Does the Artery-first Approach Improve the Rate of R0 Resection in Pancreatoduodenectomy?

A Multicenter, Randomized, Controlled Trial

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Objective: To compare the rates of R0 resection in pancreatoduodenectomy (PD) for pancreatic and periampullary malignant tumors by means of standard (ST-PD) versus artery-first approach (AFA-PD).

Background: Standardized histological examination of PD specimens has shown that most pancreatic resections thought to be R0 resections are R1. ''Artery-first approach'' is a surgical technique characterized by meticulous dissection of arterial planes and clearing of retropancreatic tissue in an attempt to achieve a higher rate of R0. To date, studies comparing AFA-PD versus ST-PD are retrospective cohort or case-control studies.

Methods: A multicenter, randomized, controlled trial was conducted in 10 University Hospitals (NCT02803814, ClinicalTrials.gov). Eligible patients were those who presented with pancreatic head adenocarcinoma and periampullary tumors (ampulloma, distal cholangiocarcinoma, duodenal adenocarcinoma). Assignment to each group (ST-PD or AFA-PD) was randomized by blocks and stratified by centers. The primary end-point was the rate of tumor-free resection margins (R0); secondary end-points were postoperative complications and mortality.

Results: One hundred seventy-nine patients were assessed for eligibility and 176 randomized. After exclusions, the final analysis included 75 ST-PD and 78 AFA-PD. R0 resection rates were 77.3% (95% CI: 68.4–87.4) with ST-PD and 67.9% (95% CI: 58.3–79.1) with AFA-PD, P=0.194. There were no significant differences in postoperative complication rates, overall 73.3% versus 67.9%, and perioperative mortality 4% versus 6.4%.

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This work was supported by a grant from Spain's Ministry of Economy and Competitiveness through the Carlos III Health Institute PI15/00076 and by the SCReN-Spanish Clinical Research Network (PT13/0002/0031; PT17/0017/0003; co-financed by European Regional Development Fund ''A way to make Europe'').

All the authors included in this paper declare to have received no funding for this work from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s).

All the authors declare also that neither they nor their institutions at any time have received payment or support in kind for any aspect of the submitted work (including grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

L.S. has participated in the development of teaching resources, advisory and educational programs for Abbott, Mylan, Johnson and Johnson, and Medtronic.

E.C., none declared.

A.S., none declared.

G.S.-A., none declared.

L.D.-V., none declared.

J.S.-S., none declared.

E.M.-P. has participated in the development of teaching resources, advisory, and educational programs for Mylan, Ipsen, and Novartis.

F.A. has participated in the development of teaching resources, advisory, and educational programs for Mylan and Baxter.

S.L.-B. received consulting fees from Medtronic, Baxter, and Integra.

J.M.J.-N., none declared.

M.G.-A., none declared.

M.G.-D., none declared.

M.S. has participated in the development of teaching resources, advisory and educational programs for Baxter.

E.P.-A., none declared.

B.S.-P., none declared.

M.D.M. has participated in the development of teaching resources, advisory, and educational programs for Mylan.

P.S.-d.-R., none declared.

L.F.-V., none declared

A.C., none declared.

M.C.G.-M., none declared.

A.F., none declared.

D.D., none declared.

E.M.-F., none declared.

C.F., none declared.

J.P., none declared.

The authors report no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

ISSN: 0003-4932/16/XXXX-0001

DOI: 10.1097/SLA.0000000000003535

Conclusions: Despite theoretical oncological advantages associated with AFA-PD and evidence coming from low-level studies, this multicenter, randomized, controlled trial has found no difference neither in R0 resection rates nor in postoperative complications in patients undergoing ST-PD versus AFA-PD for pancreatic head adenocarcinoma and other periampullary tumors.

Keywords: artery-first, pancreatic cancer, pancreatoduodenectomy, periampullary tumors

(*Ann Surg* 2019;xx:xxx–xxx)

Surgical resection in combination with adjuvant chemotherapy constitutes at present the only possibility for long-term survival in patients with pancreatic and periampullary tumors. However, even after curative resection, many patients nonetheless recur and die within few years.[1–3] Despite poor surgical results, published R0 resection rates were consistently >70% until Verbeke et al[4] and Esposito et al[5] showed that although most pancreatic resections were thought to be complete oncological R0 they were in fact R1. When pancreatoduodenectomy (PD) specimens are evaluated with a standard protocol,[6–8] the resection margin (RM) around the superior mesenteric artery is considered the most frequent R1 site and is an established poor prognostic factor. [9–13] The surgical challenge is therefore whether an increased RM along the superior mesenteric artery (SMA) can be technically achieved and, consequentially, whether this may impact prognosis compared with standard PD. ''Artery-first approach'' pancreatoduodenectomy (AFA-PD) is characterized by early evaluation of involvement of the main arterial vasculature before irreversible surgical steps are performed as well as meticulous dissection of arterial planes and clearance of retropancreatic tissue. Two factors have contributed to the recent widespread diffusion of AFA-PD: local resectability criteria have shifted from venous toward arterial invasion and greater understanding of the importance of the RM limited by the right edge of the SMA. The potential advantage of this approach over the standard procedure is unclear and has been evaluated only in retrospective cohort or case-control studies.[14–29] Therefore, the hypothesis to be tested in this multicenter, randomized, controlled study is whether AFA-PD improves R0 resection rate in malignant pancreatic head and periampullary tumors.

PATIENTS AND METHODS

This investigation was conducted in 10 university hospitals with specialized hepatopancreatobiliary surgery units. The study was registered as NCT02803814 at ClinicalTrials.gov, and the protocol was approved by each participating center's ethics committee. All patients included provided specific written informed consent.

TRIAL DESIGN

Multicenter, randomized, controlled trial to compare the rate of free resection margin in patients with pancreatic head and periampullary malignant tumors undergoing PD by either standard (ST-PD) or artery-first approach. The primary endpoint of the study was R0 resection rate. Secondary endpoints were postoperative complications, intra- and postoperative transfusions, operative time, lymph node retrieval, reoperation, hospital stay, readmissions, and mortality.

Surgical specimens were evaluated according to a previously published standard protocol [4-7] (Supplementary Table, http://links.lww.com/SLA/B734) by pathologists blinded to surgical approach.

Independent data monitors from the Spanish Clinical Research Network (SCReN)-Spanish Clinical Research Network (PT13/0002/0031; PT17/0017/0003) from the National Plan Institute of Health Carlos III (Ministry of Economy and Competitiveness) reviewed all procedures and data included in the trial. Data was recorded in electronic case report form and sent directly to the statistics core facility. Centers participating in the study had to have a minimum volume of 20 pancreatic resections per year and surgeons were to be widely experienced in both surgical procedures. The maximum number of patients included by a single center was 25, to avoid unbalanced recruitment among centers. Before the recruitment of patients, there was a consensus meeting to discuss the technical details of operative procedures for standardization in participating institutions.

PATIENTS

Between January 2016 and December 2017, all patients ≥ 18 years with resectable pancreatic and periampullary malignant tumors (pancreatic head, ampullary, or duodenal adenocarcinoma or distal cholangiocarcinoma) were evaluated for trial inclusion. Exclusion criteria included liver metastases or peritoneal carcinomatosis; high surgical risk (ASA IV); neoadjuvant treatment; other previous tumors; residual macroscopic disease (R2); and definitive histopathological diagnosis different from pancreatic, ampullary, or duodenal adenocarcinoma or distal cholangiocarcinoma.

RANDOMIZATION

Random assignment by blocks and stratified by center assigned patients to ST-PD or AFA-PD, so as to balance the groups within each of the participating centers, until reaching the sample size. Data was coded with 3 letters for the center followed by the patient's number and accessed only by the research team of each center. Treatment allocations were sealed in numbered envelopes, which were opened in the operating room once the tumor was proven respectable.

SAMPLE SIZE

Sample size was calculated with the GRANMO program. According to previous studies, R1 resection rate with standardized analysis of the surgical specimen is around 50% for pancreatic and periampullary malignant tumors.[4,13,30] In the few publications on artery-first approach, resection margin invasion is 18% to 27%.[14–29] Based on these considerations, a clinically significant reduction of R1 rate from 50% in ST-PD to 25% in AFA-PD was estimated. To achieve a power of 80% and 5% significance level, with a 1:1 ratio of experimental to reference units and considering a 20% drop-out, sample sizes of 72 per arm (144 patients in total) were calculated. The ARCSINUS approach was used for this calculation.

SURGICAL TECHNIQUE

Standard Pancreatoduodenectomy

After exploration of the abdominal cavity, combined mobilization of the right colon and wide Kocher maneuver is performed (Fig. 1). The greater omentum is separated from the mesocolon and removed. After separating the colonic mesentery from the anterior surface of the duodenum, the superior mesenteric vein and pancreatic neck are exposed. The gastro-colic trunk is dissected and divided, allowing the dissection of the anterior surface of the superior mesenteric vein below the pancreas. Cholecystectomy is performed, the lesser sac is opened, and complete dissection of the hepatoduodenal ligament and division of the gastroduodenal artery is performed. The bile duct is divided, and the portal vein is dissected, removing all lymphatic tissue circumferentially. The stomach is cut by a linear stapler device at the level of the antrum or duodenum. The angle of Treitz is dissected and the jejunum sectioned and passed to

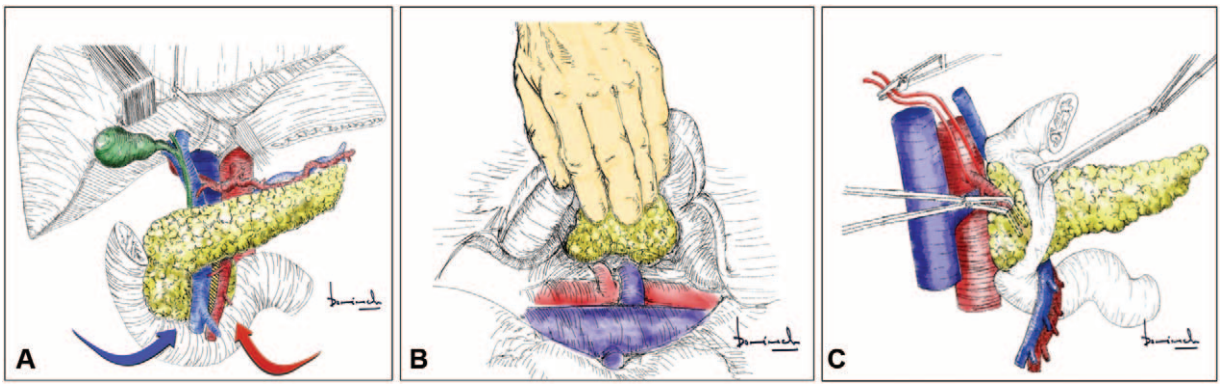

FIGURE 1. A, The most complex anatomical area of the PD operation was approached in 1 of 2 ways: from the portal vein-superior mesenteric axis (standard approach, blue arrow) or from the superior mesenteric artery (artery-first approach, red arrow). B, In the AFA-PD, the SMA is dissected just above the left renal vein, facilitated by the assistant lifting the SMA upright holding the mesentery toward the left shoulder. C, Once the SMA is encircled with a vessel-loop, dissection proceeds dividing all the attachments between the SMA, uncinate process and portal vein, identifying and dividing the inferior and posterior pancreatoduodenal arteries.

the right behind the mesenteric vessels. The pancreatic neck is divided, and small vessels from the porto-mesenteric axis to the head of the pancreas are ligated and cut. The surgical specimen is removed after sectioning the retroperitoneal border of the pancreas.

Artery-first Approach

A wide Kocher maneuver is performed, exposing the anterior surface of the inferior cava vein and the left renal vein. The assistant retracts the mesentery to the left shoulder, and the SMA is dissected above the left renal vein. The SMA is encircled with a vessel-loop, and attachments between the SMA, uncinate process, and portal vein are divided, taking care to identify and divide the inferior and posterior pancreatoduodenal arteries. Then the hepatic pedicle and hepatoduodenal area are dissected. The stomach or duodenum, jejunum, and division of the pancreatic neck are carried out as in ST-PD. The posterolateral aspect of the portal vein is dissected, dividing its tributary branches to access the retroperitoneal tissue on the right lateral edge of the SMA, and the specimen is removed.

In both techniques, the standard lymph node stations (5, 6, 8a, 12, 13, 14a&b, and 17) are removed.[31] Intraoperative analysis of the pancreatic transection margin is performed; when positive, additional pancreas is resected. Completion pancreatectomy is indicated in the case of a second positive transection margin or when the pancreatic remnant is too small to carry out a safe pancreatic anastomosis.

END-POINT DEFINITIONS

R0: Noninvolvement of circumferential margins, with minimum distance between tumor and resection margin >1 mm. The histopathological protocol included the identification and painting of the various resection margins with different inks: pancreatic transection margin and circumferential resection margin, which in turn comprises the medial circumferential or vascular margin and the posterior circumferential or retroperitoneal margin.

Morbidity: Postoperative complications were defined according to the International Study Group for Pancreatic Surgery for pancreatic fistula,[32] delayed gastric emptying,[33] and hemorrhage,[34] and biliary leak according to the International Study Group for Liver Surgery.[35] Chylous fistula was defined as the presence of milky, amylase-poor, and triglyceride rich drain effluent.[36] Diarrhea was defined according to the common Terminology Criteria for Adverse Events as an increase in frequency and/or loose or watery bowel movements >3/d. Complications were classified according to Clavien-Dindo[37] and the Comprehensive Complication Index (CCI).[38]

Intraoperative transfusions: Administration of blood or blood products during the operation or immediately after.

Reoperation: Any procedure requiring general anesthesia.

Readmission: Rehospitalization within 30 days after discharge.

Mortality: Death during the same hospital admission or within 90 days after the operation.

STATISTICAL ANALYSIS

Patient data was analyzed on an intention-to-treat basis. Categorical variables are expressed as count (percentage) and quantitative variables as mean ± standard deviation or median (25%–75% interquartile range), unless otherwise specified. A log-binomial regression model including the surgical group as covariate was used to compare the percentage of patients with R0 between groups. Continuous secondary variables were analyzed using Student *t* test, categorical secondary variables using Fisher exact test, and ordinal variables using Mann–Whitney *U* test. The level of significance was established at the 2-sided 5% level. The primary end-point, the percentage of patients with R0, was also analyzed in the subgroup of patients with pancreatic adenocarcinoma. Statistical analysis was carried out by the Medical Statistics Core Facility, IDIBAPS-Hospital Clinic Barcelona, a platform for investigation and clinical trials from the SCReN, which was not participating in the trial as recruiting center. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Between January 2016 and December 2017, 179 patients were screened as potential participants and 176 randomized. After exclusions, 153 patients were analyzed, 75 with ST-PD, and 78 AFA-PD. The Consolidated Standards of Reporting Trials flowchart is shown in Figure 2.

PATIENT AND SURGICAL CHARACTERISTICS

Table 1 reflects variables related to the patients and surgical interventions performed. Rates of pylorus-preserving PD, venous resection, completion pancreatectomy, and types of pancreatic anastomosis were similar between the 2 study groups.

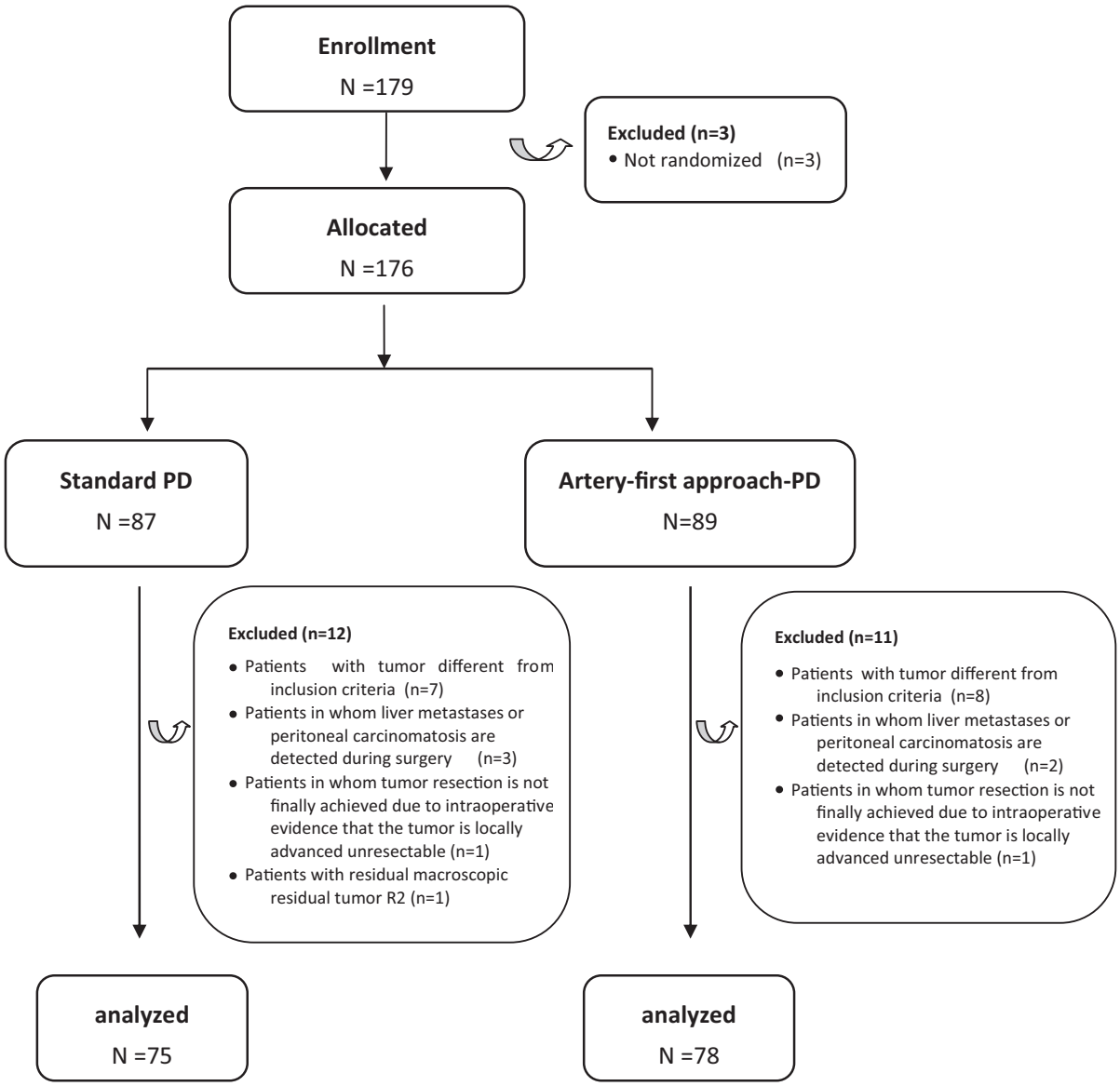

FIGURE 2. CONSORT flow diagram.

OUTCOMES

Table 2 provides information regarding surgical outcomes. R0 resection rates were 77.3% for ST-PD and 67.9% for AFA-PD. In the subgroup of patients with pancreatic adenocarcinoma (n=87), R0 resection rates were 57.9% and 58.8%, respectively. Seventeen cases undergoing ST-PD (22.7%) and 25 undergoing AFA-PD (32.1%) had at least 1 affected margin, the most frequent being the posterior circumferential margin: 15/17 (88%) with ST-PD versus 14/25 (56%) for AFA-PD (P=0.069).

Overall morbidity rates were 73.3% in the ST-PD group versus 67.9% in the AFA-PD group (P=0.484). There were no differences between groups in rates of pancreatic fistula, postoperative hemorrhage, delayed gastric emptying, biliary leak, severity of complications (Clavien-Dindo grade $\geq$3 and mean CCI), reoperation, readmission or postoperative hospital stay. Diarrhea was observed in 4% of cases undergoing ST-PD versus 8% undergoing AFA-PD (P=0.495). Ninety days mortality for the whole series was 5.8%: 4% with ST-PD and 7.7% with AFA-PD (P=0.267).

DISCUSSION

This study represents the first multicenter, randomized, controlled trial comparing R0 resection rates with 2 different surgical approaches to pancreatoduodenectomy for pancreatic and periampullary malignant tumors. The most complex anatomical area of the PD operation was approached in 1 of 2 ways: from the portal vein-superior mesenteric axis (standard approach) or from the superior mesenteric artery (artery-first approach). According to our results, approach had no impact on the rates of affected surgical margins.

Despite the recent widespread diffusion of AFA-PD, it was first described in the 1990s by Nakao and Takagi[39] and Leach et al.[40] In 2001, Machado et al[41] reported the posterior approach in a series of patients, highlighting the advantages of this technique for cases

TABLE 1. Patient Characteristics and Surgical Procedures.

Variable	Category	ST-PD (n=75)	AFA-PD (n=78)	Total (n= 153)
Age (yr)		67.7 ± 10.2	67.9 ± 67.9	67.8 ± 9.7
Sex	Male	45 (60%)	44 (57%)	89 (58%)
	Female	30 (40%)	34 (43%)	64 (42%)
Diabetes Mellitus		23 (35%)	24 (32%)	47 (33%)
ASA III		42 (56.0%)	39 (50%)	81 (53%)
Preop biliary drainage		44 (59%)	43 (55%)	87 (56%)
Pathological Diagnosis	Pancreatic cancer	38 (50.6%)	51 (65.4%)	89 (58%)
	Ampullary cancer	26 (34.7%)	22 (28.2%)	48 (31.4%)
	BileDuct Cancer	9 (12%)	5 (6.4%)	14 (9.2%)
	Duodenal Cancer	2 (2.7%)	0 (0%)	2 (1.3%)
Whipple /PP	Whipple	70 (93%)	76 (97%)	146 (95.4%)
	Pylorus-preserving	5 (7%)	2 (3%)	7 (4.6%)
Pancreatic anastomosis	PJ	56 (81%)	59 (86%)	115 (83%)
	PG	13 (19%)	9 (14%)	22 (17%)
Completion pancreatectomy		6 (8.0%)	10 (12.8%)	16 (10.5%)
Vascular resection		12 (16.0%)	18 (23.1%)	30 (19.6%)

Continuous variables expressed as mean ± standard deviation, and categorical expressed as n and frequencies (%).
PP indicates pylorus-preserving; PJ, pancreatojejunostomy; PG, pancreatogastrostomy; ASA, American Society of Anesthesiologists.

with portal vein invasion requiring resection and reconstruction. Pessaux et al[42] and Varty et al[43] subsequently published clarifying papers on the resection of the retroportal pancreatic lamina with initial dissection of the SMA and defined the technique as ''superior mesenteric artery first'' approach. In 2010, the term ''artery-first approach'' was coined from the title of a study by Weitz et al[44] describing the SMA approach from the infracolic compartment. Since then, this terminology has expanded internationally to describe

TABLE 2. Primary and Secondary End-point: R0 Resection Rate, Margin Invasion, and Postoperative Outcomes.

Variable	Category	ST-PD (n=75)	AFA-PD (n=78)	Total (n= 153)	*P* Value
R0 n (%)	Pancreatic and periampullary tumors	58 (77.3%)	53 (67.9%)	111 (72.6%)	0.194
R0 n (%)	Pancreatic cancer	22 (57.9%)	30 (58.8%)	52 (58.3%)	0.930
At least 1 margin affected		17 (22.7%)	25 (32.1%)	42 (27.4%)	0.806
Margin affected (1 or more simultaneously)	Transection	2 (12%)	7 (28%)	9 (21%)	0.167
	Medial	15 (88%)	18 (72%)	33 (78%)	0.776
	Posterior	15 (88%)	14 (56%)	29 (69%)	0.069
Isolated lymph nodes		18 ± 8	18 ± 8	18 ± 8	0.969
Operation time (min) median [IQR]		330 [285–390]	360 [300–420]	340 [300–395]	0.430
Blood loss (mL)		303 ± 408	344 ± 304	324 ± 359	0.525
Intraoperative Blood Transfusion		9 (12.2%)	14 (18.2%)	23 (15.2%)	0.249
Complications	Yes	55 (73.3%)	53 (67.9%)	108 (70.6%)	0.484
	Clavien-Dindo ≥3	18 (24%)	16 (20.5%)	34 (22.2%)	0.699
	CCI (mean ± SD)	26 ± 19.5	29.7 ± 24.3	27.8 ± 21	0.390
Hemorrhage		8 (10.7%)	8 (10.3%)	16 (10.5%)	1.000
Pancreatic fistula (A/B/C)		23 (31%) 11 (15%)/ 9 (12%)/3 (4%)	16 (21%) 7 (9%)/ 7 (9%)/2 (3%)	39 (25%) 18 (12%)/ 16 (10%/5 (3%)	0.194
DGE		13 (17.3%)	14 (17.9%)	27 (17.6%)	1.000
GI fistula		3 (4.0%)	3 (3.8%)	6 (3.9%)	1.000
Biliary fistula		4 (5.3%)	3 (3.8%)	7 (4.6%)	0.714
Abdominal abscess		17 (22.7%)	17 (21.8%)	34 (22.2%)	1.000
Chylous fistula		5 (6.7%)	6 (7.7%)	11 (7.2%)	1.000
Diarrhea		3 (4.0%)	6 (7.7%)	9 (5.9%)	0.495
Postop. transfusion		21 (28.0%)	18 (23.1%)	39 (25.5%)	0.578
Reoperation		5 (6.7%)	5 (6.4%)	10 (6.5%)	1.000
Readmission		12 (16.0%)	5 (6.4%)	17 (11.1%)	0.073
Hospital stay (d) (median, range)		15 (11-22)	17 (13-25)	16 (11-23)	0.182
30-d Mortality		3 (4.0%)	5 (6.4%)	8 (5.2%)	0.721
90-d Mortality		3 (4.0%)	6 (7.7%)	9 (5.8%)	0.267

Continuous variables are expressed as mean ± standard deviation or median and range; categorical variables as n (%) and [IQR].
DGE indicates delayed gastric emptying; GI, gastrointestinal.

TABLE 3. Summary of Previous Studies Comparing AFA Versus ST Pancreatectomy.

	Year of Publication	Type of SMA Approach	Study Type	No Patients Included	Operative Time* (min)	Intraoperative Blood Loss*	Need for Transfusion (%)	R0/R1 (%)	Lymph Node*	Morbidity (%)	Mortality (%)
Horiguchi et al	2007	IPDA first	Cohort study	36							
ST-PD				18	503 ± 186	†1225 ± 375					
AFA-PD				18	451 ± 89	678 ± 329 (g)	–	–	–	–	–
Figueras et al	2008	Posterior	Cohort study	56							
ST-PD				18	383 ± 67		†100	89/11		†94	5.5
AFA-PD				38	380 ± 79	–	33	82/18	–	50	5.3
Kawai et al	2008	IPDA first	Cohort study	96							
ST-PD				48	†357 (255–560)	†867 (120–4640)	†56.25			25	2
AFA-PD				48	339 (255–559)	728 (120–3130)(mL)	27	–	–	14.5	0
Dumitrascu et al	2010	Posterior	Case-control	42							
ST-PD				21	†332.38 ± 85.84	†435.71 ± 219.17		57.14/42.85		47.6	0
AFA-PD				21	228.57 ± 75.78	292.86 ± 195.12 (mL)	–	57.14/42.85	–	42.85	0
Ishizaki et al	2010	IPDA first	Cohort study	287							
ST-PD				112	†360 ± 108	†1062 ± 605	†46			†61	†4.5
AFA-PD				175	578 ± 112	446 ± 302 (mL)	2	–	–	45	0
Kurosaki et al	2011	Left posterior	Cohort study	75							
ST-PD				35	526 ± 95	1352 ± 823		71.4/28.6		42.9	0
AFA-PD				40	516 ± 95	1307 ± 823 (mL)	–	72.5/27.5	–	30	0
Shrikhande et al	2011	Posterior	Case-control	44							
ST-PD				14	450 (360–540)	600 (300–1.600)	–	92.85/7.14	9 (2–14)	14.3	0
AFA-PD				30	457.5 (330–630)	800 (200–4000) (mL)		96.6/3.33	8 (0–26)	40	6.67
Kawabata et al	2012	tMPDe	Cohort study	39							
ST-PD				25	614 (384–787)	1330 (230–4820)	†68	†60/40	†18 (5–40)	56	0
AFA-PD				14	568 (453–974)	1070 (340–2300) (mL)	35.7	93/7	26 (13–50)	50	0
Gundara et al	2013	IPDA first	Cohort study	42							
ST-PD				17	395 (340–410)	†627 ± 41		82.4/17.6		24	0
AFA-PD				25	380 (330–405)	385 ± 31 (mL)	–	100/0	–	36	0
Aimoto et al	2013	Left posterior	Cohort study	38							
ST-PD				19	481.16	†1.568,05		68/30	†3.4	11	0
AFA-PD				19	489.84	973.16 (mL)	–	74/26	7.9	26	0
Shah et al	2013	Superior	Cohort study	110							
ST-PD				38	†332 ± 33.8	†1371.5 ± 471.8	†63.2	–	–	31.5	0
AFA-PD				72	208.1 ± 46.3	601 ± 250.3 (mL)	13.9			19.4	0
Nakamura et al	2013	FME	Cohort study	36							
ST-PD				20	414 (310-585)	†1094 (200–3522)	†70	66.7/33.3	–	20	5
AFA-PD				16	374 (240–718)	569 (100–1339) (g)	31	86.7/13.3		25	0
Zhou et al	2014	Retrograde	Cohort study	30							
ST-PD				15	264 ± 54	423 ± 253	13.3	100/0	9.5 ± 5.7	40	0
AFA-PD				15	255 ± 57	407 ± 202 (mL)	20	100/0	10 ± 6.2	47	0
Inoue et al	2015	SMD	Cohort study	162							
ST-PD				80	†484 (273–989)	†642.5 (180–2400)	-	-	-	61.25	1.25
AFA-PD				82	453.5 (295–780)	435 (40–2400) (mL)				70.73	0
Vallance et al	2017	Posterior	Case-control	154	—	—	—	†18.2/81.8	†21 (17–27) 28	14.3	3.9
ST-PD				77				35.1/64.9	(22–34)	20.8	3.9
AFA-PD				77							
Hirono et al	2017	Mesenteric	Case-control	116							
ResectableST-PD				30	†371 (254–520)	†501.5 (60–2.230)	†20	†86.7/13.3	23.5 (11–48)	10	3.3
AFA-PD				28	416.5 (314–535)	312.5 (40–1500)(mL)	3.6	100/0	23 (11–53)	17.9	0
BorderlineST-PD				28	452 (322–570)	†920 (115–3.610)	†46.4	85.7/14.3	26 (9–49)	17.9	0
AFA-PD				30	459 (374–620)	507.5 (115–2225)(mL)	16.7	80/20	26.5 (10–53)	13.3	0

*Mean ± SD or median (range).
†Statistical significance ($P < 0.05$).
IPDA indicates inferior pancreatoduodenal artery.

procedures in which the surgeon initially evaluates the main arteries before any irreversible step is taken and dissects the planes along the SMA axis. Several other potential advantages have been attributed to AFA-PD, such as increased number of lymph nodes retrieved, shorter operative time, reduction in intraoperative blood loss, and transfusion due to early ligation of the inferior pancreatoduodenal artery before ligation of the afferent veins. Nevertheless, all these theoretical advantages have never been demonstrated. All previous studies are retrospective case-control or cohort studies[14-29] (Table 3) with 2 major drawbacks: heterogeneity in the artery-first approaches used [45] and lack of a standardized pathological reporting.

There are 2 meta-analyses comparing artery-first approach versus standard PD. In the report by Negoi et al[46] including 14 studies, AFA-PD was associated with a reduction in blood loss and transfusions, less pancreatic fistula, less delayed gastric emptying, shorter hospital stay, lower local recurrence, and a higher rate of postoperative diarrhea. There were no differences in R0 resection, major postoperative complications, reinterventions, mortality, number of resected lymph nodes, extrapancreatic plexus invasion, liver metastasis, and survival at 1, 2, or 3 years. More recently, a meta-analysis by Ironside et al[47] including 17 studies demonstrated significant differences favoring AFA-PD in terms of intraoperative blood loss, transfusion requirements, general perioperative morbidity, duration of hospital stay, grade B/C pancreatic fistula, R0 resection, and overall survival. Interestingly, in our series AFA-PD showed a tendency toward a prolonged operative time, a similar blood loss and transfusion rate, and no increased risk of chylous leak and diarrhea as shown in other series.[16,17,19,21,22,24,25] No differences were observed in the severity of complications classified according to Clavien-Dindo and CCI.

In the before mentioned meta-analyses, a study by Gall et al[48] is included as an RCT with 12 patients. However, this study compares the ''no-touch isolation technique'' versus standard PD; there is no description regarding management of the SMA. ''No-touch'' isolated PD is a different technique developed to avoid the risk of squeezing and shedding cancer cells into the portal vein secondary to grasping the pancreatic head during surgery. The confusion may arise because in some instances the ''no-touch PD'' is associated with an artery-first approach,[49] but this was not the case in the Gall study.

In our investigation periampullary and pancreatic head tumors have been included. As most studies regarding R0/R1 resection rate in PD have focused on pancreatic adenocarcinoma, the inclusion of periampullary tumors can be considered a limitation of the study. The controversial decision to include periampullary and not only ductal adenocarcinoma was driven by 2 main reasons: first, many patients come to surgery without a definitive diagnosis, since preoperative biopsy is not mandatory in resectable tumors[50]; second, there is relevant information indicating other factors such as perineural growth as more important prognostic factors than tumor localization.[3] Thus, we decided to include all periampullary tumors, so as to establish whether AFA-PD can be useful for all cases of malignant tumors of the periampullary area.

The results of our study show no difference in the rates of R0 resection achieved with ST-PD and AFA-PD when considering all tumor types. A trend toward less posterior circumferential margin invasion was observed in AFA-PD group, but the difference did not reach statistical significance. When considering only the subgroup of pancreatic adenocarcinoma, differences in R0 resection rates were so similar that it makes extremely improbable to be able to obtain statistical differences increasing the sample size. In Japan, the MAPLE-PD RCT comparing the mesenteric approach versus conventional approach for pancreatic adenocarcinoma was opened for recruitment in January 2018, and the sample size was calculated based on an estimated 2-year overall survival but not on the R0 resection rate.[51]

In summary, despite theoretical advantages associated with AFA-PD and evidence coming from low-level studies, this multicenter, randomized, controlled trial has found no difference in R0 resection rates nor postoperative complications for patients undergoing ST-PD versus AFA-PD for pancreatic head adenocarcinoma and other periampullary malignant tumors.

ACKNOWLEDGMENTS

The authors thank Mrs Landy Menzies for assistance in revising the English content of the manuscript; monitors from the SCReN-Spanish Clinical Research Network; and Alberto Domenech for illustrations.

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DISCUSSANTS

Kevin C.P. Conlon (Dublin, Ireland):

This is a well-constructed multicenter, randomized trial, which studies the value of an ''arterial-first approach" in the obtainment of an R0 resection following a pancreaticoduodenectomy. Over a two-year period, 75 patients were randomized to a standard approach (ST-PD) and 78 were randomized to an arterial-first approach (AFA-PD). The results demonstrated no difference between R0 resection rates and postoperative complications in patients undergoing ST-PD versus AFA-PD for pancreatic head adenocarcinoma and other peri-ampullary tumors.

The manuscript is well written and the authors should be congratulated for the trial design and execution.

I have a number of questions:

First, the main perceived advantage of an arterial-first approach is to obtain a negative histological margin in pancreatic ductal adenocarcinoma. In this study, 42% of patients had peri-ampullary carcinomas. Previous work would suggest that this group has an R1 resection rate, which is considerably less than for PDAC. Can the authors comment on whether, despite their sub-group analysis, the inclusion of these patients has weakened the main conclusion that AFA-PD is similar to the standard procedure for patients with PDAC?

Second, regarding the number of patients (10.5%), who underwent a completion pancreatectomy, this percentage appears somewhat high. Were these in fact patients with borderline resectable disease? If not, what was the rationale for proceeding with a completion procedure? If these patients were excluded from the analysis, would this have altered the results?

Again, the authors should be congratulated for their work. I have enjoyed reading the manuscript.

Response From Luis Sabater (Valencia, Spain):

Thank you for your comments and questions. In our study, we have included pancreatic ductal adenocarcinoma and peri-ampullary malignant tumors after lengthy discussions whilst designing the study. Two factors conditioned this decision. First, all included cases, according to the inclusion criteria, were potentially resectable tumors, for which a biopsy is not mandatory. We wanted to evaluate whether AFA-PD would be useful in all resectable cases with suspected pancreatic and peri-pancreatic malignancy, and not only in patients with a proved preoperative ductal adenocarcinoma. Second, there is increasing evidence of other factors, such as lymph nodes or a perineural invasion, which are even more important for prognosis than the location of the tumor. The inclusion of all peri-ampullary tumors enabled us to study the ability of each technique for obtaining R0 resections as well as for clearing lymph nodes and perineural tissues, regardless of the type of tumor. No differences between the two techniques were found when only taking pancreatic cancer or all tumors into consideration; this is why, in our opinion, the inclusion of all patients has not weakened the conclusions of the study.

We agree that completion pancreatectomy is probably somewhat high. There were no borderline cases included in the study. The complete pancreatectomy criteria was the same as for the other groups, and was indicated after intraoperative analysis of the transection margin. When a positive transection margin was observed, a second margin was analyzed. If positive, or when the pancreatic remnant was too small after this second margin extension, completion pancreatectomy was performed. Excluding these patients from the analysis, since there were no differences in the two groups and the number of completion pancreatectomy is similar in both groups, should not alter the final results.

Christiane Bruns (Cologne, Germany):

Thank you very much for your presentation. I also have one question regarding the R1 status. Did you also consider that an R0 resection could be an R0, in terms of the circumferential resection margin, even though you have a lymphangiosis and haemangiosis? Would this still be considered a R0 according to your pathologist, or would this be a R1 now? Also, you said that you do not have any borderline resectable patients in your study, so could you please explain how you perform the pre-operative diagnostic to justify resectable cancer where you could identify some difference in these two different approaches? Finally, you talk about recurrence. In my opinion, most pancreatic cancer patients recur in the form of a systemic disease, rather than a local recurrence. So, what is your hypothesis on differentiating between these two approaches with respect to systemic disease recurrence?

Response From Luis Sabater (Valencia, Spain):

Thank you for your comments. In our study, we analyzed histopathology according to a standard protocol, which considers the 1 millimeter rule to be a free resection margin. In other words, an R0 resection is when the tumor is at least 1 millimeter away from the resection margin. Positive lymph nodes, perineural tissue or microvascular invasion observed within this millimeter is considered to be a R1.

The preoperative diagnosis was performed via a CT-scan, MRI or endoscopic ultrasonography. Since a biopsy was not mandatory, in some cases, the final diagnosis did not meet the inclusion criteria. Most were neuroendocrine or benign tumors, and therefore, excluded from the study. We were not looking for differences to justify the use of one technique over another in any particular type of tumor, but for the usefulness of AFA-PD in malignant resectable peri-ampullary tumors, not only when a pancreatic adenocarcinoma had been preoperatively diagnosed.

Finally, we agree that most pancreatic cancer patients recur in the form of a systemic disease. However, it is also true that most of these patients have local as well as systemic recurrence; hence, it could be hypothesized that systemic and local recurrence may be related. Both techniques aim to avoid local recurrence, but their role in improving systemic recurrence of the disease is very controversial and unclear.

Irinel Popescu (Bucharest, Romania):

I have two comments. One is related to the terminology. I think that the term ''artery-first'' is misused or not well explained. As you mentioned, total meso-pancreatic excision may have been better than an artery-first one, due to the fact that out of the 6 types of artery-first, at least 3 are main operations, and there are big technical differences between those 3 types.

Second, as Christiane Bruns remarked, 153 is a big number of resections. How many portal vein resections were amongst those cases? How many borderline?

Response From Luis Sabater (Valencia, Spain):

Thank you, I appreciate your comments. Regarding terminology, there are at least 6 types of AFA-PD, with the common feature of evaluation of the superior mesenteric artery before any irreversible step. We decided to carry out the posterior approach because this is the easiest, fastest and less complex, according to the experience of the participating centers. However, this was a decision solely made by the members of the study. The concept of mesopancreas was coined in parallel with mesorectum in rectal cancer, but despite the attractiveness of the idea and the possibility of performing a total mesopancreas excision in analogy with total a mesorectal excision, the concept of meso, when applied to retropancreatic tissue, is not widely accepted because it does not meet the criteria of a mesentery definition. Whatever the term, the concept of mesopancreas reflects the surgeons' concern regarding retropancreatic tissue and margin, and AFA-PD is considered an adequate procedure for clearance of this tissue.

The number of portal vein resections in the study is 19%. This figure is frequent in PD series for malignancy, as shown in your relevant paper of 2010, which compared the posterior and the standard approach on a retrospective case-match study where vascular resection was 14%, which is only slightly lower than the present study.