Cancer Control
Volume 30: 1–13
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DOI: 10.1177/10732748231153094
journals.sagepub.com/home/ccx
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Surgical Treatment of Pancreatic Cancer: Currently Debated Topics on Vascular Resection

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Abstract

Vascular resections involving the superior mesenteric and portal veins (SMV-PV), celiac axis (CA), superior mesenteric artery (SMA) and hepatic artery (HA) have multiplied in recent years, raising the resection rate for pancreatic cancer (PDAC) and the related morbidity and mortality rates. While resection is generally accepted for resectable SMV-PV, the usefulness of associated arterial resection in borderline resectable (BRPC) and locally-advanced PDAC (LAPC) is much debated. Careful selection of splenic vein reconstruction is very important to prevent left-sided portal hypertension (LSPH). During distal pancreatectomy (DP), CA and common HA resection is largely accepted, while there is debate on the value of SMA and proper HA resection and reconstruction. Their resection is useless according to several reviews and meta-analyses, and some international societies, although some high-volume centers have reported good results. Short- and long-term reconstructed vessel patency varies with the type of reconstruction, the material used, and the surgeon's experience. Laparoscopic and robotic pancreaticoduodenectomy and DP are generally accepted if done by surgeons performing at least 10 such procedures annually. The usefulness of associated vascular resection remains highly controversial. Surgeons need to complete numerous minimally-invasive procedures to overcome the learning curve, and prevent an increase in complications and surgical mortality. Higher resectability rates and satisfactory long-term results have been reported after neoadjuvant therapy (NAT) for BRPC and LAPC requiring vascular resection. It is essential to select the most appropriate NAT for a given patient and to assess PDAC resectability preoperatively.

Keywords

pancreas, pancreatic cancer, pancreaticoduodenectomy, standard distal pancreatectomy, distal pancreatectomy with celiac axis resection, vascular resection, minimally invasive surgery, adjuvant chemotherapy, neoadjuvant chemotherapy

Received October 26, 2022. Received revised December 21, 2022. Accepted for publication January 9, 2023.

Introduction

The incidence of pancreatic ductal adenocarcinoma (PDAC) varies across regions and populations. It is the fourth leading cause of cancer-related death worldwide, with a poor prognosis and low resection rate.[1,2] Surgery is the main component of potentially curative treatment for patients with resectable disease, but most develop recurrences despite seemingly adequate procedures obtaining negative resection margins.[3,4] Unfortunately, less than 20% of all patients have resectable disease at initial diagnosis, with surgery affording a median relapse-free survival of 10-11.7 months,[5,6] and 5-year survival rates of 12-27%.[2,7,8] Historically, PDAC was judged to be resectable or locally advanced by the surgeon at the time of the operation. A preoperative definition of resectable or locally-advanced PDAC was needed, however, to identify patients eligible for enrolling in clinical trials. Computed tomography was therefore used to establish and stage pancreatic cancer

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preoperatively.[9] It soon became clear that a gray zone existed between cases of resectable and locally-advanced PDAC, which led to the definition of borderline resectable PDAC.[10,11] This term was used to define patients with arterial abutment and short-segment superior mesenteric and portal vein (SMV-PV) occlusions who would have been considered cases of locally-advanced disease. Thanks to recently expanded neo-adjuvant treatment options and increasing confidence with vascular resections (and arterial resection and reconstruction in particular), many patients previously deemed to have borderline resectable or locally advanced disease underwent successful pancreatic surgery, with or without vascular resection.[12,13] This review summarizes and analyzes recent advances in the surgical treatment of PDAC relating to the management of peripancreatic vessels during the resection procedure.

Vascular Resection

The first cases of pancreaticoduodenectomy (PD) with SMV-PV resection were reported by Moore et al[14] in 1951, and then by Asada et al[15] in 1963. Vascular resection for the surgical treatment of PDAC really started in the 1970s, however, when Joseph G. Fortner first described a series of patients treated with total pancreatectomy combined with venous (Type 1) or venous and arterial (Type 2) resection and reconstruction.[16,17] Regional pancreatectomy followed the basic principle that *en bloc* resection of the primary cancer with wide negative tissue margins and regional lymphatic drainage was needed to cure most fully malignant cancers. This involved removal of the pancreatic segment of the portal vein, and end-to-end anastomosis without a graft. The base of the transverse mesocolon and a generous margin of soft tissue around the pancreas containing regional lymph nodes were also removed *en bloc* with the pancreas and portal vein segment. In 1984, Fortner reported the results obtained in 61 patients treated with regional pancreatectomy for PDAC or ampullary and periampullary cancers: the morbidity rate was high, and the surgical mortality rates were 32% (12/37) in the years from 1972 to 1978, and 8% between 1979 and 1982.[18] Up until the 1990s, pancreatic surgeons remained reluctant to perform Fortner's proposed regional pancreatectomy due to the complexity of the procedure, the high morbidity and mortality rates, and the lack of significant long-term improvements in patients.

Venous Resection and Reconstruction

It was only during the 1990s that some authors suggested that a suspected isolated portal vein involvement should not contraindicate pancreatic resection in patients with PDAC.[19-21] Ishikawa et al[22] classified SMV-PV involvement in five ways: type 1: normal; type 2: smooth shift; type 3: unilateral narrowing; type 4: bilateral narrowing; and type 5: bilateral narrowing with collateral veins. Nakao et al[23] suggested a radiographic classification of SMV-PV invasion by pancreatic head cancer: A, normal; B, unilateral narrowing; C, bilateral narrowing; or D, complete obstruction with collateral veins. According to these Authors, histological involvement of the vein ranged from 0% in types 1-2 or A, to 51% in type 3 or/B, 74% in type 4 or C, and 93% in type 5 or D.[22,23] The extent of venous resection required depends strictly on the extent of venous invasion, and can be predicted preoperatively, enabling adequate planning instead of on-table decisions.[24] Several types of vascular reconstruction have been described in the international literature, for different extents and types of SMV-PV resection. They include: primary venous closure; end-to-end anastomosis; interposition grafts using autologous veins; autologous substitute grafts constructed from various parts of parietal peritoneum, including the falciform ligament; and cryopreserved and synthetic allografts.[25] The International Study Group for Pancreatic Surgery (ISGPS) proposed four types of SMV-PV resection: Type 1, tangential resections with venorrhaphy; Type 2, resections with patch reconstruction; Type 3, resection with end-to-end anastomosis; and Type 4, resections with graft interposition.[26] The optimal method for venous reconstruction after segmental SMV-PV resection remains a matter of debate. Although an end-to-end anastomosis is simple and preferable to an interposition graft, be it for PD,[26-35] distal pancreatectomy (DP)[33,36,37] or total pancreatectomy (TP),[26,28,33-35] the distance from the residual PV to the SMV or its branches may be too long for an end-to-end anastomosis. Even when an end-to-end anastomosis is technically feasible, the rate of thrombosis and stricture/occlusion may increase if the reconstruction creates excessive tension.[28] According to Fujii et al.[28] "when tension-free anastomosis cannot be guaranteed, generally in cases requiring ≥31 mm of SMV/PV resection, venous autografting may decrease the likelihood of anastomotic stenosis". All their 197 reported patients nonetheless underwent end-to-end anastomosis, with the aid of a Cattell-Braasch maneuver (ie, mobilization of the right colon) in some cases.[28] Younan et al[38] also reported that an end-to-end anastomosis is feasible even after long SMV-PV resections thanks to the addition of procedures like the Cattell-Braasch maneuver and splenic vein (SV) resection. More recently, Irie et al[32] proposed the parachute technique for patients undergoing PD when the distance between the resected PV and SMV is relatively long. The overall patency rates obtained using the above-mentioned reconstruction techniques ranged between 70% and 94.6%.[31,32,39-45] In a series of recent articles,[26,32,34-37] the SMV-PV resection techniques used in a total of 1183 patients - based on the ISGPS classification - were distributed as follows: Type 1: 202, Type 2: 73, Type 3: 768, Type 4: 140. In the same series, the early thrombosis rate was 8.0% (95/1183).[26,32,34-37] Hackert et al[26] reported their results for 2265 PDAC resections performed from 2006 to 2018, involving SMV-PV resections in 694 (30.6%) patients: 149 (21.5%) tangential resections with venorrhaphy; 21 (3.0%) resections with patch reconstruction; 491 (70.7%)

end-to-end anastomoses; and 33 (4.8%) resections with graft interposition. The 90-day mortality rate was 2.6% after standard resection, and 6.3% after SMV-PV resection (P < .0001). Postoperative portal vein thrombosis and pancreas-specific surgical complications occurred most frequently after SMV-PV resection with graft interposition (in 7/33 and 16/33 cases, respectively. Roch et al[34] reported on 220 patients undergoing pancreatectomy involving SMV-PV resection for any indication between 2007 and 2019. Thrombosis occurred in 36 (16.4%) patients a median 15.5 days later. Its frequency varied for the different SMV-PV reconstruction techniques, occurring in 12.8% of venorrhaphies, 13.2% of end-to-end anastomoses, 22.6% of autologous vein grafts, and 83.3% of synthetic interposition grafts (*P* < .0001). Ninety-day mortality for the whole SMV-PV resection/reconstruction cohort was 6.8%. A systematic review to identify the optimal type of graft for SMV-PV resection (ISGPS Type 4) in pancreatic surgery considered 34 studies published between January 2000 and March 2020 (concerning 603 patients).[46] The results obtained with four types of graft (autologous vein, autologous parietal peritoneum/falciform ligament, allogeneic cadaveric vein/artery, and synthetic grafts) were analyzed. The incidence of early and overall graft thrombosis was 7.5% and 22.2%, respectively, for synthetic grafts, 5.6% and 11.7% for autologous vein grafts, 6.7% and 8.9% for autologous parietal peritoneum/falciform ligaments, and 2.5% and 6.2% for allografts. There were no synthetic graft infections. The authors concluded that autologous, allogeneic or synthetic grafts were safe and feasible for SMV-PV reconstruction in selected patient groups, but the graft thrombosis rate was higher for synthetic grafts.

Four meta-analyses examined the short- and long-term outcomes of SMV-PV resection associated with PD or standard distal spleno-pancreatectomy (SDP).[47-51] Compared with pancreatic resection alone, adding SMV-PV resection significantly increased 30-day postoperative mortality,[47,50] but not 90-day mortality,[51] morbidity,[47,50] the rates of certain complications,[48,51] the length of hospital stay,[48] or the proportion of non-radical resections.[47-51] Long-term survival was also significantly shorter for patients undergoing SMV-PV resection.[47,49-51]

An interesting comparison can be drawn between the benchmarks targeting surgical performance, morbidity, mortality, and oncological parameters in patients undergoing PD or PD plus SMV-PV resection, based on data collected by 23 international centers expert in pancreatic surgery (Table 1).[52,53] Two multicenter studies analyzed consecutive patients undergoing standard PD (2012-2015)[52] and PD plus SMV-PV resection (2009-2018).[53] There was a marked variation in the morbidity and mortality rates reported by the participating centers around the world, although they were all carefully selected for their high level of expertise.[52,53] It is worth noting the relatively small difference between the morbidity and mortality reference thresholds adopted in the two studies.

Table 1. Outcome Benchmarks After PD With PVR in 840 Low-risk Cases 48,49.

Benchmark Cutoffs	PD	PD with SMV-PV Resection			
Operation duration	≤7.5 h	≤8 h			
Intraoperative blood transfusion rate	≤23%	≤27%			
Intensive therapy unit stay	NR	≤1 d			
Hospital stay	≤15 d	≤14 d			
Postoperative morbidity	At discharge	At discharge	At 90 d	At 6 m	
Any complication	≤73%	≤79%	≤83%	≤83%	
Clavien-Dindo Grade ≥3a	≤30%[a]	≤28%	≤34%	≤36%	
Comprehensive complications index (CCI)	≤20.9	≤21.0	≤23	≤26	
Pancreatic leak rate (all grades) (ISGPF)	NR	≤19%			
Clinically relevant POPF (Grades B or C)	≤19%	≤14%			
Severe postoperative bleeding grade ≥3a	≤7%	≤7%			
In-hospital mortality	≤1.6%	≤4%			
1-yr hospital readmission rate	≤21%	≤32%			
Portal vein thrombosis rate	NR	≤14%			
Occlusive only rate	NR	≤4%			
Oncological outcomes (PDAC only, n = 679)	R0 rate	R0 rate	R1 rate	R2 rate	
Resection margin status	≥61%	≥35%	≤63%	≤2%	
Portal vein positive resection margin state	NR	≤3%			
Total number of lymph node resected	≥16	≥16			
Survival (PDCA only, n = 589)	1-yr	1-yr	2-yr	3-yr	5-yr
Overall survival rate	NR	≥68%	≥37%	≥21%	≥9%
Disease-free survival rate	≥53%	≥22%	≥9%	≥2%	≥0%

[a]Clavien-Dindo Grade ≥ III.

According to Machairas et al,[54] adding neoadjuvant therapy (NAT) or neoadjuvant chemoradiotherapy (NACRT) for patients undergoing PD with SMV-PV resection significantly increased the R0 resection rate, and 1-, 3-, and 5-year overall survival (OS). It is important to bear in mind, however, that this was a multicenter retrospective study that spanned 10 years (from 2009 to 2018); it involved 23 high-volume participating centers in Asia, Europe, and America; different combinations of NAC/NACRT were used; and not all centers shared the same definition of R0.

In a retrospective study concerning the years 2006 to 2020, Addeo et al[55] found that NAC afforded a statistically significant survival benefit ($P = .02$) in the setting of PDAC with venous involvement. Unfortunately, over this quite long study period, significantly more patients (35/55; $P = .0001$) received chemotherapy after 2016. As the Authors themselves put it: "the fact that comparison was made across two different patient populations treated in two different periods with different chemotherapy regimens could bias the results". The promising preliminary results of the ESPAC 5F trial,[56] and other randomized trials[57] suggest that NAT may contribute to a survival benefit in PDAC patients with venous involvement.

In conclusion, when compared with standard PD, adding SMV-PV resection increases the resection rate but appears to be associated with a greater risk of complications,[26,34,47,48,50,51] and a higher mortality rate,[47-50] even at very high-volume centers.[26,34] These findings make careful patient selection mandatory when a major venous invasion is suspected prior to surgery. Any decision should be shared with patients after informing them about the risks. SMV-PV resection should only be performed at high-volume centers, which achieve better outcomes.[51] An increasing body of data suggests that NAT is useful in the treatment of patients with SMV-PV involvement, especially in cases of borderline resectable PDAC.[55] That said, a statistically significant demonstration of its value in patients with SMV-PV involvement is not yet available.

Splenic Vein Ligation or Reconstruction

SMV-PV resection poses the problem of how to treat the SV. Ligation is usually the preferred solution, but it may be responsible for left-sided portal hypertension (LSPH), leading to variceal bleeding and hypersplenism-associated thrombocytopenia. According to the systematic review by Petrucciani et al,[58] LSPH occurred in 28 (7.7%) of 336 patients who underwent SV reconstruction, and in 99 (29.4%) of 337 who had SV ligation. Gastrointestinal bleeding was reported in 14 cases a mean 28 months (range 8-99) after PD. The mortality rate was 7.1%. The varices occurred in the esophagus (4 patients), stomach (5), jejunum (2), pancreas (4), and colon (7), and at multiple sites (6 patients). Tanaka et al[59] identified the left gastric vein, middle colic vein, and superior right colonic vein arcade as crucial to the prevention of LSPH, and showed that the risk of varices depended on how many of these crucial veins were preserved. None of the patients with ligated SV, or occlusions after SV reconstruction developed LSPH if two or more critical veins were preserved, as opposed to 24% of patients with only one crucial vein preserved and 100% of those with no crucial veins preserved. This information can be very helpful when deciding whether or not to reconstruct a SV. In all cases, careful patient follow-up is advisable to ensure a timely diagnosis and treatment of LSPH. The most common options for SV reconstruction involve reimplanting the SV in the SMV-PV axis or creating a spleno-renal shunt whenever an insufficient venous drainage is expected. Unfortunately, the Authors wrote: "The definition of LSPH is not homogeneous, and the boundary between LSPH as a radiologic finding vs a clinically relevant problem is not clear".

In conclusion, an increasing incidence of LSPH due to more patients undergoing PD with venous resection, and to better survival rates, should be expected and, if possible, prevented by a careful selection of patients for SV reconstruction.

Arterial Resection and Reconstruction Associated With PD or TP

The superior mesenteric artery (SMA), common hepatic artery (HA) and proper HA are functional end arteries. If they are invaded by advanced PDAC, they cannot be resected without reconstructing them to ensure appropriate perfusion of the liver and bowel downstream. Their invasion is considered an expression of more advanced disease and a poor prognosis. The debate on the usefulness of AR during PD has evolved considerably in recent years: while it was once thought to be unnecessarily risky, it is now seen as feasible under certain conditions.

According to a systematic review,[60] and to a systematic review and meta-analysis[61] AR in patients undergoing pancreatectomy for PDAC is associated with poor short- and long-term outcomes, so there is currently no evidence to support SMA resection during PD or TP. In our opinion, however, these two reviews presented biased results: they included studies on patients undergoing both arterial and venous resections, without clearly distinguishing between them, and the quality of the data on the use of neoadjuvant or adjuvant chemotherapy/chemoradiotherapy was poor.[61] Interestingly, Mollberg[60] suggested that pancreatectomy with AR may be justified in carefully-selected patients because of the potential survival advantage over no resection. In 2014, the ISGPS issued a consensus statement[11]: "There is no good evidence that arterial resections during right-sided pancreatic resections are of benefit. Such resections may be harmful with increased morbidity and mortality, and should not be recommended on a routine basis (strong recommendation). Patients categorized as borderline resectable, based on features of arterial involvement seen at imaging, should undergo surgical exploration to obtain further verification of any arterial infiltration (strong recommendation). In case of verification of arterial involvement, palliative treatment is the standard of care (strong recommendation)." It is worth emphasizing that this statement is based largely on Mollberg's systematic review and meta-analysis,[60] and on the definition of resectability status in the NCCN guidelines (version 1.2013). According to French recommendations (drafted on behalf of the French National Institute of Cancer),[62] "a PD with planned arterial resection (except for SMA) may be proposed in selected patients with stable tumors or after tumor response to NAT. This must be evaluated according to the location of the tumor and the type of arterial extension (Grade B). In case of SMA invasion, NAT is recommended, followed by laparotomy with dissection and biopsy of peri-arterial tissues in case of tumor stability or tumor response. If the frozen section examination is positive, a PD with arterial resection is not recommended (Grade C)." Here again, it should be stressed that these French recommendations[62] are based on: four studies concerning 424 AR (with simultaneous VR in 155/248 cases described in two of the studies); on the systematic reviews and meta-analyses conducted by Mollberg and Jegatheeswaran[60,61]; and on a survey by the Association Française de Chirurgie on venous resection during PD or TP for PDAC, involving 25 AR[63] Unfortunately, no meta-analysis was performed on the data collected.

A systematic review and meta-analysis published by Małczak et al[64] concerned 19 studies with a total of 2955 patients (including 1913 who had PD, 574 who had DP, and 276 who had TP). The SMA was resected in 58 cases, the HA or proper HA in 122, and the celiac axis (CA) in 44. Mortality and morbidity rates were significantly higher after AR (11.02% vs 3.6% [$P < .001$], and 48.3 vs 33.7 [$P < .01$], respectively). One-year survival was similar after standard resection with or without AR (P = .7), while 3-year survival after standard resection alone was 40% better than that after standard resection with AR ($P < .04$). According to the Authors, adding AR in patients with PDAC is associated with a higher risk of mortality and complications than for standard resections. They also suggested that AR may nonetheless become a viable treatment for selected patients at high-volume centers.

Another systematic review and meta-analysis published by Haines et al [65] included 13 studies with a total of 1330 patients (712 had PD, 246 had DP, and 324 had TP). The SMA was resected in 199 patients, the HA or aberrant HA in 583, and the CA in 427. The reported median 90-day mortality and morbidity rates after AR were respectively 5% (range 0%-17%) and 52% (37%-100%). The median survival time was 17 months (range 7-29 months), with median survival rates of 59% (16-92%) at 1 year, 17% (0%–23%) at 3 years, and 10% (0%–23%) at 5 years. The median disease-free survival time was 17 months (range 15-31 months), and the median 3-year disease-free survival rate was 11% (range 0%-12%). According to the Authors, pancreatectomy with AR may be performed safely at high-volume centers in carefully-selected patients with acceptable survival results. The creation of a multi-institutional registry of pooled data would enable a more accurate assessment of the safety and efficacy of this treatment strategy.[65]

A systematic review and meta-analysis performed by Rebelo et al[66] included 31 studies with a total of 6925 patients (4094 had PD, 2256 had DP and 174 had TP). The SMA was resected in 82 patients, the HA or proper HA in 166, and the CA in 648. When the groups with and without AR were compared, neither overall morbidity (48% vs 39%, $P = .1$) nor mortality (3.2% vs 1.5%, $P = .27$) differed significantly. As expected for more advanced disease, the R0 resection rate was lower in the AR group, both in patients who were given NAT (50% vs 86%, $P < .001$) and in those who were not (69% vs 89%, $P < .001$). The weighted median survival time was 18.6 months (range 14.8-25 months) for patients who underwent pancreatic surgery with AR, and 32 months (range 19-43.1 months) for patients who had a standard procedure ($P = .037$). According to the Authors, AR adds to the complexity of pancreatic surgery, as confirmed by the high morbidity and mortality rates. Careful patient selection and multidisciplinary planning remain important.

Differences in the perioperative results described in the three reviews are at least partly attributable to a prevalence of older studies (14/19 conducted before 2010) in Małczak's study,[64] and of studies on distal pancreatectomy with celiac axis resection (DP-CAR) (19/31 studies) in the review by Rebelo et al[66]

Arterial and Venous Resection and Reconstruction Associated With PD or TP

The term locally-advanced pancreatic cancer (LAPC) is broadly used for "unresectable" non-metastatic PDAC, as defined by the ISGPS[11] in 2014. In LAPC there is an extensive involvement (>180°) of the SMA, CA, aorta or vena cava, and encasement of the SMV-PV, making surgical reconstruction out of the question. Simultaneous SMV-PV and SMA resection is therefore usually considered excessively risky. In a recent SSAT debate (2021), Boggi et al[67] explained why the technical complexity of pancreatectomy with SMA resection appears to exceed that of pancreatectomy with CA/HA resection. "First, SMA always requires arterial reconstruction and sometimes it is necessary to reconstruct multiple arterial and venous branches of the superior mesenteric vessels. Second, in almost all patients, SMA resection is associated with superior mesenteric vein (SMV) resection. In about a quarter of patients, the SMV is occluded, thus posing further technical problems. Third, most cancers that require resection of the SMA are found in the uncinate process and therefore require at least a PD, while in many patients with CA/HA involvement, the pancreatic head can be spared. Fourth, transient SMA/SMV cross-clamping is associated with intestinal ischemia/reperfusion injury that can impair kidney, lung, and heart functions, affects intestinal permeability, and reduces intestinal barrier integrity, thus facilitating bacterial translocations. The systemic consequences of CA/HA resection are often less obvious." A lack of radiological disease progression, and a decrease in Ca 19.9 levels (in patients expressing Ca 19.9) after NAC/NACRT, along with a good clinical condition, are generally accepted criteria for proposing a procedure that includes SMA resection with or without SMV resection.[67]

Loos et al[68] recently reported the largest series of pancreatic resections for LAPC (385 patients) performed between 2003 and 2019. After completing NAT, pancreatectomy with periadventitial dissection (PAD) or pancreatectomy with arterial resection (PAR) were performed in 190 and 195 patients, respectively. The SMV-PV were resected in 41.6% of the PAD and 47.2% of the PAR. Overall, the Authors performed 183 TP, 113 PD, 79 DP, and 10 other procedures. The median survival time after surgery for LAPC was 20.1 months, and the 5-year OS rate was 12.5%. In-hospital mortality was 8.8% for the whole patient cohort, but dropped to 4.8% among the last 186 patients undergoing surgery after 2013 ($P = .005$) thanks to the surgeons' growing expertise. While a learning curve was unnecessary for PAD, experienced pancreatic surgeons needed to perform 15 procedures to obtain good results with PAR.

Arterial Resection and Reconstruction Associated With DP

Body/tail PDAC involving the CA or HA is staged as T4 according to the eighth AJCC Cancer Staging Manual,[69] regardless of tumor size and resectability. It was considered unresectable in the past and, according to some experts, it still is. In 1953, Lyon H. Appleby[70] was the first to report a total gastrectomy and DP combined with en bloc CA resection for the treatment of a locally-advanced gastric cancer. DP-CAR for PDAC was first described by Nimura in 1976, in an article in Japanese.[71] Since then, it has been performed more and more frequently, becoming the most often-used AR[65,66] for several reasons: (1) there is no need for an arterial reconstruction because a collateral circulation to the liver and stomach is assured by the SMA via the gastroduodenal artery; (2) preoperative arterial embolization of the CA and/or its branches can be used to enhance this natural collateral arterial circulation[72]; and (3) there is no need for pancreatico-enteric reconstruction. About one in five DP performed in patients with body/tail PDAC are DP-CAR.[73-75] Operating times,[73-75] transfusion rates,[73,75] portal vein resections,[73-75] lymph node positivity rates,[75] delayed gastric emptying,[73,75] postoperative bleeding,[73] mortality rates,[73,74] lengths of hospital stay,[73] and recurrence rates[73] were all significantly worse after DP-CAR than after SDP, and the R0 resection rate was significantly lower.[73,75] Feng et al[75] also reported a significantly worse OS after DP-CAR than after SDP, while neither Liu et al[73] (at 1-2 year OS), nor Nigri et al[74] found any difference. Disease-free survival was not reported. Doubts have been cast on the usefulness of HA embolization prior to DP-CAR by the findings of a multicenter (15 centers) study reported by Ramia et al[76]: major morbidity (Clavien > IIIa) and 90-day mortality (60% vs 23% and 26.6% vs 11.6% respectively, $P < .004$) rates were higher among the 15 patients who underwent embolization than for the 26 who did not. No statistical difference in OS emerged between the two groups ($P = .14$). Addeo et al[77] successfully performed HA reconstructions during DP-CAR in 50/60 patients to lessen the risk of postoperative ischemic events. Associated SMA and SMV-PV resections were performed in 2 and 44 patients, respectively. After surgery, the median survival time was 17.7 months, with 1-, 3-, and 5-year OS rates of 58%, 18%, and 8%, respectively.

As experience was gained with reconstructions of the HA and SMA, the resectability of body/tail PDAC was extended to cases with involvement of the gastroduodenal and proper HA bifurcation (which impairs the collateral system on which a traditional Appleby procedure relies for hepatic and gastric perfusion) and/or of the proximal SMA, especially after NAC/NACRT.[78] Based on 90 DP-CAR performed for PDAC between 1995 and 2019, Truty et al[78] proposed a 3-level classification of CAR to simplify a comparison of the levels of experience gained by centers performing DP-CAR (Table 2). The Authors considered on 41 CAR in Class I, 33 in Class II, and 16 in Class 3, with arterial and venous revascularizations performed in 66%. Ninety-day mortality dropped to 4% among the last 50/90 patients, but the major morbidity rate remained unchanged (55%). Hepatic and gastric ischemia occurred in 20% and 10% patients, respectively, and arterial revascularization had a protective effect. The R0 resection rate (88%) was associated with preoperative chemo-radiotherapy. The median survival time was 36.2 months.

Table 2. Celiac Axis Resection Classification System.

Celiac Class	Artery Resection	Need for Revascularization	Pancreatectomy Type	Gastric Preservation
1A	Celiac only	No	Distal	Possible
1B	Celiac only	Yes	Distal	Possible
1C	Celiac only	Yes	Distal	No
2A	Celiac/PHA	Yes	Subtotal	No
2B	Celiac/PHA	Yes	Total	No
3A	Celiac/SMA	Yes	Distal	Possible
3B	Celiac/PHA/SMA	Yes	Subtotal/total	No

PHA: proper hepatic artery; SMA: superior mesenteric artery. Reprinted from Truty MJ with permission.[76]

In a multicenter retrospective cohort study, Klompmaker et al[79] investigated 191 patients who underwent DP-CAR: 71 at 20 centers in 12 European countries, and 120 at three very-high-volume centers in the United States and Japan). The 90-day mortality rate was 5.5% (95% confidence interval [CI] 2.2-11%) for 128 patients treated at five DP-CAR high-volume centers (3 in the United States and Japan and 2 in Europe), and 18% (95% CI 9-30%) for those 63 patients managed at 18 European DP-CAR low-volume centers (P = .015).

The Vessels' Fate After AR and Reconstruction

Alva-Ruiz et al[80] recently examined what happened to the vessels after an arterial reconstruction in 108 patients who underwent HA resection, associated with CA or SMA resection in 50% of cases. TP was performed in 49/108 patients, PD in 33, and subtotal DP in 26. Reconstruction with graft interposition was used in 66/108 patients, and primary end-to-end anastomoses in 42. Early and late complete arterial occlusions (CAO) occurred in 8 and 11 of the 108 patients, respectively, with arterial interposition grafts less likely to become occluded. CAO-related perioperative mortality was 4.6%, and significantly higher for early than for late CAO (P = .046). The median time to CAO was 126 days.

In conclusion, SMV-PV resection associated with SMA, HA or CA should only be considered at high-volume centers capable of assuring surgeons an adequate learning curve, and only for carefully-selected patients. No prospective randomized controlled trials (RCT) on the topic are available or ongoing.

Alternatives to Arterial Resection

An interesting sub-adventitial divestment procedure was recently proposed to avoid AR during surgery for PDAC.[81] After an artery-first approach in patients undergoing PD or DP, the plane between the tunica adventitia and the white, glossy external elastic lamina is identified using careful dissection with an electrocautery or ultrasonic scalpel at a site of an uninvolved segment of the involved or encased artery (CA, HA, proper HA, and/or SMA), just proximal or distal to the area of tumor involvement. Blunt dissection is used to proceed along the plane above the external elastic lamina towards the tumor from either one or both directions. The plane is developed both longitudinally and circumferentially until the artery has been freed from any tumor. Small arterial branches must be ligated, then divided. If the dissection plane cannot be clearly identified and clearly developed as required, then the dissection should be stopped and artery resection could be considered, or the curative intended resection should be ceased, as this usually means that the tumor has invaded the external elastic lamina into the smooth muscle of the tunica media.[81] The above-described approach warrants further validation in prospective studies.

Visceral Debranching

An interesting prospective trial (NCT04136769) has begun to examine whether "visceral debranching" - ie the surgical reconstruction of arterial blood vessels supplying the liver or bowel - prior to chemotherapy and final tumor resection is a feasible approach for patients with locally-advanced PDAC. Visceral debranching is defined as a vascular reconstruction aimed at ensuring a sufficient arterial blood flow to the mesentery and liver after a planned tumor resection, which usually comprises ligation of the gastroduodenal artery or other relevant collateral vessels. The subsequent tumor resection should be performed 2-4 weeks after completing chemotherapy. Before proceeding with the resection, the patient undergoes restaging and the patency of the vascular reconstruction is checked. The trial is expected to be completed by July 2026.

Role of Minimally-Invasive Pancreatic Surgery in the Treatment of PDAC

The first laparoscopic PD (LPD) was described by Gagner and Pomp[82] in 1994, and the first laparoscopic DP (LDP) by Cuschieri et al[83] in 1996, both procedures being performed for chronic pancreatitis. In 2003, Giulianotti et al[84] reported on their first experience with robotic surgery for pancreatic disease, performed in 13 patients (8 PD and 5 DP) with one death (due to Boerhaave's syndrome) after PD, and none after DP. As experience was gained with the procedure, the indications were expanded to include SMV-PV resection and reconstruction.[85,86] MIPS has been slow to take on, compared with other minimally-invasive abdominal procedures, because of the difficult position of the pancreas within the abdomen, the important vessels with which it is in contact, the need for reconstruction (as in the case of PD), the limited freedom of movement afforded by conventional laparoscopic instruments, and the two-dimensional view it offers. Robotic pancreaticoduodenectomy (RPD) is more expensive than laparoscopic surgery, but it gives surgeons three-dimensional stereoscopic views of the field, a greater dexterity from endo-wristed instruments, the filtration of tremors, and the ability to perform complex dissections, sutures and knots with unprecedented precision.[87] Reported cases of RPD tripled from around 150 a year in 2010 to around 450 in 2016,[87] but its use remains low (less than 5% of PD performed in USA) because of its complexity.[88] The main, commonly-recognized benefits of MIPS[87,89-95] over open surgery (OPS) are less blood loss during the procedure and a shorter hospital stay, but the operating time is reportedly longer.[87,89-96] The number of lymph nodes removed with MIPS is much the same as with OPS,[87,92,93,95] or even higher.[90,96] Similar complication,[87,90-95] reoperation,[87,91,93-95] unplanned readmission,[87,92,96] and mortality[87,90-96] rates are reported for OPS and MIPS. On the other hand, 30- and 90-day mortality rates after LPD were 5.2% and 8.6%, respectively, at hospitals performing

1-4 procedures a year, as opposed to 2.4% and 2.5%, respectively for centers performing >10 a year.[89] In other words, providing it is done at high-volume centers, MIPS is usually considered as safe as OPS for resectable PDAC, with some advantages in perioperative outcomes.[90-92,94,97] The complexity of MIPS makes it technically demanding, however.

The number of cases needed to complete the steep learning curve for pancreaticoduodenectomies is reportedly similar: 34.1 for LPD and 36.7 for RPD (P = .8241); and for distal pancreatectomies the figures are 25.3 for LDP and 20.7 for RDP (P = .5997) 97. An additional learning curve is needed to perform a vascular resection safely during MIPS. Using a modified Delphi consensus study, international experts on MIPS agreed on a set of fundamental items for the selection and training of participating surgeons and centers.[98] Criteria were established for centers and surgeons to be eligible to receive MIPS training, and for proctors in MIPS. After training, at least 20 MIPS procedures annually are recommended, and vascular and multivisceral resections should be done only after performing 50-100 procedures.[98] In 2017, Nassour et al [99] reported on 428 patients drawn from the 2014-2015 pancreas-targeted American College of Surgeons National Surgical Quality Improvement Program (NSQIP) who underwent LPD (235, 55%) or RPD (193, 45%). RPD and LPD were associated with similar operating times, lengths of hospital stay, and 30-day overall complication and mortality rates. The robotic procedures included significantly fewer vascular resections (LPD 55, 23.4%, RPD 24,12.4% P = .004) and multivisceral resections (LPD 29, 12.3%; RPD 9, 4.7%, P = .005), however.[99] Wach MM et al[100] recently retrieved 1954 patients who underwent PD (open in 1708, 87.4%; LPD in 165, 8.4%; and RPD in 81, 4.2%) in 2016-2018 from the New York State Planning and Research Cooperative System database. The incidence of vascular resection/reconstruction was 12.1% for open PD, 13.3% for LPD and 2.5% for RPD (P = .01). Unfortunately, details on the extent of vascular resections performed in the three groups were not available. The mean annual hospital volume of any PD operation was 11.0 for open PD, 14.0 for LPD and 26.2 for RPD (P < .01). One of the reported benefits of laparoscopic resections of the colon and esophagus, compared with open surgery, is a reduced inflammatory response (judging from the postoperative levels of inflammatory markers IL-6, IL-8 and CRP).[94] Unfortunately, this is not the case when LPD is compared with open PD. This supports the argument that the approach alone (ie MIPS) is not enough to alleviate the stress of PD or - rather more perilously - the procedure-related complications of LPD may even exacerbate the surgical stress.[94]

In conclusion, the feasibility and safety of MIPS in the hands of experienced surgeons at high-volume centers is generally accepted. Minimally-invasive vascular surgery is still in an early stage of development, however, especially for segmental vascular resections and reconstructions. The large-scale use of MIPS for PDAC also remains controversial for now, due to a lack of literature on the long-term outcomes.[91,93,101]

Role of NAT in the Surgical Treatment of PDAC

Lo et al[102] recently published a detailed review on the role of NAT for borderline resectable pancreatic cancer (BRPC) and LAPC, based on the results of the ESPAC-5F, NEOLAP-AIO-PAK-0113, SWOG1505, PREOPANC, HyperAcutePancreas, and ALLIANCE A021501 trials. According to the Authors, NAT is associated with a longer survival for patients with BRPC, but its broader efficacy in cases of resectable PDAC, and the optimal treatment strategy have yet to be established. In borderline resectable-locally advanced PDAC (BR/LAPC) patients NAT reportedly significantly increases the resection rate, the R0 resection rate, the node-negativity rate, and the median DFS and OS,[12,103-105] making it the treatment of choice for these patients.

Several upcoming trials (NorPACT-1, PANACHE01-PRODIGE48, PREOPANC3, ALLIANCE A021806, CONKO-007, PANDAS-PRODIGE44, and PIONEER-PANC) will focus directly on the efficacy of NAT vs adjuvant therapy, chemo-radiotherapy in the NAT setting, and chemotherapy selection driven by molecular testing.

The most important issue regarding whether or not to perform a surgical exploration after NAT is how to assess resectability, and the usefulness of surgical resection in cases of BR/LAPC for the purpose of preventing the tumor from relapsing in the short term after surgery. According to Mie et al,[106] CA19-9 levels <100 U/ml, or a more than 70% reduction in CA19-9 levels after four months of NAT was associated with a good prognosis. Hartlapp et al[107] found that a decrease in CA 19-9 levels to <61 U/ml predicted a successful R0 resection with a sensitivity of 72% and a specificity of 62%, while CA 19-9 non-responders (whose levels dropped by <20% or increased) had no chance of a successful R0 resection. Anatomical imaging (CT/MRI) is of little value in predicting response, and biochemical markers (CA 19-9) are not useful in many patients (non-secretors, or those whose levels are not elevated).[108] The Authors reviewed the baseline and interval (post-NAT) FDG-PET (CT or MRI) parameters in a total of 202 patients and defined as a major metabolic (FDG-PET) response a tumor uptake of FDG below the hepatic FDG uptake, and indistinguishable from background pancreatic tissue; a minor metabolic response was defined as persistent or higher FDG activity than in adjacent background tissues, and compared with a baseline FDG-PET, if available. There were major metabolic responses in 51% of patients, and pathological responses in 38%,[108] respectively. Median relapse-free survival (RFS) and OS times were 21 and 48.7 months, respectively. After multivariate adjustment, metabolic response was the greatest single, independent preoperative predictor (P < .001) of pathological response, RFS and OS.[108]

Unlike genes affected by epigenetic regulation, and proteins with posttranslational modifications, metabolites can be used as direct markers of biological activity, and can be used to facilitate the characterization of disease phenotypes.[109] In Guo's study,[109] 1H NMR spectroscopy was used to analyze serum samples of 76 PDAC. Three metabolic subtypes - basic (in 13 samples), choline-like (in 29), and amino acid enriched (in 34) - were identified by hierarchical cluster analysis of the serum metabolites and disturbed metabolic pathways. Of the three metabolic subtypes, the choline-like type was associated with a better long-term prognosis than the other two.[109] According to the Authors,[109] metabolic subtypes are of clinical importance and come closer to expressing the heterogeneity in the real-life behavior of pancreatic cancer than molecular typing. The identification of metabolic subtypes of PDAC is still little used, however, and its usefulness for patients given NAT before any surgical resection has yet to be established. To conclude, CA 19-9 and FDG-PET are currently the parameters of choice to support decisions regarding whether to perform a surgical resection after NAT in patients with BR/LAPC.

Recently-reported preliminary tests on the effects of NAT on PDAC metabolism showed a significantly lower expression of metabolic proteins, and of glycometabolic pathway markers in particular.[110] NAT-induced systemic metabolic changes were documented by the reduced serum levels of lactate and cholesterol. Both in vivo and in vitro, there was an increased cancer stem cell (CSC) marker expression by cancer cells that survived the cytotoxic treatment.[110] Unfortunately, the Authors did not mention the possible metabolic subtypes in the 22 patients who were given NAT and the 20 who were not. The proportion of BR/LAPC was 73% among patients given NAT, and 10% among the others.[110] Further studies are needed to examine the real usefulness of the interesting idea of assessing NAT-induced systemic metabolic changes in PDAC patients.

Conclusion

The relatively low mortality rate after pancreatic resection (approximately 2% for PD, and 1% for DP at high-volume centers), the increasing efficacy of chemo/chemoradiotherapy, a greater confidence with vascular resections, and improved postoperative patient rescue have enabled more aggressive surgical procedures in the last 30 years, including venous and arterial resections, and the surgical management of primary or secondary PDAC previously considered unresectable. The introduction of very complex procedures that may take surgeons a while to learn to perform with acceptable results has further reinforced the indication for this type of surgery to be concentrated in multidisciplinary reference centers. NAT increases the resectability rate and ensures satisfactory long-term results in cases of BRPC and LAPC requiring vascular resections. It is essential to select the most appropriate NAT for each patient, and to reassess the resectability of their PDAC preoperatively. Standardizing the surgical procedures will reduce the variability in the outcomes of surgery in prospective RCT aiming to identify the best adjuvant and/or neoadjuvant oncological treatment, thereby improving the chances of pinpointing real differences in their efficacy.

Appendix

Abbreviations

AR	arterial resection
CA	celiac axis
BRPC	borderline resectable pancreatic cancer
BR/LAPC	borderline resectable-locally advanced PDAC
DP	distal pancreatectomy
CAO	complete arterial occlusion
CI	confidence interval
DP-CAR	DP with CA resection
HA	hepatic artery
ISGPS	International Study Group on Pancreatic Surgery
LPD	laparoscopic PD
LDP	laparoscopic DP
LAPC	locally-advanced pancreatic cancer
LSPH	left-sided portal hypertension
MIPS	minimally-invasive pancreatic surgery
NAT	neoadjuvant therapy
NACRT	neoadjuvant chemoradiotherapy
OPS	open surgery
OS	overall survival
PAD	periadventitial dissection
PAR	pancreatectomy with arterial resection
PD	pancreaticoduodenectomy
PDAC	pancreatic ductal adenocarcinoma
RCT	randomized controlled trial
RDP	robotic DP
RFS	relapse-free survival
RPD	robotic PD
SDP	standard distal spleno-pancreatectomy
SMA	superior mesenteric artery
SMV	superior mesenteric vein
SMV-PV	superior mesenteric and portal veins
SV	splenic vein
TP	total pancreatectomy

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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