
Zhou [32]	Y	Y	N	N	N	63	32 (100)	0	0	End–end Graft reconstruction	1,420
Koniaris [20]	N	Y	N	N	N	100	11 (100)	0	0	End–end Graft reconstruction Interposition	2,090
Li [21]	Y	Y	Y	Y	Y	42	79 (100)	0	0	End–end Graft reconstruction Interposition	NR

Table 2 (continued)

First author	Vascular involvement					Patients with true vessel Invasion (%)	Type of pancreatic resection			Reconstruction techniques	Estimated blood loss (ml)
	Portal vein	Superior mesenteric vein	Celiac axis	Hepatic artery	Superior mesenteric artery		PD (*n*, %)	TP (*n*, %)	DP (*n*, %)		
Poon [24]	Y	N	N	N	N	50	12 (100)	0	0	End–end	800
Tseng [28]	Y	Y	N	N	N	NR	141 (100)	0	0	End–end Interposition	1,675
Nakagohri [39]	Y	Y	N	N	N	52	27 (82)	6 (18)		NR	NR
Capussotti [15]	Y	Y	N	N	N	82	24 (100)	0	0	End–end	2,100
Howard [17]	Y	Y	N	N	N	100	13 (100)	0	0	Venorrhaphy End–end Interposition	1,567
Kawada [34]	Y	Y	N	N	N	75	23 (82)	5 (18)	0	Venorrhaphy End–end Interposition	3,083
Bachellier [14]	Y	Y	N	N	N	67	10 (48)	11 (52)	0	End–end Graft reconstruction Venorrhaphy	NR
Shibata [26]	Y	Y	N	N	N	43	23 (82)	3 (11)	2 (7)	End–end Patch	1,583
Van Geenen [29]	Y	Y	N	N	N	44	34 (100)	0	0	End–end Graft reconstruction Interposition	1,800
Launois [38]	Y	Y	N	N	N	21	14 (100)	0	0	End–end Graft reconstruction Venorrhaphy	NR
Harrison [40]	Y	Y	N	N	N	NR	42 (72)	8 (14)	8 (14)	End–end Venorrhaphy	1,900
Roder [36]	Y	Y	N	N	N	61	26 (84)	5 (16)	0	End–end Graft reconstruction	NR

PD pancreaticoduodenectomy, *TP* total pancreatectomy, *DP* distal pancreatectomy

parison of survival between patients who underwent extended pancreaticoduodenectomy with vascular resection versus standard pancreaticoduodenectomy. Nine of 10 (90%) studies reported statistically similar survival outcomes.[14,16,18,22,25,28,31,36,40] The median survival of patients undergoing extended pancreaticoduodenectomy with vascular resection was 15 months (range, 9 to 23 months).

In the analysis of prognostic factors after extended pancreaticoduodenectomy with vascular resection, 11 studies[14,16,18,22,27–29,31,32,36,37] reported univariate analysis of clinicopathological factors associated with survival. There were no consistent adverse factors associated with a poor survival. Venous tumor infiltration was commonly identified as having no effect on survival. Seven studies[14,16,23,25,28,36,40] reporting a combined univariate analysis of patients undergoing both extended pancreaticoduodenectomy with vascular resection and standard pancreaticoduodenectomy reported that undergoing vascular resection was not associated with a poorer survival (Table 5).

Discussion

Surgery remains the only curative option for pancreatic cancer. It is commonly performed in selected patients with localized disease of the pancreas (T1 and T2 tumors). In the past, this procedure has been morbid with mortality rates of up to 25% in early series. However, improved techniques and training in the last decade have led to improved operative

Table 3 Complications of Extended Pancreaticoduodenectomy with Vascular Resection and Reconstruction

First author	Mortality (*n*, %)	Bleeding (*n*, %)	Collection/ abscess (*n*, %)	Thrombosis (*n*, %)	Pancreatic fistula (*n*, %)	Biliary leak (*n*, %)	Pancreatic duct leak (*n*, %)	Reoperation (*n*, %)	Average length of hospital stay (day)
Kaneoka [19]	2 (5)	NR	NR	NR	2 (5)	1 (2)	NR	0	NR
Martin [22]	0	0	3 (8)	0	0	0	1 (3)	0	11
Muller [23]	4 (4)	3 (3)	3 (3)	NR	4 (4)	NR	NR	10 (9)	18
Yekebas [31]	5 (4)	6 (4)	NR	3 (2)	9 (7)	9 (7)	NR	NR	NR
Illuminati [18]	1 (3)	1 (3)	0	0	1 (3)	0	2 (7)	0	16
Stitzenberg [37]	2 (17)	1 (8)	1 (8)	0	0	0	2 (17)	3 (25)	21
Wang [30]	1 (1)	3 (4)	0	3 (4)	14 (18)	2 (3)	NR	4 (5)	16
Al-Hadad [13]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Riediger [25]	2 (4)	4 (8)	4 (8)	NR	4 (8)	NR	NR	4 (8)	16
Nakao [35]	10 (5)	NR	NR	NR	NR	NR	NR	NR	NR
Carrere [16]	2 (4)	7 (16)	2 (4)	2 (4)	3 (7)	7 (16)	NR	10 (22)	23
Shimada [27]	1 (1)	5 (6)	2 (2)	0	14 (16)	1 (1)	0	2 (2)	44
Jain [33]	0	3 (6)	0	1 (2)	0	0	0	4 (8)	12
Zhou [32]	0	0	2 (6)	0	0	0	0	2 (6)	NR
Koniaris [20]	1 (9)	1 (9)	1 (9)	0	1 (9)	0	0	1 (9)	16
Li [21]	4 (5)	3 (4)	NR	0	0	0	0	NR	NR
Poon [24]	0	1 (8)	1 (8)	0	0	0	1 (8)	0	15
Tseng [28]	3 (2)	9 (6)	8 (6)	NR	NR	NR	2 (1)	4 (3)	13
Nakagohri [39]	2 (6)	NR	NR	NR	NR	NR	NR	NR	NR
Capussotti [15]	0	0	0	0	1 (5)	0	0	3 (13)	26
Howard [17]	1 (8)	0	2 (15)	0	2 (15)	0	0	2 (15)	14
Kawada [34]	1 (4)	2 (7)	8 (29)	NR	NR	NR	NR	NR	69
Bachellier [14]	1 (3)	1 (3)	1 (3)	0	1 (3)	0	0	3 (10)	22
Shibata [26]	1 (4)	NR	1 (4)	NR	NR	NR	1 (4)	NR	NR
Van Geenen [29]	0	3 (9)	3 (9)	NR	NR	NR	3 (9)	3 (9)	15
Launois [38]	0	NR	NR	NR	NR	NR	NR	NR	NR
Harrison [40]	3 (5)	NR	NR	NR	NR	NR	NR	10 (17)	22
Roder [36]	0	1 (3)	0	0	NR	NR	5 (16)	3 (10)	28

results and long-term survival outcomes for patients with pancreatic cancer following pancreaticoduodenectomy, hence leading to a renewed interest in the surgical oncologic management of this disease.[41] Through cumulated experience in the operative and perioperative management of patients undergoing pancreatic surgery, the criteria for resectability has gradually expanded. Extended pancreaticoduodenectomy with vascular resection has been offered in various institutions to treat patients with tumors that has involved or invaded the adjacent blood vessels. This would represent a large number of patients as the siting of the pancreas and its relationship with the adjacent critical blood vessels make these structures a common site of tumor involvement through direct invasion. Performing vascular resection during pancreaticoduodenectomy would often be the goal of a surgeon who seeks to attempt a total resection. With now established safety, it appears that such a procedure may be considered given the grim outlook of patients with unresectable tumors even after treatment. It is unlikely that the conduct of a randomized trial to determine if extended pancreaticoduodenectomy with vascular resection versus a comparator group such as a standard pancreaticoduodenectomy with adjuvant chemoradiation to treat the remnant tumor burden or a treatment of chemoradiation alone would be feasible given the known prognosis of incomplete resections. Therefore, a systematic review that critically examines the important aspects of this procedure, namely the safety, survival outcomes in relation to the resection of involved vessels in the context of expert centers, would be invaluable in achieving consensus and acceptance of this procedure.

Results from this review show that vascular resection is commonly performed in patients with venous only involvement. The median mortality rate of 4% of extended pancreaticoduodenectomy with vascular resection, the similar rates of postoperative complications that occur, and a median average length of hospital stay of 17 days suggest that the

Table 4 Survival Outcomes After Extended Pancreaticoduodenectomy with Vascular Resection and Reconstruction

First author	R0 resection (%)	R1 resection (%)	Median survival (months)	1-Year survival rate (%)	3-Year survival rate (%)	5-Year survival rate (%)
Kaneoka [19]	76	24	VR=12	NR	NR	17
Martin [22]	78	22	VAR=18	58	8	0
Muller [23]	49	49	VR=15	55	14	NR
Yekebas [31]	88	12	VAR≈20	72	35	20
Illuminati [18]	100	0	VR=19	76	17	17
Stitzenberg [37]	50	50	VAR=17	83	17	0
Wang [30]	NR	NR	VR=13	VR=56	VR=19	VR=13
			AR=7	AR=16	AR=0	AR=0
Al-Hadad [13]	NR	NR	VR=10	48	20	NR
Riediger [25]	69	31	VR=22	62	21	12
Nakao [35]	NR	NR	VR=9	VR=40	VR=9	VR=4
			VAR=3	VAR=26	VAR=0	VAR=0
Carrere [16]	82	18	VR=15	63	22	18
Shimada [27]	62	38	VR=14	65	20	12
Jain [33]	100	0	VR=40[a]	NR	NR	18
Zhou [32]	84	16	VR=17	59	16	NR
Koniaris [20]	NR	NR	VR=16	NR	NR	NR
Li [21]	NR	NR	NR	NR	49	16
Poon [24]	92	8	VR=20	88	45	0
Tseng [28]	78	22	VR=23	86	33	25
Nakagohri [39]	76	24	VR=15	58	9	9
Capussotti [15]	NR	NR	NR	NR	NR	NR
Howard [17]	75	25	VR=13	83	NR	NR
Kawada [34]	36	64	VR=11	41	9	9
Bachellier [14]	62	38	VR=12	54	NR	NR
Shibata [26]	NR	NR	VR=6	31	13	9
Van Geenen [29]	47	53	VR=14	55	NR	NR
Launois [38]	14	86	VR=5	23	15	0
Harrison [40]	73	27	VR=13	55	22	10
Roder [36]	32	68	VR=9	28	0	0

VR vein resection, *AR* artery resection, *VAR* vein and artery resection

[a] Mean

perioperative outcome is similar to that of a standard pancreaticoduodenectomy. In 16 centers which were classified as high-volume centers where at least 20 pancreatectomy procedures were performed per annum, the median survival of patients undergoing extended pancreaticoduodenectomy with vascular resection was 15 months. These survival results when compared with their independent cohorts who underwent standard pancreaticoduodenectomy procedures were not different. Studies that analyzed prognostic factors showed that undergoing vascular resection was not associated with a poorer survival. A 75% chance of a clear margin (R0) rate after this radical procedure further supports the rationale of undertaking extended pancreaticoduodenectomy with vascular resection when total resection of a locally advanced tumor is achievable.

Pancreatic cancer involvement of key vessels on preoperative imaging may not necessarily imply vascular invasion of the tumor into macroscopic vessels. It is not easy to determine definitively based on imaging the texture of the tumor and its associated adherence. Intraoperatively, the involvement or encasement that is present may occur as part of a peritumoral inflammatory reaction of the peripancreatic stromal tissue that leads to fibrotic change that may mimic tumor.[42] However, even in instances when there is true tumor involvement after histopathological examination of the resected vessel, venous tumor infiltration was not identified to affect survival. This may lead to a proposal for a change in surgical approach in patients with venous involvement on preoperative imaging scans and when examined at laparotomy. An en bloc vascular resection after adequate mobilization of proximal

Table 5 Critical Analysis of Outcomes from High Volume Centres Performing Extended Pancreatectomy with Vascular Resection

First author	Comparison of median survival (months)		$p<0.05$ (Y/N)	Analysis of prognostic factors (PVR/PVR & P)	Prognostic factors for survival after extended pancreatectomy with vascular resection
	Vascular resection	No vascular resection			
Martin [22]	VAR=18	19	N	PVR	Adverse factors: lymph node positive disease, body and tail location of tumors, no adjuvant therapy
					No effect: venous tumor infiltration
Muller [23]	VR=15	NR	NR	PVR & P	Adverse factors: operating time >420 minutes, age >70, occurrence of postoperative complications
					No effect: venous tumor infiltration, tumor size, blood loss, lymph node status, lymph node ratio, neoadjuvant treatment, technique of reconstruction, preoperative CA 19-9, CEA, ASA
Yekebas [31]	VAR≈20	16	N	PVR	Adverse factors: lymph node positive disease, poorly differentiated tumors
					No effect: venous tumor infiltration, sex, age, tumor size, margin status
Illuminati [18]	VR=19	21	N	PVR	Adverse factors: nil
					No effect: tumor differentiation, lymph node status, retroperitoneal margin status, tumor location
Stitzenberg [37]	VAR=17	NR	NR	PVR	Adverse factors: neoadjuvant chemoradiation
					No effect: age, sex, lymph node status, preoperative CA 19-9, margin status, undergoing arterial resection
Wang [30]	VR=13 AR=7	NR	NR	NR	NR
Riediger [25]	VR=22	15	N	PVR & P	Adverse factors: R1 margin status, poorly differentiated tumors
					No effect: undertaking venous resection, venous tumor infiltration
Carrere [16]	VR=15	20	N	PVR & P	Adverse factors: R1 margin status, reoperation, tumor diameter >30 mm, lymph node positive disease, perioperative blood transfusion
					No effect: age, sex, ASA, preoperative CA 19-9, undertaking venous resection, age, sex, perineural invasion, neoplastic intravascular embolism, tumor grade, adjuvant therapy
				PVR	No effect: venous tumor infiltration, type of venous resection
Shimada [27]	VR=14	35	Y	PVR & P	Adverse factors: undertaking venous resection, CA 19-9>240, tumor size >35 mm, serosal invasion, duodenal invasion, portal vein invasion, extrapancreatic nerve plexus invasion, node positive disease, R1 margin status, intraoperative radiation therapy
					No effect: age, sex, retropancreatic tissue invasion, bile duct invasion, tumor grade, peritoneal cytology, adjuvant chemotherapy
				PVR	Adverse factors: CA 19-9>240, tumor size >35 mm
					No effect: venous tumor infiltration
Jain [33]	VR=40[a]	NR	NR	NR	NR
Zhou [32]	VR=17	NR	NR	PVR	Adverse factors: R1 margin status
					No effect: venous tumor infiltration
Tseng [28]	VR=23	27	N	PVR & P	Adverse factors: lymph node positive disease
					No effect: undertaking venous resection
				PVR	No effect: venous tumor infiltration

Bachellier [14]	VR=12	15	N	PVR & P	No effect: undertaking venous resection
				PVR	No effect: venous tumor infiltration
					Adverse factors: venous tumor infiltration
Van Geenen [29]	VR=14	NR	NR	PVR	No effect: margin status, type of venous resection
Harrison [40]	VR=13	17	N	PVR & P	No effect: undertaking venous resection
Roder [36]	VR=9	12	N	PVR & PPVR	No effect: undertaking venous resection

PVR & P pancreatectomy with vascular resection and pancreatectomy, *VAR* vein and artery resection, *VR* vein resection, *AR* artery resection

[a] Mean

and distal ends to facilitate an end to end or graft reconstruction may be performed instead of an attempted dissection along the superior mesenteric-portal vein that risk injuring the thin and friable venous intima.

Clearly, the key of a successful surgical treatment arises from appropriate patient selection that preoperatively determines the extent of venous or arterial involvement, nodal disease, and absence of distant metastatic sites together with a patient's overall performance status and fitness for surgery. The majority of studies (71%) performing vascular resections reported arterial involvement as a contraindication to surgery. However, in centers such as that reported by Martin et al.,[22] Yekebas et al.,[31] and Stitzenberg et al.,[37] with expertise in en bloc resection of the hepatic artery, superior mesenteric artery, or even the celiac trunk itself, this may be performed with equivalent survival outcomes with median survival of 18, 20, and 17 months reported, respectively. In contrast, less experienced centers who have undertaken this procedure have shown poorer outcomes following arterial resection than after venous only resection.[35]

Improved survival in pancreatic cancer has evolved from standard pancreatectomy to extended pancreatectomy in selected patients in the setting of an expert referral center through increasing the resectability rates in borderline resectable patients after careful selection and achieving high R0 resection rates. Vascular resection and reconstruction of the adjacent vein and in some highly selected instances, the arteries appear to be feasible, without compromising R0 resection rates, and allow for patients with "unresectable tumors" to undergo a curative procedure for a chance at having long term survival. Presently, further surgical advancement to resect pancreatic cancer in patients with nonlocalized disease is unlikely to be beneficial. To improve the survival from now, the search for an effective systemic chemotherapeutic agent and testing of these agents in trials of neoadjuvant and/or adjuvant therapy with radiotherapy as well as with immunotherapy is necessary to complement the oncological benefit achieved after a complete surgical resection.

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