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Multimodal treatment of resectable pancreatic ductal adenocarcinoma

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ABSTRACT

After a timing preoperative staging, treatment of resectable pancreatic adenocarcinoma (PDAC) includes surgery and adjuvant therapies, the former representing the initial therapeutic option and the latter aiming to reduce the incidence of both distant metastases (chemotherapy) and locoregional failures (chemoradiotherapy). Herein, we provide a critical overview on the role of multimodal treatment in PDAC and on new opportunities related to current more active poli-chemotherapy regimens, targeted therapies, and the more recent immunotherapy approaches. Moreover, an analysis of pathological markers and clinical features able to help clinicians in the selection of the best therapeutic strategy will be discussed. Lastly, the role of neoadjuvant treatment of initially resectable disease will be considered mostly in patients whose malignancy shows morphological but not clinical or biological criteria of resectability. Depending on the results of these investigational studies, today a multidisciplinary approach can offer the best address therapy for these patients.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer death in Europe and United States with a 5-year overall survival (OS) rate around 7% (Siegel et al., 2015). Resectable disease comprises only 15–20% of patients at diagnosis and many of them are found to have microscopically positive margins at the time of surgery. Even after curative surgery, most patients will recur with 5-year survival rate around 10%, with locoregional and systemic recurrence rates from 50% to 80% and greater than 70%, respectively (Kamisawa et al., 2016).

Adjuvant treatments include systemic therapy that aims to reduce the incidence of distant metastases and chemoradiotherapy (CRT) potentially able to decrease the risk of locoregional failure. While the role of the former is well established according to the results of randomized clinical trials, the usefulness of the latter remains controversial (Oyasiji and Ma, 2015). Evaluation by a multidisciplinary team of each patient should be mandatory (Pawlik et al., 2008).

Herein, we provide a critical overview on the role of multimodal treatment in PDAC and on new opportunities related to current more active poli-chemotherapy regimens, targeted therapies, and the more recent immunotherapy approaches. Moreover, an analysis of pathological markers and clinical features able to help clinicians in the selection of the best therapeutic strategy will be discussed. Lastly, the role of neoadjuvant treatment of initially resectable disease will be considered mostly in patients whose malignancy shows morphological but not clinical or biological criteria of resectability (Russo et al., 2016).

2. Morphological and clinical/biological criteria of resectability

After a preoperative staging (Silvestris et al., 2016) surgical resection is the initial therapeutic option of patients with resectable PDAC (Barugola et al., 2013; Serrano et al., 2015). Surgical indication is mainly influenced by the involvement of vessels but the underpinning disease biology as well as the general patients' conditions should also be considered. Vessel involvement is one of the most important features that needs to be carefully assessed in the initial evaluation of resectability. Regarding tumors involving the pancreatic head, there is a general agreement in excluding from immediate surgery patients with PDAC invading the superior mesenteric artery. The main limitations of pancreatectomy with arterial resection are represented by a poor short- and long-term outcome and the absence of prospective studies aimed to clarify a possible survival benefit in highly selected patients (Mollberg et al., 2011). The MD Anderson Cancer Center proposed a classification of PDAC resectability based on vessel involvement in which lesions marginally invading the superior mesenteric artery are defined as borderline resectable pancreatic carcinoma (BRPC) (Katz et al., 2011, 2013). The same classification identifies the superior mesenteric/portal vein grade of invasion as another key element for distinguishing resectable tumors from borderline and locally advanced forms. The role of superior mesenteric/portal vein resection in patients with PDAC is still a matter of debate. Several meta-analyses reported conflicting results on the possible advantages in terms of survival in patients who underwent pancreatectomy with vein resection (Siriwardana and Siriwardena, 2006; Yu et al., 2014; Giovinazzo et al., 2016). A recent meta-analysis focusing on this issue reviewed 27 studies showing increased postoperative mortality, higher rates of non-radical surgery and shorter survival after pancreatic resection with superior mesenteric/portal vein resection (Giovinazzo et al., 2016).

A distinction has to be made between PDAC involving the head of the pancreas and tumors localized in the pancreatic body/tail due to the high rate of splenic vessels infiltration in the latter group. Several reports analyzed the impact that the invasion of splenic vessels has among patients with distal PDAC (Partelli et al., 2011; Kanda et al., 2010). In particular, the invasion of the splenic artery, contrary to that of the splenic vein, is a crucial prognostic factor of PDAC localized in the body and tail. Vascular involvement is not the only criterion that could preclude immediate surgery. In the absence of clear metastatic disease, the occurrence of distant tumor localization should be suspected when Ca 19.9, the only biomarker with demonstrated clinical usefulness for PDAC, is significantly elevated in the absence of obstructive jaundice (Goonetilleke and Siriwardena, 2007). Ferrone et al. demonstrated a close correlation between the Ca 19.9 value and survival after pancreatic resection (Ferrone et al., 2006). A value of preoperative Ca 19.9 > 200 U/mL in patients with resectable PDAC has been proposed to identify patients with disease that is not suitable for up-front surgery in combination with duration of symptoms and pathological grading (Barugola et al., 2009). The performance status of patients is another important variable to be considered (Boeck et al., 2007). Intriguingly, time interval between preoperative image staging and surgery correlate with the rate of unanticipated metastasis (UM) observed at operation. It was demonstrated that the frequency of UM for 3 shorter time interval groups (0–6, 7–13, and 14–20 days) was 12%. The longest 3 groups (35–41, 42–48, and 49–86 days) showed similar frequencies of UM of 35%, 29%, and 30%, with a linear relationship (Glant et al., 2011). So far, Authors recommend an imaging no longer than 2–3 weeks old by the date of surgery, in all new diagnosed PDAC patients.