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REVIEW ARTICLE

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Cutting-edge strategies for borderline resectable pancreatic cancer

Rajesh S. Shinde | Manish Bhandare | Vikram Chaudhari | Shailesh V. Shrikhande

GI & HPB Service, Department of Surgical Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India

Correspondence
Shailesh V. Shrikhande, Division of Cancer Surgery, GI & HPB Surgical Services, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra 400012, India.
Email: shailushrikhande@hotmail.com

Abstract

Worldwide, pancreatic ductal adenocarcinoma (PDAC) accounts for more than 400 000 deaths every year, being the 12th most common cancer and the seventh most frequent cause of death from cancer. Regardless of the advances in diagnosis and treatment, PDAC continues to have dismal outcomes and fewer than 25% of patients survive for 1 year. In the absence of metastatic disease, radical surgery remains the most important factor for improving survival and possibly offer cure. However, approximately 80% of patients cannot be offered surgery owing to locally advanced or metastatic disease at presentation. At presentation, only 10%–20% patients are eligible for resection, 30%–40% are unresectable/locally advanced and 50%–60% are metastatic. One promising development in recent years has been the inclusion of a new subgroup within the locally advanced tumors of borderline resectable pancreatic cancer (BRPC) comprising approximately 5%–10% of the total patient population. Although its exact definition has been refined over the past few years depending on the vascular involvement around the tumor, the term was initially proposed for tumors that are at a high risk of having margin positivity after resection. Various treatment approaches are still evolving for this entity. Herein, we reviewed the current status of different treatment modalities for BRPC.

KEYWORDS
borderline, borderline resectable pancreatic cancer, pancreatic cancer, pancreaticoduodenectomy

1 | INTRODUCTION

Worldwide, pancreatic ductal adenocarcinoma (PDAC) accounts for more than 400 000 deaths every year, being the 12th most common cancer and the seventh most frequent cause of death from cancer.[1] Regardless of the advances in diagnosis and treatment, PDAC continues to have dismal outcomes and fewer than 25% of patients survive for 1 year. Poor outcome in this disease is attributed to several factors including aggressive tumor biology and late stage at presentation. In the absence of metastatic disease, radical surgery with R0 resection remains the most important factor for improving survival and possibly offering cure. However, approximately 80% of patients cannot be offered surgery owing to locally advanced or metastatic disease at presentation. At

Rajesh S. Shinde and Manish Bhandare contributed equally to the manuscript.

presentation, only 10%–20% patients are eligible for resection, 30%–40% are unresectable/locally advanced and 50%–60% are metastatic.[2]

Conventionally, PDAC has been broadly classified clinicoradiologically into resectable, locally advanced and metastatic stage. One promising development in recent years has been the inclusion of a new subgroup within the locally advanced tumors of borderline resectable pancreatic cancer (BRPC) comprising approximately 5%–10% of the total patient population. The term BRPC became formal after its recognition and inclusion as a unique subcategory by the National Comprehensive Cancer Network (NCCN) in 2006. Although its exact definition has been refined over the past few years depending on vascular involvement around the tumor, the term was initially proposed for tumors that are at high risk of having margin positivity after resection. This concept was proposed with a view to extend the benefits of surgery and to improve survival of these advanced tumors and, so far, the results have been encouraging.

2 | HISTORICAL EVOLUTION OF BRPC

Recognition of BRPC as a distinct entity in PDAC evolved over a period of time and is based on several clinical observations made. Long-term prognosis or outcomes of PDAC patients undergoing surgical treatment is influenced by margin status; margin-negative (R0) resection cases fare better than microscopic/macroscopic residual (R1/R2) resections.[3–5] Historically, absence of liver/peritoneal metastasis and vascular infiltration (celiac axis [CA], superior mesenteric artery/vein [SMA/SMV], portal vein [PV]) defined resectability in PDAC. However, evolving data reported similar outcomes of vein resections and standard resections.[6–8] In 1992, Ishikawa et al[9] proposed a classification for venous involvement based on radiological findings and described five patterns of infiltration of the SMV-PV axis as: (i) normal; (ii) smooth shift without narrowing; (iii) unilateral narrowing; (iv) bilateral narrowing; and (v) bilateral narrowing and the presence of collateral veins. In 1997, Lu et al[10] proposed a grading system based on the degree of circumferential contact with vessels and circumferential contact exceeding one-half circumference of the vessel (>180°) was highly suggestive of unresectable tumor. Length of tumor contact with the vessel and presence of venous deformity on radiological evaluation were also reported to be useful for defining BRPC and deciding the treatment approach.[11,12] During the same period, data supporting neoadjuvant chemotherapy and radiotherapy emerged with possible downstaging of the tumors and increasing the chances of margin-negative resection. These studies also confirmed feasibility, safety and survival benefit with the neoadjuvant approach.[13–17] However, these studies had variable response rates to neoadjuvant treatment but clearly suggested that a small yet real proportion of patients will benefit by this approach. Such observations made over time introduced the concept of BRPC in clinical practice.

3 | DEFINITION

The initial definitions for BRPC were based on tumor extent and involvement of the surrounding vasculature such as SMA, SMV/PV, CA and hepatic artery (HA) seen on multidetector-row computed tomography (MD-CT) scans. Improvements in modern radiology have enabled superior assessment of vascular involvement and resectability in the arterial, pancreatic parenchymal and portal venous phases of pancreas protocol CT scan. The present anatomical definition of BRPC as proposed by NCCN 2016 divided tumors into pancreatic head/uncinate process and pancreatic body/tail and the extent of vascular invasion was detailed for each of the named veins and arteries. This definition avoided the use of ambiguous terms in previous definitions such as vascular abutment, impingement, narrowing, encasement, invasion, adherence etc., and the degree of interface between tumor and vessels was defined as <180° or ≥180° in an attempt to provide uniformity and standardization in reporting and documentation. However, the decision to offer resection should not be based on anatomical criteria alone. The biological behavior of the cancer and the ability of the patient to withstand the physiological stress of complex and demanding surgery should play a very important role in the decision-making process. The recent international consensus on definition and criteria of BRPC[18] has defined patients according to three distinct dimensions: anatomical (A), biological (B), conditional (C):

- The anatomical definition of BRPC includes tumor that is at high risk for margin-positive resection (R1 or R2).
- The biological definition of BRPC includes findings that raise the possibility (but not certainty) of extrapancreatic metastatic disease (high serum Ca 19-9 levels/radiologically suspected but unproven metastases).
- The conditional definition of BRPC includes patients at high risk for morbidity or mortality after surgery because of performance status and comorbidities.

4 | MANAGEMENT OF BRPC

Treatment of BRPC requires a multimodal approach including surgery, chemotherapy, and radiation therapy. In addition to the stage, baseline performance status and comorbidities should be considered before planning treatment. In BRPC, likelihood of an R1 resection is high; hence, the preferred approach is attempted downstaging with neoadjuvant chemotherapy or chemoradiotherapy and then reassessment for possible curative resection. The current available management strategies include:

- Upfront surgery followed by adjuvant chemotherapy +/− radiotherapy;
- Neoadjuvant chemotherapy (NACT) followed by surgery;
- Neoadjuvant chemoradiotherapy (NACT-RT) followed by surgery.

International Study Group for Pancreatic Surgery (ISGPS) consensus statement recommends upfront resection for tumors with isolated venous involvement [19] especially in high-volume centers of experience. However, numerous studies using different neoadjuvant protocols are published in the literature with reported benefits.[20–22]

5 | ROLE OF NEOADJUVANT THERAPY

Although the aim of neoadjuvant therapy in BRPC is to downsize the tumor and enable margin-negative resection, a proportion of these patients can also receive R0 resection without any neoadjuvant treatment (eg, small-volume disease with short segment of SMV/PV involvement of <180°). Also, during neoadjuvant therapy, there is always a risk of disease progression that is reported in the range of 10%–40%.[22] Clearly, upfront surgery in BRPC merits strong consideration among the various treatment approaches. In our own experience, all patients need not receive neoadjuvant treatment and well-selected patients in a dedicated pancreas unit can receive margin-negative upfront surgical resections.[23,24] However, rationale for neoadjuvant therapy is not only to minimize the risk of a margin-positive resection, but also to treat occult systemic disease. Until now, there is only one randomized trial addressing the impact of neoadjuvant therapy on overall survival versus upfront surgery.[25] This study reported better outcomes with the neoadjuvant approach versus upfront surgery. Low level of evidence does suggest improvement in R0 resections but that has not translated into improved overall or disease-free survival. Larger, more robust clinical trials are needed to determine actual long-term benefits with neoadjuvant approaches.

6 | NEOADJUVANT CHEMOTHERAPY OR CHEMORADIATION?

Currently, there is no consensus on the best suited neoadjuvant protocol for all BRPC patients. A recent systematic review failed to reach any conclusion on this and, hence, the best regimen for neoadjuvant therapy is still unknown. Among the various chemotherapy regimens available, currently FOLFIRINOX appears to be the most effective protocol, resulting in significantly better resection rates and overall survival as compared to the other regimens.[22] However, FOLFIRINOX has greater toxicity, especially in the elderly, with comorbidities approaching approximately 30%–40%. These factors should be considered carefully in the light of the new anatomical, biological and conditional definition of BRPC.

Combination of chemotherapy with radiation in a neoadjuvant setting was thought to result in higher response rates and better sterility of margins in BRPC. A recent and the only randomized controlled trial (RCT) using neoadjuvant chemoradiation for BRPC showed a survival advantage with chemoradiation over upfront surgery.[25] In the absence of more evidence and the lack of consensus on dose and mode of delivery of radiation (conventional vs stereotactic body radiotherapy [SBRT]), it still cannot be considered as standard of care despite the promising results of this study. Currently, a phase III Alliance trial (A021501) is ongoing to compare neoadjuvant chemotherapy versus chemotherapy + SBRT. The results of this trial will hopefully solve the problem of the type of neoadjuvant approach for BRPC.[26]

7 | SURGERY FOR BRPC

Achieving margin-negative resection remains the guiding principle and challenge in pancreatic cancer surgery and it is even more challenging in BRPC. A meta-analysis by Zhou et al[27] found similar overall survival between the cohorts with or without vascular resections. ISGPS consensus guidelines were published in 2014, addressing the role of vascular resection in BRPC.[19] Following are the ISGPS recommendations on venous/arterial resection.

7.1 | International Study Group for Pancreatic Surgery guidelines on upfront vein resection

- In the event of reconstructible mesenterico-portal axis involvement, straightforward operative exploration and upfront vein resection can be advised on the basis of the currently available evidence.
- In view of a lack of high-level evidence for neoadjuvant treatment in BRPC, patients with isolated venous involvement can be offered surgery, provided technical options of reconstruction are available and resection is R0.
- Vascular resections should be preferred in high-volume centers with experienced surgical and multidisciplinary teams.

7.2 | International Study Group for Pancreatic Surgery guidelines on arterial resection

- There is no good evidence to support arterial resections and such resections are not advised routinely as a result of increased morbidity and mortality.
- Patients with BRPC on the basis of arterial involvement on imaging, should undergo exploration in order to confirm arterial infiltration.
- Palliative treatment is the standard of care in confirmed arterial involvement.
- Neoadjuvant protocols may be evaluated considering age, comorbidities, tumor biology, and performance status.

Despite these complex vascular resections, SMA margin is often positive.[28] To triumph over this problem of margins, artery-first approaches have been increasingly adopted over the past few years. The term 'artery-first' approach was used first in 2010 and is usually applied to the SMA, although may also refer to other arteries, including the HA and CA, depending on the location and relations of the primary tumor. A total of six different 'artery-first' approaches

are described, each with a specific indication and technical justification and proven safety and feasibility.[29,30] A recent systematic review and meta-analysis showed that the artery-first approach was associated with better perioperative outcomes and improved survival.[31,32] However, such complex pancreatic surgeries are technically demanding and should be carried out at high-volume centers by experienced surgeons to achieve the best possible outcomes and reduce morbidity.

In summary, borderline resectable pancreatic cancer has evolved as a clearly distinct subgroup of potentially curable pancreatic cancer. Multidisciplinary evaluation with careful selection of treatment modality or appropriate sequencing of different modalities, such as surgery, chemotherapy and radiotherapy, is of paramount importance in successful management of this subgroup. Further studies/trials are needed to identify the optimum neoadjuvant protocols and to define its indications.

DISCLOSURE

Conflicts of interest: Authors declare no conflicts of interest for this article.

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ORCID

Rajesh S. Shinde https://orcid.org/0000-0001-9478-8676

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