

International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017

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ABSTRACT

This statement was developed to promote international consensus on the definition of borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC) which was adopted by the National Comprehensive Cancer Network (NCCN) in 2006, but which has changed yearly and become more complicated. Based on a symposium held during the 20th meeting of the International Association of Pancreatology (IAP) in Sendai, Japan, in 2016, the presenters sought consensus on issues related to BR-PDAC. We defined patients with BR-PDAC according to the three distinct dimensions: anatomical (A), biological (B), and conditional (C). Anatomic factors include tumor contact with the superior mesenteric artery and/or celiac artery of less than 180° 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. Biological factors include potentially resectable disease based on anatomic criteria but with clinical findings suspicious for (but unproven) distant metastases or regional lymph nodes metastases diagnosed by biopsy or positron emission tomography-computed tomography. This also includes a serum carbohydrate antigen (CA) 19–9 level more than 500 units/ml. Conditional factors include the patients with potentially resectable disease based on anatomic and biologic criteria and with Eastern Cooperative Oncology Group (ECOG) performance status of 2 or more. The definition of BR-PDAC requires one or more positive dimensions (e.g. A, B, C, AB, AC, BC or ABC). The present definition acknowledges that resectability is not just about the anatomic relationship between the tumor and vessels, but that biological and conditional dimensions are also important. The aim in presenting this consensus definition is also to highlight issues which remain controversial and require further research.

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Introduction

Since first adopted by the National Comprehensive Cancer Network (NCCN) in 2006, the definition of borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC) has been based solely

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on anatomic criteria, and more specifically on the extent of venous and arterial involvement by the tumor. While BR-PDAC has been widely used for recruitment into clinical trials and for selecting treatment modalities the definition is variable, published by different societies and there is no internationally agreed consensus.

The final determination of whether a tumor is able to be resected with negative margins has customarily been made by the surgeon undertaking a trial dissection. Improvements in radiologic imaging have allowed enhanced assessment of potential resectability. Both the surgical and radiologic criteria for resectability are currently based on anatomic criteria alone. In practice, the decision about whether a patient is offered a resection is not based solely on anatomic criteria. The biological behavior of the cancer is an important consideration and will become more so with increasing knowledge of the genomic basis for local invasion and metastases. Another important consideration in make a decision about the appropriateness of resection is the ability of the patient to withstand the physiological challenge of surgery. Biological and conditional criteria for resectability were first published in 2008 [1] but these have not been incorporated into other definitions of BR-PDAC. The original biological criteria was the presence of possible metastatic disease and the conditional criteria was the presence of suboptimal performance status and/or severe medical comorbidities. It has been widely considered that there is scope to improve these biological and conditional criteria.

To address these issues and to seek an international consensus on BR-PDAC, a symposium was arranged during the 20th meeting of the International Association of Pancreatology (IAP) held in Sendai, Japan, in 2016. The symposium was chaired by Professors Shuji Isaji and Christopher L Wolfgang who selected eastern and western experts for symposiasts based on their published studies on BR-PDAC. Prior to the consensus meeting, the moderators developed key questions on the definitions and criteria of BR-PDAC, representing areas requiring consensus, and these were sent to each expert. The expert speakers spoke to current perspectives and the issues with respect to the definitions and criteria of BR-PDAC. The speakers drafted a series of consensus statements for the symposium, based on the issues and these were refined by further discussion after the symposium. Our goal was not to provide any new criteria or knowledge, but to develop an international consensus on the definitions and criteria of BR-PDAC in 2017. These consensus statements should provide direction for future advances. For instance, genomic studies will yield valuable information about subgroups of PDAC with different biological behaviors.

Main concept of definition of BR-PDAC at the IAP in 2016

The consensus view was that a broader definition of BR-PDAC was required than those in current use. This is because the anatomical definition of BR-PDAC does not take into account the biology of the tumor or the physiology of the host, both of which are determinants of resectability. The approach that is presented here is derived from the 'ABC' method, that was developed at the MD Anderson Cancer Centre [1]. The following statement captures this broader definition as agreed to at the IAP symposium:

- The anatomical definition of BR-PDAC is a tumor that is at high risk for margin-positive resection (R1, R2) when surgery is used as an initial treatment strategy. Neoadjuvant chemotherapy and/or radiotherapy is considered to increase the chance of a R0 resection and should be considered in patients with BR-PDAC.
- The biological definition of BR-PDAC is when there are findings that raise the possibility (but not certainty) of extra-pancreatic metastatic disease.

- The conditional definition of BR-PDAC is when the patient has a high risk for morbidity or mortality after surgery because of host-related factors including performance status and comorbidities. These criteria apply even when margin-negative resection (R0) is considered likely following a surgery-first strategy.

Patients after neoadjuvant treatment for BR-PDAC are considered for pancreatic resection when there is no anatomical contraindication to resection, there has not been the development of metastatic disease and patients have an acceptable performance status.

Literature review of neoadjuvant multimodality clinical treatment for BR-PDAC

The definition of BR-PDAC is used to estimate the likelihood of a positive margin with resection, the prognosis of surgical patients and to help decide the optimal strategy for treatment. Accumulating evidence indicates that patients with BR-PDAC can benefit from neoadjuvant multimodality therapy, including chemotherapy and/or radiation therapy, because of the high probability of treatment failure with a surgery-first approach. There are some reports regarding this evidence, from series with more than 20 patients [2–8]. The most common chemotherapy regimens were FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin) and gemcitabine. The resection rates after neoadjuvant therapy ranged from 48% to 90%. Those not resected developed distant metastasis or progression of local disease during neoadjuvant treatment. The median survival time (MST) ranged from 17 to 29 months for all patients and from 24 to 33 months in those patients who were resected. Limitations of this published literature is the variable BR-PDAC definition used and the lack of consensus on the best regimen of neoadjuvant therapy.

Anatomic criteria for defining borderline resectable PDAC

Achieving a margin-negative (R0) resection is important in ensuring the best prognosis of patients with pancreatic ductal adenocarcinoma (PDAC). Determining the likelihood of an R0 resection is currently based on multidetector-row computed tomography (MD-CT) images with triphasic technique and 1–2 mm slices. Localized tumors are classified as resectable (R), borderline resectable (BR), or locally advanced (LA). Identifying BR-PDAC is important because in contrast to a 'surgery-first' approach, these patients may benefit from neoadjuvant chemo and/or radiotherapy to reduce the likelihood of an R1 resection and are more likely to require a vascular resection at the time of pancreatoduodenectomy (PD). This category of BR-PDAC is a helpful concept to estimate prognosis and to decide the treatment strategy.

In 2001, Mehta et al. [9] firstly reported the concept of BR-PDAC. They used the term 'marginal resectable' for a tumor with a high risk of margin-positive resection when a surgery-first approach was performed. Their patients with 'marginal resectable'-PDAC were treated with 5-FU and radiation therapy and underwent resection after re-staging. The result of resection was that 9 of 15 patients had an R0 resection. In 2006, the term of 'borderline resectable' was firstly adopted by the National Comprehensive Cancer Network (NCCN). It was defined as patients with PDAC who were at high risk for a margin-positive resection and for whom neoadjuvant therapy should be considered. Since then, several groups, including MD Anderson Cancer Center (MDACC) [10], Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract (AHPBA/SSO/SSAT) [11], NCCN [12], and Intergroup Alliance [13], have separately

reported different definitions of BR-PDAC. These definitions of BR-PDAC are summarized in Table 1.

In MD Anderson Cancer Center [10], AHPBA/SSAT/SSO [11], and NCCN 2012 [12], the definition of interface between tumor and vessels in BR-PDAC was described using ambiguous terms including 'abutment, encasement, occlusion, and impingement'. According to Intergroup radiographic definitions in 2013, the degree of interface between tumor and vessels was defined more precisely as "less than 180°" or "180 or more degrees", but the ambiguous term "reconstructable" was still included. This is problematic because the potential for reconstruction differs between surgeons and institutions. For example, if an interposition venous graft is used it is possible to reconstruct regardless of the length of vessel occlusion, invasion or abutment. In the NCCN 2016, the definition of resectability was divided 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. The principles of diagnosis, imaging, and staging of PDAC are based on the consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association [14]. However, the ambiguous sentence "allowing for safe and complete resection and vein reconstruction" was still described in it and BR-PDAC is not subclassified according to venous or arterial invasion [15].

In JPS classification 7th edition, BR-PDAC is subclassified into

venous invasion alone or arterial invasion [15]. BR-PV refers to tumor invades SMV/PV alone, while BR-A refers to tumor involving arteries, including SMA, CA, or CHA. In the situation where there is both venous and arterial involvement this is graded as BR-A. This is based on the study that BR-A had significantly worse prognosis and a greater risk of incomplete resection compared with BR-PV [16]. The difference between UR-PDAC and BR-PDAC was considered in relation to SMV/PV involvement and was whether the tumor 'exceeded or did not exceed the inferior border of the duodenum', as former was not considered to be reconstructable. Fig. 1a and b shows an example of BR-PV where the tumor invades the SMV/PV for more than 180° but does not exceed the inferior border of the duodenum and reconstruction with a venous graft was achieved after resection. Fig. 1c and d revealed UR PDAC tumor which invades the SMV/PV with exceeding the inferior border of the duodenum.

Before adapting the duodenal margin criteria for determination of unresectability of PV/SMV invasion, the duodenal margin of SMV invasion was classified into the following four groups: Group A (not exceeding the superior border of the duodenum), Group B (not exceeding the middle of the duodenum), Group C (not exceeding the inferior border of the duodenum) and Group D (exceeding the inferior border of the duodenum) on the line of SMV (Fig. 2). According to this classification, Hayasaki et al. prospectively reviewed

Table 1
Criteria defining resectability status in Intergroup, JPS classification 7th edition, and NCCN 2016.

	Alliance A021101 ^[13]	JPS classification 7th edition (2016) ^[15]	NCCN 2016 ^[12]
Resectable: R		<ul style="list-style-type: none"> SMV/PV: no tumor contact or contact of less than 180° without occlusion SMA, CA, CHA: no tumor contact/invasion 	<ul style="list-style-type: none"> SMV/PV: no tumor contact, or contact of less than 180° without vein contour irregularity. SMA, CA, CHA: no arterial tumor contact
Borderline resectable: BR	No subclassification according to SMV/PV invasion alone/arterial invasion.	Subclassified according to SMV/PV invasion alone or arterial invasion.	No subclassification according to SMV/PV invasion alone or arterial invasion.
BR-PV (SMV/PV invasion alone)	<ul style="list-style-type: none"> SMV/PV: tumor-vessel interface 180 or more degree and/or reconstructable occlusion 	<ul style="list-style-type: none"> SMV/PV: tumor contact/invasion of 180° or more/occlusion, not exceeding the inferior border of the duodenum. SMA, CA, CHA: no tumor contact/invasion 	<ul style="list-style-type: none"> SMV/PV: solid tumor contact of 180° or more, contact of less than 180° with contour irregularity of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. IVC: solid tumor contact
BR-A (arterial invasion)	<ul style="list-style-type: none"> SMA, CA: tumor-vessel interface less than 180°. CHA: reconstructable, short-segment tumor-vessel interface of any degree 	<ul style="list-style-type: none"> SMA, CA: tumor contact/invasion of less than 180° without showing stenosis/deformity. CHA: tumor contact/invasion without showing tumor contact/invasion of the PHA and/or CA. <p>(In case of contact/invasion to both portal vein and peripancreatic arteries, it was graded as BR-A.)</p>	<ul style="list-style-type: none"> Pancreatic head/uncinate process: <ul style="list-style-type: none"> SMA: solid tumor contact of less than 180° CHA: solid tumor contact without extension to CA/hepatic artery bifurcation allowing for safe and complete resection and reconstruction. Presence of variant arterial anatomy (RHA, CHA) and the presence of tumor contact as it may affect surgical planning Pancreatic body/tail: <ul style="list-style-type: none"> CA: solid tumor contact of less than 180° CA: solid tumor contact of 180 or more degree without involvement of the aorta and with intact and uninvolved GDA <p>(some members prefer this criteria to be in the UR category)</p>
Unresectable: UR		Subclassified according to the status of distant metastasis	No subclassifications according to the status of distant
UR-LA (locally advanced)		<ul style="list-style-type: none"> SMV/PV: tumor contact/invasion of 180 or more degree/occlusion, exceeding the inferior border of the duodenum. SMA, CA: tumor contact/invasion of 180 or more degree. CHA: tumor contact/invasion showing tumor contact/invasion of the PHA and/or CA. AO: tumor contact or invasion 	<ul style="list-style-type: none"> Venous <ul style="list-style-type: none"> Head/uncinate process: <ul style="list-style-type: none"> SMV/PV: unreconstructible due to tumor involvement/occlusion Contact with most proximal draining jejunal branch into SMV Body and tail <ul style="list-style-type: none"> SMV/PV: unreconstructible due to tumor involvement/occlusion Arterial <ul style="list-style-type: none"> Head/uncinate process: <ul style="list-style-type: none"> SMA, CA: solid tumor contact of 180 or more degree Solid tumor contact with the 1st jejunal SMA branch Body and tail <ul style="list-style-type: none"> SMA, CA: solid tumor contact of 180 or more degree Solid tumor contact with the CA and aortic involvement
UR-M		<ul style="list-style-type: none"> Distant metastasis including non-regional lymph node metastasis. 	<ul style="list-style-type: none"> Distant metastasis (including non-regional lymph node metastasis)

SMV: superior mesenteric vein, PV: portal vein, SMA: superior mesenteric artery, CA: celiac artery, CHA: common hepatic artery, PHA: proper hepatic artery, RHA: right hepatic artery.

Table 2

International consensus of classification of BR PDAC based on anatomical definition using CT imagings including coronal and sagittal sections.

Resectable: R	<ul style="list-style-type: none"> • SMV/PV: no tumor contact or unilateral narrowing • SMA, CA, CHA: no tumor contact
Borderline resectable: BR	Subclassified according to SMV/PV involvement alone or arterial invasion.
BR-PV (SMV/PV involvement alone)	<ul style="list-style-type: none"> • SMV/PV: tumor contact 180° or greater or bilateral narrowing/occlusion, not exceeding the inferior border of the duodenum.
BR-A (arterial involvement)	<ul style="list-style-type: none"> • SMA, CA, CHA: no tumor contact/invasion • SMA, CA: tumor contact of less than 180° without showing deformity/stenosis. • CHA: tumor contact without showing tumor contact of the PHA and/or CA. (The involvement of the aorta is categorized as unresectable. Presence of variant arterial anatomy is not taken into consideration)
Unresectable: UR	Subclassified according to the status of distant metastasis
Locally advanced: LA	<ul style="list-style-type: none"> • SMV/PV: bilateral narrowing/occlusion, exceeding the inferior border of the duodenum. • SMA, CA: tumor contact/invasion of 180 or more degree[#]. • CHA: tumor contact/invasion showing tumor contact/invasion of the PHA and/or CA. • AO: tumor contact or invasion
Metastatic: M	<ul style="list-style-type: none"> • Distant metastasis \$.

SMV: superior mesenteric vein, PV: portal vein, SMA: superior mesenteric artery, CA: celiac artery, CHA: common hepatic artery, PHA: proper hepatic artery, #: In the cases with CA invasion of 180° or more without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a distal pancreatectomy with en bloc celiac axis resection (DP-CAR) [21], some members prefer this criteria to be in the BR-A category. \$: including macroscopic para aortic and extra abdominal lymph node metastasis.

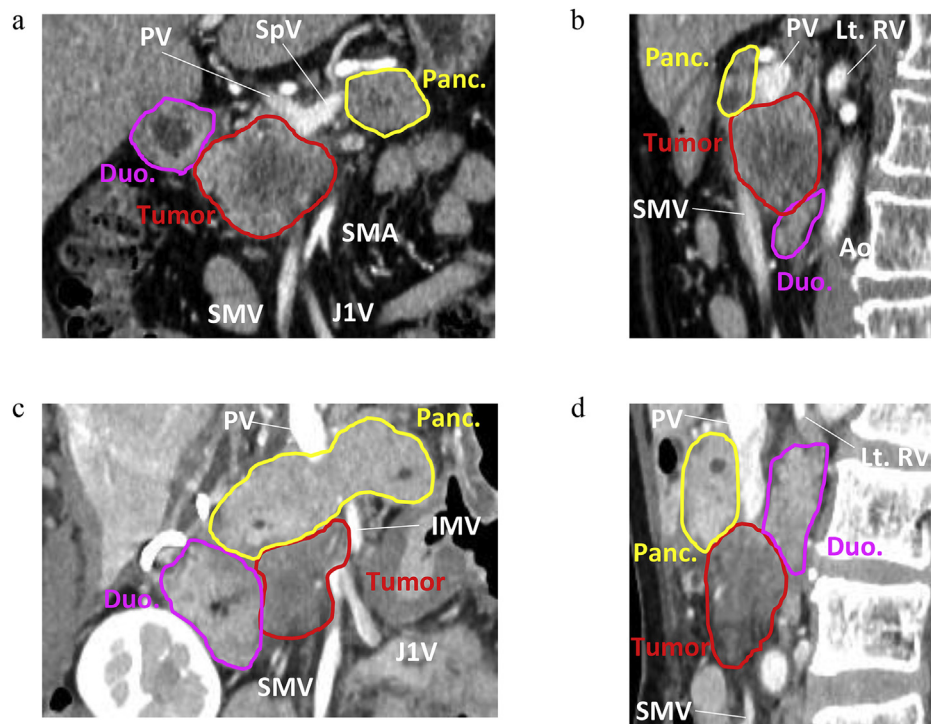


Fig. 1. CT findings of BR and UR PDAC. BR-PV (a: coronal, b: sagittal): The tumor of pancreatic head has invasion of the SMV/PV, but not exceeding the inferior border of the duodenum. UR (c: coronal, d: sagittal): The tumor of pancreatic head has invasion of the SMV/PV, and exceeding the inferior border of the duodenum. PV: portal vein, SpV: splenic vein, Panc.: pancreas, Duo.: duodenum, SMA: superior mesenteric artery, SMV: superior mesenteric vein, J1V: 1st jejunal vein, RV: renal vein, Ao.: aorta. JPS classification of pancreatic cancer, 7th edition (permission from Kanehara & Co., Ltd., Tokyo, Japan).

electronic charts of the 307 cytologically or histologically proven PDAC patients without distant metastases who had been enrolled for chemoradiotherapy (CRT) followed by surgery (CRT-S) at Mie University Hospital [16] from February 2005 to December 2016 (Fig. 3). Among 235 patients with PV/SMV invasion, the duodenal margin of SMV invasion was classified into Groups A (n = 188), B (n = 34), C (n = 11) and D (n = 2). The resection rate was 62.2% (117/188) in Group A, 64.7% (22/34) in Group B, and 81.8% (9/11) in Group C, while the two patients in Group D were not resectable. These data demonstrated that tumor resection is challenging when SMV invasion exceeds the inferior border of the duodenum (unpublished data).

As to the issue of tumor extension of PDAC, the NCCN guideline in 2016 proposed that the definition of BR-PDAC include that there is “no contact with most proximal draining jejunal branch into SMV”. It is often difficult to identify which tributary of the SMV is invaded by the tumor, whether it is the first (J1V) or second jejunal vein (J2V). The variations in the anatomy of the jejunal veins have been reported by Ishikawa et al. [17]. It is suggested that J1V and J2V usually form a common trunk, and that separate J1V and J2V drainage into the SMV is uncommon. Because it is difficult to identify the invasion of jejunal veins, this aspect of the definition was not included in the consensus statements. Nonetheless, some of our members favor the NCCN guideline definition, and therefore

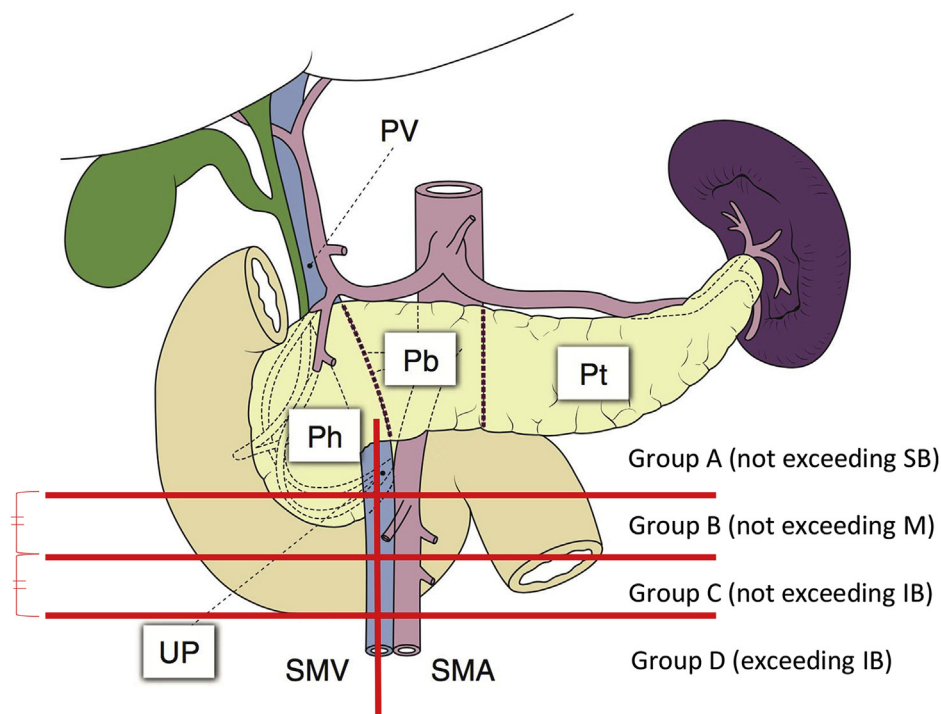


Fig. 2. Classification of the duodenal margin of SMV invasion. Group A: SMV invasion not exceeding the superior border of the duodenum (SB), Group B: SMV invasion not exceeding the middle of the duodenum (M), Group C: SMV invasion not exceeding the inferior border of the duodenum (IB), and Group D: SMV invasion exceeding the inferior border of the duodenum (IB). SMV: superior mesenteric vein, PV: portal vein, SMA: superior mesenteric artery, UP: uncinate process, Ph: pancreatic head, Pb: pancreatic body, Pt: pancreatic tail. Anatomical scheme of the pancreas in Japanese classification of pancreatic cancer 7th edition with modifications. (permission from Kanehara & Co., Ltd., Tokyo, Japan).

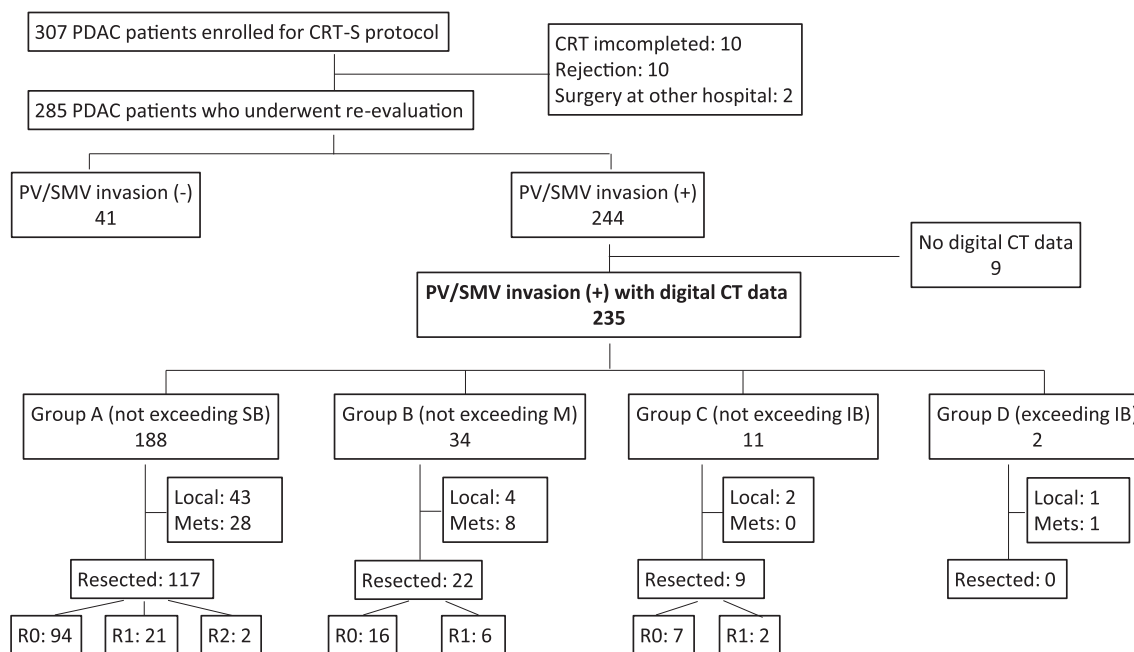


Fig. 3. Flow diagram of the 307 patients who had been enrolled for treatment of chemoradiotherapy (CRT) followed by surgery (CRT-S) at Mie University Hospital from February 2005 to December 2016, and surgical outcomes in the subjects of 235 patients according to classification of duodenal margin of SMV invasion (Groups A, B, C and D). Invasion (-): invasion negative, invasion (+): invasion positive, Local: unresected due to local factors such as major artery invasion, Mets: unresected due to the development of distant metastases.

duodenal margin criteria should be considered a surrogate to a more refined knowledge of the venous tributaries.

The extent of SMV/PV involvement has also been defined in terms of the degrees (extent of circumferential involvement) and is

considered an important factor in the definition of BR-PDAC. The number of degrees is best determined by maximum intensity projection (MIP) or three-dimensional volumetric thick section using MDCT [18]. Many of the definitions of BR-PDAC refer to '180

or more' degrees of SMV/PV invasion [12,13,15]. However, limitations in spatial resolution on CT scanning can make it difficult to determine the degree of vessel invasion. Nakao et al. [19] classified of PV invasion of PDAC of the pancreatic head by portography or computed tomography into four types (Fig. 4): A (normal), B (unilateral narrowing), C (bilateral narrowing), or D (complete obstruction with collateral veins). They reported that type A or B had a significantly better prognosis than the type C or D ($p = 0.002$). They noted that the only patients that survived more than 5 years had type A and B. On this basis, the consensus statement includes the degree of tumor involvement of the SMV/PV to the classification of BR-PDAC.

It has been reported that neoadjuvant chemotherapy was effective (resection rate 85%) when tumor contact with the SMA was less than 180° [20]. In another study, there was a significant difference in resection rates between BR-A and UR-LA when tumor contact with the SMA and/or CA was less than 180° . The resection rates after chemoradiotherapy for BR-A and UR-LA were 67.9% and 43.5%, respectively ($p < 0.01$). Similarly, the R0 resection rates were 80.6% and 60.0%, respectively ($p = 0.03$) [16] (including unpublished data). Accordingly, there was consensus on the imaging-based NCCN criteria of the SMA invasion for BR-PDAC based on the degree of tumor contact "less than 180° ". Compared with SMV/PV invasion, however, the evaluation of SMA invasion by using coronal section CT is difficult partly due to the elasticity of the arterial wall and merely the tumor contact of less than 180° may be insufficient to determine the presence or absence of arterial invasion, given that there is no clinical evidence. Therefore, we defined the BR-A as "tumor contact with the SMA and/or CA less than 180° without showing stenosis or deformity".

There are other anatomic criteria which have been considered in relation to the definition of BR-PDAC. Tumor involvement of the root of gastroduodenal artery (GDA) is nearly equivalent to that of short segment of CHA. In regards radical distal pancreatectomy with enbloc celiac axis resection (DP-CAR) [21] can be successfully performed in some patients even when the invasion of CA is more

than 180° without GDA involvement. DP-CAR is not a common procedure and these tumors are defined as locally advanced (LA).

The definition of regional lymph nodes of PDAC, remains controversial and differs between countries and societies. Para-aortic lymph nodes are categorized as distant metastasis in UICC 7th edition [22], but in 8th edition [23], lateral aortic nodes in the pancreatic body and tail cancer are defined as regional LN. In the meta-analysis study [24], survival rate is significantly decreased in patients with microscopically positive para-aortic LNs, but tumor involvement of them is not independent predictor of survival in these patients. Although the definition of regional LN is still debated, we defined metastatic PDAC (M) as distant metastases including macroscopic para-aortic and extra abdominal lymph node metastases revealing an enlargement of more than 10 mm in the shorter diameter based on the CT imagings.

Anatomical definition of BR-PDAC at the IAP in 2016 (Table 2)

BR-PV (SMV/PV invasion alone)

- Tumor contact 180° or greater or invasion of the SMV/PV with bilateral narrowing or occlusion, and not exceeding the inferior border of the duodenum.

BR-A (arterial invasion)

- Tumor contact with the SMA and/or CA less than 180° without showing stenosis or deformity. Tumor abutment of the CHA without showing tumor contact with the proper hepatic artery and/or CA.

Biological and conditional factors of BR-PDAC

Biological and conditional factors were taken into consideration

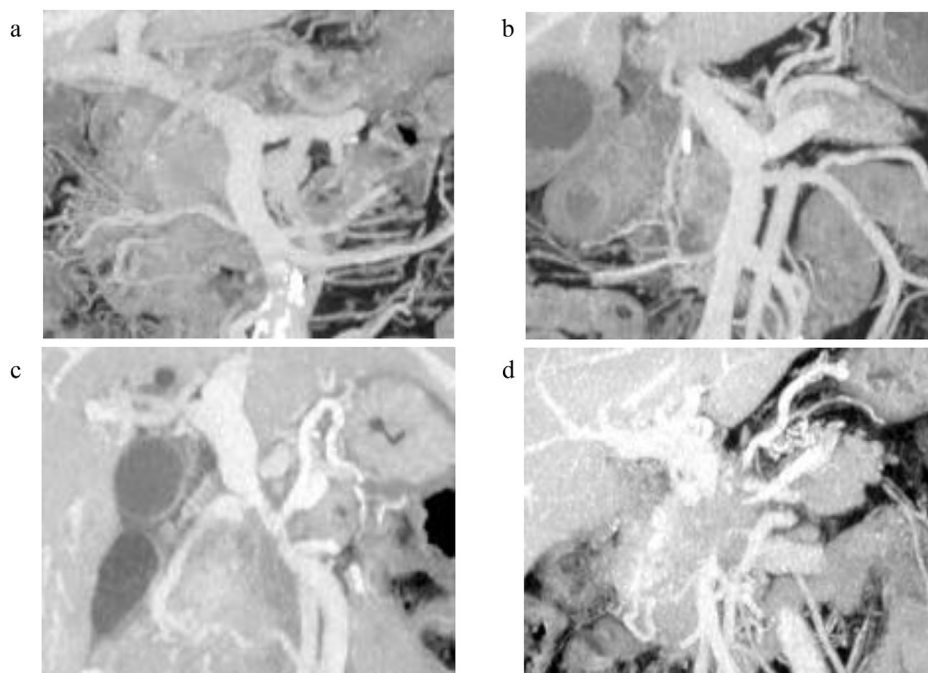


Fig. 4. Radiographic classification of PV/SMV invasion by CT (1 mm slice four phase). a) absent of PV/SMV invasion, b) unilateral narrowing, c) bilateral narrowing, or d) stenosis or obstruction with collaterals. Cases at Mie University Hospital.

in this consensus, even they are relevant for patients who are categorized as with anatomically resectable PDAC, and both of them were considered in relation to BR-PDAC. This was initially proposed by Katz et al., in 2008 [1] and modified by Dr. Tzeng et al., in 2012 [25]. They proposed two additional subsets of PDAC patients; those with questionable metastatic disease (biological factor) and those with a suboptimal performance status or severe medical comorbidities (conditional factors). Another biological indicator is the serum level of CA 19-9. When the preoperative serum level of CA 19-9 is > 1000 U/ml in patients with anatomically resectable PDAC or biopsy-proven regional lymph nodes metastasis, 20 out of 41 (46.3%) patients developed metastases after neoadjuvant chemotherapy and/or radiotherapy. In the patients who had anatomically resectable PDAC with severe comorbidities or depressed PS (Eastern Cooperative Oncology Group (ECOG) score >2, distant metastases were detected in 10 out of 36 (27%) patients after neoadjuvant therapy, which means that these patients had a potential metastasis and were not suitable for a surgery-first strategy [25].

The recent American Society of Clinical Oncology clinical practice guidelines [26] have incorporated the biological and conditional criteria of BR-PDAC. They indicate that neoadjuvant therapy is recommended for PDAC patients whose radiographic findings are suspicious but not diagnostic of extrapancreatic disease, a performance status or comorbidity profile not currently appropriate for a major abdominal operation, or a CA 19-9 level suggestive of disseminated disease.

Literature review of biological definition of BR-PDAC

Preoperative CA19-9 levels are associated with PDAC stage and prognosis, although these studies are mostly based on small to moderate-sized patient cohorts [27,28]. Hartwig et al. [29] reported the usefulness of preoperative CA19-9 levels based on a large cohort of more than 1600 patients with potentially resectable PDAC, and investigated the correlation between CA19-9 levels and tumor resectability and prognosis (Table 3). In patients with preoperative CA19-9 levels more than 500 IU/ml, the resectability ratio was less than 70% and the median survival time after pancreatectomy was less than 20 months. It was on this basis that our consensus view was that preoperative CA19-9 of 500 IU/ml should be included in the definition of BR-PDAC as a biological factor.

As to regional lymph nodes metastasis, the existence of positive node strongly impacted the prognosis of PDAC patients regardless of tumor resectability or tumor stage. Fig. 5 shows the survival curves of all PDAC patients according to the number of positive regional lymph node based on the Japanese Pancreatic Cancer Registry in the JPS classification 7th edition [16]. When the patients were divided into three groups according to the total numbers of lymph node metastasis, overall survival was significantly better in the patients with no lymph node metastasis followed by the patients with 1–3 lymph node metastases and those with 4 or more

lymph node metastases in UICC (7th edition)-T1, T 2, and T3, respectively. However, in UICC-T4, there were no association between positive lymph node and prognosis. These results suggest that the positive lymph node is associated with poor prognosis even in the patients with anatomically resectable PDAC. The American Joint Commission on Cancer (AJCC) 8th edition changed the N definition similar to the JPS classification 7th edition, and positive lymph node was associated with poor prognosis regardless of T stage [30].

Biological definition of BR-PDAC at the IAP in 2016

Consensus statement

- Tumor potentially resectable anatomically with clinical findings suspicious but not proven distant metastasis, including CA 19–9 level more than 500 units/ml, or regional lymph nodes metastasis diagnosed by biopsy or PET - CT.

Literature review of conditional host-related factor of BR-PDAC

Conditional host-related factors are important because they are associated with resistance to the neoadjuvant therapy, post-operative morbidity/mortality and poor overall prognosis. According to the 8th edition of the UICC TNM classification [31], ECOG status is described as a host-related “essential” prognostic risk factor for PDAC. Tas et al. [32] reported that the prognostic factor that best predicted survival was performance status for all stages of PDAC. This is shown in Table 4 which compares the prognosis of patients with performance status of 0, 1 and 2 or more. In patients with anatomically resectable PDAC (TNM stages I and II) there was a significantly shorter median survival for those with PS 2 or more compared with patients with PS of 0 and 1 ($p = 0.015$) [32]. Regarding the indication for pancreatic surgery, patients with PS 3 or 4 were not suitable for operation regardless of tumor stage, but patients with PS 2 are considered as a candidate to undergo surgery. However, some patients with marginal PS might be reversible and be targeted for medical consultation, nutritional supports and prehabilitation, to prepare for a surgical treatment [33].

Another conditional host-related factor to be considered in the definition of BR-PDAC is the systemic inflammatory response, which is a prognostic factor. This includes the modified Glasgow Prognostic Score (mGPS) [34] and neutrophil/lymphocyte ratio (NLR) [35]. It was considered that systemic inflammatory response (SIR) is likely to be included as an aspect of the definition of BR-PDAC in the future, but the consensus view was that it should not be included at this time.

Table 3

The relationship between CA19-9 levels and tumor resectability and prognosis in patients who underwent surgery for potentially resectable PDAC (Ref. [26] with modifications).

CA19-9 (U/ml)	Number of patients	Resection rate (%)	MST (months) after resection
5 - <37	281	79.7	28.5
37 - <100	216	83.3	26.9
100 - <250	247	82.2	22.5
250 - <500	204	72.1	20.1
500 - <1000	184	67.4	15.4
1000 - <2000	126	61.1	12

MST: median survival time.

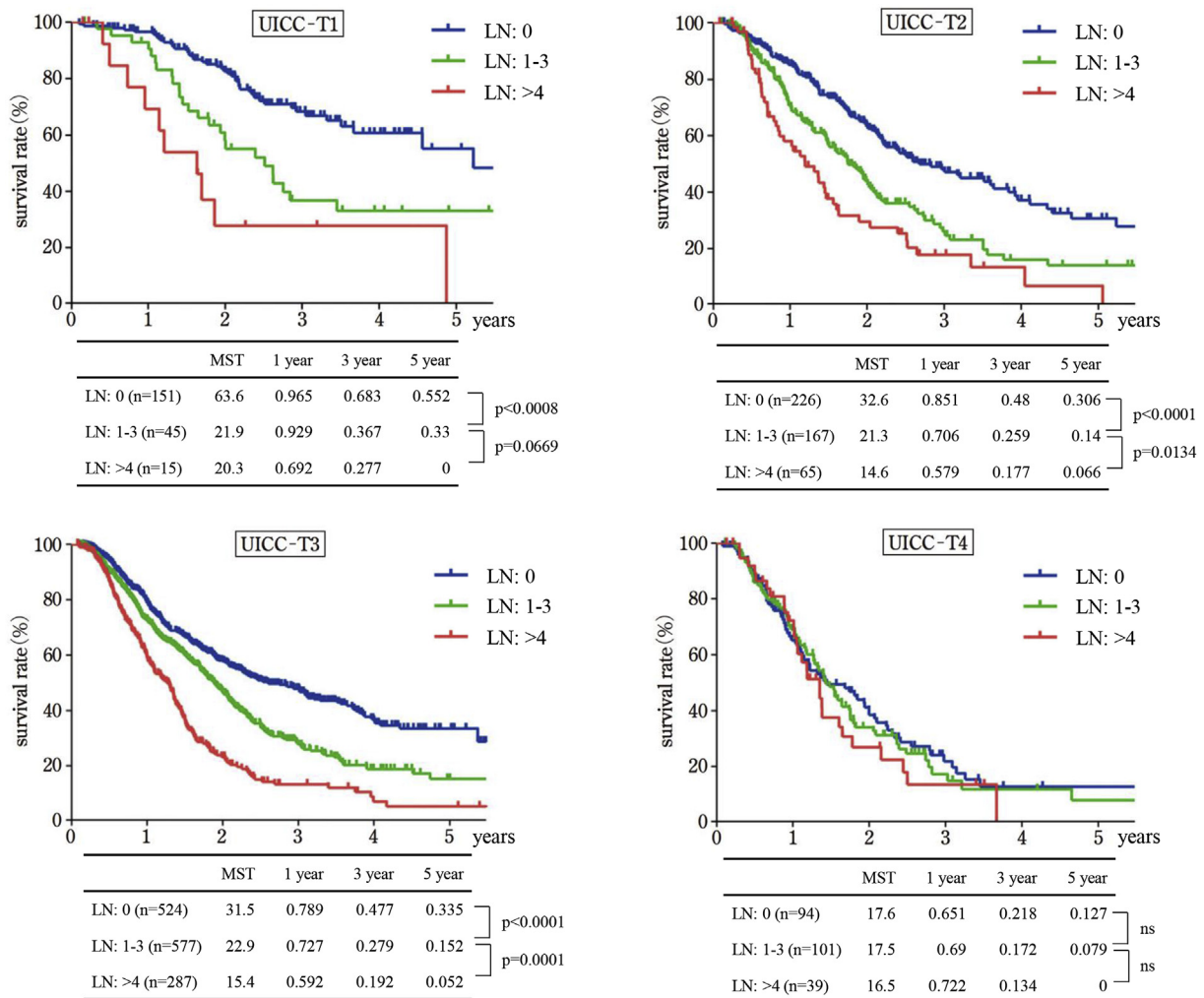


Fig. 5. Survival curves of all PDAC patients according to the number of positive regional lymph node based on the Japanese pancreatic cancer registry (n = 3315). UICC (7th edition)-T1, UICC-T 2, UICC-T3, and UICC-T4. (Kanehara & Co., Ltd., Tokyo, Japan).

Table 4

The comparison of prognosis between PDAC patients with PS 0, 1 and those with PS = />2 in each stages (ref [29] with modifications).

	MST (months) in all patients	MST in patients with PS 0 or 1	MST in patients with PS = />2	p-value(PS 0,1 v.s. PS = />2)
Local diseaseStage I/II	22.1 (n = 59)	23.5 (n = 52)	12.4 (n = 7)	0.015
Locally advancedStage III	10.3 (n = 122)	10.7 (n = 100)	4.6 (n = 22)	0.01
MetastaticStage IV	6.0 (n = 154)	7.4 (n = 102)	3.1 (n = 52)	<0.001

MST: median survival time, PS: Eastern Cooperative Oncology Group (ECOG) performance status.
Stage: the International Union Against Cancer TNM classification 5th edition.

Conditional definition of BR-PDAC at the IAP in 2016

Consensus statement

- Patients with anatomically resectable PDAC and with performance status of 2 or more are defined as BR –PDAC.

International consensus statements of BR-PDAC

With these considerations consensus was reached for the definition of BR-PDAC, summarized in Table 5, including anatomical,

biological and conditional factors. It was agreed that distinguishing resectable (R), borderline resectable (BR), locally advanced (LA) PDAC was of benefit, based on *anatomic definitions* (Table 3). This includes tumor abutment or invasion of the SMV/PV with bilateral narrowing or occlusion, not exceeding the inferior border of the duodenum, tumor contact with the SMA and/or CA less than 180° without showing stenosis or deformity, or tumor abutment of the CHA without showing tumor contact with the proper hepatic artery and/or CA. To the anatomic definition is added the *biological definitions* of a serum CA 19-9 of >500 IU/ml and/or positive regional lymph node metastases (biopsy or PET-CT). And to this is added the *conditional definitions* of poor performance status (PS of 2 or more).

Table 5

Classification of BR-PDAC based on anatomical, biological, and clinical aspects.

Type of definition	Anatomical	Biological	Conditional
R	R-Type A	No: R-Type A	No: R-Type A
		Yes: BR-Type B	Yes: BR-Type C
BR	BR-Type A	No: BR-Type A	No: BR-Type A
		Yes: BR-Type AB	Yes: BR-Type AC
Locally advanced: LA	LA-Type A	No: LA-Type A	No: LA-Type A
		Yes: LA-Type AB	Yes: LA-Type AC

Biological definition:

- CA 19-9 more than 500 IU/ml
- Regional lymph node metastasis (biopsy or PET-CT)

Conditional host-related definition:

- Depressed performance status (PS: 2 or more)

Tumor is classified based on combination of A, B, and C

(for example, a patient with both Type B and Type C features would be classified as Type ABC).

Nomenclature of BR-PDAC

When PDAC is considered borderline resectable, patients can be classified on the basis of 3 dimensions: BR-A (based solely on anatomic criteria), BR-B (based solely on biological criteria), BR-C (based on conditional criteria) or a combination of these criteria: BR-AB, BR-BC, BR-AC, BR-ABC.

Conclusion

In this consensus statement of definition of BR-PDAC, we have added the biological and conditional host-related factors as well as reaching consensus on the anatomical factors. There are aspects which remain controversial and there is the need for further improvements. Therefore, this consensus statement must be considered an interim statement that will be further refined.

Conflicts of interest

Shuji Isaji and other co-authors have no conflict of interest of this study.

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