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Neoadjuvant multimodal treatment of pancreatic ductal adenocarcinoma

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Contents

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ABSTRACT

Treatment of pancreatic ductal adenocarcinoma (PDAC) is increasingly multidisciplinary, with neoadjuvant strategies (chemotherapy, radiation, and surgery) administered in patients with resectable, borderline resectable, or locally advanced disease. The rational supporting this management is the achievement of both higher margin-negative resections and conversion rates into potentially resectable disease and *in vivo* assessment of novel therapeutics. International guidelines suggest an initial staging of the disease followed by a multidisciplinary approach, even considering the lack of a treatment approach to be considered as standard in this setting. This review will focus on both literature data supporting these guidelines and on new opportunities related to current more active chemotherapy regimens.

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Locally advanced
Neoadjuvant
Radiotherapy
Chemotherapy
Target therapy

An analysis of the pathological assessment of response to therapy and the potential role of target therapies and translational biomarkers and ongoing clinical trials of significance will be discussed.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is projected to become the second leading cause of cancer death by 2030 with a 5-year overall survival (OS) rate around 7% (Siegel et al., 2015; Rahib et al., 2014). At first diagnosis, only 10–20% of PDAC patients present with primarily resectable disease, whereas a locally advanced disease affects approximately 30% of patients, recently subdivided into locally advanced nonresectable (LAPC) and borderline resectable (BRPC) PDAC according to tumor involvement of the adjacent vasculature (Hidalgo, 2010). Even in patients undergoing primarily radical resection, the 5-year survival rate is around 15–20%, with 30% of deaths associated with locally relapsed disease alone (Hishinuma et al., 2006). So far, localized PDAC remains one of the most challenging human malignancies to treat. The advancement of technology in radiology and nuclear medicine has allowed clinicians to improve the definition of the vascular involvement state, which is critical for an accurate classification of locally advanced PDAC. Currently, there are no studies in the literature able to give considerable categories of evidence. Nevertheless, on the basis of available literature data, international guidelines suggest an initial staging of the disease followed by a multidisciplinary approach, including different multimodal strategies such as chemotherapy and/or chemoradiotherapy (CRT) in order to convert tumor to resection and improve RO resection rate (NCCN Guidelines, 2015; Seufferlein et al., 2012; AIOM Guidelines, 2014).

This review will focus on literature data supporting these guidelines and on new opportunities related to current more active chemotherapy regimens and ongoing clinical trials of significance. An analysis of the pathological assessment of response to therapy and the potential role of target therapies and translational biomarkers will be discussed.

2. Definition of initially resectable PDAC, BRPC and LAPC

Differentiation between initially resectable PDAC, BRPC and LAPC is performed mostly based on vascular involvement. PDAC is considered to be clearly initially resectable in the absence of superior mesenteric vein (SMV) or portal vein (PV) distortion with a clear cleavage plane around the celiac axis, hepatic artery and superior mesenteric artery (SMA). Obviously, tumor resectability must also be assessed according to patient performance status and comorbidities (Callery et al., 2009). It is crucial to detect the possibility of achieving radical resection, since, a macroscopically clear resection may be microscopically incomplete. In this regard, differentiating R0 resection (no tumor cells within 1 mm of any surface) from R1 (one or more tumor cells visible within 1 mm of any surface) and R2 (macroscopically incomplete resection) resections (Esposito et al., 2008; Campbell et al., 2009) becomes significant as many surgical procedures on resectable PDAC are R1 resections with only a marginal benefit in terms of OS with respect to R2 ones. Furthermore, the median OS of R2 resected PDAC is similar to that of BRPC/LAPC patients treated with chemotherapy alone (Tol et al., 2015). Consequently, patients who will achieve a R2 resection should not be considered resectable.

According to NCCN guidelines, BRPC has been defined as a tumor with limited involvement of mesenteric veins, in which resection is technically possible, although with a high risk of a positive margin and consequently an increased risk of recurrence. Regarding arterial involvement in BRPC there is a general consensus to include patients with interface between the tumor and vessel measuring <180° of the circumference of the superior mesenteric artery (SMA) or of the celiac axis, or short segment encasement of the hepatic artery amenable to resection/reconstruction (Katz et al., 2008, 2013). Further vascular involvement is considered to characterize LAPC. A variability in the definition of SMV-PV impingement has been reported. In particular, the MD Anderson Cancer Center group definition of BRPC allows for short segment occlusion of the SMV-PV with a suitable vein for reconstruction above and below the area involved by the tumor (Katz et al., 2013). While, the definition used in the intergroup Alliance trial A021101 has been recently endorsed by NCCN, consisting in tumor ≥180° of the circumference of the vessel wall and/or reconstructible occlusion. In addition to the purely radiological criteria, Katz et al. considered also patient-related factors and identified three distinct subgroups of BRPC patients: group A, defined by radiological criteria alone; group B, including patients with findings suggestive, but not diagnostic, of metastasis; and group C, characterized by contraindications for major abdominal surgery (Katz et al., 2008). Nevertheless, universally accepted set of characteristics to define BRPC patients still remains to be established.

3. Preoperative PDAC staging

Even if the mortality rate for PDAC surgery has reduced significantly in the last 30 years, its morbidity remains clinically relevant (30–50%) even in centers of excellence (Lewis et al., 2013). As a consequence, patient selection for surgery represents a crucial aspect. Optimal preoperative work up of PDAC requires the use of high quality imaging. Computer tomography (CT) is mandatory in these patients and should be performed using a pancreas protocol, consisting of three-phasic contrast (non-contrast, arterial pancreatic parenchymal, portal venous) and thin cross sectional cuts (≤3 mm) with multiplanar reconstruction (Callery et al., 2009). Although 70–85% of patients defined by CT as having a resectable tumor were able to undergo resection, the sensitivity of CT for small hepatic and peritoneal metastases is limited (Wong and Lu, 2008). In this regard, magnetic nuclear resonance (MNR), which showed a similar capacity in the evaluation of tumor extension and vascular involvement with respect to CT, may be useful to identify subcentimetric liver metastases (Vachiranubhap et al., 2009; Park et al., 2009; Koelblinger et al., 2011).

Several studies have shown a higher rate of distant metastases detection with positron emission tomography (PET)/CT than with conventional imaging (Kauhanen et al., 2009). Moreover, the metabolic activity of the pancreas tumor, measured by PET through standardized uptake value (SUV), seems to correlate with prognosis and response to treatment of LAPC patients (Topkan et al., 2011; Chang et al., 2014). However, the role of PET/CT in the evaluation of potentially resectable PDAC remains unclear. A recent metanalysis of 39 studies concluded that PET can be used as a valuable tool for PDAC diagnosis, whereas it has a moderate sensitivity for staging, due to a poor detection of local lymph node metastases and local tumor spread (Wang et al., 2013).

Differently from patients referred to upfront surgery, a biopsy is required prior to starting a neoadjuvant therapy. Fine nee-