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## Review Article

## Clinical significance of defining borderline resectable pancreatic cancer

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## ABSTRACT

Since the introduction of the concept of borderline resectable pancreatic cancer (BRPC), various definitions of this disease entity have been suggested. However, there are several obstacles in defining this disease category. The current diagnostic criteria of BRPC mainly focuses on its expanded 'technical resectability'; however, they are difficult to interpret because of their ambiguity using potential subjective or arbitrary terminology. In addition, limitations in current imaging technology and a lack of evidence in radiological-pathological-clinical correlation make it difficult to refine the criteria. On the other hand, neoadjuvant treatment is usually applied to increase the R0 resection rate of BRPC focusing on the 'oncological curability'. However, evidence is needed concerning the effect of neoadjuvant treatment by quality-controlled prospective randomized clinical trials based on a standardized radiologic and pathologic reporting system. In conclusion, there are two aspects in the current concept of BRPC, which are technical resectability and oncological curability. Although the recent evolution of surgical techniques is expanding the scope of technical resectability, it should not be overlooked that the disease entity must be defined based on the evidence of oncological curability.

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## Introduction

Pancreatic cancer has the lowest 5-year relative survival rates among all types of cancer, and only 9% and 28% of the patients have localized or regional disease at the time of diagnosis [1]. Despite various multi-disciplinary efforts to improve the prognosis of pancreatic cancer, radical surgical resection is still the best treatment option to obtain long-term survival [2]. However, patients with positive resection margin after surgical resection have a significantly poor prognosis compared with those with a negative resection margin [3]. Therefore, the importance of defining proper surgical candidates who can achieve R0 resection has been emphasized.

The NCCN guideline classifies localized pancreatic cancer as resectable, borderline resectable, and locally advanced unresectable pancreatic cancer [4]. When upfront surgery is indicated for resectable pancreatic cancer, neoadjuvant treatment (NAT) is recommended before considering surgical treatment in borderline

resectable pancreatic cancer (BRPC). Although the term 'borderline resectable' has not been used, the recent ASCO guideline [5] also recommends preoperative therapy for patients with a radiographic interface between a primary tumor and the mesenteric vasculature. As a consequence, there are two aspects in the current concept of BRPC. One is a technical concept which is expanding the scope of technical 'resectability' based on the recent evolution of surgical techniques and improvements in surgical outcomes. However, when having a high probability of R1 resection with an uncertain oncological outcome, the 'curability' concept emerges with an effort to increase the chance of R0 resection with NAT, and it is should not be overlooked that the disease entity must be defined based on the evidence of the oncological outcome.

However, we encounter several obstacles in managing BRPC. This review focuses on refining the definition of BRPC, a brief overview of current limitations in radiological and pathological diagnosis, and evidence of NAT in BRPC.

## Summary of the published diagnostic criteria for BRPC

With improving surgical techniques and their outcomes, keen efforts were made to overcome the limitations of surgical resection.

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In 1990s, evidence emerged supporting the technical and oncological feasibility of superior mesenteric vein (SMV)/portal vein (PV) resection in patients with pancreatic cancer involving venous structures. The reports revealed comparable outcomes for patients undergoing combined vascular resection with those undergoing conventional resections, and the outcome was superior to those being treated nonoperatively [6–8].

Based on the background, the MD Anderson Cancer Center group introduced the term 'borderline resectable' in 2006 to define tumors with a short segmental occlusion of the SMV/PV, which is an abutment with the celiac axis, hepatic artery, or superior mesenteric artery (SMA) that blur the distinction between resectable and locally advanced disease [3]. The concept was slightly extended in terms of the SMV/PV abutment by a consensus statement from the American Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract (AHPBA/SSO/SSAT) in 2009 [9,10]. In 2013, the Alliance for Clinical Trials in Oncology (Alliance), in cooperation with the Southwest Oncology Group, Eastern Cooperative Oncology Group, and Radiation Therapy Oncology Group initiated a multi-institutional treatment trial for patients with BRPC (Alliance A021101) based on their revised criteria with the concept of a tumor-vessel interface of 180° [11,12]. The International Study Group of Pancreatic Surgery (ISGPS) announced a consensus statement adding a criterion of venous distortion or narrowing of the SMV/PV, which supported the 2013 NCCN guideline [13]. Most recently, the 2017 NCCN guideline integrating the previous criteria has been published [4].

However, there are practical problems in interpreting these criteria including the variability of definitions and potential subjective or arbitrary terminology. Table 1 summarizes the aforementioned BRPC criteria concerning the SMV and PV. The terms used vary as 'abutment', 'interface', or 'contact'; however, all of the criteria adopted technical feasibility to resection and reconstruction of the SMV/PV. The artery criteria are summarized in Table 2. However, the terms also vary; the artery criteria connote the oncological concept for the celiac axis and SMA and the technical concept for resection and reconstruction of the hepatic artery.

### Difficulties in interpretation of the BRPC criteria

The major difficulty in interpreting the diagnostic criteria of BRPC is its potential subjective or arbitrary terminology.

First, concerning tumor-vessel contact/interface (abutment/encasement), what is the rationale of the 180° criteria? For the SMV/PV, there have been various attempts to describe radiological SMV/PV invasion. Focusing on the concept of tumor-vessel interface, some authors have suggested that the risk of SMV/PV invasion increases when the tumor-vessel contiguity is higher than 90°

[14,15]. A recent report classified the tumor-vein interface using the 180° criteria, which was revealed to be a predictor of needing a vein resection, pathologic invasion and survival [16]. Another group of researchers used the percentage of the tumor-vessel contact to describe the lesion. Resectability was best predicted with a tumor-vessel contiguity cutoff of 25–50% [14,17–19], and the positive predictive value of unresectability based on pre-operative CT imaging was 73.5–95% when the tumor-vessel contiguity cutoff was set at 50% [17,18]. On the other hand, some focused on the change of vessel morphology, which can be roughly summarized as the uni-/bilateral involvement based criteria [20–24]. When unilateral invasion of the vessels were identified in the pre-operative CT, there was less true pathologic invasion [23,24] and higher margin negative resection and survival rates [22,23] compared with those with bilateral involvement. Therefore, the earlier BRPC criteria mainly focused on technical resectability for resection and reconstruction of the SMV/PV, but the later BRPC criteria are trying to reflect the oncological disease severity among patients with the tumor-SMV/PV interface adopting the 180° criteria.

Concerning the SMA, there is little evidence to correlate the degree of radiologic abutment with pathological invasion and survival outcome. From a radiological point of view, it was suggested that arterial invasion is more difficult to predict with pre-operative imaging compared with venous invasion raising the necessity for different criteria for a proper evaluation [25,26]. From a technical and oncological aspect, on the basis that the SMA margin is the most commonly positive resection margin which is positive in up to 45% of the patients undergoing an operation with a curative intent [27], some preferred circumferential dissection of the SMA [28,29]. However, a recent review of prospective randomized trials concerning the value of extended surgery concludes that circumferential dissection of the SMA is no longer recommended considering its morbidity and oncological necessity, although it may be technically feasible [30]. Therefore, the 180° criteria for the SMA is more focused on the oncological concept without definite evidence of radiological-pathological correlation. With the introduction of a standardized pathologic [31,32] and radiologic [33] reporting system, it is expected that quality controlled studies will provide more evidence in the near future.

Another point of view is the oncological equivalence of the 'venous' and 'arterial' BRPC criteria. There are limited data comparing the oncological outcome of patients with the positive 'venous' or 'arterial' BRPC criteria. However, it is widely accepted that patients undergoing arterial resection have a lower survival outcome compared with those undergoing venous resection [34,35]. Therefore, it should be revisited whether the 'venous' and 'arterial' criteria could be applied at the same level and categorized in one disease entity.

Second, the length and extent of narrowing or occlusion of the

**Table 1**  
Vein criteria.

Criteria	Year	SMV/PV
MDACC [3]	2006	• Short-segment occlusion <sup>a</sup>
AHPBA/SSO/SSAT [10]	2009	• Tumor abutment • Encasement, but without encasement of the nearby arteries • Short segment venous occlusion resulting from either tumor thrombus or encasement <sup>a</sup>
Intergroup [11] (Alliance)	2013	• Interface between tumor and vessel $\geq 180^\circ$ • Occlusion <sup>a</sup>
ISGPS [13]	2014	• Distortion or narrowing • Occlusion <sup>a</sup>
NCCN 2017 [4]	2017	• Contact $>180^\circ$ • Contact $\leq 180^\circ$ with contour irregularity of the vein or thrombosis of the vein <sup>a</sup>

SMV, superior mesenteric vein; PV, portal vein.

<sup>a</sup> With suitable vessel proximal and distal.

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