ORIGINAL ARTICLE

Patency rates of hepatic arterial resection and revascularization in locally advanced pancreatic cancer

Roberto Alva-Ruiz[1], Amro M. Abdelrahman[1], Patrick P. Starlinger[1], Jennifer A. Yonkus[1], David N. Moravec[1], Joel J. Busch[1], Chad J. Fleming[2], James C. Andrews[2], Bernardo C. Mendes[3], Jill J. Colglazier[3], Rory L. Smoot[1], Sean P. Cleary[1], David M. Nagorney[1], Michael L. Kendrick[1] & Mark J. Truty[1]

[1]Division of Hepatobiliary & Pancreas Surgery, Department of Surgery, [2]Division of Vascular & Interventional Radiology, Department of Radiology, and [3]Division of Vascular & Endovascular Surgery, Department of Surgery, Mayo Clinic Rochester MN, USA

Abstract

Background: Arterial resection (AR) for pancreatic adenocarcinoma is increasingly considered at specialized centers. We aimed to examine the incidence, risk factors, and outcomes of hepatic artery (HA) occlusion after revascularization.

Methods: We included patients undergoing HA resection with interposition graft (IG) or primary end-to-end anastomoses (EE). Complete arterial occlusion (CAO) was defined as "early" (EO) or "late" (LO) before/after 90 days respectively. Kaplan–Meier and change-point analysis for CAO was performed.

Results: HA resection was performed in 108 patients, IG in 61% (66/108) and EE in 39% (42/108). An equal proportion (50%) underwent HA resection alone or in combination with celiac and/or superior mesenteric artery. CAO was identified in 18% of patients (19/108) with arterial IG least likely to occlude (p=0.019). Hepatic complications occurred in 42% (45/108) and correlated with CAO, symptomatic patients, venous resection, and postoperative portal venous patency. CAO-related operative mortality was 4.6% and significantly higher in EO vs LO (p = 0.046). Median CAO occlusion was 126 days. With change-point analysis, CAO was minimal beyond postoperative day 158.

Conclusion: CAO can occur in up to 18% of patients and the first 5-month post-operative period is critical for surveillance. LO is associated with better outcomes compared to EO unless there is inadequate portal venous inflow.

Received 12 January 2022; accepted 13 June 2022

Correspondence

Mark J. Truty, Division of Hepatobiliary and Pancreas Surgery, Department of Surgery, Mayo Clinic, 200 First St. Southwest, Rochester, MN, 55905. E-mail: Truty.Mark@mayo.edu

Introduction

Pancreatic cancer (PDAC) is an aggressive malignancy that often presents with locally advanced (LA) tumors involving critical vasculature that would historically preclude resection.[1,2] With advances in more effective neoadjuvant combinatorial chemotherapy regimens and increasing surgical experience, a larger fraction of patients are being considered for pancreatectomy with concomitant *en bloc* arterial resection and revascularization.[3–9] However, such arterial resections are associated with potentially life-threatening complications of postoperative complete arterial occlusion (CAO). Pancreatic cancers can have isolated encasement of the common and/or proper hepatic artery (HA) as well as replaced hepatic arteries or can be more extensive and involve the celiac and/or SMA and therefore resectional procedures can be simple segmental resections with primary anastomotic reconstruction or require more complex multivisceral resection and revascularization procedures with interposition grafting. Presently, there are few institutions performing high-volume HA vascular resections in general for LA PDAC and thus the reported incidence and consequences of HA graft or anastomotic occlusions after resection and revascularization is relatively unknown.[10–13] Given the increased risks associated with hepatic arterial complications after revascularization, our institutions' significant recent experience in the modern era, and

scarce literature on the topic, the aim of this exploratory study was to examine the incidence, timing, consequences, and risk factors of HA occlusion after HA resection and revascularization during pancreatectomy for LA PDAC.

Methods

After institutional review board approval was obtained, a retrospective review of a prospectively maintained PDAC surgical database was performed. All sequential patients with LA PDAC undergoing segmental HA resection and revascularization with either end-to-end (EE) reconstruction or interposition graft (IG) revascularization were included. The majority of cases were performed in the modern neoadjuvant era, 2011–2021, however we did include 8 cases from the previous upfront surgery era for completeness. We specifically excluded any patients that underwent hepatic artery resection alone without formal revascularization (i.e. Class 1 A celiac axis tumors, diminutive or non-dominant accessory vessels).[4] Choice of EE vs. IG was determined by the operative surgeon based on intraoperative anatomical considerations. For those patients undergoing IG the proximal and distal interposition graft size (mm) was recorded. In our current practice a minimal distal arterial revascularization target of 3 mm is required for consideration of revascularization. Cadaveric arterial grafts included either superficial femoral artery or aortoiliac grafts. These were cryopreserved vascular allografts that are commercially available (CryoLife, Inc, Kennesaw, GA). We routinely use intraoperative Doppler ultrasound to assess and confirm IG/EE anastomotic patency prior to abdominal closure. In addition, indocyanine green angiography is often used to assess for adequate liver perfusion. We also perform computed tomography (CT) arterial/venous imaging on postoperative day 1 to assure early technical patency. IG or EE anastomotic patency during follow up was assessed using serial contrast enhanced cross-sectional CT or dedicated Doppler ultrasound if CT results were indeterminate during surveillance imaging and dichotomized as: complete arterial graft/anastomotic occlusion (CAO) and non-occluded arterial graft/anastomosis (NAO). Arterial graft/anastomotic patency time was calculated from date of index operation to date of last follow up or occlusion. "Early" (EO) and "late" (LO) HA occlusion was defined as before or after 90 days of index pancreatectomy and hepatic revascularization respectively. Incidental identification of CAO was defined as patients with occlusions identified on postoperative screening. Symptomatic presentations were defined as patients having imaging secondary to clinical symptoms or laboratory values necessitating imaging additional to standard screening. Portal venous (PV) patency was determined at time of hepatic CAO. Patients who died as a direct result of occlusion (hepatic failure) or from a complication related to graft occlusion were defined as occlusion-related mortalities. Hepatic complications included hepatic infarction, liver abscess, and postoperative ascites and were determined radiographically. Pancreas-specific complications were defined according to the International Study Group for Pancreatic Surgery.[14]

Statistical analysis

Mean and standard error of the mean (SEM), median and standard deviation, and interquartile ranges were calculated for continuous variables. Differences between groups with continuous variables were determined with student-t test and either a x^2 test or a Fisher's exact test was used for categorical variables as appropriate. Univariate associations for CAO and any hepatic complication or occlusion-related mortality were assessed using logistic regression. Kaplan–Meier was used to assess the probability of vascular occlusion over the study period. A Cox proportional hazards model was not used as the low number of CAO events precluded the creation of a stable multivariate model to identify independent predictors of CAO. The mean time between occlusions and rate of occlusions were calculated using a clinically determined change point cutoff of 90 days post-pancreatectomy. In addition, an unbiased-detected change point was determined through Piecewise Weibull NHPP Change Point Detection analysis.[15] This analysis was performed using JMP Pro 14.1.0. Statistical tests were two-sided, and results considered significant when $p < 0.05$. SPSS software was used for analysis of continuous and categorical variables (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp).

Results

A total of 108 patients with LA PDAC that underwent segmental HA resection and revascularization that had adequate postoperative contrast enhanced surveillance imaging to review were included in the study analysis (Table 1). The overwhelming majority of patients (93%) received preoperative chemotherapy followed by chemoradiation prior to resection. Open operative approaches were utilized in 88% (95/108) of patients. Of the entire cohort, total pancreatectomy was most commonly performed in 45% (49/108) of patients, with 31% (33/108) undergoing pancreaticoduodenectomy, and 24% (26/108) subtotal/distal pancreatectomy. Segmental isolated HA resection and revascularization was performed in 50% (54/108) of patients while multi-arterial (HA + celiac and/or SMA) resection with revascularization was performed in the remaining 50% (54/108) of patients. 39% (42/108) of patients underwent HA resection with celiac axis trunk resection, 9% (10/108) of patients underwent HA resection with celiac trunk and SMA resection, and 2% (2/108) of patients underwent replaced HA with SMA resection. There were 15 patients with hepatic artery variations in this series. Variations included: 11 replaced right hepatic arteries, 3 replaced common hepatic arteries, and 1 patient involving an accessory right hepatic artery. Segmental HA resection was feasible in 91% (10/11) of replaced right hepatic artery cases, and 80% were reconstructed with an end-to-end anastomosis. The

Table 1 Patient Cohort Demographics and Variables: Hepatic Interposition Graft (IG) vs. End-to-End Anastomosis (EE); No Arterial Occlusion (NAO) vs. Complete Arterial Occlusion (CAO); Early Occlusion (EO) vs. Late Occlusion (LO)

Variable	Total (n = 108)	IG (n = 66)	EE (n = 42)	p	NAO (n = 89)	CAO (n = 19)	p	EO (n = 8)	LO (n = 11)	p
Complete Arterial Occlusion (%)				0.079						
Yes	19 (18%)	15 (23%)	4 (10%)							
No	89 (82%)	51 (77%)	38 (90%)							
Median time to CAO ± SD, days	126 ± 148	126 ± 114	83.5 ± 258	1		126 ± 148		26.5 ± 26	138 ± 151	0.001
Age at surgery				0.010			0.129			0.181
Median ± SD	63 ± 8	62 ± 8	67 ± 7		63 ± 8	59 ± 9		63 ± 7	58 ± 9	
Range	37–77	37–77	49–76		42–76	37–77		55–77	37–69	
Sex				0.354			0.429			0.845
Male (%)	60 (56%)	39 (59%)	21 (50%)		51 (57%)	9 (47%)		4 (50%)	5 (46%)	
Female (%)	48 (44%)	27 (41%)	21 (50%)		38 (43%)	10 (53%)		4 (50%)	6 (54%)	
Preoperative chemoradiation (%)				0.155			0.567			0.202
Yes	100 (93%)	63 (95%)	37 (88%)		83 (93%)	17 (90%)		8 (100%)	9 (82%)	
No	8 (7%)	3 (5%)	5 (12%)		6 (7%)	2 (10%)		0 (0%)	2 (18%)	
Pancreatectomy type (%)				<0.001			0.457			0.301
Total	49 (45%)	38 (58%)	11 (26%)	0.001	38 (43%)	11 (58%)	0.140	4 (50%)	7 (64%)	0.366
Pancreaticoduodenectomy	33 (31%)	4 (8%)	29 (69%)	<0.001	29 (33%)	4 (21%)	0.276	3 (38%)	1 (9%)	0.317
Distal	26 (24%)	24 (36%)	2 (5%)	0.006	22 (24%)	4 (21%)	0.798	1 (12%)	3 (27%)	0.317
Type of Arterial Resection (%)				<0.001			0.448			0.552
HA only	54 (50%)	15 (23%)	39 (93%)		46 (52%)	8 (42%)		4 (50%)	4 (36%)	
HA + Celiac and/or SMA	54 (50%)	51 (77%)	3 (7%)		43 (48%)	11 (58%)		4 (50%)	7 (64%)	
Distal Hepatic Artery Target (%)				0.003			0.119			0.120
CHA	22 (20%)	16 (24%)	6 (14%)	0.033	19 (21%)	3 (16%)	0.673	1 (13%)	2 (18%)	0.877
PHA	47 (44%)	32 (48%)	15 (36%)	0.013	36 (41%)	11 (58%)	0.101	3 (38%)	8 (73%)	0.107
RHA	27 (25%)	8 (12%)	19 (45%)	0.034	24 (27%)	3 (16%)	0.330	3 (38%)	0 (0%)	0.279
LHA	1 (1%)	1 (2%)	0 (0%)		0 (0%)	1 (5%)	0.873	1 (11%)	0 (0%)	0.809
>1 target vessel	11 (10%)	9 (14%)	2 (5%)	0.035	10 (11%)	1 (5%)	0.612	0 (0%)	1 (9%)	0.828
Revascularization Type (%)							0.079			0.719
Interposition Graft					51 (57%)	15 (79%)		6 (75%)	9 (82%)	
End-to-End Anastomosis					38 (43%)	4 (21%)		2 (25%)	2 (18%)	
Interposition Graft Type (%)							0.019			0.013
Arterial (autologous/cadaveric)		52 (79%)			44 (86%)	8 (53%)	<0.001	2 (33%)	6 (67%)	0.188
Venous		9 (13%)			5 (10%)	4 (27%)	0.367	4 (57%)	0 (0%)	0.095
Synthetic		5 (8%)			2 (4%)	3 (20%)	0.460	0 (0%)	3 (33%)	0.320
Proximal Graft Size (mm)										
Median ± SD		6.4 ± 1.1			6.3 ± 1.1	6.6 ± 0.9	0.537	6.9 ± 0.7	6.3 ± 0.9	0.619
Distal Graft Size (mm)										
Median ± SD		5.5 ± 1.1			5.4 ± 1.2	5.6 ± 1	0.831	5.6 ± 1.2	5.5 ± 0.5	1
Venous Reconstruction (%)				0.238			0.105			0.348

(*continued on next page*)

Table 1 (*continued*)

Variable	Total (n = 108)	IG (n = 66)	EE (n = 42)	p	NAO (n = 89)	CAO (n = 19)	p	EO (n = 8)	LO (n = 11)	p
Yes	74 (69%)	48 (73%)	26 (62%)		58 (65%)	16 (84%)		6 (75%)	10 (91%)	
No	34 (31%)	18 (27%)	16 (38%)		31 (35%)	3 (16%)		2 (25%)	1 (9%)	
Anticoagulation, Type (%)				0.121			0.469			0.377
ASA Only	2 (2%)	1 (1%)	1 (2%)	0.954	1 (1%)	1 (5%)	1	0 (0%)	1 (9%)	0.201
ASA + Unfractionated Heparin	39 (36%)	19 (29%)	20 (48%)	0.087	32 (36%)	7 (37%)	0.927	2 (25%)	5 (46%)	0.429
ASA + LMWH	67 (62%)	46 (70%)	21 (50%)	0.018	56 (63%)	11 (58%)	0.555	6 (75%)	5 (45%)	0.167
Anticoagulation, Dosing (%)				0.472			0.820			0.348
Prophylaxis	89 (82%)	53 (80%)	36 (86%)		73 (82%)	16 (84%)		6 (75%)	10 (91%)	
Therapeutic	19 (18%)	13 (20%)	6 (14%)		16 (18%)	3 (16%)		2 (25%)	1 (9%)	
Portal Vein Status (%)				0.872			0.181			0.719
Occluded/Compromised	37 (34%)	23 (35%)	14 (34%)		33 (37%)	4 (21%)		2 (25%)	2 (18%)	
Patent	71 (66%)	43 (65%)	28 (66%)		56 (63%)	15 (79%)		6 (75%)	9 (82%)	
Operative Approach (%)				0.003			0.318			0.228
Open	95 (88%)	63 (95%)	32 (76%)		77 (87%)	18 (95%)		7 (88%)	11 (100%)	
MIS	13 (12%)	3 (5%)	10 (24%)		12 (13%)	1 (5%)		1 (12%)	0 (0%)	
***POPF (%)**				0.001			0.554			0.285
Yes	12 (20%)	11 (39%)	1 (3%)		11 (22%)	1 (12%)		1 (25%)	0 (0%)	
No	47 (80%)	17 (61%)	30 (97%)		40 (78%)	7 (88%)		3 (75%)	4 (100%)	
PPH (%)				0.402			0.286			0.008
Yes	12 (11%)	6 (9%)	6 (14%)		8 (9%)	4 (21%)		4 (50%)	0 (0%)	
No	96 (89%)	60 (91%)	36 (86%)		81 (91%)	15 (79%)		4 (50%)	11 (100%)	
****DGE (%)**				0.193			0.475			0.038
Yes	9 (12%)	4 (8%)	5 (19%)		6 (10%)	3 (20%)		3 (43%)	0 (0%)	
No	66 (88%)	44 (92%)	22 (82%)		54 (90%)	12 (80%)		4 (57%)	8 (100%)	
Any Hepatic Complication (%)				0.072			<0.001			0.912
Yes	45 (42%)	33 (49%)	13 (31%)		28 (32%)	17 (90%)		6 (75%)	8 (73%)	
No	63 (58%)	34 (51%)	29 (69%)		61 (68%)	2 (10%)		2 (25%)	3 (27%)	
Hepatic Infarct (%)				0.383			<0.001			0.040
Yes	17 (16%)	12 (18%)	5 (12%)		7 (8%)	10 (53%)		6 (75%)	3 (27%)	
No	91 (84%)	54 (82%)	37 (88%)		82 (92%)	9 (47%)		2 (25%)	8 (73%)	
Liver Abscess (%)				0.038			0.035			0.127
Yes	21 (19%)	17 (26%)	4 (10%)		14 (16%)	7 (37%)		1 (16%)	5 (45%)	
No	87 (81%)	49 (74%)	38 (91%)		75 (84%)	12 (63%)		7 (88%)	6 (55%%)	
Post-operative Ascites (%)				0.05			0.484			0.435
Yes	17 (16%)	14 (21%)	3 (7%)		13 (15%)	4 (21%)		1 (12%)	3 (27%)	
No	91 (84%)	52 (79%)	39 (93%)		76 (85%)	15 (79%)		7 (88%)	8 (73%)	
Median length of stay ± SD, days	12 ± 21	16 ± 25	8 ± 5	<0.001	11 ± 13	19 ± 40	0.107	17.5 ± 11	19 ± 52	1
Occlusion Detection Type (%)							0.330			0.026
Incidental						8 (42%)		1 (12%)	7 (64%)	
Symptomatic						11 (58%)		7 (88%)	4 (36%)	

Table 1 (*continued*)

Variable	Total (n = 108)	IG (n = 66)	EE (n = 42)	p	NAO (n = 89)	CAO (n = 19)	p	EO (n = 8)	LO (n = 11)	p
Occlusion-Related Mortality				0.958			0.246			0.046
Yes	5 (5%)	3 (5%)	2 (5%)		0 (0%)	5 (26%)		4 (50%)	1 (9%)	
No	103 (95%)	63 (95%)	40 (95%)		89 (100%)	14 (74%)		4 (50%)	10 (91%)	

CAO, complete arterial occlusion; NAO, no arterial occlusion; IG, interposition graft; EE, end-to-end anastomosis; HA, hepatic artery; SMA, superior mesenteric artery; PV, portal vein; *excludes total pancreatectomies; **excludes total gastrectomies; POPF, postoperative pancreatic fistula; PPH, post-pancreatectomy hemorrhage; DGE, delayed gastric emptying; LMWH, low molecular weight heparin; ASA, aspirin.

most common hepatic artery revascularization target was either the distal common hepatic or the distal proper hepatic artery (PHA) in 64% (69/108) of the cohort. Overall, 61% (66/108) of patients underwent revascularization with IG while 39% of (42/108) patients underwent EE. Amongst all IG types, arterial (autologous/cadaveric) grafts were most frequently utilized at 79% (52/66), and the median proximal and distal graft diameters were 6.4 mm and 5.5 mm respectively. Concomitant venous resection and reconstruction was performed in 69% (74/108) of patients. All patients received intraoperative heparinization during resection and revascularization and anti-platelet therapy (ASA) peri-postoperatively with the remaining patients also receiving some form of postoperative subcutaneous heparin most commonly with prophylactic dosing in 82% (89/108). Postoperative pancreas specific complications included POPF in 20%, PPH in 11%, and DGE in 12% of the cohort. Any hepatic complications occurred in 42% (45/108) of patients with liver abscess most common in 19% and hepatic infarction and ascites in 16% and 16% of the cohort respectively. Overall median length of stay was 12 days. At last imaging 66% (71/108) of patients had patent portal venous anatomy and the remaining third had either occlusion or significant compromise (>50% stenosis).

With a median follow-up of 15.4 months, complete hepatic arterial occlusion was identified in 18% (19/108) of patients. Median patency time for CAO patients was not reached at last follow up (Fig. 1). Amongst CAO patients, median time to detection of occlusion was 126 days (2–571) and for EO and LO was 26 days (2–89) and 138 days (94–571) respectively. Amongst NAO patients, median patency time was 461 days (180–761). Probability of complete vascular occlusion can be seen in Fig. 1. Using change point analysis, the mean time to CAO during the initial 90-day post-operative period was in a range between 4 and 17 days and the rate of CAO was constant over the initial 90-day post-operative period ($\beta = 0.6$, (95% CI: 0.29 to 1.26)). Between the 90-day post-operative period and the unbiased detected change point (158 days), the mean time to CAO was in a range between 10 and 18 days and the rate of CAO was constant (90-days post-operative period to 158-days: $\beta = 1.17$, (95% CI: 0.56 to 2.46)). However, after the unbiased change point time of 158 days, the mean time to CAO improved to a range between 48 and 128 days and the rate of CAO significantly decreased ($\beta = 0.24$, (95% CI: 0.1 to 0.57)) (Fig. 2).

Of these occlusions, a minority (42%) were incidentally diagnosed and the majority (58%) were late (>90 days) presentations. The overall occlusion related mortality rate was 4.6% (5/108). Fulminant hepatic failure (FHF) after occlusion was the ultimate cause of death in 80% (4/5) of patients with 2 patients being secondary to initial POPF and resultant fatal bleed or compressive hematoma with subsequent graft occlusion. One death from occlusion occurred during an endovascular attempt at dilating a high-grade but asymptomatic arterial anastomotic stricture. Case-specific mortality details can be seen in Table 2.

When we assessed variables associated with revascularization type (IG vs. EE) we found IG patients were younger, more likely to undergo open approaches, most often underwent either total or distal pancreatectomy and less often pancreaticoduodenectomy, more often underwent multi-arterial resection, and more often had distal vascular targets (PHA and beyond). There were significantly higher rates of POPF, postoperative liver abscess, ascites, and length of stay in the IG group but post-pancreatectomy hemorrhage (PPH) was not significantly different. There was a non-significant trend in higher occlusion rates in IG ($p = 0.079$) but this did not result in higher occlusion related mortality. The utilization of arterial conduits was statistically protective for complete arterial occlusion compared to venous or synthetic grafts. Amongst IG patients, CAO occurred at a rate of 15% (8/52) amongst arterial grafts, 44% (4/9) of venous grafts, and 60% (3/5) amongst synthetic grafts ($p = 0.019$). Median proximal and distal interposition graft sizes (mm) were not significantly different between CAO and NAO cohorts (6.6 ± 0.9 mm vs 6.3 ± 1.1 mm, $p = 0.537$; 5.6 ± 1 mm vs 5.4 ± 1.2 mm, $p = 0.831$). Patients with complete arterial occlusion had significantly higher rates of hepatic complications as expected. Preoperative rates of chemoradiation between CAO and NAO cohorts were similar (90% vs. 93%, $p = 0.567$). The majority of symptomatic occlusions were identified early (<90 days) whereas the majority of incidental occlusions were identified late. In those patients with early occlusion, there were higher rates of occlusion with venous grafts. Hepatic infarction, PPH, and DGE also associated with early occlusion. There was a

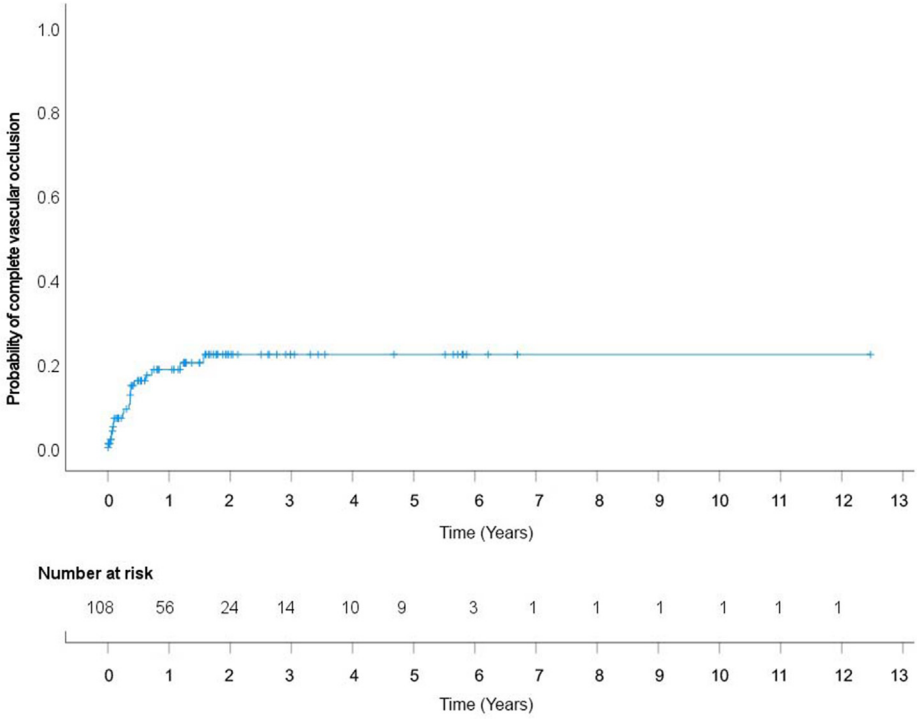

Figure 1 Probability of complete vascular occlusion using Kaplan–Meier analysis

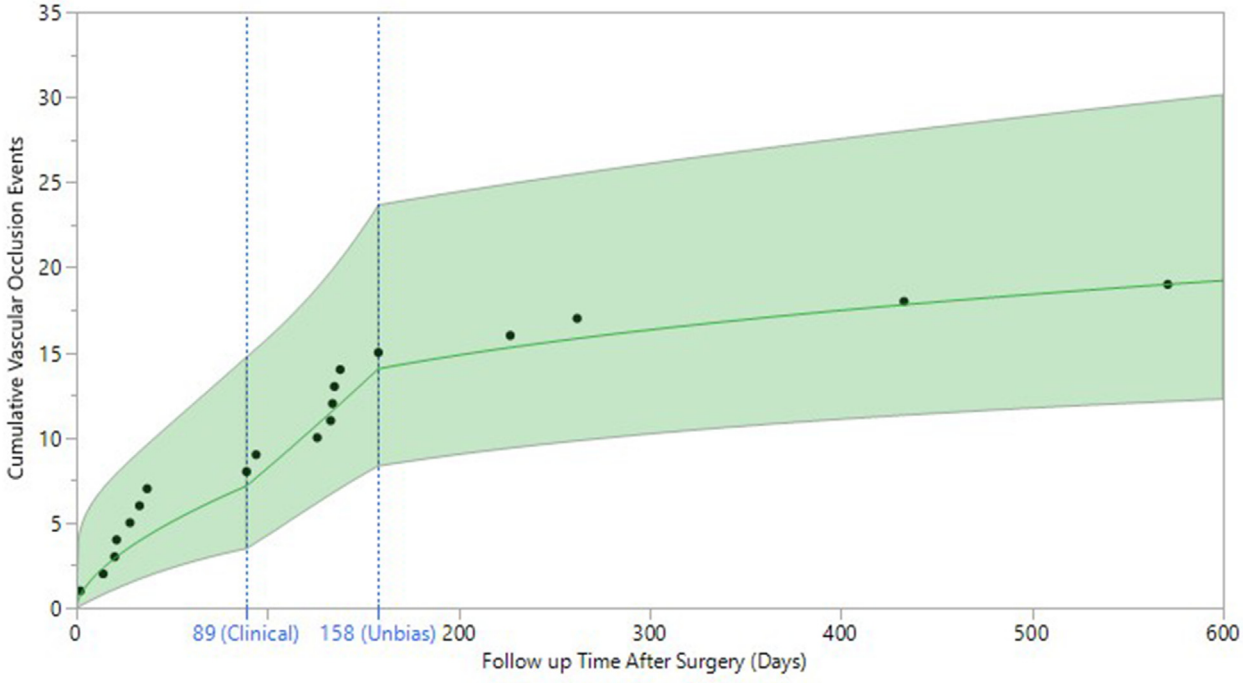

Figure 2 Cumulative vascular occlusion events using change point detection analysis in relation to two determined points: a clinically-determined change point of 90 days and an unbiased-detected change point at 158 days

Table 2 Univariate analysis of variables associated with any hepatic complication or occlusion related mortality

Variable	Any Hepatic Complication	
	HR (95% CI)	*P*-value
Sex		
Female	1.0 (reference)	
Male	0.983 (0.457–2.114)	0.965
Pancreatectomy Type		
Pancreaticoduodenectomy	1.0 (reference)	
Distal	1.250 (0.428–3.650)	0.683
Total	2.261 (0.905–5.649)	0.081
Arterial Reconstruction Type		
End-to-End Anastomosis	1.0 (reference)	
Interposition Graft	2.00 (0.896–4.463)	0.091
Venous Reconstruction		
No	1.0 (reference)	
Yes	2.400 (1.008–5.712)	0.048
Type of Arterial Resection		
HA only	1.0 (reference)	
HA + Celiac and/or SMA	1.078 (0.504–2.308)	0.846
Hepatic Interposition Graft by Type		
Synthetic + Venous	1.0 (reference)	
Arterial	0.476 (0.243–2.586)	0.234
PV Status at last F/U or at CAO		
Occluded/Stenotic	1.0 (reference)	
Patent	0.388 (0.161–0.939)	0.036
Open Approach		
No	1.0 (reference)	
Yes	1.861 (0.536–6.463)	0.328
*POPF		
No	1.0 (reference)	
Yes	0.295 (0.058–1.498)	0.141
PPH		
No	1.0 (reference)	
Yes	1.341 (0.403–4.461)	0.632
**DGE		
No	1.0 (reference)	
Yes	0.760 (0.207–2.794)	0.680
Preoperative chemoradiation		
No	1.0 (reference)	
Yes	0.754 (0.178–3.188)	0.702
In-Hospital Anticoagulation, Dosing		
Prophylactic	1.0 (reference)	
Therapeutic	0.932 (0.342–2.541)	0.891
In-Hospital Anticoagulation, Type		
ASA Only	1.0 (reference)	
ASA + Unfractionated Heparin	0.773 (0.045–13.268)	0.773
ASA + LMWH	0.763 (0.046–12.722)	0.763
Post-operative anticoagulation status		
No	1.0 (reference)	
Yes	0.886 (0.277–2.836)	0.838
Occlusion Detection Type		
Incidental	1.0 (reference)	
Symptomatic	3.600 (0.959–13.515)	0.058

HA, hepatic artery; SMA, superior mesenteric artery; PV, portal vein; *excludes total pancreatectomies; **excludes total gastrectomies; POPF, postoperative pancreatic fistula; PPH, post-pancreatectomy hemorrhage; DGE, delayed gastric emptying; CAO, complete arterial occlusion; LMWH, low molecular weight heparin; ASA, aspirin.

significant difference in occlusion related mortality in early (4/8, 50%) vs late (1/11, 9%) occlusions ($p = 0.046$). In the late occlusions, portal venous system patency appeared to correlate with occlusion mortality where this did not in early occlusions, suggesting the development of hepatic inflow collaterals (arterial and/or venous) have not yet developed in the early postoperative setting, and are likely potentially protective in the later setting. Table 3 summarizes univariate associations with any hepatic complications and occlusion-related mortality. Only concurrent venous resection and patency of portal venous hepatic inflow were independent predictors of any hepatic complication and occlusion-related mortality.

Discussion

Since the introduction of modern and effective combinatorial neoadjuvant chemotherapy regimens for anatomically advanced PDAC, the frequency with which pancreatectomy with AR is being performed for LA PDAC has significantly increased at our center with the largest proportion of operations requiring HA resection and revascularization. Although many studies have reported peri-operative outcomes following AR for LA PDAC, many are limited by sample size, and few report hepatic arterial graft/anastomotic patency rates.[16,12,17,18,13] Given the highly variable patient vascular anatomy combined with tumor location and extent, such advanced operations are truly custom and bespoke for any given patient. Any given operation for LA PDAC requiring en bloc arterial resection can include a variety of pancreatectomy types, need for associated multivisceral resection, and host of complex revascularization procedures and as such cannot be simply classified. Each surgical variation can either eliminate or introduce various postoperative risks that can affect surgical outcomes. In those patients that require hepatic arterial resection and revascularization the concerns are for hepatobiliary ischemic insults that may be significantly difficult

Table 3 Occlusion-related mortality, specifics

Case	Operation Type	Arterial Resection	IG or EE	Venous Resection	Anticoagulation (PPX vs TX)	Porto-mesenteric Patency	Occlusion Details	Early or Late Occlusion	Cause of Death
1	Total pancreatectomy	HA +	IG	Yes	PPX	Patent	Occlusion after endovascular intervention	Early	Liver failure
2	Pancreaticoduodenectomy	HA only	IG	Yes	PPX	Patent	POPF with PPH (pseudoaneurysm)	Early	Hemorrhage
3	Pancreaticoduodenectomy	HA only	EE	No	PPX	Occluded/ Stenotic	PPH (pseudoaneurysm)	Early	Liver failure
4	Total pancreatectomy	HA +	IG	Yes	PPX	Occluded/ Stenotic	Occlusion of HA conduit and SMA	Late	Liver failure
5	Total pancreatectomy	HA +	IG	Yes	TX	Patent	Occlusion of conduit	Early	Liver failure

HA, hepatic artery; SMA, superior mesenteric artery; PPX, prophylaxis; TX, therapeutic; CAO, complete arterial occlusion, POPF, postoperative pancreatic fistula; PPH, post pancreatectomy hemorrhage; IG, interposition graft; EE, end-to-end-anastomosis.

to manage above and beyond those seen for standard pancreatic operations and the typical treatment interventions are not always possible due to significantly altered anatomy thus higher potential for morbidity or fatal outcomes. Thus, for any surgeons contemplating such operations in this modern era of pancreatic cancer surgery, having a complete and thorough understanding of associated anatomical considerations and unique specific risks and outcomes of these procedures is critical.

To our knowledge, this is the largest single institution experience of pancreatectomy with HA resection and reconstruction in LA PDAC patients, and one of the few to report short and long-term hepatic arterial graft/anastomotic patency rates. With a median follow up time of 15.4 months, CAO was identified in 18% of the cohort. Importantly, occlusion-related mortality was significantly higher amongst patients with EO versus LO, with half of EOs resulting in occlusion-related mortality (ORM). Amongst IG patients, arterial conduits were associated with the least risk of CAO as compared to venous and synthetic conduits. We found no association between CAO and in-hospital anticoagulation dosing and our current protocol is consensus based. Any hepatic complications developed in approximately 40% of the cohort regardless of CAO, and were predictably highest in those with occlusion. In those patients with ORM, the primary cause of death was FHF with 80% (4/5) of these occurring in the early setting. We did note and observe patency of portal venous hepatic inflow in all but one of these early occlusion mortalities possibly suggesting that in the acute setting, the damage incurred from loss of hepatic arterial inflow in the absence of developed arterial collaterals cannot be mitigated with adequate portal venous inflow alone. EO is associated with a high mortality rate, and if the initial insult is survivable, significant morbidity can be expected. Strikingly, only 1/11 LO patients developed ORM, and this single patient notably had a high-grade stenosis of the PV system. The remaining LO survivors had either a patent portal venous system or had undergone portal venous stenting postoperatively to improve venous inflow. Although still associated with significant morbidity, our data suggests that LO is associated with significantly better outcomes than EO unless there is an associated high-grade stenosis or occlusion of the portal venous system, and this is evident in that the majority of LO were incidentally identified. In our practice we have a low threshold to consider transhepatic portal venous stenting in any patients with compromised venous anatomy to increase hepatic inflow.[19] In addition to using a clinical cutoff period of 90 days to dichotomize CAO patients into EO or LOs, we performed a previously described unbiased change point detection analysis[15] to describe this cohort of CAO patients. This analysis revealed that between the 90 day post-operative period and 158 day post-operative period (unbiased change point detection) the rate of CAO was constant. However, after the unbiased change point cutoff, the rate of CAO significantly decreased. The slope of the mean time between CAOs decreased considerably after the unbiased cutoff. These results suggest that the first 5-month post-surgical window is critical for the surveillance and detection of complete graft/anastomotic occlusion in these high risk patients and can potentially influence future surveillance programs.

Although successful arterial graft salvage has been reported in the liver transplant literature, in our experience arterial graft procedures are rarely performed and reserved only in the immediate postoperative setting due to early technical complications (thrombectomy). Endovascular procedures are typically limited primarily to the setting of acute bleeding from pseudoaneurysm, however these have become significantly less common with understanding the critical need to wrap these grafts with coverage flaps (omentum, round ligament, etc.). Additional studies are needed to adequately guide decision-making surrounding arterial revascularization procedures following pancreatectomy.[20,21] The data herein still cannot ascertain best practice for those patients with significant stenoses of the hepatic arterial revascularization. We did have one patient with acute and fatal occlusion after endovascular attempts to dilate/stent an arterial anastomotic stricture. In general, in the

absence of symptoms or radiologic/biochemical signs of impending ischemia we rarely intervene on such cases as the risk of converting an asymptomatic radiologic stenosis to a complete occlusion from endovascular complications likely outweigh the risks. In our experience as long as the arterial occlusion occurs slowly over time as opposed to acutely, there is typically development of collaterals with minimal clinical morbidity, with the exception in those with inadequate portal venous inflow. And as stated earlier we tend to intervene on these venous strictures empirically with transhepatic venous stenting. Most patients with CAO presented symptomatically, with the overwhelming majority of EO patients presenting with symptoms. The opposite was true of LO patients. Given the lack of symptoms in the LO group there should be routine imaging after such operations despite lack of symptoms so that hepatic inflow via the portal system can be optimized if necessary. No current imaging guidelines exist, but our current practice is to obtain formal computed tomography angiography/venography on post-operative day 1 to evaluate the arterial graft/anastomoses with subsequent in-hospital and post-discharge imaging guided by the patient's clinical condition.

The role of post-operative anticoagulation in preventing CAO is unclear. Guidelines regarding anticoagulation administration after pancreatectomy with AR are lacking as most published work focuses on anticoagulation after venous resections. A recent systematic review by Chandarasegaram et al. examined post-operative anticoagulation in patients undergoing pancreatectomy with portal venous resection. They found significant heterogeneity amongst centers with established anticoagulation practices, and noted that even in centers with such practices, only 50% of patients received anticoagulation postoperatively.[22] In addition, the systematic review excluded studies where patients underwent concomitant AR. In this study, we found no difference in either in-hospital type of anticoagulant (heparin vs enoxaparin) or in-hospital therapeutic versus prophylactic anticoagulation dosing amongst patients who developed CAO versus those that did not. It is our practice to routinely provide both post-operative prophylactic anticoagulation and antiplatelet therapy. Changes to therapeutic dosing changes are dictated by patient specific factors, such as development of arterial graft stenosis or development of portal venous thrombosis.

While this study includes a large sample size of HA resection and revascularizations for LA PDAC, it has several significant limitations. Firstly, as it is a single-institution retrospective review, there is significant information and selection bias as uniform reporting of various outcomes is unlikely over time. Secondly, with the exception of 5 patients, the majority of the cohort underwent extensive neoadjuvant treatment including long-course chemotherapy and chemoradiation, therefore our results will be difficult to generalize to other LA PDAC cohorts as neoadjuvant regimens are variable at different centers. Furthermore arterial resections were performed amongst various teams of pancreatic and vascular surgeons, and therefore variation in surgical technique could not be accounted for and given the heterogeneity of patient anatomy and tumor location, a host of different total procedures were included in this current series that cannot be simply classified.

Despite these limitations, this study represents one of the largest experiences of hepatic artery resection and revascularization for LA PDAC and provides important clinical insights for anticipated outcomes. It highlights the incidence rate of hepatic complications and complete arterial occlusion after such operations and the impact of early occlusion. Given the significant frequency and severity of post-operative morbidity that is associated with these operations, this study further reinforces the importance of neoadjuvant treatment sequencing and stresses appropriate patient selection. As these operations continue to be adopted, future studies examining arterial graft failure are warranted and should expound upon predictive factors (surgical or medical) that may help identify patients at risk of complete arterial occlusion. In addition, other future directions of study include: the optimization of arterial graft revascularization procedures; ideal post-operative graft surveillance schedules; discerning how HA reconstruction technique effects CAO; and understanding the role of prophylactic anticoagulation to prevent HA thrombosis in this high risk patient population.

Conflicts of interest

None to declare.

References

1. Reames BN, Blair AB, Krell RW, Groot VP, Gemenetzis G, Padussis JC *et al*. (2019) Management of locally advanced pancreatic cancer: results of an international survey of current practice. *Ann Surg* 273. https://doi.org/10.1097/SLA.0000000000003568.
2. Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA *et al*. (2016) FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. *Lancet Oncol* 17:801–810. https://doi.org/10.1016/S1470-2045(16)00172-8.
3. Truty MJ, Kendrick ML, Nagorney DM, Smoot RL, Cleary SP, Graham RP *et al*. (2019) Factors predicting response, perioperative outcomes, and survival following total neoadjuvant therapy for borderline/locally advanced pancreatic cancer. *Ann Surg*. https://doi.org/10.1097/sla.0000000000003284. Publish Ah:1.
4. Truty MJ, Colglazier JJ, Mendes BC, Nagorney DM, Bower TC, Smoot RL *et al*. (2020) En bloc celiac Axis resection for pancreatic cancer: classification of anatomical variants based on tumor extent. *J Am Coll Surg* 231: 8–29. Elsevier.
5. Hartwig W, Gluth A, Hinz U, Koliogiannis D, Strobel O, Hackert T *et al*. (2016) Outcomes after extended pancreatectomy in patients with borderline resectable and locally advanced pancreatic cancer. *Br J Surg* 103:1683–1694. https://doi.org/10.1002/bjs.10221.
6. Tee MC, Krajewski AC, Groeschl RT, Farnell MB, Nagorney DM, Kendrick ML *et al*. (2018) Indications and perioperative outcomes for pancreatectomy with arterial resection. *J Am Coll Surg* 227:255–269. https://doi.org/10.1016/j.jamcollsurg.2018.05.001.

7. Loos M, Kester T, Klaiber U, Mihaljevic AL, Mehrabi A, Muller-Stich BM *et al*. (2020) Arterial resection in pancreatic cancer surgery. *Ann Surg*. https://doi.org/10.1097/sla.0000000000004054. Publish Ah(June).
8. Del Chiaro M, Rangelova E, Halimi A, Ateeb Z, Scandavini C, Valente R *et al*. (2019) Pancreatectomy with arterial resection is superior to palliation in patients with borderline resectable or locally advanced pancreatic cancer. *HPB* 21:219–225. https://doi.org/10.1016/J.HPB.2018.07.017.
9. Alva-Ruiz R, Yohanathan L, Yonkus JA, Abdelrahman AM, Gregory LA, Halfdanarson TR *et al*. (2021) *Neoadjuvant chemotherapy switch in borderline resectable/locally advanced pancreatic cancer*. Ann Surg Oncol. Published online.
10. Miyazaki M, Yoshitomi H, Takano S, Shimizu H, Kato A, Yoshidome H *et al*. (2017) Combined hepatic arterial resection in pancreatic resections for locally advanced pancreatic cancer. *Langenbeck's Arch Surg* 402:447–456. https://doi.org/10.1007/s00423-017-1578-5.
11. Glebova NO, Hicks CW, Tosoian JJ, Piazza KM, Abularrage CJ, Schulick RD *et al*. (2016) Outcomes of arterial resection during pancreatectomy for tumor presented at the vascular and endovascular surgery society paper session 2 at the 2015 Vascular Annual Meeting of the Society for Vascular Surgery, Chicago, Ill, June 17-20, 2015. In: *Journal of vascular surgery*, vol. 63. Mosby, pp. 722–729.
12. Sakuraba M, Miyamoto S, Nagamatsu S, Kayano S, Taji M, Kinoshita T *et al*. (2012) Hepatic artery reconstruction following ablative surgery for hepatobiliary and pancreatic malignancies. *Eur J Surg Oncol* 38:580–585. https://doi.org/10.1016/j.ejso.2012.04.004.
13. Yang F, Wang X, Jin C, He H, Fu D. (2019) Pancreatectomy with hepatic artery resection for pancreatic head cancer. *World J Surg* 43:2909–2919. https://doi.org/10.1007/s00268-019-05106-8.
14. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M *et al*. (2017) The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years after. *Surgery* 161:584–591. https://doi.org/10.1016/j.surg.2016.11.014.
15. Meltzer AJ, Graham A, Connolly PH, Karwowski JK, Bush HL, Frazier PI *et al*. (2013) Risk factors for early failure after peripheral endovascular intervention: application of a reliability engineering approach. *Ann Vasc Surg* 27:53–61. https://doi.org/10.1016/J.AVSG.2012.05.002.
16. Nakao A, Takeda S, Inoue S, Nomoto S, Kanazumi N, Sugimoto H *et al*. (2006) Indications and techniques of extended resection for pancreatic cancer. *World J Surg* 30:976–982. https://doi.org/10.1007/s00268-005-0438-6.
17. Mollberg N, Rahbari NN, Koch M, Hartwig W, Hoeger Y, Buchler MW *et al*. (2011) Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. *Ann Surg* 254:882–893. https://doi.org/10.1097/SLA.0b013e31823ac299.
18. Zhang Q, Wu J, Tian Y, Duan J, Shao Y, Yan S *et al*. (2019) Arterial resection and reconstruction in pancreatectomy: surgical technique and outcomes. *BMC Surg* 19:1–10. https://doi.org/10.1186/s12893-019-0560-2.
19. Thompson SM, Fleming CJ, Yohanathan L, Truty MJ, Kendrick ML, Andrews JC. (2020) Portomesenteric venous complications after pancreatic surgery with venous reconstruction: imaging and intervention. *Radiographics* 40:531–544. https://doi.org/10.1148/RG.2020190100/ASSET/IMAGES/LARGE/RG.2020190100.FIG16.JPEG.
20. Sheiner PA, Varma CV, Guarrera JV, Cooper J, Garatti M, Emre S *et al*. (1997) Selective revascularization of hepatic artery thromboses after liver transplantation improves patient and graft survival. *Transplantation* 64:1295–1299. https://doi.org/10.1097/00007890-199711150-00011.
21. Grodzicki M, Anysz-Grodzicka A, Remiszewski P, Cieslak B, Kotulski M, Kalinowski P *et al*. (2011) Treatment of early hepatic artery thrombosis after liver transplantation. *Transplant Proc* 43:3039–3042. https://doi.org/10.1016/J.TRANSPROCEED.2011.08.028.
22. Chandrasegaram MD, Eslick GD, Lee W, Brooke-Smith ME, Padbury R, Worthley CS *et al*. (2014) Anticoagulation policy after venous resection with a pancreatectomy: a systematic review. *HPB* 16:691–698. https://doi.org/10.1111/HPB.12205.

