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Upfront surgery in borderline resectable pancreatic cancer

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Abstract
Introduction: The definition of Borderline resectable pancreatic cancer (BRPC) is evolving. In general BRPC is considered when high rate of margin positivity is possible without neoadjuvant therapy. Though neoadjuvant therapy is emerging in BPRC there is still role of upfront surgery in some patients with BRPC.
Aim: The aim of the present study was to study the surgical feasibility and perioperative outcomes in patients with BRPC undergoing upfront surgery.
Material and methods: The study was done from data collected from prospectively maintained database between 2013 to 2018. Patients with pancreatic and periampullary tumors who were classified BRPC according to NCCN 2018 classification. In addition solid tumor contact of tumors to PV/SMV of less than 180 degrees were also included as BRPC. Tumors with abutment of PV and SMV with thrombosis or obliteration of lumen were excluded. The surgical feasibility, complication and R0 resection rate was studied.
Results: A total of 22 patients were included in the study. Eleven (11/22, 50%) patients underwent vascular resection. In 5 (5/22, 22.7%) patients pancreaticoduodenectomy could be done without the need for vascular resection. In 6 (6/22, 27%) patients palliative therapy was done due to metastatic disease (2) or locally advanced disease (4).Of the 11 patients who underwent vascular resections Grade A pancreatic fistula was seen in 3 (3/11), Grade B pancreatic fistula 1(1/11) Delayed gastric emptying in 3 (3/11) and wound infection in 2 (2/11) There was no mortality. The resection margin was positive in 3 patients (3/16, 18%).
Conclusion: Upfront vascular resection is possible in carefully selected patients with good resectability and R0 resection rates.

Keywords: Borderline resectable pancreatic cancer, upfront surgery

Introduction

The definition of Borderline resectable pancreatic cancer (BRPC) is evolving since its first description by Mehta *et al.* [1]. Resectable disease is tumor without contact with the celiac artery, hepatic artery, Superior mesenteric artery (SMA), or superior mesenteric vein (SMV), suggesting a high likelihood that margin-negative resection can be achieved without preoperative therapy [2]. However the definition of borderline resectable pancreatic cancer is evolving. Abutment of SMV and Portal vein (PV) confluence without obstruction of vessels is considered resectable according to MD Anderson cancer center definition [3]. According to NCCN tumor abutment of less than 180 degrees of SMV or PV without contour irregularity or thrombosis is still considered resectable [4]. However even abutment of SMV or PV confluence is considered BRPC according to AHPBA /SSO/SSAT definition [2]. In general BRPC is considered when high rate of margin positivity is possible without neoadjuvant therapy.

According to NCCN 2018 [4] BRPC is defined as following

1. BRPC for Arterial involvement in head and uncinate tumors
   a. Solid tumor contact with common hepatic artery without extension to celiac axis or hepatic artery bifurcation.
   b. SMA of ≤180°
   c. Solid tumor contact with variant arterial anatomy (ex. accessory right hepatic artery, replaced CHA, and the origin of replaced or accessory artery)

2. BPRC for arterial involvement for Pancreatic body or tail tumors
a. Celiac axis of ≤180°
b. Celiac axis of >180° permitting a modified Appleby

3. BPRC for PV/SMV involvement in pancreatic tumors
a. Solid tumor contact with the SMV or PV of >180°contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction.
b. Solid tumor contact with the inferior vena cava (IVC)
In the present study we report the surgical feasibility and early outcomes of patients who underwent upfront surgery for BRPC.

Aim

The aim of the present study was to study the surgical feasibility and perioperative outcomes in patients with BRPC undergoing upfront surgery.

Material and methods

The study was done from data collected from a prospectively maintained database between 2013 to 2018. All cases were done by a single surgeon who is working in a high volume center.

Inclusion criteria

1. Patients with pancreatic and periampullary tumors who were classified BRPC according to NCCN 2018 classification.
2. Tumor contact to PV/SMV of less than 180 degrees were also included.

Exclusion criteria

1. Tumors with abutment of PV and SMV with thrombosis or obliteration of lumen.
2. Tumors considered beyond criteria for BPRC on NCCN 2018.

Surgical technique

All patients underwent laparotomy. After exclusion of distant metastasis careful dissection was done to rule out involvement of SMA, Celiac axis and Hepatic artery. Artery first approach was used to rule out SMA involvement. The approach to SMA depended on location of tumor. After ruling out SMA involvement the tumor was dissected and made to hang on SMV/PV. Splenic vein was ligated and cut if required. Routine revascularisation of splenic vein was not done. Small jejunal branches of SMV were ligated to increase the length of distal vessel. Portal vein was mobilised up to hepatic hilum if required. An end to end anastomosis was done if tension free anastomosis was possible. Otherwise conduit was used.

The surgical feasibility, complication and R0 resection rate was studied. The number of patients with tumor abutment on CT and didn't require vascular resection were studied. Intraoperative and postoperative complications were studied.

The type of vascular resections were classified according to Tseng *et al.* [5, 6] (VR1 to VR5)

Results

A total of 22 patients were included in the study. The mean age of patients was 54yrs.The patients were categorised as BRPC based on preoperative CT. The findings are summarised in Table 1 All patients underwent laparotomy

Table 1: Site of involvement of vessel

	n= 22 (some had more than 1 site of involvement)
BRPC for Arterial involvement in head and uncinate tumors	
Solid tumor contact with commom hepatic artery without extension to celiac axis or hepatic artery bifurcation.	2
SMA of ≤180°	3
Solid tumor contact with variant arterial anatomy (ex. accesory right hepatic artery, replaced CHA, and the origin of replaced or accesory artery)	2
BPRC for arterial involvement for Pancreatic body or tail tumors	
Celiac axis of ≤180°	2
Celiac axis of>180° permitting a modified Appleby	1
BPRC for PV/SMV involvement in pancreatic tumors	
Solid tumor contact with the SMV or PV of >180°	3
contact of ≤180°	13
Solid tumor contact with the inferior vena cava (IVC)	2

Eleven (11/22, 50%) patients underwent vascular resection. In 5 patients pancreaticoduodenectomy could be done without the need for vascular resection. In 6patients palliative therapy was done due to metastatic disease (2) or locally advanced disease (4).The results are summarised in Table 2.

Table 2: Vascular resections

portal vein sleeve resection	**4**
VR2 (ligation of splenic vein and end to end portal vein anastomosis Fig 1	2
VR4 (SMV resection) Fig 2	1
Resection of jejunal and ileal branch and end to end anastomosis of portal vein to ileal branch of SMV followed by jump graft with saphenous vein from jejunal vein to portal vein Fig 3	1
Modified Appleby procedure Fig 4	1
IVC sleeve	1
GDA resection	1
resection without requirement of portal vein resection	5
palliative bypass	6

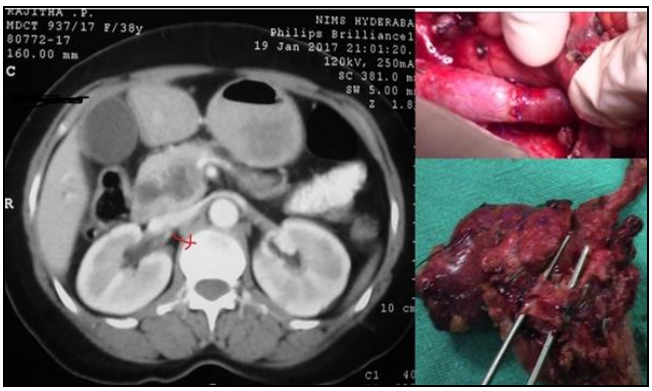

Fig 1: VR2 (ligation of splenic vein and end to end portal vein anastomosis

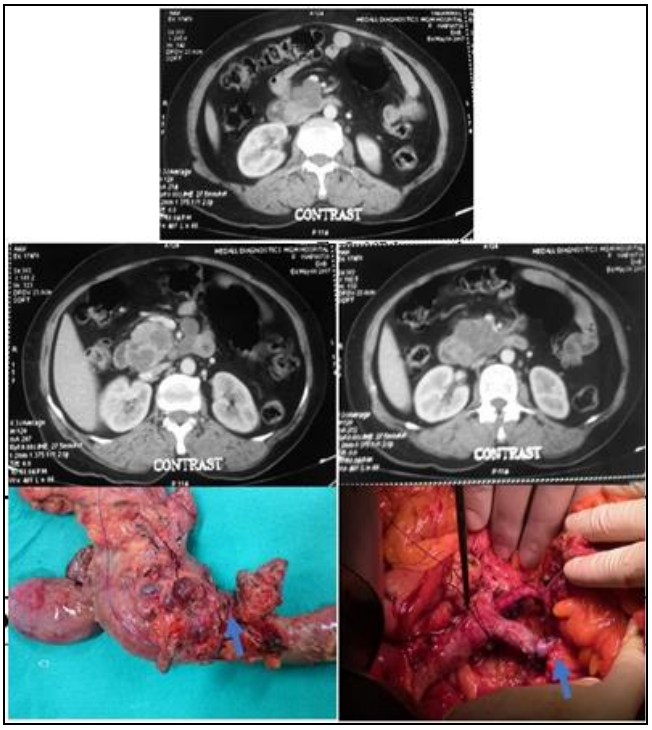

Fig 2: VR4 resection. CECT showing abutment of SMV and engulfment of SMA with uncinate mass. Specimen shows groove of SMA in uncinate mass (arrow) the infrapancreatic SMV was resected and end to end anastomosis done

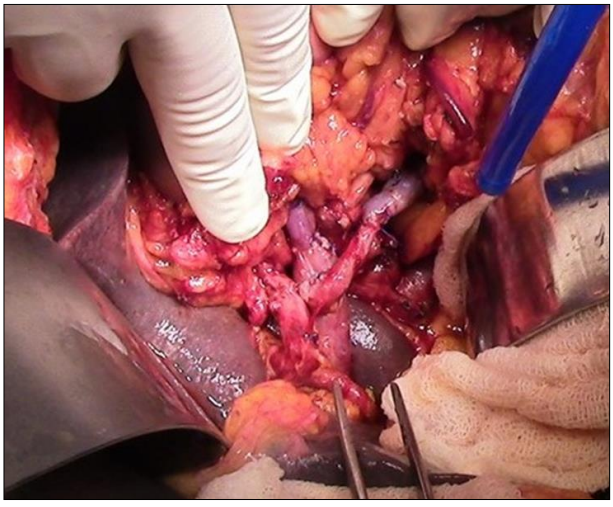

Fig 3: Resection of jejunal and ileal branches and end to end anastomosis of portal vein to ileal branch of SMV followed by jump graft with saphenous vein from jejunal vein to portal vein.

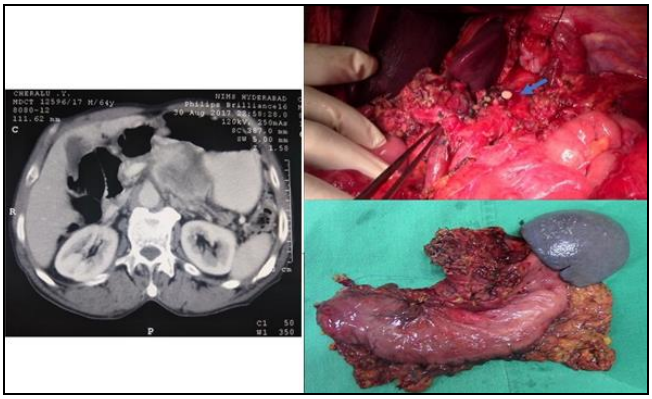

Fig 4: Modified Appleby procedure. Total gastrectomy, distal pa ncreatectomy and splenectomy with celiac axis excision was done. Patient had a replaced common hepatic artery from SMA (Forceps pointing).The excised celiac axis stump is shown by blue arrow

Of the 11 patients who underwent vascular resections Grade A pancreatic fistula is seen in 3 (3/11), Delayed gastric emptying in 3 (3/11) and wound infection in 2 (2/11).The resection margin was positive in 3 patients (3/16, 18%).

Discussion

Tumor abutment of SMV/PV confluence less than 180 degrees without contour irregularity or thrombosis is considered resectable according to MD Anderson and NCCN whereas it is BRPC according to AHPBA /SSO/SSAT definition[2].So these are the tumors which can undergo upfront surgery. In our study 16 of 22 (72.7%) underwent resection surgery. In 5/22 (22.7%) resection could be done without vascular resection. In a recent metaanalysis the overall resection rate was lower in patients who had neoadjuvant treatment than in those who had upfront surgery (66·0 versus 81·3 per cent; $P< 0·001$) [7]. The resection rate may be higher because these were carefully selected cases and may be subjected to selection bias [7].

The resection margin was positive in 3 patients (3/16, 18%). The R0 resection rate after upfront surgery is comparable to rates of 29–81 per cent, depending on the R0 criteria being used [7]. Patients treated with neoadjuvant therapy who underwent exploratory laparotomy followed by resection, the R0 resection rate was 86·8 (range 38·9–100) per cent [7].

There is no controversy that patients with locally advanced pancreatic cancer should be considered for neoadjuvant therapy rather than upfront resection [8].

In BRPC the decision for upfront surgery or neoadjuvant therapy depends on venous or arterial involvement. In venous BRPC, upfront surgery should be considered and the venous resection performed along with specimen [8-10]. According to the consensus recommendation of the ISGPS, this group of patients should undergo upfront resection [9]. Meta-analysis comparing neoadjuvant therapy vs upfront surgery for BRPC and resectable pancreatic cancer showed that neoadjuvant therapy tends to improve patients' long-term outcomes. However, the evidence level remains too low for a firm conclusion [11]. In a recent study from Korea the overall 2-year survival rate was 51.1% in the upfront surgery group and 36.7% in the neoadjuvant group [12]. However in patients who could undergo surgery after neoadjuvant therapy the survival was comparable.

In our study we have included all patients with venous involvement which are potentially resectable into upfront

surgery. However we have excluded patients with venous thrombosis or obliteration and attained a good resectability rate and R0 resections.

Sleeve resection was done in 4 patients in our study. It can be safely done if significant luminal narrowing can be avoided.

In our series 2 patients underwent splenic vein ligation and end to end anastomosis. After the division of splenic vein the access and exposure of SMA is easier so that R0 resection can be achieved. It also provides increased length of SMV and PV to facilitate a tension free end to end anastomosis [13, 14].

Splenic vein preservation will limit mobilisation of PV for end to end anastomosis. Usually a vascular graft is required. In our study one patient underwent SMV resection and end to end anastomosis preserving the splenic vein. In that case Cattle brausch manoeuvre was performed to increase the mobility. The portal vein was also mobilised till hilum.

The problem with splenic vein liagtion is sinistral hypertension. If left gastric vein and right gastric and right gastroepiploic veins are also ligated along with splenic vein congestion of stomach can happen. If IMV is draining into splenic vein then some retrograde flow will happen. If IMV drains into SMV than a shunt will be required after ligation of splenic vein [13, 14]. In our study there was no congestion of stomach.

When suspected arterial BRPC is found intraoperatively to be a true arterial involvement, neoadjuvant treatment should be considered. Direct arterial resection considered in exceptional cases [8]. In our case arterial resection was done in 2 cases (One underwent GDA resection, 1 Modified Appleby procedure). The Appleby procedure evolved as an answer to the question of resection of the celiac axis because of tumor encasement [15, 16]. For pancreatic body tumors celiac axis resection is possible as after resection blood flow through GDA and peripancreatic arcade will provide hepatic artery perfusion. Sometimes a supercharging may be required [17]. In our case the patient had a replaced common hepatic artery arising from SMA which permitted a safe celiac axis resection.

As the results of resectable pancreatic cancer are also poor there is definitely a role of neoadjuvant therapy in pancreatic cancer. As studies are evaluating the ideal neoadjuvant therapy there is still a role of upfront surgery in some selected BRPC.

There are a number of ongoing studies on this issue that evaluate the effect of neoadjuvant therapy in the above-mentioned situations [8].

Our study evaluated the feasibility of vascular resection in carefully selected cases. There may be a selection bias in our study as patients who underwent surgery only are included.

Conclusions

Upfront vascular resection is possible in carefully selected patients with good resectability and R0 resection rate.

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