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Surgical management of borderline resectable pancreas cancer in the era of neoadjuvant therapy

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Introduction

Pancreatic Cancer remains a devastating disease with high mortality rates worldwide. Surgery remains the cornerstone of curative treatment. Conventionally, pancreatic cancers have been classified as resectable (Stage I / II / III), locally advanced resectable or unresectable (Stage III) or metastatic (Stage IV). However, over the past few years, a distinct subset of patients with pancreatic cancer has emerged, i.e. borderline resectable pancreatic cancer. BRPC are those which satisfy any one of the following criteria:

1. 180° tumour abutment with the SMA
2. Short segment (1.5 cm) encasement or occlusion of the PV/SMV
3. Encasement of short segment of hepatic artery, but not up to celiac axis
4. Encasement of GDA up to hepatic arterial origin
5. 180° tumour abutment with the PV and SMV (1).

Latest AJCC staging system (8th edition), do not consider this subgroup as operable because any venous occlusion or arterial encasement is defined currently as unresectable; hence patients with BRPC have a high probability of being classified as unresectable disease. The International Study Group of Pancreatic Surgery (ISGPS) suggests that preoperative evaluation of resectability should be based on pancreatic protocol contrast enhanced CT scan. However, with refinements in imaging, distinction between resectable and locally advanced disease may be difficult in specific cases. Careful evaluation of CT scan for following details helps to better define these tumors on preoperative imaging (1):

1. Length of Contact (LC)
2. Circumferential Contact (CC) (Grades I – IV)
3. Venous Deformity (VD) (Grades 0 – 2).

It is generally inferred that greater the degree of CC and VD, higher is the chance of venous resection.

Another important aspect in deciding the appropriate treatment for this subset of patients is the likelihood of ending up in R+ resection. Based on our own institutional publication, incidence of R1 resection was 7%, in common bile duct tumors 20%, and 57% in head of pancreas and uncinated process tumors. Posterior and SMA margins were the most commonly involved margins. To overcome this issue, artery first or SMA first approach, along with peri-adventitial (LV3) approach or sub-adventitial approach can used to minimize rates R1 resection in BRPC and even locally advanced pancreatic cancer with arterial involvement.

ISGPS classification of venous resections:

Type 1: partial venous excision with direct closure (venorraphy) by suture closure;
Type 2: partial venous excision using a patch;
Type 3: segmental resection with primary veno-venous anastomosis; and
Type 4: segmental resection with interposed venous conduit and at least two anastomoses.

ISGPS guidelines on Upfront Venous resection in BRPC (2):

1. On the basis of the currently available evidence suggesting similar survival rates to those reported for

patients undergoing a standard resection, there is clear evidence supporting straightforward operative exploration and resection in the presence of reconstructible mesenterico-portal axis involvement.
2. There is currently evolving but not convincing evidence for neoadjuvant treatment protocols in BRPC patients with isolated venous involvement, provided technical options of reconstruction are given.
3. After intraoperative evaluation of tumour extent, venous resection is indicated if complete tumour excision (R0) is possible, although this may lead to greater overall rates of intraoperative and postoperative morbidity rates.
4. The ISGPS strongly suggests that these vascular resections should be limited to high-volume centres with experienced surgical and multidisciplinary teams.

ISGPS guidelines on arterial resection in BRPC (2):
1. There is no good evidence that arterial resections during right-sided pancreatic resections are of benefit. Such resections may be harmful with increased morbidity and mortality and should not be recommended on a routine basis.
2. Patients categorized as borderline resectable on the basis of features of arterial involvement seen at imaging, should undergo surgical exploration in order to obtain further verification of any arterial infiltration.
3. In case of verification of arterial involvement, palliative treatment is the standard of care.
4. Respecting patients' age, grade of comorbidities, tumour biology, and performance status, neoadjuvant approach may be evaluated in addition to the standard of care: There is no level I evidence to recommend neoadjuvant therapy regimens in patients with arterial infiltration; therefore, evaluation of neoadjuvant therapeutic options is only recommended in the setting of prospective trials. If neoadjuvant therapy regimes are applied, an exploratory laparotomy and attempt at resection should be considered in the absence of disease progression after neoadjuvant treatment (distant metastasis) and if patients' performance status is adequate.

Role of Neoadjuvant Therapy in BRPC
Neoadjuvant therapy may increase the possibility of R0 resection and eradicate systemic micro metastasis and is therefore considered a reasonable approach for treating BRPC. In a meta-analysis by Tang et al. (3), which included 18 studies, they found that 2.8% patients had CR, 28.7% had partial response, 45.9% had stable disease while 16.9% patients progressed on neoadjuvant therapy. A total of 65.3% patients underwent resection and R0 resection was achieved in 57.4% patients. The authors concluded that resection and R0 resection rates in the group of borderline resectable tumour patients after neoadjuvant therapy are similar to the resectable tumour patients, but much higher than those in unresectable tumour patients. The survival estimates of borderline resectable tumour patients after neoadjuvant therapy were similar to resectable tumour patients. Patients with borderline resectable pancreatic cancer should be included in neoadjuvant protocols and subsequently be re-evaluated for resection.
A more recent meta-analysis by Versteijn E et al. consisting of 38 studies with 3484 patients of resectable and borderline resectable pancreatic cancer showed better R0 resection rates (86.8% v/s 66.4%) and improved overall survival (median OS 18.8 months' v/s 14.8 months) with neoadjuvant therapy (4).
In one of the most recent meta-analysis published in 2022, Van Dam JL et al. included 7 randomised controlled trials including 938 patients of resectcable and BRPC. All studies included neoadjuvant chemotherapy. They reported improved survival with neoadjuvant therapy with median OS improvement from 19 months in upfront surgery v/s 29 months in neoadjuvant chemotherapy group (5).
In recent years, selected cases of pancreatic neck and body tumours with celiac axis involvement can be resected after optimal neoadjuvant therapy. A pan European multicentric study showed 2-year survival of

45% in patients undergoing celiac axis resection with distal pancreatectomy after undergoing neoadjuvant therapy (6).
In 2017, International Association of Pancreatology (IAP) proposed new classification BRPC based on anatomical (SMA and/or CA < 1800 without stenosis or deformity, CHA without tumor contact with proper HA and/or CA, SMV and/or PV including bilateral narrowing or occlusion without extending beyond the inferior border of the duodenum), biological (clinical suspicious for distant metastases or nodal metastases diagnosed by biopsy or PET-CT, CA 19-9 level more than 500 units/ml), and conditional factors (resectable disease based on anatomic and biologic factors but with ECOG status of 2 or more). Patients are classified as: BR-A (based on anatomic criteria), BR-B (based on biological criteria), BR-C (based on conditional criteria) or a combination of these criteria: BR-AB, BR-BC, BR-AC, BR- ABC. Future studies will define the feasibility of such classification system (7).
Extensive venous involvement by tumour with distal non reconstructible vein is considered to be unresectable disease. However, in few selected cases, even in the absence of availability of vein available for reconstruction, resection can be done without the need of reconstruction owing to crucial collateral formation as reported by our institutional experience (8).
Our institutional experience with BRPC also suggests that neoadjuvant therapy in BRPC is associated with significant tumour down staging, improved R0 resection rates and improved survival in patients undergoing surgery after neoadjuvant therapy (9).

Conclusions

BRPC is a distinct subset of pancreatic cancer that blur the distinction between resectable and locally advanced disease. BRPC should be treated with multidisciplinary approaches using neoadjuvant treatment of pancreatic cancer, because it is frequently associated with loco-regional or systemic failure, even if the tumour is resected. Presently, neoadjuvant chemotherapy, sometimes coupled with radiotherapy is the major treatment strategy for resectable pancreas cancer with vascular involvement.

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