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Source / Izvornik: **World Journal of Clinical Cases, 2021, 9, 5398 - 5407**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.12998/wjcc.v9.i20.5398>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:549397>

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Download date / Datum preuzimanja: **2025-02-03**



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## Borderline resectable pancreatic cancer and vascular resections in the era of neoadjuvant therapy

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**Author contributions:** Mikulic D and Mrzljak A made contributions to the conception and design of the study, collecting of data and in drafting and revising the manuscript; both authors read and approved the final manuscript.

**Conflict-of-interest statement:** The authors have any conflict of interest to declare.

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**Manuscript source:** Invited manuscript

**Specialty type:** Surgery

**Country/Territory of origin:** Croatia

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### Abstract

While pancreatic cancer is still characterized by early systemic spread and poor outcomes, the treatment of this disease has changed significantly in recent years due to major advancements in systemic therapy and advanced surgical techniques. Broader use of effective neoadjuvant approaches combined with aggressive surgical operations within a multidisciplinary setting has improved outcomes. Borderline resectable pancreatic cancer is characterized by tumor vascular invasion, and is a setting where the combination of potent neoadjuvant chemotherapy and aggressive surgical methods, including vascular resections and reconstructions, shows its full potential. Hopefully, this will lead to improved local control and curative treatment in a number of patients with this aggressive malignancy.

**Key Words:** Pancreatic adenocarcinoma; Borderline resectable; Neoadjuvant therapy; Venous resection; Arterial resection; Vascular reconstruction

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**Core Tip:** Curative treatment of pancreatic ductal adenocarcinoma is only possible after margin negative surgical resection. Borderline resectable pancreatic cancer is characterized by vascular tumor involvement and the need to perform vascular resection to achieve radical resection. This report reviewed the characteristics of borderline resectable pancreatic cancer and the current treatment perspectives, including aggressive surgical approaches in the era of neoadjuvant therapy.

**Citation:** Mikulic D, Mrzljak A. Borderline resectable pancreatic cancer and vascular resections in the era of neoadjuvant therapy. *World J Clin Cases* 2021; 9(20): 5398-5407

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
 Grade B (Very good): B, B  
 Grade C (Good): C  
 Grade D (Fair): 0  
 Grade E (Poor): 0

**Received:** January 27, 2021**Peer-review started:** January 27, 2021**First decision:** February 25, 2021**Revised:** March 1, 2021**Accepted:** May 27, 2021**Article in press:** May 27, 2021**Published online:** July 16, 2021**P-Reviewer:** Tan CL, Wang YF, Wang XB**S-Editor:** Ma YJ**L-Editor:** Filipodia**P-Editor:** Yuan YY**URL:** <https://www.wjgnet.com/2307-8960/full/v9/i20/5398.htm>**DOI:** <https://dx.doi.org/10.12998/wjcc.v9.i20.5398>

## INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease with a dismal prognosis, currently the tenth most common cancer and the fourth leading cause of cancer-related mortality[1]. Its incidence is rising, and the current 5-year overall survival is only about 5%[2]. While major advancements have recently been made with systemic treatment, only a radical surgical resection gives the possibility of long-term survival and cure[3]. Long-term survival in non-resected patients has been reported only exceptionally[4]. Unfortunately, most pancreatic cancer patients are diagnosed with locally advanced or metastatic disease that precludes curative resection. Due to the aggressive nature of the disease and late onset of symptoms, only 10%-20% of patients present with resectable or borderline resectable disease[5].

Numerous studies have reported beneficial effects of neoadjuvant chemotherapy (NAT) in different cancers of the digestive system, namely rectal, gastric and esophageal carcinomas[6-8]. In recent years, promising results have appeared from clinical research of neoadjuvant chemotherapy and chemoradiotherapy for PDAC[9-12]. There are several possible benefits of NAT in PDAC. Firstly, the margin negative (R0) resection rates could be improved in borderline resectable pancreas cancer (BRPC). Only an R0 resection gives the chance of cure in PDAC, and it has been shown that an R0 resection with at least 1 mm margin correlates with improved survival[13, 14]. Secondly, some patients with locally advanced (LA) PDAC, initially not amenable to surgical resection, could be downstaged with NAT, converting them from unresectable to resectable disease[9-12]. Finally, while adjuvant chemotherapy should be the standard of care after upfront resection for PDAC, almost half of the patients never receive adjuvant chemotherapy due to postoperative complications or poor performance status[15]. NAT, being independent of surgical morbidity, can increase the number of patients that receive chemotherapy leading to better systemic and local control of the disease translating into improved outcomes[16].

Due to the retroperitoneal location of the pancreas and its intimate contact with the neighboring vessels, vascular invasion by the tumor is a hallmark of PDAC. However, thanks to advancements in surgical techniques and perioperative management, tumor infiltration of the superior mesenteric vein/portal vein (SMV/PV), superior mesenteric artery (SMA), hepatic artery (HA), or celiac artery (CA) is no longer a contraindication to surgery. Over the last 20 years, resections and reconstructions of the diseased vessels have become the standard of care in experienced centers, and they play a major role when securing a curative resection. A number of innovative surgical modifications have appeared with the goal of safe and radical resection of all of the tumor-infiltrated tissue regardless of vascular involvement. Promising results of NAT appear to be central in the attempt to achieve optimal effects of these complex and challenging surgical procedures[3,17,18].

## BRPC

The National Comprehensive Cancer Network first adopted the definition of borderline resectable pancreatic cancer (BRPC) in 2006, and it is based on the extent of arterial and venous involvement by the tumor. Specific anatomic factors include tumor contact with the superior mesenteric artery and/or celiac artery of less than 180 degrees without showing stenosis or deformity, tumor contact with the common hepatic artery without showing tumor contact with the proper hepatic artery and/or celiac artery, and tumor contact with the superior mesenteric vein and/or portal vein including bilateral narrowing or occlusion without extending beyond the inferior border of the duodenum[19]. Apart from anatomic factors, recent expert attempts were directed to broaden the definition of BRPC by including biologic and conditional dimensions (*e.g.*, positron emission tomography (PET) positivity, CA 19-9 Levels, Eastern Cooperative Oncology Group (ECOG) performance status), acknowledging the fact that resectability is not defined solely by anatomic factors, but that the biology of the tumor and performance status of the patient bear equal importance[20]. Different classifications of borderline resectable pancreatic cancer are presented in

**Table 1**[18-20].

Despite surgical resectability in experienced centers, BRPC is burdened with an increased risk of positive resection margins and postoperative recurrence[21,22]. This is the rationale behind the idea of NAT for BRPC, and the current National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recommend NAT for patients with BRPC[23].

A number of studies, some of them within a controlled randomized setting, show promising data with NAT in BRPC. A Dutch multicenter controlled randomized study (PREOPANC) was recently published including patients with resectable PC and BRPC. The patients were randomized either to upfront surgery or NAT with gemcitabine combined with radiation, followed by surgery and adjuvant gemcitabine. The BRPC subgroup undergoing NAT had a significant advantage in survival (overall survival: 17.6 mo *vs* 13.2 mo), a higher R0 resection rate, and less chance of having positive lymph nodes[24]. A study by authors from Korea compared neoadjuvant chemoradiation with gemcitabine to upfront surgery in patients with BRPC and found better 2-year survival and median survival (40.7% and 21 mo *vs* 26.1% and 12 mo) for patients with NAT[25]. In a study from Japan, patients with resectable PC and BRPC were randomized to NAT with gemcitabine and S-1 or upfront surgery followed by adjuvant chemotherapy with gemcitabine. Patients from the NAT group had better overall survival (36.7 mo *vs* 26.6 mo) without differences in resectability rates or resection margins[26]. However promising, it should be noted that the results of these studies should be interpreted with caution. Some of the concerns include heterogeneity of NAT regimens, variable application of concurrent radiation, and lack of differentiation between cases with arterial abutment and the patients with venous involvement only. There are several more ongoing randomized trials that will supposedly shed more light on the effects of NAT on survival, resectability, and R0 rates in BRPC. The results from recent systematic reviews and meta-analyses are also encouraging, particularly those that are based on comparative studies with intention-to-treat analysis[27-29]. Resection rates and R0 rates in the analyzed reports are highly variable, again highlighting the heterogeneity of the patient populations. While resectability rates after NAT are not always superior to upfront surgery, R0 rates for BRPC after NAT reported in these systematic reviews are encouraging and often comparable to initially resectable PC.

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## VENOUS RESECTIONS

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Almost 50 years ago, Joseph Fortner first reported a series of patients treated with pancreatectomy combined with vascular resection and reconstruction[30]. Reported perioperative morbidity and mortality rates were high, but still comparable to the rates achieved with conventional pancreas resections performed at the time[31,32]. Despite such evidence, pancreatic surgeons were mostly reluctant to perform vascular resections and reconstructions concomitantly with pancreas resections well into the 1990s. Over the years, wider familiarity with vascular reconstruction techniques, centralization of PDAC patients in high volume centers, advancements in perioperative management and evolution of systemic therapies including NAT have led to pancreaticoduodenectomies (PD) being associated with venous resection in up to 25% in Europe and even more in Japan[33-36]. Distal splenopancreatectomies, on the other hand, require venous resections less often[37]. Radiologic classification of SMV/PV invasion includes: Type A: no invasion, Type B: unilateral narrowing, Type C: bilateral narrowing, Type D: stenosis or obstruction with development of collateral circulation [38]. The same group defined three grades of pathological vessel invasion: grade 0: no invasion, grade 1: tunica adventitia invasion, grade 2: tunica media invasion, grade 3: tunica intima invasion[39]. Notably, the extent of tumor venous invasion is often poorly evaluated in pathology reports, and its prognostic value is debatable[40,41]. Interestingly, the rate of true vascular infiltration is relatively low (between 47% and 60%), reflecting the difficulty to intraoperatively differentiate between venous tumoral invasion and fibrotic changes secondary to peritumoral inflammation, especially after NAT[42-44].

As for the surgical technique, reconstruction after resection of the SMV/PV can be performed as a lateral, tangential resection and primary suture, repair using a venous patch, end-to-end anastomosis, or reconstruction using an autologous or synthetic interposition graft, depending on the type and length of vessel involvement by the tumor[22]. Adequate mobilization of the mesenteric root usually provides for a safe, tension-free end-to-end anastomosis, even in vein resections ranging up to several

Table 1 Definition of borderline resectable pancreatic cancer in different classifications

	AHPBA classification[20]	NCCN classification[20]	JPS classification[18]
VenousPV/SMV	Contact or encasement	Contact > 180 or ≤ 180 with contour irregularity or thrombosis of the vein	SMV/PV: Tumor contact/invasion of 180° or more/occlusion not exceeding the inferior border of the duodenum.
	Short venous segment occlusion		
	Reconstructible	Reconstructible	SMA, CA, CHA: No tumor contact/invasion.
	Arterial		
SMA, CA: Tumor contact/invasion of less than 180° without stenosis/deformity.	SMA	Contact ≤ 180°	Contact ≤ 180°
	CHA	Direct contact	Contact without extension to CA or HA bifurcation
CHA: Tumor contact/invasion without showing tumor.		Short segment encasement	
	CA	No contact	Contact ≤ 180°
Contact/invasion of the PHA and/or CA. (In case of contact/invasion to both portal vein and peripancreatic arteries, it was graded as BR-A.)			Contact > 180° without contact of aorta/uninvolved GDA

AHPBA: American Hepato-Pancreato-Biliary Association; CA: Celiac artery; CHA: Common hepatic artery; GDA: Gastroduodenal artery; HA: Hepatic artery; JPS: Japan Pancreas Society; NCCN: National Comprehensive Cancer Network; PHA: Proper hepatic artery; PV: Portal vein; SMA: Superior mesenteric vein; SMV: Superior mesenteric vein.

centimeters[17]. The use of synthetic grafts may be associated with the risk of infection, particularly worrying in the setting of a pancreatic fistula and the associated risk of postoperative hemorrhage[45]. However, the type of reconstruction technique does not affect the outcomes in terms of perioperative morbidity or mortality[43,46]. Distal locations of SMV involvement are more challenging than proximal when it comes to reconstruction because of the smaller diameter and branching of the SMV. According to current guidelines, involvement of the SMV below the inferior margin of the duodenum is considered to be the marker of unresectability of BR PDAC[20]. The alternative classification proposed by the NCCN in 2016 defined resectability based on the contact of the tumor with the first and second jejunal venous branches; however, this is often difficult to assess intraoperatively[20].

Venous resection performed concomitantly with pancreas resection in patients with vascular involvement seems to result in similar surgical mortality and perioperative morbidity rates when compared to standard pancreas resections. A number of single and multi-center studies have reported no difference in overall complication rates and postoperative mortality after PD with or without venous resection in patients who underwent upfront surgery[47-49]. Notably, most of the patients in these studies had not undergone NAT before surgery. On the other hand, when considering factors that affect overall and disease-free survival, several studies have shown higher R1 rates in patients undergoing venous resection without NAT[50,51]. Other negative prognostic characteristics associated with tumors requiring venous resection include larger tumor size, higher lymph node invasion rates, and worse tumor differentiation[52]. Several meta-analyses compared the outcomes of VR with conventional resections. They have confirmed the higher incidence of negative prognostic characteristics in patients undergoing VR without NAT (R1 resections, larger tumors, higher perineural invasion rates), and they suggest that NAT should be recommended in the setting of a planned venous resection[53-55].

## ARTERIAL RESECTION

Not long ago, PDAC resection requiring concomitant arterial resection and reconstruction was performed only exceptionally and considered a controversial procedure limited to a small number of centers[56,57]. Reasons are manifold. Firstly, there are the apparent surgical technical challenges and inherent risks that reportedly portend increased surgical mortality due to possible complications such as graft thrombosis

and mesenteric/hepatic ischemia or fatal hemorrhage[58]. Secondly, the celiac trunk and the SMA are invested within dense neural and lymphovascular tissue, making a margin negative resection technically demanding. Finally, infiltration of the arteries and the perivascular tissue can be considered to be a marker of a biologically aggressive disease, so the oncologic rationale of arterial resection for local tumor clearance in such cases may be questioned.

The use of potent and effective NAT followed by more aggressive and complex operative resections has improved local and systemic control providing improved outcomes in patients with BRPC and LA PC[59-61]. Even in BRPC with arterial infiltration where upfront resection is possible from the technical standpoint, recent evidence leans towards NAT first[17]. This is based on the results of several studies that have reported 5-year survival rates of up to 20% for selected patients who undergo arterial resection after NAT[62,63]. Regardless of the NAT regimen applied, surgical exploration should be carried out after restaging, provided there are no signs of systemic spread. Notably, the historical criteria of resectability by cross-sectional imaging are no longer appropriate in patients after potent NAT therapies. Current imaging techniques are often unable to distinguish between post-NAT fibrosis and viable tumor and patients without the signs of systemic spread or tumor progression after NAT should be surgically explored[64].

Over recent years several innovative surgical techniques have appeared when dealing with PDAC with arterial involvement. One of the widely used techniques is the “artery first” approach, where the SMA involvement is first assessed by dissection of the vessel from its origin. This can be accomplished *via* several anatomical routes, both inframesocolically and from the supracolic approach, from the left or right sides [65-67]. Once the infiltration of the SMA is confirmed or excluded, the type of reconstruction can be decided upon. The techniques used in arterial reconstruction include direct anastomosis, transposition of another artery (*e.g.*, splenic artery), and graft interposition with a venous graft, autologous or allogeneic artery. Microsurgical techniques used in liver transplantation have proven helpful and yielded excellent outcomes with minimal incidence of complications[68]. While splenic and left gastric artery can usually be resected and sacrificed without reconstruction, proper or common hepatic artery must be reconstructed to ensure hepatic perfusion. Distal pancreatectomy with celiac axis resection (DP-CAR) is an example of a long-known procedure that has shown excellent results in the era of NAT, sometimes combined with innovative techniques like aorto-hepatic bypass[69,70]. While there are some concerns regarding the safety of this procedure after reports of high postoperative mortality, most of the recent data show that this operation can be performed safely with acceptable median survival[71-73].

The struggle to achieve local control in patients with BR or LA PDAC has recently taken a new turn with the adoption of surgical strategies that take maximal advantage of the results of tumor downstaging in the era of NAT. The new techniques of periadventitial dissection or arterial divestment are applicable when the arterial adventitia is not affected by tumor invasion, and the periarterial neurolymphatic tissue can be dissected off the arterial wall by sharp dissection. This must include all of the soft tissue along the SMA and in the triangle between the CA, SMA, and the PV/SMV (mesopancreas excision or the triangle operation)[66,74,75]. This way, radical tumor clearance can be achieved without arterial resection and the associated morbidity[66, 76,77]. In conclusion, survival rates after arterial resection for BRPC are encouraging, and postoperative morbidity and mortality rates, while once controversial, are acceptable today without a significant increase of the perioperative risk.

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## CONCLUSION

The combination of modern chemotherapy regimens, including those applied in the neoadjuvant setting and aggressive surgical methods, has shown promising results in the treatment of patients with pancreatic cancer. While most of patients with resectable PDAC still undergo upfront surgery, evidence shows that neoadjuvant therapy has benefits in patients with borderline resectable pancreatic cancer and locally advanced pancreatic cancer. Surgery for pancreatic cancer has taken advantage of several surgical innovations over the last 20 years. Venous resections are now part of a routine surgical approach to PDAC. Pancreatectomy combined with arterial resection is also feasible and should be considered in selected patients. Survival benefit exists in patients who undergo NAT before arterial resection. In conclusion, in the era of potent and effective systemic treatment, aggressive surgical operations for borderline

resectable pancreatic cancer are justified and bring a clear survival benefit to a group of patients fraught with a history of poor outcomes.

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