REVIEW ARTICLE

Concepts and techniques for revascularization of replaced hepatic arteries in pancreatic head resections

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Abstract

Background: The relationship of pancreatic ductal adenocarcinoma (PDAC) to important peripancreatic vasculature dictates resectability. As per the current guidelines, tumors with extensive, unreconstructible venous or arterial involvement are staged as unresectable locally advanced pancreatic cancer (LAPC). The introduction of effective multiagent chemotherapy and development of surgical techniques, have renewed interest in local control of PDAC. High-volume centers have demonstrated safe resection of short-segment encasement of the common hepatic artery. Knowledge of the unique anatomy of the patient's vasculature is important in surgical planning of these complex resections. Hepatic artery anomalies are common and insufficient knowledge can result in iatrogenic vascular injury during surgery.

Methods and Results: Here, we discuss different strategies to resect and reconstruct replaced hepatic arteries during pancreatectomy for PDAC to ensure restoration of adequate blood flow to the liver. Strategies include various arterial transpositions, in-situ interposition grafts and the use of extra-anatomic jump grafts.

Conclusion: These surgical techniques allow more patients to undergo the only available curative treatment currently available for PDAC. Moreover, these improvements in surgical techniques highlight the shortcoming of current resectability criteria, which rely mainly on local tumor involvement and technical resectability, and disregards tumor biology.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is projected to be the second leading cause of cancer death in the United States by 2030.[1] The dismal prognosis can in part be attributed to its aggressive tumor biology and a delay in diagnosis. Nearly 30% of patients present with unresectable locally advanced pancreatic cancer (LAPC) without apparent metastasis.[2] Surgical resection is an essential part of the multimodality treatment of PDAC and provides the best chance at long-term survival or cure. The National Comprehensive Cancer Network (NCCN) guidelines define LAPC as extensive, unreconstructible, venous involvement and/or >180° tumor encasement of one of the major peripancreatic arteries.[3] Extensive vascular involvement dictates resectability both in technical and oncologic terms, as the chances of a complete oncologic resection are lower.

In recent decades, major progress in surgical techniques and systemic therapy have renewed the focus on local control. This progress has resulted in a significant decrease in postoperative morbidity and mortality, and has increased long-term survival.[4] Within this context, surgeons have increased resectability rates by including previously considered inoperable disease. Around the world, high-volume centers perform venous resections and reconstructions with comparable outcomes to standard pancreatic resections.[5–8] In contrast, arterial resections remain controversial. Historically, arterial resections are associated with a high morbidity and mortality, but lack evidence of oncological benefit.[9] With the advent of more efficacious multiagent chemotherapy, such as gemcitabine/nab-paclitaxel and FOLFIRINOX, specific arterial resections and reconstructions are increasingly being performed for biologically favorable localized tumors in which the tumor cannot be dissected off of the involved artery.[10–14] A recent systematic review showed that rates of microscopic positive margin were comparable between patients who underwent preservation (i.e. conventional dissection) versus resection and reconstruction of replaced hepatic arteries. However, resection of involved arteries is often necessary even in the era of multimodality neoadjuvant therapy; in particular when the tumor displays a string sign on CT-imaging, conferring true arterial invasion.[14,15] In some cases, a "halo sign" can be seen on CT-imaging, meaning that periadventitial dissection of the artery is possible without resection and reconstruction of the hepatic artery.[14]

Previous studies have demonstrated that short-segment hepatic artery involvement can safely be resected *en bloc* and reconstructed in an end-to-end fashion owing to the redundancy of the hepatic artery.[16] In planning these complex surgical resections, the unique anatomy of the patient's vasculature needs to be carefully appreciated. Hepatic artery anomalies are common; the presence of a replaced and/or accessory hepatic artery occurs in 24–49% of the population.[17–20] Knowledge of hepatic artery anomalies is of considerable importance as it can reduce the risk of iatrogenic vascular injury during surgery. Injury to these vessels can result in severe intra- or postoperative morbidity, such as liver ischemia, biliary fistulae and biliary-enteric anastomotic leaks, and perioperative mortality.[21–24] However, current literature lacks a comprehensive overview on strategies and techniques for the resection and revascularization of replaced hepatic arteries.

In this technical report, we review our patient evaluation and selection in a multidisciplinary setting during the preoperative planning stage for patients with LAPC. We discuss criteria that are considered in determining if the patient may benefit from complex hepatic arterial resection and reconstruction. Moreover, we elaborate on the different surgical techniques that can be deployed to resect and revascularize hepatic artery anomalies, through end-to-end-anastomosis, interposition grafts, and transposition of arteries.

Preoperative management and patient selection

PDAC is a complex disease that is most effectively treated in a multidisciplinary setting. The multidisciplinary team enables optimal patient selection for more extensive resections, while considering patients' overall health, tumor biology, quality of life, therapy toxicity, and chance of long-term survival. According to the NCCN guidelines, the relationship of the tumor to the peripancreatic vasculature defines resectability. Abutment, which is less than 180° tumor involvement, of the celiac axis (CA) and greater than 180° involvement of the superior mesenteric artery (SMA) is termed locally advanced disease, and, was historically considered to be unresectable.[3] Abutment of the SMA is considered borderline resectable (BRPC).[25]

Preoperative chemotherapy is now frequently used by experienced centers.[26] The use of preoperative radiation remains controversial and is often center dependent.[26] Preoperative chemotherapy serves three general purposes – potential control of micrometastatic disease, selection of favorable biology, and enhancement of the ability to achieve an R0 resection. Of these three, the control of micrometastatic disease and selection of tumor biology are the most important aspects in achieving long-term survival. The "downstaging" of LAPC to borderline resectable or resectable by induction therapy is rare, although the occasional exceptional responder is observed. In contrast, many large series report a margin-negative resection (R0) in the range of 80% among BRPC patients who receive neoadjuvant therapy.[27,28]

A dual-phase CT scan is the primary modality for the clinical staging of patients with PDAC. The CT-imaging is combined with a post-processing technique, called a 3D-rendering, which generates detailed vascular maps with improved depth perception[29,30] (Fig. 1). These vascular maps assist surgeons in determining tumor resectability, and the need for vascular resection and reconstruction. In addition, cinematic rendering is applied to the CT-imaging data creating photorealistic 3D-images that are physically accurate representations of the imaging data (Fig. 1).[29,30] This provides improved visualization of potential vascular abutment, encasement, or invasion. Moreover, it generates meticulous vascular maps that can highlight vascular variations, such as replaced or accessory hepatic arteries.

Anatomic variations

Ten basic anatomic hepatic arterial variations were first described in Michels' autopsy series of 200 dissections (Table 1).[31] In Michels' report, a distinction is made between replaced hepatic arteries and accessory hepatic arteries. The latter supply a portion of the lobe along with the conventional arterial supply, while replaced hepatic arteries are the sole arterial supply to the hepatic lobe. In this technical report we address the surgical strategies classified by three main categories.

1. *The presence of a replaced right hepatic artery (rRHA) or a replaced common hepatic artery (rCHA).* This arterial variation is the most common and present in 10–18% of the population, whereby the replaced artery arises from the SMA or more rarely, the celiac trunk, aorta, left gastric artery (LGA) or the posterior inferior pancreaticoduodenal artery or gastroduodenal artery (GDA) (Fig. 1).[32]
2. *The presence of a replaced left hepatic artery (rLHA).* This anomaly is less common, with a prevalence of around 7–8%

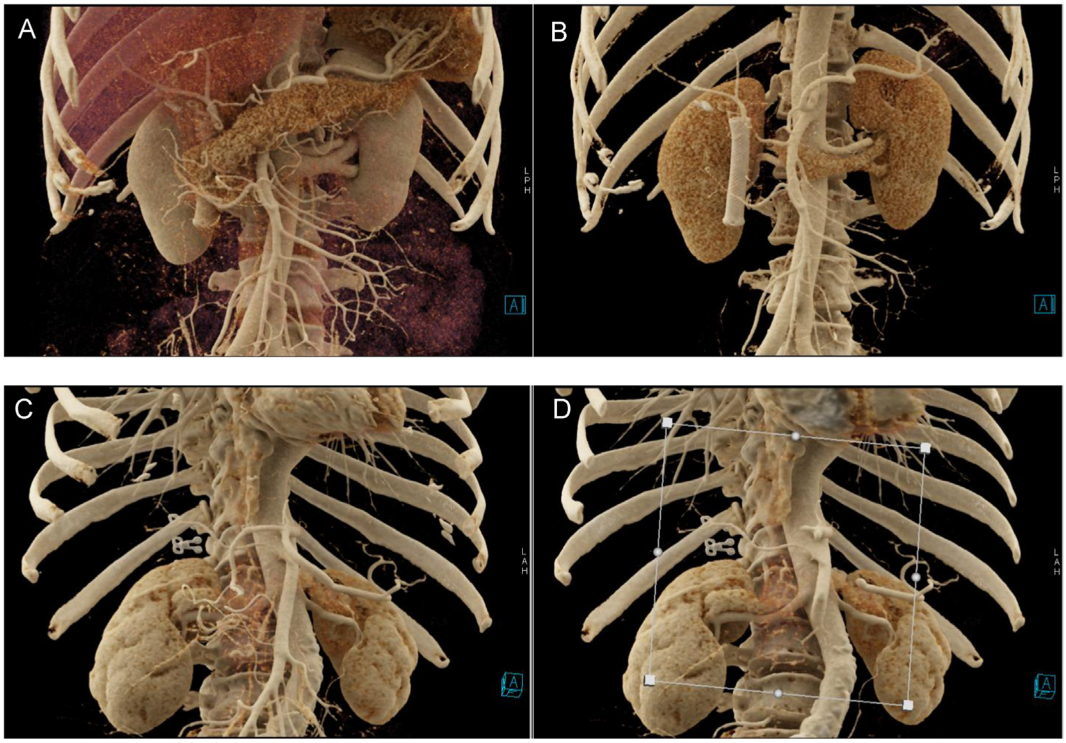

Figure 1 The 3D-rendered images depict two patients with anatomical variations. A replaced common hepatic artery, arising from the superior mesenteric artery (Michels classification IX) with surrounding parenchymal tissue (A) and without to better visualize the arterial anatomy (B). This patient has encasement of the CHA by a tumor in the head of the pancreas. Note the metallic stent in the CBD. The second patient has a replaced right hepatic artery, arising from the superior mesenteric artery (Michels classification III) before (C) and after use of anatomic cut planes (box) to better visualize the replaced right hepatic artery (D)

of the population [33]. Due to its anatomic location, left replaced hepatic arteries are less frequently involved by pancreatic head cancers, but might be inadvertently injured during dissection of the gastrohepatic ligament and the pars flaccida during a Whipple procedure.

3. *The presence of an accessory left or right hepatic artery.* Accessory arteries provide additional arterial supply to the liver and occur in 21–45% of people.[33] They can often be sacrificed, but otherwise need to be reconstructed if the liver demarcates with test-clamping of the accessory artery.

Operative techniques

Resection and reconstruction of rRHA from SMA

The rRHA is often encased with posterior head or uncinate tumors, in these cases, the replaced vessel is often the only vessel involved. A key principle in this case is to leave the arterial resection as the very last step in order to minimize liver ischemia. This is usually possible, unless there are multiple vessels involved (i.e., superior mesenteric vein [SMV], portal vein [PV]/SMV and rRHA) in which reconstruction may have to be performed before the specimen is removed. Once the surgeon determines that the tumor is localized (i.e., no metastatic disease), the Whipple procedure commences in a standard fashion, making sure to divide the jejunum and the stomach early on, the hepatoduodenal ligament is dissected with identification and vascular control of the common hepatic artery (CHA), GDA and the distal portion of the rRHA at the porta hepatis. It is critical to perform a generous dissection of the GDA to allow for a long stump once it is divided. Then the SMV-PV tunnel is created, and the pancreatic neck is divided, followed by the common bile duct (CBD), and the uncinate dissection. At this point, the tumor should be hanging by the encased portion of the rRHA. The origin of the rRHA is ligated at the SMA and the distal portion is divided above the tumor making sure to leave as much length as possible, without compromising the R0 resection. At this stage, the specimen is passed off the field, and systemic anticoagulation is started using unfractionated heparin with 80 units per Kg and a target activated clotting time (ACT) of 200–300 in preparation for the arterial reconstruction.

There are multiple options for arterial reconstruction in this case; the easiest and most preferred is GDA stump transposition, in which an end-to-end anastomosis is performed between cut ends of the rRHA and the GDA stump, which lie in close proximity. This is done using interrupted Prolene sutures (6–0 or 7-0 depending on diameter) or a running fashion utilizing a parachute technique given the small diameter. A tension-free

Table 1 Michels's classification

Type	Description
I	Normal anatomy
II	Replaced left hepatic artery from left gastric artery
III	Replaced right hepatic artery from superior mesenteric artery
IV	Replace left hepatic artery from left gastric artery and replaced right hepatic artery from superior mesenteric artery
V	Accessory left hepatic artery from left gastric artery
VI	Accessory right hepatic artery from superior mesenteric artery
VII	Accessory left hepatic artery from left gastric artery and accessory right hepatic artery from superior mesenteric artery
VIII	Accessory left hepatic artery from left gastric artery and replaced right hepatic artery from superior mesenteric artery, or Accessory right hepatic artery from superior mesenteric artery and replaced left hepatic artery from left gastric artery
IX	Common hepatic artery from superior mesenteric artery
X	Common hepatic artery from left gastric artery

anastomosis must be constructed to prevent risk of disruption and stricture. This approach is appealing as it requires only one anastomosis, and no requirement for a conduit (less risk of thrombosis), and thus has been widely utilized by many surgeons.[22,34]

If the GDA stump (or the rRHA) is too short, then the proximal and distal ends of the rRHA are anastomosed using an in-situ interposition graft. The choice of graft is surgeon and institution dependent. In our experience, autogenous vein graft (e.g., reversed greater saphenous vein) is the conduit of choice, given the matching size, ease of harvesting, eliminating the infectious risks associated with prosthetic (e.g., ringed PTFE) grafts, while also decreasing the thrombotic complications associated with cryopreserved cadaveric allografts, and decrease the need for lifelong systemic anticoagulation. Arterial grafts such as the gastroepiploic artery, middle colic artery or right gastric artery have been reported but are usually more technically challenging and may not provide enough conduit length.[35]

If the proximal rRHA stump off the SMA is too short, then another option is a splenic artery (SA) transposition with or without graft, depending on the length needed, which would require a concomitant splenectomy.[36] Other options include an extra-anatomic jump graft from the right renal artery or right iliac artery.

When the CHA is originating from the SMA (Michels' type 9 variant; Table 1) and encased in tumor, which is considered locally advanced but not a contraindication for resection, an *en bloc* pancreaticoduodenectomy (PD) resection with the CHA should be performed to obtain an R0 resection. Tumor involvement of the type 9 CHA variant is more akin to involvement of the GDA, as both structures are not retroperitoneal/posterior in location. As such, when tumor involvement of the CHA as a type 9 hepatic arterial variant is encountered, this should not be considered a contraindication to proceeding with an *en bloc* PD resection with the CHA to obtain an R0 resection. Particularly, revascularization with inflow from the right renal or right iliac artery is typically required. In this case, reconstruction can be more complex with the need for an extra-anatomic interposition branching "jump" bypass graft to both right and left hepatic arteries using either autogenous (e.g. greater saphenous vein [GSV], Fig. 2) or synthetic graft especially when a long graft is needed (e.g., external iliac artery [EIA] as donor artery), it is essential to make sure the anastomosis is tension-free in order to prevent anastomotic disruption. Having a vascular surgeon involved in these complex and high-risk anastomoses is highly recommended, even with experienced Hepato-Pancreato-Biliary (HPB) surgeons but who do not routinely perform arterial reconstructions. Microvascular anastomosis by a plastic surgeon might be necessary in cases of rCHA reconstruction using LGA transposition to both RHA and LHA with a Y-shaped graft. The diameter of the RHA and LHA stumps in the hilum can be small requiring microanastomosis using 9–0 Prolene sutures.

Reconstruction of rCHA from LGA (Michels' type 10 anatomy) follows the same principles, with SA transposition with anastomosis to the distal rCHA stump being the favorable option. Other options include a jump graft from the aorta, right renal artery, SA or right common iliac artery using an autogenous or a synthetic graft. For any arterial reconstruction, pulsatile flow has to be confirmed immediately following the release of the vascular clamps and rechecked again before abdominal closure (and confirmed with Doppler examination). Some authors routinely perform a liver duplex test the night of surgery post-operative day 1 and whenever there is a sharp rise in liver enzymes (i.e., above 1000U/L).

Of note, there are reports of simple resections of the rRHA following inadvertent injury during a Whipple procedure, with no associated severe morbidity, as the liver may have cross-perfusion from the contralateral artery. However, this may not be safe in patients who received multiple cycles of neoadjuvant chemotherapy where they commonly develop chemotherapy-associated steatohepatitis (CASH) and their liver regeneration might be impaired, risking post-operative hepatic failure, especially when combined with a pancreatoduodenectomy. And thus, reconstruction is considered the standard of care and should be attempted if at all possible, even when technically challenging.[37]

Resection and reconstruction of rLHA originating from LGA (Michels' type 2/4 anatomies)

Encasement of an rLHA is most likely encountered in tumors of the pancreatic neck and body and, when locally advanced, these tumors sometimes require a concomitant CA resection and distal pancreatectomy and splenectomy (DP-CAR).[38] In this operation,

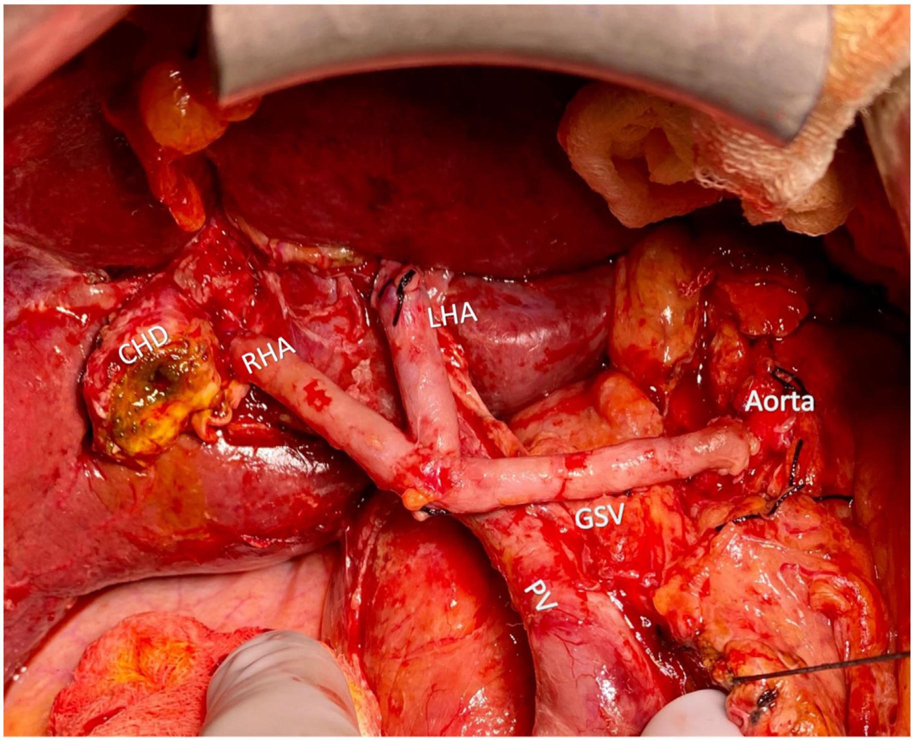

Figure 2 CHA reconstruction using GSV (Greater Saphenous Vein) graft from the aorta to the right and left hepatic artery stumps (RHA, LHA) in a branched Y-fashion. CHD= Common Hepatic Duct. PV= Portal Vein

when the hepatic arterial anatomy is conventional (i.e., Michels' type I) the hepatic arterial flow is dependent on retrograde flow from the SMA through the pancreatoduodenal arcade and the GDA into the CHA. When a Michels' type 2/4 anatomy is present, the surgeon must reestablish flow to the left hepatic lobe via one of the techniques described below.

As previously discussed, the surgeon should perform as many steps of the pancreatectomy as possible before addressing the arterial encasement, in order to minimize liver ischemia time. Of note, in this aberrant variety, the liver occasionally can tolerate resection of the rLHA without reconstruction, however, if the liver demarcates following ligation of the rLHA (and especially with a concomitant DP-CAR) reconstruction is warranted. This is achievable by transposing the LGA and performing an end−end anastomosis to the distal rLHA stump. Another option would be transposition of the rLHA stump and "tapping it" into the CHA, or the GDA stump. If these options are not achievable (e.g., when a DP-CAR is also performed) then an in-situ interposition graft between the LGA and the rLHA stump is performed, as described above, using any available conduit, preferably autogenous vein or arterial grafts.

Accessory RHA/LHA/both (Michels' types 5/6/7/8 anatomies)

When the hepatic artery variant is an accessory one (i.e., there is another dominant artery supplying that liver lobe), test clamping should be performed to confirm the lack of liver demarcation and the use of Doppler is recommended to assess and confirm arterial flow. In most cases reconstruction can be deferred.

Postoperative anticoagulation

The protective effects of postoperative anticoagulation following arterial resection and reconstruction are currently theoretical and evidence is lacking. Globally, surgeons have adopted varying protocols based on individual experiences. In our practice, we keep all patients who underwent arterial reconstruction on anticoagulation in the immediate postoperative period (heparin drip, standard goal). We then switch to therapeutic anticoagulation with low molecular weight heparin (LMWH) or an oral anticoagulant for 1−3 months. However, the advantages and risks of therapeutic anticoagulation should be carefully considered on a patient-to-patient basis.[39] Immediately after surgery we routinely start patients with rectal aspirin and then switch to oral aspirin once oral intake is tolerated and continued. Some recommend lifelong anticoagulation, but this is a very controversial topic with a wide variation in practice among different surgeons and institutions. As experience in these resections increases, future research is warranted to investigate the use of anticoagulation. Lastly, these anastomoses are also susceptible for stenotic complications, which would require endovascular procedure such as balloon angioplasty to reestablish patency.

Discussion

The advent of more effective systemic therapies, such as FOLFIRINOX and gemcitabine/nab-paclitaxel, has increased the role of local control in LAPC. Neoadjuvant therapy followed by radical oncologic resection can provide survival outcomes in patients with LAPC similar to those of patients with resectable pancreatic cancer or BRPC.[40] In light of these advancements, the definition of resectability continues to evolve to include venous resections and increasingly arterial resections. For instance, distal pancreatectomy in combination with a celiac axis resection (DP-CAR, also known as a modified Appleby) is widely adopted as a strategy to resect pancreatic cancer in the neck or body of the pancreas involving the CA or CHA.[12,41] Similarly, surgeons at high-volume centers have continuously performed more arterial resections with reconstructions in cases of short-segment hepatic artery invasion.[13,42] This report provides a detailed description of surgical techniques and practical strategies for resection and reconstruction of hepatic artery anomalies during pancreatic head resections for LAPC.

Michels' autopsy series published in 1966, first mapped out the hepatic artery variations with the intention to inform surgeons who perform procedures around the porta.[31] Variations of the hepatic arterial supply are common, occurring in 24–49% of the patients. Knowledge of these vascular anomalies is essential to safely perform these complex surgeries and prevent a catastrophic iatrogenic injury. Injury to, especially, replaced hepatic arteries can lead to severe complications, such as liver ischemia with subsequent abscess formation and biliary tract anastomotic leaks or fatal liver failure, and even mortality.[21,22] Hence, familiarity with various arterial variants and the operative techniques for arterial reconstruction in these cases is essential for the modern HPB surgical oncologist when dealing with pancreatic cancer. Most importantly, the surgeon should always have the arterial reconstruction planned before heading to the operating room, based on the pre-operative pancreas-protocol CT scan or MRI. Cinematic rendering (or 3D reconstruction) provides additional help when planning these complex reconstructions by providing detailed vascular maps (Fig. 1).

Numerous reconstruction methods are available to HPB-surgeons, varying from primary reconstruction to extra-anatomic reconstructions. The choice of reconstruction strategy is dependent on a number of factors, including but not limited to the patient's inherent anatomy, concurrent comorbidities, and extent and location of arterial involvement. Primary end-to-end anastomosis of the native vessel is often the preferred option. However, when this is not possible the surgeon may have to resort to other techniques, such as interposition grafting in situ or extra-anatomic bypass grafting in order to achieve a tension free anastomosis. When it comes to interposition grafts, autologous grafts are preferred, as they carry a lower risk of introducing contamination and perigraft seromas compared to synthetic grafts.[43] Inherent to reconstruction procedures of hepatic arteries is a risk of postoperative vascular occlusions, particularly in patients with PDAC who are prone to a paraneoplastic hypercoagulable state.[44] Early detection of vascular occlusions during postoperative follow-up can greatly improve morbidity and mortality, as these complications may be managed successfully in a multidisciplinary team of interventional radiologists, intensive care specialists, vascular and HPB-surgeons.

To date, no prospective randomized control trials have compared the outcomes of hepatic arterial resection with medical treatment for patients with PDAC. As mentioned, hepatic arterial resections carry a higher risk of postoperative morbidity and mortality. A meta-analysis demonstrated that arterial resections were associated with a significantly increased risk for perioperative mortality (Odds ratio [OR] = 5.04; $P < 0.0001$) and a worse 1 year-survival (OR = 0.49; $P = 0.002$) compared to patients without arterial resection.[45] Another recent systematic review, examining the safety following arterial resections in pancreatectomy, found that the median overall morbidity was 52% (range, 37%–100%), with major complications occurring in a median of 25% (range, 12%–54%) of patients.[46] Additionally, the median 90-day mortality rate was 5% (range, 0%–17%).[46] However, patients who underwent pancreatectomy with arterial resection had a considerably more favorable survival compared with patients who did not undergo resection for locally advanced disease. Another study focused on LAPC, also demonstrated that resection significantly extended overall survival compared to chemotherapy alone (35.3 vs. 16.3 months; $P < 0.001$).[40] PDAC treatment with chemotherapy alone is considered a temporary reprieve, as treatment-resistant clones will eventually cause progression and metastasis of disease.[40] Careful patient selection is crucial, and a multidisciplinary setting can help make up the balance for individual patients setting the inherent risks of the operation against the dismal prognosis of pancreatic cancer. One of the concerning risks following arterial resection and reconstruction is the potential occurrence of a pancreatic leak, which can subsequently lead to a severe postoperative hemorrhage. In order to minimize this risk, surgeons could opt for a total pancreatectomy. However, it is crucial to carefully consider the perceived advantages of performing a total pancreatectomy in relation to the resulting type 3 diabetes, which is a highly debilitating condition. Consequently, the decision regarding the appropriate course of action should be individualized, taking into account a thorough assessment of the potential risks and benefits in each specific case.

Currently, guidelines defining the resectability of localized PDAC make distinctions largely based on the local extent of the disease.[3] In the context of improved systemic therapy and advanced surgical techniques, these criteria are inadequate at identifying the patients who will derive the most benefit from surgery. PDAC is not merely a localized disease. Up to 80% of patients with resectable PDAC recur within 2 years after resection.[47] Over three quarters of these patients recur at distant sites, suggesting that PDAC is a systemic disease at the time of diagnosis.[47] At the same time, an autopsy study from our institution showed that 28% of patients initially diagnosed with LAPC died with only local disease without metastases.[48] Ideally, we would identify patients who are not only technically resectable, but also systemically resectable. A recent study stratified patients who underwent resection for LAPC into three categories based on prognosis: early, late, and no recurrence.[49] In this study, one third of patients was categorized into the early recurrence cohort, recurring within 6 months after surgery with a median recurrence-free survival of 3.3 months. One third of patients experienced late recurrence with a median recurrence-free survival of 11.5 months.[49] The final one third of patients experienced no recurrence at a median follow-up of 25.5 months. The latter two cohorts clearly benefit most from surgery and in order to identify these patients, current guidelines need to incorporate proxies for tumor biology. Carbohydrate antigen 19–9 (CA19-9) is a well-studied prognostic biomarker in this regard, and different postinduction thresholds have been suggested.[50,51] Other potential biomarkers, such as circulating tumor cells and circulating tumor DNA, are closer surrogate for tumor biology. These novel biomarkers are promising but require more extensive testing and validation.

In order to perform pancreatic resections with curative intent for PDAC, replaced hepatic arteries may need to be resected, because of either tumor involvement or inadvertent injury during the procedure. Hepatic artery resections, particularly of short-segment involvement, are currently safely performed. However, a significant part of the population has an anatomical variation of the hepatic artery. These arterial variations are of importance in the preoperative planning of PDAC resections. The resectability of PDAC needs to be assessed on an individual basis to determine if a successful complete oncologic resection is possible, while ensuring adequate blood flow to the liver. Herein, we have described different methods to reconstruct replaced hepatic arteries, using transpositions of a variety of arteries, as well as interposition grafts. These techniques offer patients a chance at better oncologic outcomes. In addition, these strategies challenge current resectability criteria, which are founded mainly on technical limitations. The decision to resect PDAC lies with the operator and is dependent on a myriad of factors, including technical resectability, but also tumor biology.

COI/Discloser

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