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REVIEW ARTICLE

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Surgery for Pancreatic Cancer after neoadjuvant treatment

Thilo Hackert

Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany

Correspondence
Thilo Hackert, Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Im Neuenheimer Feld 110, Heidelberg 69120, Germany.
Email: Thilo_Hackert@med.uni-heidelberg.de

Abstract

Pancreatic ductal adenocarcinoma (PDAC) remains to be a therapeutic challenge as only 15%-20% of all patients present with resectable tumor stages by the time of diagnosis. In the remaining patients, either local tumor extension or systemic spread are obstacles for a surgical therapy as the only chance for long-term survival. With regard to local tumor extension, PDAC has been classified as resectable, borderline-resectable (BR) or locally advanced (LA). While there is currently no evidence for neoadjuvant therapy in resectable PDAC, this issue remains controversial in BR-PDAC. In the case of venous tumor involvement, guidelines mostly recommend upfront resection, when technically possible; whereas arterial involvement is regarded as an indication for chemotherapy or chemoradiotherapy first. Furthermore, in locally advanced PDAC, neoadjuvant treatment approaches have recently resulted in high rates of secondary resection, thus allowing "conversion" surgery in an otherwise palliative treatment situation. The present review gives an overview on the current literature of treatment concepts in these situations and additionally focuses of evaluation of resectability after neoadjuvant therapy as well as technical aspects in this specific situation.

KEYWORDS

borderline resectable pancreatic adenocarcinoma, FOLFIRINOX, locally advanced pancreatic adenocarcinoma, neoadjuvant therapy, Pancreatic ductal adenocarcinoma

1 | BACKGROUND

Pancreatic cancer (PDAC) is one of the most aggressive solid tumor entities and the fourth leading cause for cancer-associated mortality in Western countries and shows an increasing incidence which will make it the second leading cause of cancer-associated deaths in 2030.[1,2] Currently, only 15%–20% of all patients are candidates for upfront surgery at the time of diagnosis, which offers the chance of long-term survival, a proportion that has not significantly changed during the last two decades.[3] In the remaining 80%–85% of all patients, either a locally advanced or even metastatic stage of disease is found at the initial presentation.[3] To define the option of surgical resection, several classifications have been used since the mid-2000s, including the Americas Hepato-Pancreato-Biliary Association (AHPBA)/Society of Surgical Oncology (SSO)/Society for Surgery of the Alimentary Tract (SSAT) consensus[4] and the consensus of the International Study Group of Pancreatic Surgery (ISGPS) in 2014,[5] which is mainly based on the recommendations of the National Comprehensive Cancer Network (NCCN).[6] Local resectability is generally defined as primary resectable PDAC, borderline resectable PDAC (BR-PDAC), or locally advanced PDAC (LA-PDAC). Metastatic PDAC (stage IV) is generally not included in these definitions, but must be individually considered as a situation where conversion surgery–even with metastases resection–may be feasible in selected patients after neoadjuvant systemic treatment.[7]

For stage I-III patients, resectable PDAC is characterized by a circumscript tumor without any vascular attachment (no distortion of superior mesenteric vein (SMV) or portal vein (PV) and preserved fat planes towards the important arterial structures-celiac axis (CA) with its branches and superior mesenteric artery (SMA). BR-PDAC describes 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. Consequently, findings with a cavernous collateralization of the PV axis towards the liver hilus as well as a distal tumor involvement of the jejunal vein branches are considered to be technically not resectable and do not fulfil the criteria of BR-PDAC, but are included in the LA-PDAC definition. These two latter findings (venous collateralization and jejunal branch infiltration) are very unlikely to be converted into a resectable situation after neoadjuvant therapy as a recanalization of venous vessels cannot be generally expected

Regarding the arterial structures, a semicircumferential abutment (<180 degrees) of the SMA or an attachment at the hepatic artery without contact toward the CA are regarded as BR findings. Finally, LA-PDAC is defined as a more extended involvement of the SMA, CA, aorta, or inferior vena cava as well as a venous involvement without a possibility for surgical reconstruction as mentioned above. The situations of BR and LA stages have to be regarded differently in terms of arterial and venous involvement because in these situations, the extension of disease is still locally limited and offers the potential of an either upfront or a future local, surgical, approach.[8]

For the definition of local resectability and the decision for surgery, the extension of the tumor toward the vascular structures is of utmost importance. Since the 6th edition of the International Union against Cancer tumor staging system, venous infiltration and infiltration of adjacent organs represent a T3 stage, and only arterial involvement is regarded as T4 in PDAC.[9] Tumor extension should be evaluated by contrast-enhanced computed tomography (CE-CT) because this diagnostic modality achieves sensitivity and specificity rates of 63%–82% and 92%–100%, respectively, with regards to these issues.[10] In the case of contraindications for a CE-CT, MRI may be used instead of CE-CT; however, the accuracy of MRI is inferior to CE-CT regarding features of resectability in PDAC.[11] A prerequisite for the planning of a resection is the exclusion of distant metastases, which is done with regard to the liver by the above-mentioned examinations. Furthermore, pulmonary spread should be excluded by conventional chest radiograph and thoracic CT scan in the case of any doubts.

Three recommendations are given by the above-mentioned consensus statements in the respective situations:

1. Patients with resectable PDAC should undergo surgical exploration and radical resection.
2. Patients with LA-PDAC should not be considered for upfront resection, but neoadjuvant therapy option should be evaluated, when possible included in a clinical trial protocol.
3. In BR-PDAC, therapeutic decisions have to be differentiated between venous and arterial vessel involvement. In venous BR-PDAC, upfront surgery should be performed and, if the intraoperative finding matches the presumed borderline situation as defined above, completed as an en bloc tumor removal with venous replacement. In contrast, when suspected arterial BR-PDAC is found intraoperatively to be a true arterial involvement, no general recommendation for resection is given, neoadjuvant treatment with consecutive surgical re-exploration and the option for a secondary resection is possible, as well as direct arterial resection in exceptional cases or under study conditions.

A comprehensive meta-analysis published in 2010 included 111 studies with 4394 patients and concluded that neoadjuvant treatment is recommended in LA-PDAC as in resectable disease. Outcome after upfront resection was similar to that after neoadjuvant treatment with median survival times of approximately 23 months for both groups.[12] However, this meta-analysis did not specifically evaluate BR-PDAC as a separate topic. Since 2010, BR-PDAC is an intense point of controversy as on one hand upfront resection, when technically possible is the standard of care in most centers in Europe, whereas in the United States, the trend towards neoadjuvant therapy has clearly increased.

A shortcoming of the currently used resectability definitions is the fact that they are based on anatomical criteria, which do not adequately reflect other, especially patient-related factors, that may limit the indication for upfront resection. As a consequence of this, the International Association of Pancreatology (IAP) has considered these factors in a current definition of BR resectability, published in 2017.[13] This definition has included the anatomical criteria (A) as described above as the basis and additionally included the items of biological (B) and conditional (C) factors that may convert an anatomically resectable tumor to a BR situation if an increased level of CA 19-9 (>500 iU/mL) or lymph node metastases (biopsy or high suspicion based on PET CT scan) are found (category B) and if the patient's clinical condition is comprised (depressed performance status, category C). A decision for upfront resection or an alternative approach with neoadjuvant therapy should be made taking into account all of these three columns of the definition as an aggressive tumor biology (category B) and a poor performance status (category C) may lead to poor postoperative and oncological outcomes.

2 | NEOADJUVANT THERAPY IN BORDERLINE RESECTABLE PANCREATIC CANCER

A large number of studies have investigated the effect of neoadjuvant treatment in BR-PDAC during the last decade. It needs to be emphasized that to date, all available data—except for one study—are retrieved from retrospective studies, and only one randomized controlled trial published in 2018 is available at the moment. The prior retrospective studies on BR-PDAC included between 13 and 203 patients.[14–17] Mostly, chemoradiation was administered, including dosages between 30 and 60 Gy, and chemotherapy protocols

with gemcitabine, 5-fluorouracil, or combinations with oxaliplatin and paclitaxel, respectively. These different clinical practice patterns reflect the wide variety of protocols and the lack of a standardized approach for neoadjuvant treatment in BR-PDAC. Clinically relevant toxicity in these publications depended on the chosen protocol and ranged between 9% and 58%. In a meta-analysis pooling these studies, most patients (46%) showed a stable disease stage, whereas a partial response was reported in 29%, and in 3% of the patients, a complete response was observed.[14] The remaining 17% of the patients suffered from tumor progression under the neoadjuvant therapy. The latter observation is an important aspect because it shows the potential selection effect of patients with aggressive and unfavorable tumor biology. In this subgroup of patients, a resection could have been performed at the time of diagnosis due to the BR stage of the tumor; however, they may not have had a benefit of the operation and may have suffered from very early recurrence postoperatively, which underlines the importance of considering the B category of the IAP consensus.[13] In the case of stable disease or response, a resection was possible in two out of three patients, including approximately 60% of R0 resections and a median survival time of 25.9 months, which is comparable to the outcome after upfront resection. Because of the large data heterogeneity, the overall small number of patients, and the fact that all results are based on observational studies alone, it is not valid to draw a conclusion or give recommendation for neoadjuvant treatment in BR-PDAC.

Most recently, the first randomized controlled trial on neoadjuvant therapy for BR-PDAC has been published by a multi-institutional Korean consortium.[18] In this study, 27 patients received neoadjuvant therapy (chemoradiation with gemcitabine an 54 Gray) compared to 23 patients in the control group with upfront surgery. Due to a clear benefit of the neoadjuvant arm in terms of median and 2-year survival, the study was terminated prematurely and may be the first high-level evidence work supporting a neoadjuvant approach for BR-PDAC.

A special situation may be found when tumors of the pancreatic body involve the basis of the CA and do not extend towards the common hepatic artery beyond the offspring of the gastroduodenal artery (GDA). In these situations, a distal pancreatectomy with CA resection under preservation of the GDA (DP-CAR, modified Appleby procedure) is technically feasible.

Recent studies have underlined this approach in the context of the presently available efficient chemotherapy regimens.[19,20] A US study matched seventeen patients undergoing DP-CAR after neoadjuvant therapy, mostly performed by Folfirinox chemotherapy in a 3:1 ratio with 51 patients undergoing DP alone. Although DP-CAR was associated with increased operation times and led to transient liver enzyme elevation, no differences were observed with regard to blood loss, length of hospital stay, and the rate of a microscopically radical R0 resection. Furthermore, the median survival times of 20 months (DP-CAR) versus 19 months (DP alone) did not differ between both groups. A multi-institutional Japanese study included 72 DP-CAR patients with a neoadjuvant therapy proportion of 56%.[20] In this study, morbidity was 63% and in-hospital mortality 4.2%. With a comparable median survival of 18 months, especially adjuvant therapy was found to be a significant prognostic factor in the DP-CAR collective. A recent systematic review on 19 studies included 240 patients and confirmed that, despite a considerable morbidity, this procedure can be performed with a low mortality of 3.5% and results in 15 months median survival, which increases to 18 months if resection is embedded in a multimodal therapy approach.[21]

3 | THERAPY OPTIONS IN LOCALLY ADVANCED PANCREATIC CANCER

In LA-PDAC, historically palliative treatment has been the standard of care in many institutions because the involvement of arterial structures has been regarded as a contraindication for surgery, and arterial resections in PDAC surgery have only been performed in a few patients in the past.[22,23] The reasons for this include high morbidity when pancreatic surgery is combined with an arterial anastomosis, which ranges up to 100% in some publications, as well as a postoperative mortality of up to 46% in some series.[24] Besides these unacceptably high complication rates, oncologic outcomes after arterial resections during PDAC surgery have not been convincing, which was shown in a meta-analysis published in 2011.[24] Twelve studies reporting survival data on 170 patients showed that 1- and 3-year survival were clearly inferior to that of 1640 patients who underwent standard PDAC surgery. Regarding the specific topic of SMA involvement, a 2017 systematic review including 13 retrospective studies with 70 patients[25] has shown that resection and reconstruction of this vessel is on one hand associated with a high morbidity and a postoperative mortality of 20% and on the other hand results in a median survival of 11 months, which is not superior to a palliative treatment in the FOLFIRINOX era.[26] Consequently, upfront resection in LA-PDAC does in general not seem to be surgically feasible nor justified from an oncologic point of view, but is only accepted as an individual approach in highly selected patients today.[27–29]

The Japanese Society of Hepato-Biliary-Pancreatic Surgery has published their experience with neoadjuvant therapy in initially unresectable PDAC in a 58-patient series in 2013 and has shown that an 8-month treatment before surgery is associated with a clearly superior outcome after an "adjuvant resection" than palliative treatment alone.[30]

Based on the above-mentioned considerations, it is obvious that LA-PDAC represents the clinical situation in which pretreatment can clearly enhance the number of patients who may eventually undergo surgery despite an initially not resectable finding at the time of PDAC diagnosis. This consideration can be based on two effects of neoadjuvant therapy, namely downsizing and eventually downstaging of the tumor on one hand and devitalizing the tumor without an obvious response in imaging on the other hand. Regarding downsizing or downstaging, this implies a clear response reflected in radiographic imaging after completion of the neoadjuvant treatment,

resulting in a shift from the initial cT4 stage to lower stages and delineating tissue planes toward the arterial structures, allowing a standard resection afterward.[31,32] In contrast to this clearly visible response in the case of downstaging, there is growing evidence that conventional imaging, that is, by standard CE-CT, fails to reflect the actual presence of viable tumor during restaging after completion of neoadjuvant treatment.[33,34] This has been demonstrated in a 50-patient collective by Dholakia et al.[33] including both BR-PDAC and LA-PDAC, in which a resection rate of 58% was achieved, despite no significant changes in tumor volume or degree of vessel involvement in the two groups after completion of the neoadjuvant therapy. The achievement of resection was impressively shown to be the decisive factor that determines survival in this study with a median survival of 23 months after resection, compared with 13.0 months, when resection could not be performed. Comparable results were described in 2015 by Ferrone and colleagues.[34] In this study, 40 patients were included: 26 of these patients were classified as LA-PDAC. The overall response rate was 90%, and the final R0 resection rate was 92%. Although a radiographic response was not seen in most patients, a pathologic downstaging occurred in the final histopathology compared with patients who underwent upfront resection, resulting in a decreased proportion of patients with positive lymph nodes (35% vs 79%), lymphatic invasion (35% vs 70%), and perineural invasion (73% vs 95%). All of these statistically significant changes underline the important aspect of an improved local control after neoadjuvant treatment that can be achieved not only when combined radiochemotherapy is applied but also with systemic treatment alone. The reported median overall survival of 34 months underlines the efficacy of Folfirinox as the preferable combination chemotherapy. The currently largest study on LA-PDAC surgery after pre-treatment included 575 patients who underwent various regimens of radiochemotherapy or chemotherapy alone.[35] In this cohort, 322 patients underwent gemcitabine and radiation; 125 patients received Folfirinox therapy, and 128 patients were treated by other regimens. Most patients in all groups were staged as unresectable due to arterial tumor infiltration or even the presence of distant metastases. After completion of pre-treatment, an overall resection rate of 51% was achieved. The most effective treatment option was Folfirinox with a secondary resection rate of 61%, compared with 47% after gemcitabine and radiation and 52% after other treatment schemes, respectively. Following resection, the median survival was 16 months; combined with an average 5–6 months of treatment time, this adds up to 21–22 months. An important fact in this study was the observation that the type of therapy did not have an influence on postoperative survival. Once a patient is converted to a resectable stage and this is performed, similar survival results postoperatively. Folfirinox seems to be the most effective possibility to achieve secondary resectability and consequently increase the pool of patients who can undergo pancreatectomy after a primary diagnosis of unresectability.

From the surgical point of view, exploration after completion of neoadjuvant treatment should be performed in all patients with a stable disease or obvious tumor response in the re-staging and only patients with a clear progression should be excluded from undergoing surgery. A described, conventional imaging fails to predict tumor response and even if imaging remains unchanged in many patients, a resection may be possible. When exploring these patients, surgery should follow the principle of an initial exclusion of distant metastases followed by an exploration of the critical arterial structures by an artery-first approach[36,37] before performing any surgical steps of no return. When frozen sections at these critical sites show no viable tumor, a resection is often possible without performing arterial resection and reconstruction as only fibrous tissue is found along the SMA or CA. A close periarterial dissection technique with removal of all soft tissue can be applied as an artery-sparing approach and offers the chance of radial tumor removal. Depending on the location of the tumor, this approach can be performed from the right, the left or both sides, when necessary.[38] After completion of dissection, the "TRIANGLE" between CA origin, SMA origin and the mesenterico-portal vein axis is displayed completely and all tumorous and fibrotic tissue has been removed under avoidance of any arterial resection. A synchronous portal vein resection; however, is mandatory in many of these patients. The mentioned approach is comparable to the previously described radical "level 3" dissection in upfront PDAC surgery.[39]

4 | CURRENT PERSPECTIVE

A major problem in the evaluation of neoadjuvant therapy in PDAC is the fact that the available evidence is mostly based on retrospective studies and that the applied treatment protocols differ to a great extent, that is, with regard to the use of radiation, the combination of different chemotherapy regimens, and the sequence as well as duration of treatment before surgery. Furthermore, in many studies, BR-PDAC and LA-PDAC are included, which makes comparisons difficult. Although in the last year several meta-analyses have been published, especially on the topic of Folfirinox in the neoadjuvant setting[14,40–42]; all of these fail to reach a high level of evidence due to the mentioned shortcomings. The reported resection rates after neoadjuvant therapy in these meta-analyses show a large heterogeneity, ranging between 0% and 43%, respectively. R0 resection rates vary between 55% and 100%, and median survival times between 9 and 43 months are reported. Despite these differing observations, all publications show that the achievement of resectability is the decisive factor to improve survival and that surgical resection after neoadjuvant treatment is not associated with higher rates of surgical morbidity or mortality compared with upfront resections. Although from these publications no valid conclusions can be drawn to define the most effective treatment regimens, which eventually lead to an increased rate of resectability for LA-PDAC, they show that the pool of patients who are candidates for surgery can be substantially extended when a neoadjuvant therapy is completed. A considerable number of trials are currently being conducted on national and international levels to investigate neoadjuvant therapy in BR-PDAC and LA-PDAC in a prospective setting.

Among them, gemcitabine is a standard drug in many protocols, combined with radiation, oxaliplatin, or capecitabine. Furthermore, combinations with nab-paclitaxel and radiation are under investigation for LA-PDAC, as well as Folfirinox in comparison to nab-paclitaxel and gemcitabine.

In summary, the various approaches to neoadjuvant PDAC therapy underline the importance of a multimodal strategy to improve outcomes in this fatal disease. There are encouraging results that effective chemotherapy protocols combined with or without radiation enhance the number of patients who can undergo surgical resection as the key to long-term survival despite an initially unresectable disease stage. Standardization of these protocols, however, remains poor to date. Presently recruiting and planned studies will increase evidence, and a change in clinical treatment pathways and guidelines can be expected in the near future, especially with regard to recommendations on BR-PDAC and LA-PDAC.

CONFLICT OF INTERSET

Authors declare no Conflict of Interests for this article.

ORCID

Thilo Hackert http://orcid.org/0000-0002-7012-1196

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