Review Article on Surgery for Locally Advanced Pancreatic Cancer

# Surgery for locally advanced pancreatic ductal adenocarcinoma—is it only about the vessels?

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**Abstract:** Pancreatic ductal adenocarcinoma (PDAC) is an oligosymptomatic disease, that is usually diagnosed in an advanced tumor stage. Traditionally, only the small subset of patients with tumors that showed no signs of vascular infiltration and distant metastases proceeded to surgery—still the only curative therapeutic modality to date. The remaining majority of patients received palliative chemotherapy or chemoradiation, usually with gemcitabine monotherapy. While gemcitabine monotherapy results in improved survival compared to best supportive care, most patients still succumb to the disease under therapy in a relatively short amount of time. Over the last years and decades, paradigms have shifted in PDAC treatment and potent multidrug chemotherapy protocols, including gemcitabine plus nab-paclitaxel and FOLFIRINOX, result in sufficient downstaging of advanced tumors in many patients. In this context, more and more patients are eligible for exploration and often resection. In this review we discuss the current state of the art in the clinical management and surgical treatment of patients with locally advanced pancreatic cancer, including classifications of locally advanced and borderline disease and surgical strategies for extended resections. An emphasis is put on arterial and venous resections and their outcome. In the end, we discuss current gaps in the literature and propose directions future research endeavors should focus on.

**Keywords:** Pancreatic ductal adenocarcinoma (PDAC); surgery; locally advanced; borderline; chemotherapy

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## Introduction epidemiology and definitions

Pancreatic ductal adenocarcinoma (PDAC) is associated with a dismal prognosis. Globally, in 2018, over 450,000 patients were diagnosed with PDAC, while over 430,000 died from the disease (1). Average 5-year survival rates under multimodal therapy are 9% for all stages in the United States, with a clear benefit in localized stages (5-year survival of 37%) of the disease and a negative impact of metastatic disease (5-year survival of 3%) (2). The only potentially curative treatment option is complete surgical removal of the tumor. However, only a small subset of patients is eligible for surgery, mainly due to a late diagnosis of this oligosymptomatic disease. Unlike for other malignant entities such as colorectal cancer, there is currently no screening test for PDAC available. While certain promising biomarkers, such as serum CA 19-9, early-onset diabetes mellitus and changes in body composition and metabolism are evaluated in trials (3), to date no single marker or composite score

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provides the sensitivity and specificity for safe and effective screening of the general population. In this context, the majority of PDAC cases is diagnosed at an advanced stage—either metastasized to distant organs, including lung, liver and peritoneum, or invading adjacent structures, including the duodenum and major blood vessels. Historically, all of these cases were considered inoperable, the risks of an attempted resection far outweighing potential oncologic benefits. Recent advances in medical PDAC therapy and refinement of surgical techniques are challenging this dogma and the treatment options for PDAC patients grew substantially over the last decades and years. In this review we will illustrate key concepts of contemporary PDAC treatment with an emphasis on locally advanced tumor stages.

In 2006, Varadhachary *et al.* defined three PDAC subgroups (for non-metastasized disease), according to the involvement of the vasculature. Resectable PDAC is defined as a tumor without contact to major blood vessels, specifically no contact to the superior mesenteric vein (SMV), portal vein (PV), celiac artery (CA) and the superior mesenteric artery (SMA). Borderline tumors are defined by having venous involvement that allows for venous resection and reconstruction if necessary and/or having tumor infiltration/contact of the SMA with an angle of less than 180° or focal involvement of the common hepatic artery (CHA). Locally advanced PDAC includes SMA involvement/encasement of greater than 180°, advanced CHA involvement, encasement of the celiac axis and/or an unresectable/unreconstructible venous (PV, SMV) situation (4).

This classification was rapidly adopted across centers around the world. The terminology provided will be used throughout this review. In 2010, Chun *et al.* provided a useful refinement in the classification of venous involvement by including a modified version of the scoring model established by Ishikawa in 1992, differentiating between no changes (grade 1), smooth shift of venous configuration (grade 2), unilateral narrowing (grade 3) and bilateral narrowing without (grade 4) and with (grade 5) collateralization (5,6). The most recent International Study Group for Pancreatic Surgery (ISGPS) (7) and International Association of Pancreatology (IAP) (8) guidelines adopted and refined the borderline and locally advanced PDAC definitions established in 2006. The main difference to other classifications lies in the definition of resectability not only in an anatomical matter (category A), but also in a biological (CA 19-9 >500 iU/L or positive lymph nodes in PET staging or biopsy, category B) and a conditional (performance status of the patient, category C) matter. This classification is useful to respect tumor biology and frail patients who may not benefit from surgery and—eventually—assign them to a neoadjuvant concept despite anatomical resectability. However, most studies published to date have not yet followed this classification.

In general, the ISGPS (and more recently IAP) guidelines provide a useful extension of the most recent AJCC edition, where locally advanced cancers with involvement of the CA or SMA are grouped in the T4 category (stage III PDAC when no distant metastases) (9).

## Advances in chemotherapy and surgical management of PDAC

Gemcitabine mono-therapy has been the treatment standard for PDAC since the 1990s. For stage 4 PDAC, the survival benefit compared to best-supportive care treatment is moderate with only 5.65 months, however gemcitabine mono-therapy proved to be more effective than 5-FU monotherapy (10). Gemcitabine mono-therapy also showed beneficial effects in the adjuvant setting after resection of localized disease with a 5-year survival rate after surgery of 20.4% compared to 10.7% in the observation group (11). Over time different combinational therapies with a gemcitabine backbone were tested in the adjuvant and palliative setting, with nab-paclitaxel plus gemcitabine (12) and cabecitabine plus gemcitabine (13) emerging as valuable treatment options with relatively low toxicity and an improved outcome compared to gemcitabine mono-therapy. In the last decade however, FOLFIRINOX emerged as a potentially even more effective regimen: adjuvant FOLFIRINOX after resection improved median survival to 54.4 months compared to 35.0 months after gemcitabine mono-therapy (14). After neoadjuvant FOLFIRINOX, high rates of R0 resections of 65% were demonstrated for borderline resectable PDAC in a recent single center study (15).

It is important to acknowledge, that the studies listed in this section do not allow for a final verdict of which chemotherapeutic regimen is clearly superior. The studies were heterogeneous, and gemcitabine-based combination therapies were never compared to FOLFIRINOX in a randomized controlled trial. However, it is apparent that oncologists have more effective tools now than they had in the past, resulting in more patients gaining access to surgical intervention after partial or complete response after chemotherapy.

Resection of the tumor after neoadjuvant therapy resulted in a survival benefit compared to exploration in several studies and should be the main goal of treatment. Effective

 

chemotherapy protocols lead to an increasing number of initially unresectable patients proceeding to explorative surgery, and ideally resection of the tumor. FOLFIRINOX treatment resulted in resectability in 60% of explored patients, compared with around 50% after gemcitabine and radiation in a large study from Heidelberg (16), while in another study from Boston, a R0 resection rate of 92% after FOLFIRINOX was achieved (17).

In the setting of more effective perioperative therapies, it is important to note that post-chemotherapy imaging can be deceiving: a large series from 2019 found that no established parameter reliably predicted resectability after FOLFIRINOX and the authors concluded, that all patients without signs of disease progression in follow-up imaging should be offered surgical exploration (18). In this context the term "unresectable" should be avoided after neoadjuvant therapy based on information from cross-sectional imaging, especially considering that the tumor burden is often rather over than underestimated (17). Multiphase contrast-enhanced multidetector CT (MDCT) is the current radiological standard in the assessment of resectability after neoadjuvant therapy. Functional imaging modalities, including 18-FDG-positron emission tomography (PET) and diffusion weighted magnetic resonance imaging (MRI) show promising results in terms of estimation of total response to neoadjuvant chemotherapy (reduction of vital tumor mass), but assessment of local vasculature involvement is still inferior to MDCT, due to lower spatial resolution (19-22).

Biomarkers, first and foremost serum CA 19-9, can aid in pre-operative assessment of the response to neoadjuvant therapy and should be incorporated in the follow-up monitoring (8,18,23,24). Around 10% of patients exhibit a Lewis-negative genotype, hence CA 19-9 cannot be used as a marker. This phenomenon and the interference of serum-bilirubin levels with CA 19-9 levels are limitations of the CA 19-9 system. Carcinoembryonic antigen (CEA) and carbohydrate antigen 125 (CA125) have been proposed as potential alternatives, but large-scale, prospective validation similar to CA 19-9 in the neoadjuvant setting are not available yet (25).

Once disease progression under multidrug chemotherapy is excluded (either stable disease or regression in cross-sectional imaging) and the patient is fit for surgery, exploration should be performed. It is critical for the surgeon to be familiar with the suspected extent of the disease. Diagnostic laparoscopy can be a valuable tool in selected patients to exclude/detect metastatic disease to avoid unnecessary laparotomy. Intraoperative ultrasound might aid in assessing local resectability in selected cases, as suggested by a recent prospective study (26). After occult metastatic disease is excluded, frozen section at critical sites including the SMA, CA and CHA—usually after an appropriate artery-first maneuver (27,28)—should be performed. If intraoperative frozen section reveals vital tumor cells, the procedure is usually aborted and palliative treatment is initiated. If necessary, this includes gastrointestinal or biliodigestive bypass procedures. In selected cases, arterial resection with reconstruction can be evaluated (see below). If no vital tumor residues are detected in intraoperative frozen section, sharp dissection of all soft-tissue between SMA, CA and PV, in a dissection plane directly on the arterial adventitial layer, with concurrent tumor resection and reconstruction as needed for tumors in the head, the tail or the body of the pancreas, represents a new strategy to approach patients with locally advanced disease after neoadjuvant chemotherapy. This approach, labeled the TRIANGLE operation—due to the characteristic triangle that is formed by the skeletonized vessels after completed dissection (*Figure 1*), was investigated in a pilot series including 15 patients with locally advanced PDAC after neoadjuvant chemotherapy in a single high-volume institution, with promising results: an R0 resection was achieved in 6/15 (40%) patients with all R1 resections being limited to the peripancreatic tissue. Arterial resection was avoided in all included patients. Relevant complications (Clavien-Dindo grade 3 or higher) occurred in 7/15 (47%) patients and no mortality was reported. The majority of patients (11/15, 73%) reported a good quality of life after a median follow up of 197 days. Distant tumor recurrence was observed in 2 patients (liver metastases) and local recurrence was observed in one patient (time to recurrence 3, 7 and 11 months) (29).

## Venous resection

Venous resections nowadays represent fairly standard procedures in some centers. As many as 25% of pancreaticoduodenectomies (PD) and up to around one-third of distal pancreatectomies involve venous resections in various degrees (30-33). Dependent on what center the patient is referred to, neoadjuvant chemotherapy or upfront resection are recommended. The current evidence regarding neoadjuvant therapy for borderline resectable tumors with venous involvement is inconclusive (34) and our center currently favors upfront resection

 

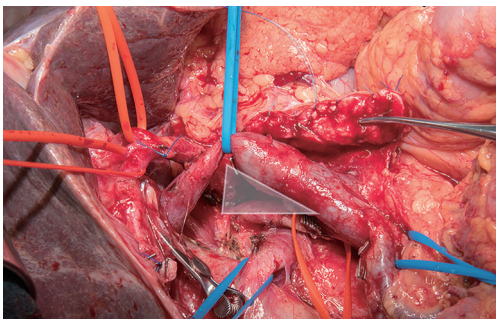

**Figure 1** Intraoperative view after completion of the TRIANGLE operation. All soft tissue in the area of SMA, celiac axis and PV has been removed (grey triangle). SMA, superior mesenteric artery; PV, portal vein.

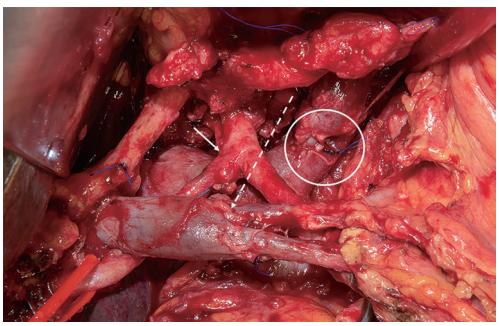

**Figure 2** Intraoperative view after porto-mesenteric vein resection ISGPS type 3. End-to-end anastomosis of two jejunal branches and PV (broken white arrow), aberrant right hepatic artery originating from the SMA (white arrow), re-insertion of the splenic vein end-to-side on the left renal vein to avoid left-sided portal hypertension (white circle). SMA, superior mesenteric artery; PV, portal vein.

followed by adjuvant chemotherapy, in line with the 2014 ISGPS guidelines (7). Planned venous resection is also associated with higher R0 rates compared to unplanned venous resection, emphasizing the need for meticulous pre-operative planning/assessment (35). A recent French study demonstrated, that SMV or PV resection was the only independent factor associated with margin positivity (R1 situation) in multivariate analysis. PV/SMV margin was invaded in around 35% of patients in this cohort, which is in line with experience from our institution. The study also demonstrated a negative impact of margin positivity at either the PV/SMV site or the SMA site, while a positive posterior margin had no impact on survival, illustrating the need for a standardized histopathological workup (36). In this context, it is important to acknowledge that the importance of the R status changes after neoadjuvant therapy: R0 status (≥1 mm margin) is independently associated with survival in the upfront situation (37), but not after neoadjuvant chemotherapy (38). Once the decision for venous resection is made, tumor location and extent dictate the resection required: SMV, PV and portal confluence are most commonly affected. Longer contact/adherence of the tumor to the vein of 2–3 cm is associated with more complex procedures and a worse prognosis compared to only focal contact/involvement (39,40). The ISGPS guidelines define several levels of venous involvement requiring different resection and reconstruction techniques: Lateral or "wedge" resections that don't require full transection of the vessel and either direct suture (type 1) or an autologous patch plastic (type 2); segmental resection with end-to-end reconstruction (type 3, *Figure 2*) and finally resections that require reconstruction by means of an interposition graft—either autologous, homologous or artificial (type 4) (41). Surgical morbidity and mortality after interposition graft is comparable to end-to-end reconstruction (42,43), however, multiple studies confirmed that the risk of thrombosis is elevated after reconstruction with any kind of graft (42,43). Overall survival after interposition graft was reduced compared to other reconstruction techniques in a recent study (44), likely reflecting more advanced tumor stages in the subgroup requiring extended venous resections.

When compared to tumors without venous involvement, requiring only standard resection, overall surgical morbidity was similar in different retrospective series after venous resection (45,46) while other series found more septic events, longer hospital stay, longer duration of surgery and higher blood loss compared to standard resection (47,48). A few retrospective studies demonstrated higher R1/lower R0 resection rates after venous resection compared to standard resection for PDAC in both the upfront setting (49) and after neoadjuvant therapy (50,51). Several studies report long-term outcome/survival to be worse after pancreatic resection with venous involvement compared to standard resection, with median survival ranging from 18.5 to 21 months after venous resection and 25.8–29 months after standard resection (39,52). Studies and a meta-analysis including large patient numbers confirm these results and find that R1 resection rate, post-operative mortality and long-term outcome are negatively impacted by venous resection compared to standard resection (52,53). While the authors of one meta-analysis (53) conclude that neo-adjuvant treatment is indicated before all planned venous resections for pancreatic cancer, it is important to recognize that high quality data to back this claim is still

 

lacking: no prospective RCT compared upfront venous resection versus resection after neoadjuvant treatment and the worse outcome found might well be explained by a selection bias, with higher tumor stages being included in the venous resection groups. Multicenter RCTs filling this gap in the literature are urgently needed to provide the highest level of evidence for this critically ill patient cohort.

## Arterial resection

First systematically described in the 1970s by Fortner (54), regional pancreatectomies including vascular resection and reconstruction have been controversially debated ever since. Key points of criticism even today include an elevated mortality and a questionable oncologic benefit (55,56). The most comprehensive analysis to date reveals increased perioperative mortality and worse survival after arterial resection compared to standard resection and even venous resection, but at the same time a benefit compared to patients not undergoing resection at all (56). It is important to acknowledge that (just like for venous resection) very few and heterogeneous prospective studies exist (57,58) and the current evidence is mainly based on retrospective studies. Several national and international guidelines (7,8,59) agree that planned upfront resection for tumors involving major arteries should be avoided and downstaging by multidrug chemotherapy might represent a favorable option.

Upon exploration, after neoadjuvant therapy, an appropriate artery-first maneuver (dependent on the location of the tumor) (27) should be performed to assess the true involvement of the vasculature and consequently resectability. As described above, if histology of obtained frozen sections shows tumor negativity, a radical, vessel-sparing sharp dissection in the triangle between PV, SMA and CA can be evaluated to avoid artery resection and reconstruction (29). In selected cases with involvement of the celiac axis, usually in locally advanced tumors of the pancreatic body, an extended resection of the CA and CHA without reconstruction plus distal pancreatectomy can be evaluated. Blood supply to liver and stomach is provided via the SMA and the gastroduodenal artery and the remaining proper hepatic artery in these patients. Mortality after this modified Appleby procedure (or DP-CAR) ranges between 3.5% and 16.4% (90-day mortality) described in recent systematic reviews and series (60-62). While the option to resect major vessels without the need for reconstruction is very intriguing, the procedure is a rare one, for few selected patients. As the operation is dependent on a sufficiently large gastroduodenal artery, preoperative conditioning via embolization of the CA represents an approach for some patients. Critical complications of DP-CAR include hepatic and gastric ischemia and severe post-operative pancreatic fistula (POPF).

Resections of the right HA, the CHA and most importantly the SMA are still a matter of lively debate in the field of pancreatic surgery. Resection and reconstruction of one or more vessels shouldn't be a major technical obstacle for experienced HPB surgeons in high-volume centers, however, looking beyond technical aspects, outcome parameters still leave a lot to be desired compared to venous resection and standard resection (56). In their series of 21 patients requiring CHA resection, Miyazaki *et al.* described no perioperative mortality and a median survival of 11 months. The authors emphasize, that serum CA 19-9 levels stratified patients with low values being associated with improved survival, and conclude that CHA resection can be safely performed with encouraging oncologic outcome in these patients. 42% of patients received neoadjuvant chemotherapy in this study (63). A recent systematic review conducted to evaluate the outcome after SMA resection for advanced PDAC found that a large subset of patients (5/25=20%) died perioperatively. Median survival in this review that summarized the available literature from 2000–2016 was 11 months. Given the discouraging outcome the authors concluded that SMA resection cannot be recommended on a routine basis (64). An even newer publication that included 118 patients in a single center retrospective series by Bachellier *et al.* reported 50 resections of the CA, 29 resections of the HA and 35 of the SMA. The majority of patients here received neoadjuvant chemotherapy (75.4%) and reconstruction after arterial resection (85.5%). Mortality was relatively low (5.1%) and R0 rates of over 50% were achieved, resulting in a median overall survival of 13.7 months. R0 had a positive impact on survival, while venous invasion was associated with a worse survival (65). The authors concluded, that for selected patients, arterial resection can be a technically safe option in a specialized setting. Del Chiaro *et al.* came to a similar conclusion in a retrospective series of 34 patients receiving arterial resection. They found, that resected patients had a superior survival with similar rates of postoperative complications compared to a cohort from the same center that received palliation (5-year survival of 23.4% compared to 0% in the palliation group) (66).

These examples illustrate the heterogeneity of studies in the field and the need for randomized trials and standardized reporting of the extent of the disease, surgical procedures and outcomes. Currently the evidence for

 

arterial resections for PDAC patients is sparse and the landscape of the disease is rapidly changing due to new therapeutic regimens. However, a few conclusions can be drawn from the data available today: (I) resectability should be evaluated intraoperatively if cross-sectional imaging shows no disease progression. (II) An appropriate artery first approach should be an early step of the operation to evaluate the extent of the disease before conducting irreversible surgical steps. (III) Patients with advanced disease and arterial involvement should be treated in high volume centers by an interdisciplinary team that includes experienced pancreatic surgeons. (IV) Effective multidrug neoadjuvant treatment should be initiated whenever possible.

It is important to point out, that total pancreatectomy should be critically evaluated in most resections for locally advanced PDAC since it offers some potential advantages, including access to the splenic artery for reconstruction purposes and avoidance of the risk of POPF and associated, potentially life-threatening complications.

## Summary and conclusions

Effective multidrug chemotherapy changed the landscape of PDAC treatment in the last decade. Conversion surgery after neoadjuvant therapy for advanced tumors is now performed routinely in centers across the world and oncological results are encouraging. The dogma that the majority of PDAC cases is unresectable, has been falsified in multiple studies and the term unresectable should be avoided to not discourage patients and caregivers. However, PDAC, despite the advances illustrated above, still represents a deadly disease and further improvements in diagnosis, stratification of patients and treatment strategies are urgently needed. While anatomical classifications have been and still are a mainstay of describing this devastating disease, other ways to assess the behavior of the tumor are needed. Some tumors that classify as locally advanced respond well to chemotherapy and patients have an encouraging survival after resection, while in other cases, even after resection and margin-negativity, patients quickly succumb to rapidly progressive disease. We as the medical and scientific community need to better predict whether the tumor behaves one way or the other, and hence need a much deeper understanding of the biology of PDAC. The most recent IAP guidelines for the diagnosis and treatment of borderline resectable PDAC acknowledge non-anatomical features including the biology of the tumor and patient factors and should be considered the standard for reporting extent of the disease and outcomes (8). Standardized assessment of patient factors/performance status according to either Eastern Cooperative Oncology (ECOG) (67) or American Society of Anaesthesiologists (ASA) (68), standardized reporting of vascular involvement according to the IAP guidelines and correct histopathologic reporting of the R status with respect to the mesopancreas (69,70) and ideally with evaluation of the extent of the tumor-free resection margin (37) should be incorporated into each study on PDAC to improve comparability. To answer the question asked in the title "*Is it only about the vessels?*": no, not anymore. Even resection and reconstruction of major arteries is feasible and associated with encouraging results in selected patients. While blood vessels still represent important landmarks in PDAC surgery and they remain one critically important determinant of resectability, many other factors, including patient fitness, tumor biology and response to chemotherapy are important aspects in surgery for locally advanced PDAC.

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