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Radical pancreatic cancer surgery—with arterial resection

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Abstract

Extended surgery with arterial resection in pancreatic cancer remains a controversial topic. Although not recommended as a standard procedure, arterial resection may be

feasible in selected patients and with the availability of new multimodal treatment approaches it may gain increasing impact in pancreatic cancer therapy as a complete tumor removal is still the only opportunity to achieve long-term survival for this disease.

With regard to the surgical approach, one must differentiate between resection and reconstruction of the celiac axis and the hepatic artery as its most important branch, and resection/reconstruction of the superior mesenteric artery. Both procedures are technically possible and require a distinct level of surgical experience as well as interdisciplinary management for preoperative diagnosis and treatment of postoperative complications to achieve good outcomes. Besides arterial resection followed by reconstruction, there are specific situations when arteries may be

resected without reconstruction, e.g., during distal pancreatectomy with celiac axis resection. In addition, in some cases arterial resections can be avoided despite a suspected tumor attachment by sharp dissection on the adventitial layer of the respective artery, especially after neoadjuvant therapy which is increasingly performed for borderline resectable and locally advanced tumor findings. This review summarizes definitions, diagnostics, technical aspects and outcomes of arterial resection in pancreatic cancer surgery in the context of the current literature and evidence.

Keywords: Arterial resection, locally advanced pancreatic cancer, pancreatic surgery

Background

Surgical resection still remains the only potentially curative option in the management of pancreatic cancer (PDAC) which is projected to be the second most common cause of cancer-related deaths in Europe in 2030 (1). The prognosis of resected PDAC has improved in recent years, mostly due to adjuvant chemotherapy which is the standard of care today (2). Simultaneously, surgical resection has become safer and indications have been extended, including vascular and multi-visceral resections which meanwhile can be performed with a postoperative mortality below 5% in specialized institutions (3). Still, morbidity of PDAC surgery remains considerably high, but most complications can be managed by an interdisciplinary approach including interventional radiology

and intensive care medicine (4). Modern radiological treatment strategies have helped to avoid re-operations including completion pancreatectomy, i.e., for postoperative pancreatic fistula (POPF) or postpancreatectomy hemorrhage (PPH) (5).

Despite the fact, that a tumor infiltration of the superior mesenteric artery or the celiac axis (especially the hepatic artery) is regarded as a contraindication for upfront surgery in general, a resection of these arteries with reconstruction can be carried out in selected patients (6) and the increasing use of neoadjuvant therapy protocols has increased the pool of patients who are regarded as candidates for surgery despite locally advanced findings (7).

This review gives an overview on the surgical management of PDAC with a focus on the aspect of arterial resection as a special

(9), and the recently published consensus of the International Association of Pancreatology (IAP) (10). All definitions are comparable regarding the anatomical findings of local tumor extension and any arterial tumor involvement fulfills the criteria of either borderline resectable (BR-PDAC) or locally advanced PDAC.

Generally, a contrast-enhanced computed tomography (CE-CT) using a pancreas-specific protocol should be the gold standard to determine local tumor extension, exclude liver metastases and evaluate a possible vascular infiltration. The CE-CT scan should offer a visualization and differentiation of normal and tumorous pancreatic tissue in an arterial and venous phase including an optimal contrast imaging of the vascular structures in both phases as well as the liver parenchyma to exclude hepatic metastases

(11). BR-PDAC comprises findings with a

(11). BR-PDAC comprises findings with a distortion/narrowing or occlusion of the respective veins but a technical possibility of reconstruction on the proximal and distal margin of the veins. With regard to the arterial structures, a semi-circumferential abutment ($<180^\circ$) of the superior mesenteric artery or an attachment at the hepatic artery without contact towards the celiac axis is regarded as a BR-PDAC. Locally advanced PDAC is defined as a more extended involvement (encasement) of the superior mesenteric artery, celiac axis, aorta or inferior vena cava, as well as involvement of the portal vein/superior mesenteric vein without a possibility for surgical reconstruction of the venous tract. The most recent definition of resectability has been provided by the International Association of Pancreatology (IAP) in 2017 and extends the consideration to define resectability beyond

merely anatomical issues (10). Besides the criterion of anatomy (A), which is mainly similar to the ISGPS consensus with a more detailed subclassification of venous tumor involvement, a biological (B) as well as conditional (C) aspect is introduced.

Borderline resectability based on biological factors (BR-B) includes patients with high CA 19-9 levels (>500 kU/L) and suspected or proven lymph node metastases (PET CT/biopsy). Conditional factor for borderline resectability (BR-C) is a poor performance status of the patient. Both considerations are based on previous studies that show poor oncological outcomes despite tumor resection in each of these patient subgroups. Consequently, patients with an anatomically resectable tumor may be shifted to biological or conditional BR-PDAC and upfront surgery may be critically

discussed in these situations, although the IAP consensus does not clearly recommend neoadjuvant therapy or general non-surgical treatment.

Surgical considerations of arterial resection and replacement

When arterial PDAC involvement is suspected, the initial step of the operation should always be an “artery first” maneuver that allows evaluating arterial involvement itself as well as the position and length of the respective required resection and reconstruction (12,13). This especially implies an evaluation of the superior mesenteric artery by different approaches and offers the possibility to stop proceeding with the operation before any irreversible steps are performed if technical

irresectability is found. The specific artery first approach to choose depends on the suspected site of involvement and may include a left or right inferior mesenteric as well as an infracolic or supracolic direction (12). Regarding the left infracolic approach, the inferior mesenteric vein is identified first on the left side of the mesenteric root and the peritoneum is incised towards the duodenojejunal flexure opening the Treitz's ligament (13). The artery is then dissected towards its aortic root under ligation of lymphatic structures to avoid postoperative chyle leakage and a potential tumor infiltration can be evaluated. Consecutively, a Kocher maneuver allows the additional evaluation of the artery from the right side. Besides this "left posterior" approach, the superior mesenteric artery can also be evaluated during a Kocher first approach

(“posterior”), the dissection of the medial uncinata process from the right side (“medial uncinata”) or by dividing the transverse mesocolon and dissecting the space between superior mesenteric vein and artery (“mesocolic”). Therefore, the terminology “artery first” is not considered a single surgical approach but rather an operative strategy to check tumor infiltration of the superior mesenteric artery. With regard to the celiac axis and the hepatic artery, respectively, an analogous evaluation of tumor infiltration can basically be done but is not specifically defined as “artery first”. Especially towards the basis of the celiac axis, an initial dissection can be difficult in obese patients if no prior respective steps (i.e., transection of the duodenum or stomach) have been performed.

From the technical point of view there are

From the technical point of view, there are various possibilities for arterial reconstruction after resection, including direct anastomosis, insertion of allografts and replacement by autologous bridging or interposition (14).

A direct anastomosis can be performed for short-segment resections of either the hepatic or the superior mesenteric artery.

Anatomically, both vessels offer the length and potential mobility to bridge segmental resection defects of app. 1.5–2 cm when the fat, connective, lymphatic and neural tissue has been dissected along the respective proximal and distal segments. A direct reconstruction is preferably performed as an end-to-end anastomosis without any artificial widening of the lumen before. Safe techniques include circular single-stitch sutures with non-resorbable monofilament

material as well as a combination of a running suture for the back wall and single stitches for the front wall. Regarding the hepatic artery, the back wall can often be rotated ventrally for suturing and de-rotated afterwards which facilitates especially single-stitch suture techniques, whereas the superior mesenteric artery does usually not show enough mobility to allow rotation and de-rotation during the suturing process. A single continuous running suture for reconstruction along the entire circumference may be possible in many situations as well, however, in case of a non-satisfactory flow after completion of the anastomosis a complete re-do is required, while single-stitches on the front wall allow a selective control of the patency by re-opening one or two stitches and performing a thrombectomy when necessary.

When grafting is required, there are basically autologous vessels as well as allografts that can be used to replace long-segment defects after resection. The splenic artery can be used as an autologous graft in many situations either by interposition or transposition for both, hepatic and superior mesenteric artery. The use of the splenic artery requires a total pancreatectomy and splenectomy with careful dissection of the splenic artery as far towards the spleen as possible. Afterwards, either an interposition graft of the splenic artery can be harvested and inserted in any position or a transposition of the splenic artery can be done if the basis of the celiac trunk is not affected by the tumor (14). The latter technique is easier as only one anastomosis is required and the inflow of the celiac axis origin is preserved.

In addition to an autologous arterial graft, venous grafts are possible, namely the internal jugular and the saphenous vein have been described as suitable vessels for arterial replacement, however, the number of reported cases for these techniques remains low (15).

Allografting of arterial vessels can be performed with either synthetic grafts or by the use of deceased donor vessels, when available (15). Both possibilities offer a wide variety of vascular replacement in nearly every position for the hepatic as well as the superior mesenteric artery by standard vascular reconstruction suture techniques as described above. However, it must be mentioned that such kinds of reconstruction have been reported only anecdotally and are certainly reserved for highly individual

situations.

In all situations of major arterial resection and reconstruction, the possibility of a total pancreatectomy should be critically considered to avoid POPF as a well-known and potentially fatal complication in case of arterial erosional bleeding (16).

Other aspects of procedure-related morbidity are ischemic complications, namely liver or stomach ischemia in case of celiac axis resection/hepatic artery replacement and small bowel ischemia when the superior mesenteric artery is approached.

Liver ischemia can occur in case of thrombotic occlusion of a reconstructed hepatic artery or celiac axis, respectively, and is characterized postoperatively by strongly increasing liver enzymes as well as a vascular flow decrease in ultrasound or CT

examination. Especially when a synchronous venous resection and reconstruction has been performed, this complication may be aggravated by venous thrombosis leading to fatal liver ischemia and requiring an immediate surgical or interventional management to restore adequate arterial (and portovenous) inflow (17).

Ischemia of the stomach needs to be kept in mind in all cases of celiac axis resection when recovery of the patient and oral intake is prolonged. The diagnosis can easily be made by endoscopic evaluation of the stomach and management usually requires surgical revision with stomach resection, occasionally a total gastrectomy may be necessary (18).

Small bowel ischemia following superior mesenteric artery resection and

reconstruction represents a severe and potentially life-threatening complication. The diagnosis can be made by CE-CT examination and consecutive exploratory laparotomy which should be performed without hesitation in case of any suspicion in the early postoperative period as otherwise the small bowel may be irreversibly damaged and extensive small bowel resections may be required. A restoration of arterial perfusion must be immediately attempted by open thrombectomy and revision of the arterial anastomosis, in selected cases interventional stenting may alternatively be performed (19).

Celiac axis and hepatic artery

Celiac axis or hepatic artery resection is performed more often than superior mesenteric artery resection. The available

literature on this topic includes app. 200 patients. Surgical morbidity is up to 100%, mortality in pancreaticoduodenectomy with arterial resection ranges between 0% and 45%, showing the inconsistent data basis of this approach. The major risk following hepatic artery reconstruction—as mentioned above—is the occurrence of arterial hepatic perfusion failure that may cause acute problems postoperatively in terms of liver ischemia, necrosis and infection with a high associated mortality. The most comprehensive meta-analysis on arterial resection during PDAC surgery by Mollberg *et al.* (20) confirms the high risk of surgery-associated morbidity and mortality. Even more importantly, it shows a poor oncological outcome with significantly impaired survival in comparison to standard PDAC resections. As most of the included

studies report on patients receiving upfront resections, it remains unclear which impact this procedure may have in the setting of neoadjuvant treatment improving patient selection and eventually oncological outcome.

Distal pancreatectomy with celiac axis resection

A surgical procedure that may be regarded differently from other arterial resections in PDAC surgery is distal pancreatectomy with celiac axis resection (DP-CAR), also called “modified Appleby” operation (21). This procedure describes the combination of distal pancreatectomy and splenectomy with the resection of the celiac axis and common hepatic artery under preservation of the proper hepatic artery which is supplied with arterial inflow by the gastroduodenal arcade

along the pancreatic head and has originally been described in gastric cancer surgery. In contrast to the original technique for gastric cancer, in PDAC surgery, the stomach is preserved and supplied by the gastroepiploic vessel arcade. This technique offers the possibility for a radical resection of pancreatic tumors located in the body/tail of the pancreas and involving the celiac axis or common hepatic artery. A prerequisite for DP-CAR is the existence of a strong gastroduodenal artery which allows sufficient arterial blood supply for the liver and may be prepared by preoperative embolization of the celiac axis/common hepatic artery leading to an enhancement of the arterial inflow via the gastroduodenal artery. Numerous case series have described this procedure with reasonable results in terms of surgical and oncological outcome

which seems to be nearly equal to the standard approaches (22-25). According to the larger series in the literature, that include more than 10 patients, these procedures can be carried out with mortality rates of 0–7% and an average overall morbidity of app. 50%. Median survival in these reports ranges between 10 and 25 months. A recent systematic review has summarized an overall number of 19 reports including 240 patients. Although in some of the publications morbidity ranged up to 100%, mortality was 3.5% which seems to be acceptable for this extended type of resection. The procedure resulted in a radical resection in 75% of all patients with a median survival of 14 months. Especially when DP-CAR was embedded in a multimodal approach with (neo-)adjuvant therapy, improved median as well as long-

term survival was observed in the respective studies (21,25). In contrast to these findings, the same group of authors collected individual patient data on DP-CAR from 20 centers including 68 patients to evaluate the reliability of the previously published systematic review (26). Analyzing this “real-world experience” showed a high proportion of multi-visceral DP-CAR as well as combination of DP-CAR and portal vein resection, but also revealed an unexpected 90-day mortality of 16.4% mostly due to ischemic gastric or liver complications as well as grade C POPF. These data show that arterial resections in PDAC surgery—even when performed with a distal pancreatectomy as a “small” resection—bear an inherent risk of severe complications and should be done only in specialized centers after careful patient selection to avoid

adverse outcomes (26).

Superior mesenteric artery

Resection and replacement of the superior mesenteric artery remains a rare procedure in PDAC surgery. The published case series show that the resection is technically possible, grafting with the saphenous vein is the most commonly used method for reconstruction. Morbidity of this approach is high and the oncological outcome is not yet convincing from the limited evidence. A current review of the literature has summarized 13 retrospective series including an overall number of 70 published cases, resulting in an institutional number of 1–12 patients in whom this operation was performed (27). The reported outcomes underline the difficulty of this surgical procedure which was usually combined with

a resection of the portovenous vessels as well and resulted in median blood losses of up to 6.6 liters, operation times of more than 12 hours and an average in-hospital mortality of 20%. Furthermore, the median survival of 11 months does not support the general performance of this approach as modern multi-agent chemotherapy may achieve similar survival times in a palliative setting (27). Despite these rather disillusioning results, it needs to be emphasized that all of the included publications reported patients in the pre-Folfirinox era and that survival in a multimodal setting with modern chemotherapy regimens may be much better. Consequently, resection of the superior mesenteric artery may be an individual option for highly selected patients in a multidisciplinary oncological approach and

should not be generally considered as contraindicated when the surgeon's and center's experience may allow to perform this procedure safely (28).

Avoidance of arterial resection

An important aspect in locally advanced PDAC surgery is the avoidance of arterial resection and reconstruction without constraining margin clearance. There are two scenarios in this context:

- I. Resection without reconstruction of the hepatic artery potentially after preoperative embolization;
- II. Sharp dissection on the adventitial layer of an involved artery after preceding neoadjuvant treatment.

Regarding the first approach, this has been described in a Japanese 21-patient series by

Miyazaki *et al.* (29) for partial and total duodenopancreatectomy. In this collective, 20/21 patients underwent hepatic artery resection without reconstruction, 12 of these patients had received a preoperative embolization of the common hepatic artery with the aim of collateral vessel formation. Except for a postoperative temporary increase of liver enzymes, there was no relevant morbidity associated with this procedure and a CA 19-9 level of 400 kU/L was shown to be an adequate cut-off for oncological patient selection for this procedure (29).

Regarding avoidance of arterial resection despite suspected tumor contact or encasement, neoadjuvant therapy can change surgical techniques as even modern cross-sectional imaging modalities fail to predict true tumor extension accurately (30,31).

Therefore, even in locally advanced findings, viable tumor is not necessarily remaining after neoadjuvant therapy and a radical resection may be possible in a high proportion of patients without arterial resection. The technique applied is comparable to a “level 3” dissection as described for upfront surgery by Inoue *et al.* (32) which implies to carry out the preparation on the adventitial layer of the arterial vessel, presumed that no viable tumor is found in frozen section during exploration. This procedure has been described as the “Triangle” operation and may be applicable for an increasing number of patients following neoadjuvant treatment (33).

Conclusions

In summary, locally advanced pancreatic

In summary, locally advanced pancreatic cancer (PDAC) with arterial infiltration of either the celiac axis, common hepatic artery or superior mesenteric artery still represents the only T4 stage of this tumor entity and current guidelines do generally not recommend surgery in this situation. Despite this, arterial resection may be beneficial in selected patients and with the availability of new multimodal treatment approaches it may gain increasing impact in PDAC therapy as a complete tumor removal with clear resection margins is still the only opportunity to achieve long-term survival. Neoadjuvant treatment should preferably be performed instead of upfront surgery in such advanced tumor stages. After neoadjuvant treatment, a surgical exploration should always be attempted in all patients with stable disease or oncological remission as cross-sectional imaging often fails to predict

the extent of remaining viable tumor and a radical resection may be achieved in a considerable proportion of these patients. In case an arterial resection is required, it has to be differentiated between resection without reconstruction which can be performed in patients with tumors of the pancreatic body and celiac axis infiltration (modified Appleby procedure) as a distal pancreatectomy if the perfusion of the liver is sufficiently preserved via the gastroduodenal artery. When hepatic or superior mesenteric artery resection requires reconstruction, the restoration of perfusion can be achieved by using the splenic artery by interposition or transposition, autologous or allograft insertions are alternatively possible. With regard to the different possibilities for arterial resection and reconstruction a consensus definition would

be desirable for better inter-study comparability of the reported postoperative outcomes. If respective extended PDAC resections are performed, a total duodenopancreatectomy should always be considered to avoid occurrence of postoperative pancreatic fistula as a complication with potentially severe consequences in case of erosional bleeding at the site of arterial reconstruction.

Although arterial resections in PDAC surgery are no standard procedure today, they are important options in individual patients and further studies should be initiated to collect more evidence on the indication and patients' selection for these approaches.

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