ORIGINAL ARTICLE

Biological and conditional factors should be included when defining criteria for resectability for patients with pancreatic cancer

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Abstract

Background: This study aimed to evaluate novel resectability criteria for pancreatic ductal adenocarcinoma (PDAC) proposed by the International Association of Pancreatology (IAP) by comparing them with the National Comprehensive Cancer Network (NCCN) guidelines.

Methods: 369 patients who underwent upfront surgery for PDAC were retrospectively analyzed. Overall survival (OS) of each group as defined by either of the guidelines were compared and preoperative prognostic factors for OS were identified.

Results: Based on the IAP-criteria, 157 patients were classified as resectable (R), 192 as borderline resectable (BR) and 20 as unresectable (UR), with the median survival time (MST) of 40 months, 17 and 11, respectively. In contrast to the NCCN-criteria, BR demonstrated significantly better OS than UR ($P = 0.023$) under the IAP-criteria. Performance status ≥ 2 (hazard ratio [HR]: 2.47, $P = 0.014$) and lymph node metastasis suspected by imaging (HR: 1.55, $P = 0.003$) were identified as independent prognostic factors by the multivariate analysis along with portal or arterial invasion, while carbohydrate antigen 19-9 $\geq$ 500 U/ml was not (HR: 1.23, $P = 0.190$).

Conclusion: The IAP-criteria, which includes biological and conditional factors, resulted in superior separation of survival curves stratified by the resectablity when compared with the NCCN-criteria.

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Introduction

The concept of borderline resectable (BR) pancreatic ductal adenocarcinoma (PDAC), a distinct subset of tumours whose prognosis is meant to be the intermediate between resectable (R) and locally advanced unresectable (UR-LA) tumours, was first identified in 2006 by Varadhachary *et al.*[1] The definition of resectability status has been established by the guidelines of the National Comprehensive Cancer Network (NCCN). However, the current authors remained concerning that it focused purely on anatomical aspects of the tumour to determine resectability[2,3] rather than incorporating potentially important biological factors.

The terminology of BR originally related to the likelihood of achieving a margin-negative resection when a tumour infiltrated the surrounding structures, especially the major blood vessels. Ideally, BR should represent a subset of patients with PDAC whose overall survival (OS) would be intermediate between those with R and those with UR-LA. However, BR patients were reported to have a prognosis that was similar to those patients with UR-LA when treated by upfront surgery.[4,5] Furthermore, even when complete resection was achieved in patients with R, the 5-year survival was reported to be modest at approximately 40%.[4–7]

Therefore it would seem important to take tumour biology and host-related conditional factors into consideration alongside

the anatomical aspects, and the MD Anderson group was the first to advocate this approach in 2008.[8] In 2014, the International Study Group of Pancreatic Surgery incorporated serum carbohydrate antigen 19-9 (CA 19-9) level, modified Glasgow Prognostic Score (m-GPS) and neutrophil/lymphocyte ratio (NLR) into its definition of BR.[9] However there was no recommendation for specific cutoff values for these factors. In 2017, the International Association of Pancreatology (IAP) released a new definition of BR,[10] in which BR was defined based on anatomical (A), biological (B), and conditional (C) dimensions with specific value or conditions.

The objective of this study was to evaluate the novel resectability criteria established by the IAP (IAP-criteria) and to compare these criteria with the NCCN guidelines version 3. 2017[11] (NCCN-criteria), focusing on differences between these two criteria.

Methods

Patient selection

Between November 2001 and April 2017, consecutive patients who underwent surgical resection of PDAC at the Department of Gastroenterological Surgery (Surgery II), Nagoya University Hospital were retrospectively considered for potential inclusion. Patients who underwent preoperative chemo- or chemoradiotherapy were excluded to eliminate the influence of neoadjuvant therapy because there was no unified protocol. Patients who did not undergo preoperative multidetector computed tomography (MDCT) were also excluded. Resected pancreatic tumours were pathologically confirmed as invasive ductal adenocarcinoma. The Ethics Committee of the hospital approved this study, and informed consent was obtained from all patients for the subsequent use of their resected tissues.

Treatment and follow-up

Endoscopic retrograde cholangiopancreatography (ERCP) and stenting were performed in patients with jaundice preoperatively. All patients were considered "resectable" at that time and pancreatectomy with extended radical lymph node dissection (D2) using a mesenteric approach and a no-touch isolation technique[12,13] was performed. Paraaortic lymph nodes were routinely sampled. The main pancreatic duct of the remnant pancreas was pathologically examined by frozen section, and additional resection (including total pancreatectomy) was performed when necessary.

All resected specimens were pathologically diagnosed. Margin negative (R0 resection) was defined that none of tumour cell was exposed on any surgical margin. Adjuvant chemotherapy including gemcitabine (Gemzar®; Eli Lilly, Kobe, Japan) and/or S-1 (TS-1®; Taiho, Tokyo, Japan) was administered unless contraindicated by patients' morbidities or by patients' refusal. Gemcitabine (1000 mg/m^2) was administered weekly for 3 weeks, followed by a week of rest (one cycle) and this administration of gemcitabine was repeated up to six cycles. S-1 was administered from days 1–14, followed by a week of rest (one cycle) and this administration of S-1 was repeated up to eight cycles. Chemotherapy was started within 2 months of surgery in all patients considered eligible for this study.

Investigational factors

The resectability status of each patient based on both NCCN-criteria and IAP-criteria was evaluated. The details of IAP-criteria are shown in Table 1. Preoperative MDCT was assessed by 2 radiologists with special focus on the following points: tumour size, tumour contact with the portal vein/superior mesenteric vein (PV/SMV) and celiac artery/superior mesenteric artery/common hepatic artery (CA/SMA/CHA) greater than 180°, and tumour invasion of the anterior pancreatic capsule, retroperitoneal tissue, duodenum, other organs or the first jejunum artery/vein (J1A/V) (Fig. 1). Regarding the evaluation of lymph node metastasis, PET-CT imaging was not deemed mandatory. Enhanced CT findings regarding lymph node metastasis were discussed and diagnosed by the 2 radiologists with focus on the following points: enlargement of more than 10 mm in the shorter diameter, homogeneous contrast enhancement and demonstrating orbicular shape. The accuracy of N status by each imaging study was later to be assessed based on the postoperative pathological diagnosis.

Table 1 Consensus statement by international association of pancreatology on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma

Anatomical definition (BR-A)
Subclassified according to SMV/PV involvement alone or arterial invasion
SMV/PV: tumor contact 180° or greater or bilateral narrowing/occlusion, not exceeding the inferior border of the duodenum.
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)
Biological definition (BR-B)
Serum CA 19-9 level more than 500 units/ml.
Regional lymph nodes metastasis diagnosed by biopsy or PET-CT.
Conditional definition (BR-C)
ECOG performance status of 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).
SMV, superior mesenteric vein; PV, portal vein; SMA, superior mesenteric artery; CA, celiac artery; CHA, common hepatic artery; PHA, proper hepatic artery; CA 19-9, carbohydrate antigen 19-9.

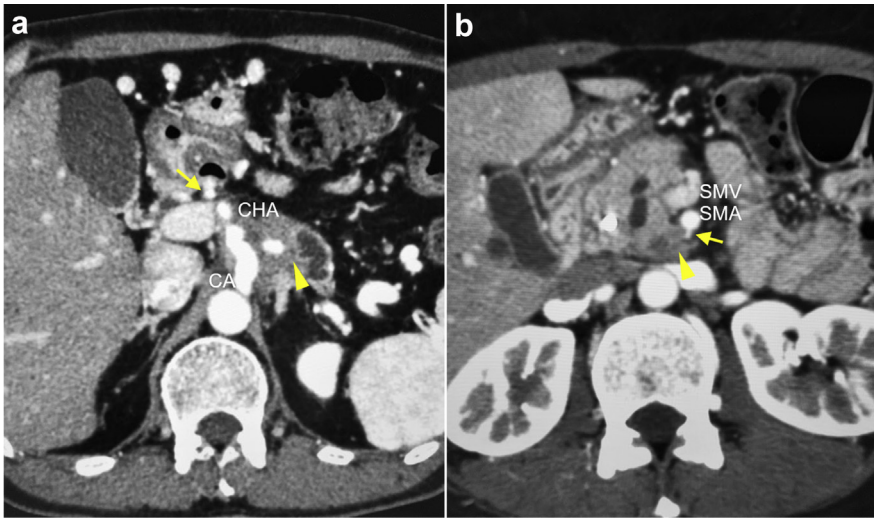

Figure 1 **a:** Carcinoma in the body/tail of the pancreas (arrow head) invades anterior pancreatic capsule, retroperitoneal tissue, around celiac artery (CA) and common hepatic artery (CHA) with more than 180°. Gastroduodenal artery (arrow) and aortic artery are intact from the tumour. The tumour is anatomically classified to UR-LA based on the IAP-criteria and is a candidate for BR in the NCCN-criteria. **b:** Carcinoma in the uncinate process (arrow head) invades retroperitoneal tissue and contact superior mesenteric artery (SMA) with less than 180°. The common artery of first jejunal SMA branch (arrow) and inferior pancreaticoduodenal artery is surrounded by the tumour. The tumour is anatomically classified to BR-A based on the IAP-criteria and is classified to UR-LA in the NCCN-criteria

Performance status (PS) and body mass index (BMI) were assessed when patients were admitted for surgery. Parameters from preoperative blood samples, including serum albumin level, lymphocyte count, serum total cholesterol level, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels, were measured 1 or 2 days before surgery. Controlling Nutrition Status (CONUT) score[14] was calculated as host-related immunonutritional factor. Diabetes mellitus was diagnosed as preoperative glycohemoglobin $\geq$6.5%. Prognostic risk factors preoperatively available were analyzed to evaluate validity of each criteria.

Statistical analysis

Continuous variables were expressed as medians (ranges) and compared using the Wilcoxon rank sum test, and categorical variables were compared using the Fisher exact test. The OS curves were constructed using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional hazards models were used to determine the independent risk factors associated with OS. OS was defined as the date of surgery to the date of death due to any cause. The level of statistical significance was set at $p < 0.05$. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[15]

Results

In total 476 patients underwent resection, of whom 100 were excluded due to neoadjuvant approach and 7 because they did not undergo preoperative MDCT. Table 2 summarizes the demographics of the 369 patients included in this study. Based on the resectability status established by the NCCN-criteria, 253 patients (69%) were classified as R, 78 (21%) as BR and 38 (10%) as UR-LA. On the other hand, based on the resectability status established by the IAP-criteria, 157 patients (43%) were classified as R, 192 (52%) as BR [BR-A: 35 (9%), BR-B: 97 (26%), BR-C: 4 (1%), BR-AB: 49 (13%), BR-BC: 3 (1%), BR-ABC: 4 (1%)] and 20 (5%) as UR-LA. Through the reclassification by IAP-criteria, 4 patients from the UR-LA classified by NCCN-criteria were promoted to R, and 14 were delegated to BR due to tumour invasion of J1A/V.

Accuracy of image diagnosis for N1 status

53 patients underwent PET-CT, and the remaining 316 patients were diagnosed using MDCT regarding preoperative diagnosis of N status. From the postoperative pathological diagnosis, the sensitivity of identifying N1 was 30.3% using PET-CT and 32.7% using MDCT ($P = 0.844$). Specificity was 90% using PET-CT and 84.3% using MDCT ($P = 0.734$). Positive and negative predictive values were also not significantly different between the two groups (Table 3).

Survival based on each resectability criterium

The median length of follow-up for censored cases was 27 months (range 1–136). The median survival time (MST) based on the NCCN-criteria was 33 months for the R group, 15 for the BR group, and 12 for the UR-LA group (Fig. 2A). Although the R group showed significantly better OS than the BR ($P < 0.001$) or

Table 2 Perioperative data of the 369 patients

Characteristics	Values
Age, median (range), y	66 (34–84)
Sex, male/female, n	227/142
PS ≥ 2, n (%)	12 (3)
BMI, median (range), kg/m^2	21.3 (13.2–33.5)
Diabetes mellitus, n (%)	145 (39)
CONUT score, median (range)	2 (0–12)
CEA, median (range), ng/ml	3.2 (0.4–124.1)
CA19-9, median (range), U/ml	161 (1–28,160)
Preoperative imaging diagnosis	
Tumor size, median (range), mm	26 (10–100)
PV/SMV encasement/abutment, n (%)	177 (48)
CA/SMA/CHA encasement/abutment, n (%)	73 (20)
Invasion of anterior pancreatic capsule, n (%)	207 (56)
Invasion of retroperitoneal tissue, n (%)	210 (57)
Invasion of duodenum, n (%)	115 (31)
Invasion of other organs, n (%)	11 (3)
Invasion of J1A/J1V, n (%)	34 (9)
Resectability (NCCN), R/BR/UR, n	253/78/38
Resectability (IAP), R/BR/UR, n	157/192/20
Operative method, PD/DP/TP/Others, n	265/75/27/2
PV/SMV resection n (%)	187 (51)
R0 resection, n (%)	253 (69)
Mortality (30 day), n (%)	0 (0)
Adjuvant chemotherapy, n (%)	268 (73)

PS, performance status; BMI, body mass index; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CONUT, controlling nutritional status; PD, pancreatoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy; J1A, 1st jejunum artery; J1V, 1st jejunum vein.

Table 3 Diagnostic accuracy of detecting N1 status

	PET-CT (n = 53)	CT (n = 316)	P
Imaging N1, n (%)	12 (23)	86 (27)	
Pathological N1, n (%)	33 (62)	214 (68)	
Sensitivity, %	30	33	0.844
Specificity, %	90	84	0.734
Positive predictive value, %	83	81	0.100
Negative predictive value, %	44	37	0.487
Accuracy rate, %	53	49	0.808

UR-LA groups ($P < 0.001$), the BR group did not demonstrate any superiority of OS compared to the UR-LA group ($P = 0.878$). However, the MST using the IAP-criteria was 40 months for the R group, 17 for the BR group, and 11 for the UR-LA group (Fig. 2B). The R group showed significantly better OS than did the BR ($P < 0.001$) or UR-LA groups ($P < 0.001$); moreover, the BR group also demonstrated significantly superior OS compared to the UR-LA group ($P = 0.023$).

Upon evaluation of the BR status using NCCN-criteria in more detail, there was no difference in OS between the BR-A group and the BR-PV group ($P = 0.217$, Fig. 2C). Equivalent evaluation using IAP-criteria in more detail indicated that although the BR-B group showed no contact with the PV/SMV or CA/CHA/SMA, it exhibited significantly worse OS than the R group ($P < 0.001$, Fig. 2D). However, the BR-B group demonstrated significantly better OS than any other type of BR group (i.e., BR-A/C/AB/BC/AC/ABC; $P < 0.001$).

Univariate and multivariate analyses associated with OS

Seventeen preoperative clinical factors were analyzed using univariate and multivariate analyses (Table 4). The multivariate analysis revealed that PS ≥ 2 (hazard ratio [HR]: 2.47, $P = 0.014$), CONUT score ≥ 3 (HR: 1.37, $P = 0.023$), imaging lymph node metastasis (HR: 1.55, $P = 0.003$), PV/SMV encasement/abutment (HR: 1.75, $P < 0.001$) and CA/SMA/CHA encasement/abutment (HR: 1.61, $P = 0.009$) were independent prognostic risk factors of OS. Neither CA 19-9 ≥ 500 U/ml (HR: 1.23, $P = 0.19$) nor invasion of the J1A/V (HR: 1.27, $P = 0.3$) were independent risk factors of OS.

As the levels of SMV/PV and CA/SMA/CHA encasement/abutment as well as tumour size increased, the risk for death increased incrementally, whereas the serum CA 19-9 level did not demonstrate a significant association with the risk for death if the levels were less than 1000 U/ml (Table 5). However, CA 19-9 ≥ 1000 U/ml was a significant risk factor for OS compared to CA 19-9 < 100 U/ml (odds ratio: 2.03, $P < 0.001$). Where the cutoff level of CA19-9 was set at 1000 U/ml, another Cox proportional hazard model revealed that CA 19-9 was an independent risk factor for OS (HR: 1.52, $P = 0.014$, Supporting Table 1).

Discussion

This study explored the prognostic impact of resectability status as defined by the NCCN guidelines and the IAP proposals in patients who underwent upfront surgery for PDAC and recognized value of the IAP resectability criteria in which some clinically important prognostic factors had been incorporated. According to the IAP-criteria, significantly different OS was observed between BR and UR-LA, but this difference was not observed in these groups classified by the NCCN-criteria. Additionally, patients defined as R by the IAP-criteria had an improved MST compared with those defined by the NCCN-criteria. The reason why these phenomena were observed would be that the IAP-criteria shifted patients with biologically more aggressive tumours from the NCCN-R group to the BR group. This suggested that the IAP-criteria has better defined resectability criteria than the NCCN-criteria in terms of patient selection for preoperative treatment.

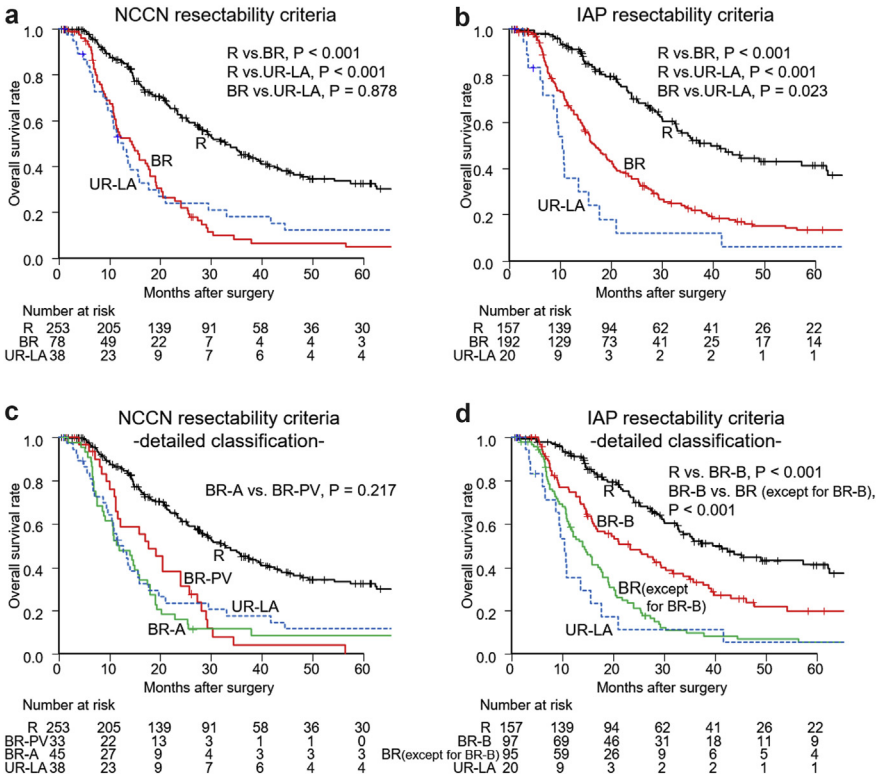

Figure 2 **a:** Overall survival (OS) curves based on NCCN-criteria. Although the R group showed significantly better OS than did the BR ($P < 0.001$) or UR-LA groups ($P < 0.001$), the BR group did not demonstrate any superiority of OS compared with that of the UR-LA group ($P = 0.878$). **b:** OS curves based on the IAP-criteria. The BR group demonstrated significant superiority of OS compared to that of the UR-LA group ($P = 0.023$). **c:** OS curves based on more detailed NCCN-criteria. There was no difference in OS between the BR-A and BR-PV groups ($P = 0.217$). **d:** OS curves based on more detailed IAP-criteria. The BR-B group showed significantly worse OS than did the R group ($P < 0.001$) and better OS than any other type of BR group (BR-A/C/AB/BC/AC/ABC) ($P < 0.001$)

Based on the IAP-criteria, patients classified as BR-B showed significantly worse OS than those classified as R, which suggested that the BR-B cohort appropriately included patients who, despite having no tumour contact with the CA/SMA/CHA or PV/SMV, had poor outcome and could be indicated for the neoadjuvant strategy as the BR group.

Nevertheless, there were some shortcoming in the IAP-criteria. Although many studies[16–19] reported that CA 19-9 was a prognostic factor in PDAC, the cutoff value of CA 19-9 deserves to be discussed. This study demonstrated that CA19-9 $\geq$ 1000 U/ml was more appropriate than $\geq$500 U/ml, which is recommended by the IAP-criteria. IAP-criteria also recommended PET-CT or biopsy for the diagnosis of lymph node metastasis, the current study demonstrated that MDCT could sufficiently replace PET-CT. A meta-analysis[20] reported that the pooled sensitivity and specificity of PET-CT for lymph node metastasis were 64% and 81%, respectively. Another retrospective study,[21] which compared the diagnostic ability of PET-CT with MDCT, reported that the accuracy rate of PET-CT for lymph node metastasis was 42%, while that of MDCT was 35%. In this study, both PET-CT and MDCT resulted in low sensitivity and high specificity for detecting N1 in the same manner.

Regarding anatomical criteria to determine the resectability of PDAC in relation to tumour involvement of major celiac or mesenteric vessels, the NCCN-criteria and IAP-criteria were almost the same. However, this study demonstrated that even less than 180° of tumour contact with the PV/SMV, which is classified as R in both criteria, significantly increased the risk for OS in the univariate analysis. Thus, patients with any degree of tumour contact with the PV/SMV might be classified into BR to be candidates for neoadjuvant treatment. There is a difference in treating tumour invasion with J1A/V contact between the IAP-criteria and NCCN-criteria. While the IAP-criteria does not treat the tumour invasion of the J1A/V as a negative prognostic factor, the NCCN-criteria classifies patients positive for this parameter into the UR-LA category regardless of the presence/absence of major venous or arterial involvement by the tumour located in the pancreatic head. One study reported that tumour invasion of the SMV proximal (away from liver) to its jejunal tributaries was unresectable due to difficulty with vascular control and potential for bowel infarction,[22] however, PD is generally

Table 4 Univariate and multivariate analyses of preoperative clinical factors associated with OS

Preoperative clinical factor	Patients	Univariate analysis	Multivariate analysis		
	n = 369	*P*	HR	95% CI	*P*
Age, ≥70 y	73	0.223			
Sex, male	227	0.913			
PS, ≥2	12	<0.001	2.47	1.20–5.06	0.014
BMI, ≥25 kg/m^2	36	0.537			
Diabetes mellitus	145	0.143			
CONUT score[a], ≥3	136	0.004	1.37	1.05–1.80	0.023
CEA, ≥15 ng/ml	17	0.039	1.69	0.90–3.17	0.100
CA19-9, ≥500 U/ml	102	<0.001	1.23	0.91–1.66	0.190
Preoperative imaging diagnosis					
Tumor size, ≥20 mm	268	0.002	1.13	0.80–1.58	0.490
Lymph node metastasis	98	<0.001	1.55	1.16–2.06	0.003
PV/SMV encasement/ abutment	177	<0.001	1.75	1.30–2.34	<0.001
CA/SMA/CHA encasement/ abutment	73	<0.001	1.61	1.13–2.29	0.009
Invasion of anterior pancreatic capsule	207	0.26			
Invasion of retroperitoneal tissue	210	0.020	1.10	0.83–1.46	0.500
Invasion of duodenum	115	0.049	0.97	0.71–1.32	0.850
Invasion of other organs	11	0.023	1.50	0.75–2.99	0.250
Invasion of J1A/J1V	34	<0.001	1.27	0.81–1.98	0.300

OS, overall survival; PS, performance status; BMI, body mass index; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; J1A, 1st jejunum artery; J1V, 1st jejunum vein.
[a] Ignacio de Ulibarri *et al.* CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp 2005; 20:38–45.

Table 5 Univariate analyses for each level of clinical factors associated with OS

Clinical factors	n	Odds ratio	95%CI	*P*
CA 19-9, U/ml				
<100	152	1		
100 - <500	115	1.06	0.77-1.45	0.73
500 - <1000	33	1.14	0.73-1.79	0.57
≥1000	69	2.03	1.45-2.84	<0.001
CA/SMA/CHA encasement/abutment				
No	296	1		
<180°	54	2.48	1.79-3.43	<0.001
≥180°	19	3.00	1.79-5.02	<0.001
PV/SMV encasement/abutment				
No	182	1		
<180°	96	1.53	1.11-2.11	0.009
≥180°	91	3.90	2.85-5.33	<0.001
Tumor size, mm				
<20	63	1		
20 - <40	251	1.67	1.15-2.43	0.007
≥40	55	2.00	1.25-3.20	0.004

CA 19-9, carbohydrate antigen 19-9; CA, celiac artery; SMA, superior mesenteric artery; CHA, common hepatic artery; PV, portal vein; SMV, superior mesenteric vein.

performed with combined resection of the J1A/V for the purpose of lymphadenectomy in Japan.[23] Even if resection of a long segment of SMV including the J1A/V is required, reconstruction could be performed safely using vascular grafts to prevent the risk of anastomotic stenosis.[24] In addition, invasion of the J1A/V was not an independent prognostic factor in this study; thus, tumour invasion of the J1A/V in itself would not be an element to classify PDAC into the UR-LA.

This study also demonstrated that PS was one of the strongest prognostic factors for OS, as has previously been reported.[25] Thus, it would be logical to incorporate PS into the resectability criteria of PDAC. However, a poor PS has not been interpreted with similar seriousness when compared with the anatomical or biological BR. Some patients with poor PS could be indicated for medical consultation, nutritional support and rehabilitation prior to surgical treatment.[26] One of the caveats may be that distinguishing a PS of 2 from a PS of 3 would be difficult in some cases. Immunonutritional status is another objective host-related factor that will need to be considered when deciding on resectability. Several parameters related to immune-nutrition, such as m-GPS,[27,28] NLR,[29,30] and PLR,[31] have been reported as prognostic factors for patients with PDAC. This study also identified the CONUT score as an independent prognostic factor for OS.

This study has several limitations, including its retrospective design and single-center setting. Thus, the current results will have to be validated using larger data sets on the multi-institutional basis. Additionally, this study contained a certain number of BR or UR-LA patients who underwent upfront surgery unlike current clinical setting because the concept of resectability was uncommon before 2009. Nowadays, resectability status decides treatment plan for patients with PDAC, therefore, more precise criteria of resectability is desirable. For this reason, this study purely focused on efficacy of resection for each resectability status.

In conclusion, the resectability status of PDAC defined by the IAP-criteia was adequate from the viewpoint of OS. Not only anatomical factors but also biological and conditional factors were important for considering resectability. Further studies are

needed to identify the optimal cutoff value of the CA 19-9 level and to decide on the most appropriate parameter to be used for evaluating host-related conditions.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2019.01.012.