

The borderline resectable/locally advanced pancreatic ductal adenocarcinoma: What should be the surgeon's choice?

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INTRODUCTION

In 2006, MD Anderson group published a new classification of pancreatic ductal adenocarcinoma (PDAC) that took into account the degree of neoplastic involvement of peripancreatic vessels.^[1] According to that, PDAC was classified as resectable, borderline resectable (BR), or locally advanced (LA).^[1] From its introduction, this classification has been universally adopted, allowing a standardization of terminology used by different pancreatic centers. If, in case of resectable PDAC, upfront radical surgery followed by adjuvant chemotherapy is the gold standard treatment,^[2] on the other hand, the optimal treatment strategy of patients with BR and LA-PDAC is complex, and it is still matter of debate.

BORDERLINE RESECTABLE PANCREATIC CANCER

BR-PDAC is defined as a tumor with abutment, encasement, or occlusion of superior mesenteric vein or portal vein, abutment of superior mesenteric

artery (SMA) $<180^\circ$, and abutment or short segment encasement of common hepatic artery.^[1]

Two questions about the optimal treatment for BR-PDAC are still open:

1. Is it oncologically more effective to perform an upfront surgery followed by adjuvant treatment or a neoadjuvant treatment followed by radical surgery?
2. In case of neoadjuvant treatment, what is the best strategy to adopt (chemotherapy, radiochemotherapy, chemotherapy + radiochemotherapy)?

The adoption of a neoadjuvant protocol treatment followed by radical surgery for BR-PDAC has some theoretical advantages: (a) early treatment of micrometastatic disease; (b) selection of patients with localized disease and more favorable tumor biology, who are most likely to benefit from surgical resection; and (c) increased likelihood of an R0 resection. In the last decade, many retrospective studies evaluating the results of neoadjuvant treatments followed by radical surgery for BR-PDAC have been published.^[3-5] In 2008, Katz *et al.*^[4] evaluated 160 patients with BR-PDAC: 78% of them completed the neoadjuvant protocol, and

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41% of them underwent pancreaticoduodenectomy. R0 resection was obtained in 94% of resected cases. Median survival was 40 months for patients who underwent preoperative therapy followed by surgery and 13 months for patients who did not undergo pancreaticoduodenectomy ($P < 0.001$). This study, as others published in the last years, demonstrated that the neoadjuvant approach allowed for the identification of a subset of patients that was most likely to benefit from surgery, as evidenced by the favorable median survival in this group. According to these results, even in the absence of randomized controlled trials, the trend of many pancreatic surgeons during the last years has been to adopt a neoadjuvant approach for patients affected by BR-PDAC.

The debate on the most effective neoadjuvant treatment scheme is currently unsolved. Conventionally, chemoradiation for BR-PDAC with gemcitabine- or 5-fluorouracil-based protocols along with radiotherapy has been adopted,^[6] showing resection rates of approximately 30%.^[7] With the introduction of other regimens, such as FOLFIRINOX or nab-paclitaxel,^[8-11] resection rates of up to 60% were achieved. Unfortunately, there are no randomized studies comparing these approaches, and consequently, evidence-based recommendations on the best treatment option cannot be given. However, a FOLFIRINOX-based regimen seems to be the most promising approach.

LOCALLY ADVANCED PANCREATIC CANCER

LA-PDAC is defined as a tumor with $>180^\circ$ abutment or encasement of the SMA, long segment common hepatic artery abutment, and encasement of the celiac axis as well as a nonreconstructible portal vein/superior mesenteric vein.^[1]

For many years, LA-PDAC has been considered an unresectable disease, and gemcitabine monotherapy (sometimes combined with radiotherapy) has been the standard palliative treatment.^[12] In the last years, the advent of more effective chemotherapeutic agents and the skills of the surgeons to perform arterial resections during pancreatectomy led to a change of this approach.

Recently, the superiority of FOLFIRINOX over gemcitabine monotherapy in patients with metastatic pancreatic cancer was demonstrated.^[13] The comparable

poor prognosis of LA-PDAC and the lack of beneficial therapies have also led to the administration of FOLFIRINOX, sometimes combined with radiotherapy, in these subset of patients. A systematic review on clinical outcomes after FOLFIRINOX-based treatment for LA-PDAC demonstrated a 28% resection rate, of which 77% were R0, and a median overall survival ranging between 8.9 and 25.0 months.^[14] These data suggest that FOLFIRINOX-based treatment is indeed a promising option for patients with LA-PDAC, with acceptable toxicity (23% Grade 3–4 complications). Future unselected prospective cohort studies are needed to determine the exact role for FOLFIRINOX in LA-PDAC.

The increasing rate of resection after neoadjuvant treatment for LA-PDAC is also a consequence of a more aggressive surgical attitude. In the last years, many studies reporting the experience with arterial resection during pancreatectomy have been published. However, the benefit of this kind of approach is still questionable according to the available literature. Published series of arterial resections during pancreaticoduodenectomy are small, often including heterogeneous anatomical reconstructions.^[15,16] Such studies reported a not negligible morbidity and mortality, perhaps countering any potential oncologic benefits.^[16]

CONCLUSIONS

BR-PDAC represents an interdisciplinary treatment challenge. Recent literature focuses on the utility of neoadjuvant treatment in this subset of cases, to obtain better oncological results. LA-PDAC was previously thought not to be amenable to surgery. However, the evolution of vascular reconstruction techniques combined with administration of active neoadjuvant therapy has allowed for the conversion of some cases to potentially resectable disease.

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