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Mini-review

Borderline resectable pancreatic cancer

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ABSTRACT

Surgery followed by adjuvant chemotherapy remains the only treatment option for pancreatic ductal adenocarcinoma (PDAC) with the chance of long-term survival. If a radical tumor resection is possible, 5-year survival rates of 20–25% can be achieved. Pancreatic surgery has significantly changed during the past years and resection approaches have been extended beyond standard procedures, including vascular and multivisceral resections. Consequently, borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC), which has recently been defined by the International Study Group for Pancreatic Surgery (ISGPS), has become a controversial issue with regard to its management in terms of upfront resection vs. neoadjuvant treatment and sequential resection. Preoperative diagnostic accuracy to define resectability of PDAC is a keypoint in this context as well as the surgical and interdisciplinary expertise to perform advanced pancreatic surgery and manage complications.

The present mini-review summarizes the current state of definition, management and outcome of BR-PDAC. Furthermore, the topic of ongoing and future studies on neoadjuvant treatment which is closely related to borderline resectability in PDAC is discussed.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive solid tumor entities and the fourth leading cause for cancer-associated mortality in Western countries with – in contrast to other malignancies – still increasing rates of incidence [1]. In 15–20% of all patients, surgery is possible and offers the chance of long-term survival. When combined with adjuvant chemotherapy, 5-year survival rates of 20–25% can be achieved [2]. The importance of postoperative adjuvant chemotherapy has been demonstrated in large randomized studies during the last two decades [3–5] and represents the standard of care for all patients that are considered to be resectable by the time of diagnosis.

With the ongoing development of specialization and centralization for pancreatic surgery since the late 1990s, not only postoperative mortality for these operations has been dramatically decreased [6,7]. In addition, the borders of resectability have been extended including approaches like vascular and multivisceral resections [8–10]. These developments have led to the need for a definition and standardization of local resectability with the aim to make publications on this topic comparable and to establish pathways for the diagnostic and therapeutic management of these patients. Today, the only situation that represents a clear contra-

indication for surgery is the finding of systemic spread, especially peritoneal carcinomatosis or diffuse liver metastases [11,12]. In contrast, locally advanced tumors without systemic spread – so-called borderline resectable tumors – should always be evaluated for either upfront surgery or neoadjuvant treatment and secondary resection in case of stable disease or remission during neoadjuvant therapy.

Diagnostic workup and classification of resectability

For the definition of local resectability in PDAC, the extension of the tumor toward the vascular structures, namely the superior mesenteric (SMV)/portal vein (PV) and the celiac axis (CA) as well as the superior mesenteric artery (SMA) is of utmost importance. A valid evaluation can be done by contrast-enhanced computed tomography (CE-CT) [13]. This diagnostic modality is available in nearly all institutions which has become a quick and relatively cheap diagnostic tool achieves sensitivity and specificity rates of 63–82% and 92–100%, respectively, with regard to PDAC diagnosis [14]. The use of a pancreas-specific CE-CT examination protocol with a 30° right-sided position of the patient and oral water intake to enhance the contrast in the gastro-duodenal region is the basis to maximize accuracy in the preoperative diagnostics [15]. In case of contraindications for a CE-CT, magnet-resonance imaging (MRI) can be used instead of CE-CT as the accuracy of MRI is comparable to CE-CT regarding diagnosis of PDAC and evaluation of the local tumor

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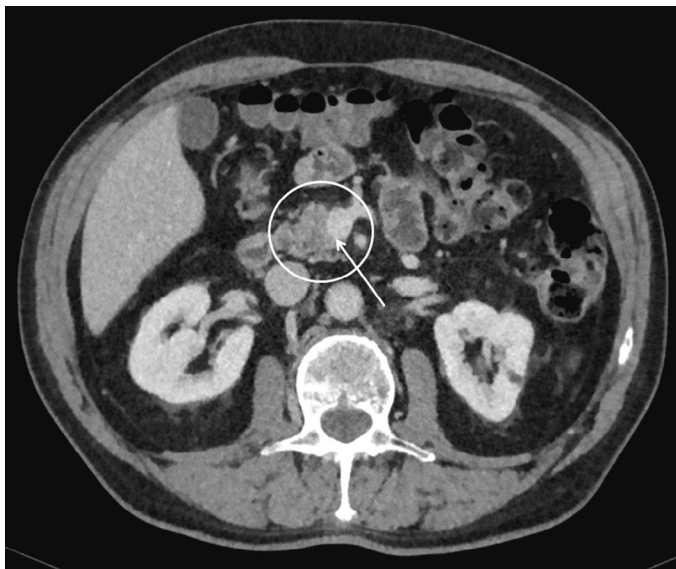


Fig. 1. BR-PDAC: axial CE-CT scan showing a hypodense PDAC (white circle) with involvement of the PV/SMV (white arrow).

extension [14]. With regard to possible vascular involvement, the use of endoscopic ultrasound (EUS) has gained widespread acceptance today. This diagnostic tool shows best rates of sensitivity and specificity compared to CE-CT and MRI as it offers a very high resolution local imaging along the vessels [14]. The possible disadvantages of EUS include that – besides the invasive character of EUS from the patients' perspective – the region of interest is limited, the accuracy of EUS is depending on the examiner's experience and the results of this dynamic examination can be reproduced only during the procedure itself. Therefore, EUS has to be regarded as a complementary tool CE-CT or MRI and is not available as a standard procedure in all institutions.

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 cross-sectional imaging modalities. Furthermore, pulmonary spread should be excluded by conventional chest X-ray and thoracic CT scan in case of any doubts.

Local resectability is defined as primary resectable PDAC, borderline resectable (BR-PDAC) or irresectable PDAC according to the criteria published by the ISGPS in 2014 [16] which are mainly based on the recommendations of the National Comprehensive Cancer Network [11].

Resectable PDAC is characterized by the absence of any vascular attachment (no distortion of SMV or PV and clearly preserved fat planes toward CA and AMS, 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 (Fig. 1). With regard to the arterial structures, a semi-circumferential abutment ($\leq 180^\circ$) of the SMA (Fig. 2) or an attachment at the hepatic artery (HA) without contact toward the CA is regarded as a borderline resectable finding. Finally, irresectable PDAC is defined as a more extended involvement of the SMA, CA, aorta or inferior vena cava as well as a SMV/PV venous involvement without a possibility for surgical reconstruction of the venous tract due to the lack of a suitable luminal diameter of the feeding and/or draining vein. This situation is most likely to be found in tumor-associated portal cavernous transformation.

Besides these definitions, two other classifications are in clinical use, namely the definition of the AHPBA/SSO/SSAT published in 2009 [17] and the M.D. Anderson criteria, that were published in 2006 [18]. Both definitions are similar to the above mentioned



Fig. 2. BR-PDAC: axial CE-CT scan showing a hypodense tumor extension to the AMS $<180^\circ$ (white arrow).

in terms of resectable PDAC. Regarding arterial involvement, there are no relevant differences between all definitions either, however, with regard to PV involvement, the M.D. Anderson definition does not include contact or narrowing of the vein, but gives occlusion as the criterion for BR-PDAC. Furthermore, in this publication, irresectability is termed “locally advanced”. An additional aspect with regard to patient management is the recommendation of the AHPBA/SSO/SSAT consensus that diagnostic laparoscopy should be performed in resectable tumors of the pancreatic head >3 cm, in all tumors of the body and tail and in patients who display CA 19-9 levels >100 U/ml. This aspect is not mentioned in any other definition or consensus and is based on the observation that a considerable proportion of patients fulfilling these criteria show unexpected peritoneal or liver metastases despite local resectability.

For the consecutive therapeutic decision, the recommendations for resectable and irresectable PDAC are clearly defined. While patients with resectable PDAC should undergo surgical exploration and radical resection, for irresectable PDAC patients the option of neoadjuvant treatment should be considered as the therapy of choice with the chance of a re-evaluation and eventually surgical exploration (see below). In BR-PDAC, therapeutic decisions have to differentiate 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 [19,20]. In contrast, when suspected arterial BR-PDAC is intraoperatively found to be a true arterial involvement, no general recommendation for resection is given, neoadjuvant treatment with a consecutive re-exploration and the option for a secondary resection is possible as well as direct arterial resection in exceptional cases or under study conditions.

Beyond the topic of vascular tumor involvement, the involvement of any adjacent organ, i.e. mesocolon, colon, stomach, adrenal gland or kidney may be regarded as BR-PDAC as well. Although this is not covered by the ISGPS definition for BR-PDAC, surgery for respective findings is defined as an extended approach by the ISGPS [21]. There is international consensus that these extended approaches are feasible in terms of surgical and oncological outcome and organ involvement should not be considered an obstacle for resection as long as a radical tumor removal is possible. Consequently, these patients should undergo upfront surgery and should not be treated in a neoadjuvant setting [21].

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