Pancreatology 19 (2019) 307–315

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

The clinical impact of portal venous patency ratio on prognosis of patients with pancreatic ductal adenocarcinoma undergoing pancreatectomy with combined resection of portal vein following preoperative chemoradiotherapy

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ARTICLE INFO

Article history:
Received 19 August 2018
Received in revised form
23 January 2019
Accepted 24 January 2019
Available online 25 January 2019

Keywords:
Borderline resectable pancreatic cancer
Aggressive surgical resection
Portal venous patency
Degree of PV contact

ABSTRACT

We analyzed the significance of portal vein (PV) patency ratio (minimum diameter/maximum diameter) during preoperative chemoradiotherapy (CRT) on the outcomes of patients with pancreatic-ductal adenocarcinoma (PDAC).

Methods: The 261 PDAC patients had been prospectively registered to our CRT protocol (Gemcitabine or S1+Gemcitabine) from 2005 to 2015. Among them, the subjects were the 84 PDAC- patients with pre-operative PV contact who underwent pancreatectomy with PV resection.

Results: The 3- and 5-year disease-specific survival (DSS) rates of all 84 patients were 44% and 39%, respectively. Pathological PV invasion (pPV) was seen in 22, and PV patency ratio after CRT (cut-off:0.62) was most relevant factor to predict pPV (sensitivity:54.8%, specificity:91.9%, accuracy:81.5%). Multivariate analysis revealed that PV patency ratio after CRT and improvement of PV patency ratio were selected as independent prognostic indicators. The 3- and 5-year DSS in 39 patients with PV patency ratio after CRT >0.6 were significantly higher than those in 45 patients <0.6: 65% and 60% vs. 24% and 20% ($p = 0.0001$). The patients with PV patency ratio >0.6, were significantly associated with the lower incidence of pPV, higher response for CRT, and better R0 resection rate. Even when severe PV strictures were seen before CRT, DSS of the patients whose PV patency ratio had recovered after CRT was excellent compared with those without improvement.

Conclusions: The PV patency ratio and its improvement are new prognostic indicators for PDAC treated with preoperative CRT. Even when PV was severely constricted, patients could obtain favorable outcomes, if its patency had recovered after CRT.

Introduction

Preoperative treatment including chemoradiotherapy (CRT) and following surgery for pancreatic ductal adenocarcinoma (PDAC) has been widely accepted as the treatment of borderline resectable (BR)-PDAC [1,2] and there have been several articles regarding the radiological evaluation of the accuracy of CT when determining resectability of PDAC after neoadjuvant therapy [3–5]. However, most of these articles mentioned that preoperative treatment for locally advanced PDAC significantly decreases the accuracy of CT scan in determining surgical operability, and tumor reassessment is difficult because of fibrotic inflammatory change effected by the treatment. Katz et al. [4] reported that radiographic downstaging was rarely observed after preoperative treatment, and Response Evaluation Criteria in Solid Tumors (RECIST) was not an effective treatment endpoint for BR-PDAC, and concluded that these patients should undergo pancreatectomy after initial therapy in the absence of metastases. Therefore, establishment of optimal radiographic evaluation for the BR-PDAC treated with preoperative CRT should be urgent.

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https://doi.org/10.1016/j.pan.2019.01.020
1424-3903/

Recently, the National Comprehensive Cancer Network (NCCN) announced the new definition of BR-PDAC, in which solid tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction [6]. On the contrary, PDAC contacting with SMV/PV or ≤180° contact without vein contour irregularity, was categorized as a resectable (R) PDAC. Except the degree of tumor contact, these criteria seem to be abstractive and its interpretation of "safe and complete resection and vein reconstruction" might be diverse in each institution. Therefore, the assessment for an objective finding of PV configuration affected by PDAC is needed.

Okabayashi et al. mentioned that pathological PV invasion (pPV) of PDAC was clearly identified as a poor prognostic indicator and an assessment of early-recurrence risk should be undertaken in such patients to avoid unnecessary and ineffective resection, even if the pancreatic cancer is considered resectable based on preoperative imaging [7]. Teramura et al. reported that accurate diagnosis of PV invasion was difficult based only upon morphological features by preoperative CT [8]. As for the change of the morphological changes of PV configuration and its influence on pathological PV invasion and surgical outcomes, there have been several reports regarding preoperative prediction of pathological PV invasion [8,9], and Klauss M et al. [9] reported the new invasion score including length of tumor contact and degree of circumstantial involvement of PV for determining the resectability of PDAC with using preoperative multi-detector computed tomography (MDCT). Whereas, these reports focused on the patients undergoing up-front surgery, so they might not fit for the patients who underwent preoperative neoadjuvant treatment, because configuration of PV/SMV nearby tumor has been dramatically changed during the treatments, which might represent the effect of preoperative treatment and patient prognosis.

Aim of our study is to elucidate the significance of the morphological change of PV configuration such as PV patency ratio, degree of PV contact and these serial changes during CRT, on the patient prognosis, the incidence of pathological PV invasion, R0 resection rate and response of preoperative Gem-based CRT. To the best of our knowledge, this is the first report focusing on the importance of PV patency ratio and its change, rather than degree of PV contact to predict the prognosis of patients who underwent pancreatectomy with concurrent PV resection for PDAC. The study protocol was approved by the medical ethics committee of Mie University Hospital (No.3188), and the study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

Methods

Patient selection

Between February 2005 and December 2015, the 261 patients with PDAC including R, BR and Unresectable (UR)-PDAC without distant metastasis treated with preoperative CRT aiming to follow curative surgery were prospectively collected in an electronical database. In all patients, the diagnosis of pancreatic cancer was confirmed by the cytology or histology of the biopsy specimens obtained by endoscopic ultrasonography-guided fine-needle aspiration biopsy (EUS-FNA).

Among the 261 patients, 157 patients underwent curative intended pancreatectomy, and concurrent PV resections were performed in 128 patients. In this study, patients with UR-PDAC with superior mesenteric artery (SMA) contact of >180 and/or celiac axis (CA) contact of >180 were not included because the arterial involvements such as SMA and CA were considered to be unrivaled influential prognostic factor rather than PV related factor. Therefore, 84 PDAC patients who underwent combined PV resection and whose preoperative MDCT were conducted in 1 to 3 mm, were eligible in this study.

Treatment plan and assessment of clinical efficacy of CRT

In an attempt to increase the R0 resection rate of locally advanced PDAC, our institution had used preoperative gemcitabine monotherapy (800 mg/m^2 on days 1, 8, 22, and 29 for one cycle) with radiation (45.0–50.4Gy) since February 2005 to October 2011 [10,11]. To obtain further improvement of prognosis, we converted the protocol of chemotherapy from gemcitabine alone to gemcitabine (800 mg/m^2, biweekly) and S-1 (80mg/m^2, 21 days every 4 weeks) combined therapy from November 2011 to now. MDCT were performed for restaging at 4–6 weeks after the completion of CRT and, in the absence of disease progression, patients were taken for surgeries. Radiographic responses were determined by a MDCT before and after CRT prior to surgery. Response was judged according to the RECIST [12].

Surgical resections

In our institution, the concept of medial-to-lateral mesenteric approach has been adopted for pancreatic head cancer regardless of proximal or distal pancreatectomy, so called "antegrade en bloc pancreaticoduodenectomy (PD)" since April. 2005 [13]. With regard to the preoperative surgical planning, we routinely decide proposed operations including whether PV resection should be required or not, according to the preoperative MDCT. For instance, if tumor showed the contact with PV surface without any soft tissue density regardless of the degree of circumferential involvement, PV resection should be conducted without dissection between tumor and PV wall, because blunt dissection results in unexpected bleeding and positive resected margin.

Evaluation of portal venous architecture before and after CRT

PV patency ratio was evaluated using coronal images on the equilibrium phase, and defined as the value calculated by the formula: minimum diameter of PV/SMV nearby the tumor (Y) divided by maximum diameter of PV which is intact and measured at the cranial side of the tumor (X) (Fig. 1A). The degree of PV contact by the tumor was evaluated using cross-section images on the equilibrium phase, and defined as the degree of angle calculated by the formula: circumferential length of PV/SMV contacting the tumor (P) divided by the circumferential length of PV/SMV without tumor contact (Q)+P, which is multiplied by 360° (Fig. 1B).

To evaluate whether PV patency ratio had improved or not before and after CRT, PV patency ratio after CRT was subtracted by that before CRT, and it was regarded as improvement when the value was positive. We calculated these values based on 3 sections and used the average of 3 values.

Association with pre- and post-CRT PV configurations and incidence of pathological PV invasion

In cases with BR or R-PDAC with PV contact, pPV has been recognized as a poor prognostic indicator. In the present study, we evaluated the influence of pre- and post-CRT PV configurations on the incidence of pPV. In addition to the various PV configurations, variables included age, sex, performance status, tumor size, levels of carbohydrate antigen (CA)19–9 and carcinoembryonic antigen (CEA), RECIST criteria and presence or absence of other arterial

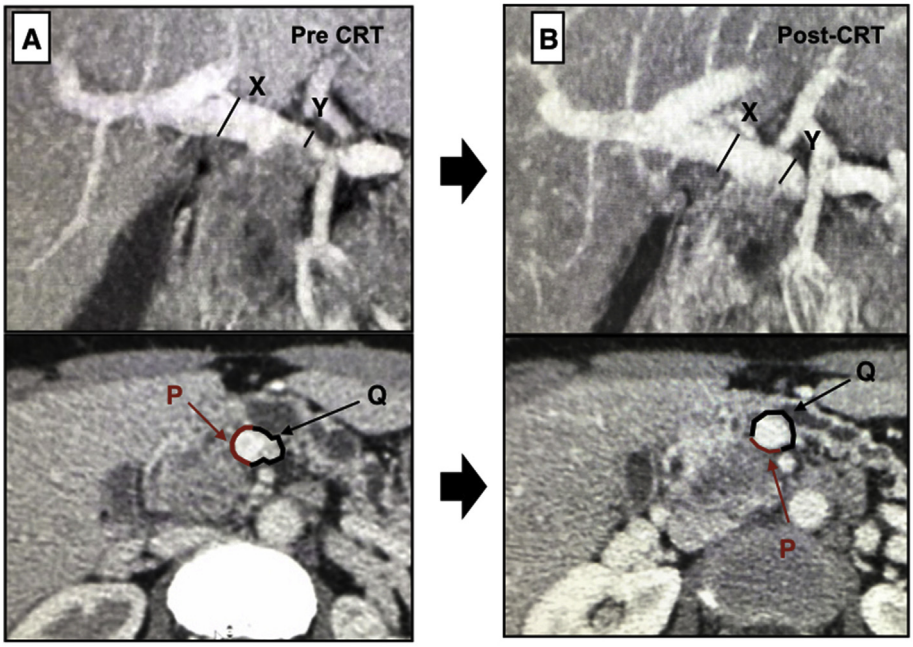

Fig. 1. A. Typical image of PV abutment before the initiation of CRT. PV patency ratio and degree of PV contact were 0.45 and 160, respectively. **B.** After the completion of CRT, the PV patency ratio and degree of PV contact were improved from 0.45 to 0.78 and 160 to78, respectively. PV: Portal vein, CRT: chemoradiotherapy. PV patency ratio = Y/X, Degree of PV contact = P/(P + Q) x360.

contacts such as SMA, CA and common hepatic artery et al. To assess whether these risk factors are valid for clinical usage or not, each optimal cutoff value are determined by receiver operating characteristic (ROC) curves.

Evaluation of the patient prognoses according to the PV configurations

For evaluating the prognostic factors of the patients, we compared the cumulative survivals, according to the various PV configurations and other prognostic factors such as age, sex, performance status, tumor size, levels of CA19-9 and CEA, RECIST criteria and presence or absence of other arterial contacts such as SMA, CA and common hepatic artery. Moreover, we identified the most independent prognostic factors using uni- and multivariate analyses among these factors.

Histological response of PDAC for CRT

The resected specimens were fixed in a formalin solution, sliced into 5-mm sections, and embedded in paraffin blocks. A 3-μm section was obtained from each block and stained with hematoxylin-eosin. The histological response of CRT was evaluated according to the Evans grading system [14]. Based on the results, the patients were divided into 2 groups: high responders, in whom tumor destruction was greater than 50%, and low responders, in whom tumor destruction was 50% or less.

Statistical analysis

All statistical analyses were performed using the statistical software package IBM SPSS Statistics version 24.0 for Macintosh (International Business Machines Co., Armonk, NY, USA). The results of the continuous variables were expressed as median and range, and Student's t-test or Mann–Whitney *U* test, determined the statistical significance. Discrete variables were evaluated by $\chi 2$ analysis or Fisher's exact test, as appropriate. Kaplan–Meier curves of estimated overall survival were generated, and comparisons between groups were performed using a two-sided log-rank test. To clarify the most influential prognostic factors, multivariate analysis by Cox proportional hazard model was performed, examining potential interactions among the entered covariates. In multivariate analyses, only variables whose p-value was less than 0.05 by univariate analysis were included in the multivariate analysis.

Results

Clinical and demographical variables of 84 patients with concurrent PV resection and its disease-specific survival

The patient characteristics of 84 patients were summarized in Table 1. Shortly, even though the levels of tumor markers such as CEA and CA19-9 after the Gem-CRT, were markedly decreased compared to those before initiation of the treatments, averages of PV patency ratio and degree of PV contacts were comparable between pre- and post-CRT settings.

As shown in Fig. 2A, the 3- and 5-year disease-specific survival (DSS) rates of all 84 patients with PV resection were 44% and 39%, respectively. With regard to the significance of pPV in patient survival, the 3- and 5-year DSS of the 22 cases with pPV positive were significantly worse than those of the 62 cases with pPV negative: 25% and 13% vs. 50% and 48% ($p = 0.018$), showing the clinical importance of PV invasion on patient outcomes (Fig. 2B).

Uni- and multivariate analysis for identifying risk factors for pathological PV invasion and optimal cut-off values of risk factors chosen by univariate analysis

Since pPV was regarded as the dismal prognostic factor in patients with PV resection for PDAC, we conducted the uni- and multivariate analysis for identifying its preoperative risk factors. As

Table 1
Background of 84 cases who underwent combined PV resection for PDAC Feb. 2005–Dec. 2015.

Variables	N = 84
Age	67.7 ± 9.5
Sex (male/female)	30/54
Performance status 0/1/2/3/4	50/30/3/1
Tumor size	30.0 ± 10.8
Initial chemotherapy (Gem alone vs Gem + S1)	37/47
CA19-9 level before the initiation of CRT	142.4 (1–17268.9)
CEA level before the initiation of CRT	4.2 (1.0–59.0)
CA19-9 level after CRT (U/ml)	34.9 (1.0–2406.3)
CEA level after CRT	3.8 (1.0–369.0)
RECIST (PD/SD/PR)	5/60/19
PV patency rate before CRT	0.47 ± 0.31
PV patency ratio after CRT	0.46 ± 0.31
Improvement of PV patency ratio (no/yes)	42/42
Degree of PV contact before CRT	224.5 ± 99.3
Degree of PV contact after CRT	229.01 ± 99.73
Improvement of degree of PV contact (no/yes)	52/32
SMA contact (absent/present)	59/25
Celiac axis contact (absent/present)	76/8
CHA contact (absent/present)	65/19
UICC T classification (=<T3/T4)	54/30
UICC N classification (N0/N1)	60/24
Surgical procedures (PD/DP/TP)	80/3/1
JPS 7th resectability criteria (R/BR-PV/BR-A)	31/23/30
Pathological PV invasion (yes/no)	22/62
R0 resection rate (%)	87% (73/84)
Pathological tumor response for CRT (necrosis>50%/<50%)	41/85

Gem: gemcitabine, CA19-9: carbohydrate antigen 19–9, CEA carcinoembryonic antigen, RESIST: Response evaluation criteria in solid tumors, PD: progressive disease, SD: suppressive disease, PR: partial response, PV: portal vein, CRT: chemoradiotherapy, SMA: superior mesenteric artery, CHA: common hepatic artery, UICC: Union for International Cancer Control PD: pancreaticoduodenectomy, DP: distal pancreatectomy, TP: total pancreatectomy, JPS: Japan Pancreas Society, R: resectable, BR: borderline resectable.

shown in Table 2, CA19-9 level after CRT, CEA level after CRT, PV patency rate before CRT, PV patency ratio after CRT, degree of PV contact before CRT and degree of PV contact after CRT were chosen as the significant risk factors for pPV positive. Nevertheless, any significant independent risk factors for pPV positive were not identified by multivariate analysis. The optimal cutoff values of these continuous variables selected as significant factors by univariate analysis for predicting pPV were evaluated by ROC curves (Fig. 3). As a results, PV patency ratio after CRT (cut-off value:0.62) was most relevant and accurate factor to predict pathological PV invasion (sensitivity:54.8%, specificity:91.9% accuracy:81.5%) in terms of its accuracy (Table 3).

Analysis for identifying prognostic factors for survivals of 84 patients who underwent concurrent PV resection

According to the univariate analysis, PV patency ratio before and after CRT, improvement of PV patency ratio, and degree of PV contact before and after CRT, were selected as the significant prognostic factors among the various prognostic factors (Table 4). By multivariate analysis, PV patency ratio after CRT, and improvement of PV patency ratio were selected as the independent prognostic factors (Table 4). Next, when we compared the Kaplan-Meier curves according to the PV patency ratio before >0.6 or not, the prognosis of the 33 patients whose PV patency ratio ≥ 0.6 before CRT, was significantly better than that of 51 patients with <0.6, but this difference of prognosis was not as strong as that according to the PV patency ratio after CRT (Fig. 4A). In fact, the 3 and 5 year DSS of the 39 patients whose PV patency ratio ≥ 0.6 after CRT, were 65% and 60%, which were significantly superior than those of the 45 patients with <0.6 (3-year DSS:24%, and 5-year DSS:20%) (Fig. 4B).

Moreover, as shown in Fig. 5, the better survival in patients with PV patency ratio after CRT >0.6 was associated with significantly lower incidence of pPV positive (7.6% vs. 42.2%), higher tumor response for CRT (Pathological response >50%:64.1% vs. 35.6%), and excellent R0 resection rate (97.4% vs. 77.8%).

Favorable prognosis of patients even if PV patency ratio is slightly improved during CRT

We performed further analysis to show the importance of improvement of PV patency ratio from pre-to post-CRT since the improvement of PV patency ratio was selected as the independent favorable prognostic factor by multivariate analysis. Thus, we compared the DSS between the two groups; improved group: the patients whose PV patency ratio was improved from pre to post-CRT status, and non-improved group, according to the severity of preoperative PV stricture determined by PV patency ratio before

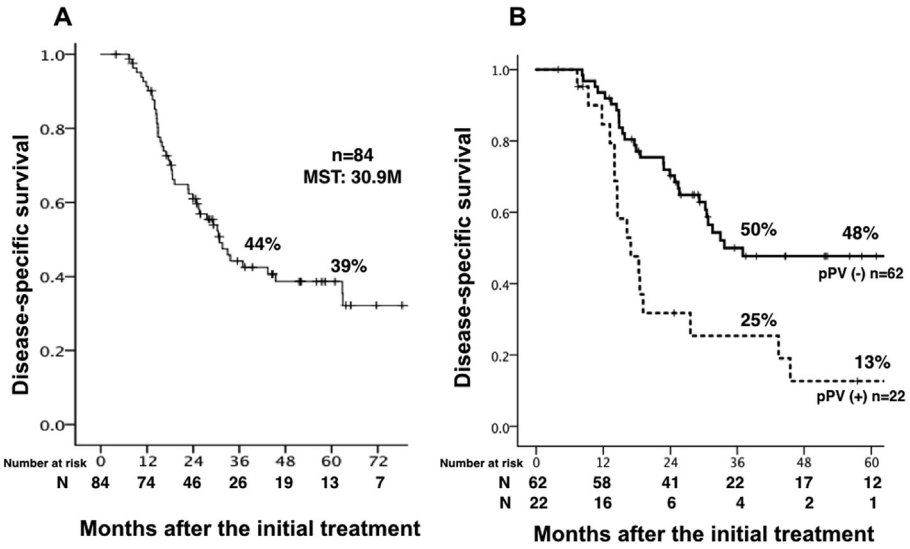

Fig. 2. Disease-specific survival (DSS) of 84 patients (A) and DSS according to the presence or absence of pPV(B) MST: median survival time, pPV: pathological portal venous invasion.

Table 2
Uni and multivariate analysis for identifying risk factors for pathological PV invasion (n = 84).

Perioperative variables	Pathological PV Invasion (Univariate)			Multivariate		
	Positive (n = 22)	Negative (n = 62)	P-value	HR	95% CI	P-value
Age	69.23 ± 9.45	67.11 ± 9.48	0.291			
Sex (male/female)	9/13	21/41	0.609			
Performance status 0/1/2/3/4	12/9/1/0	38/21/2/1	0.853			
Tumor size	29.64 ± 9.61	30.18 ± 11.28	0.976			
CA19-9 level before the initiation of CRT	210.9 (5.4–3666.0)	120.9 (1.0–17268.9)	0.703			
CEA level before the initiation of CRT	4.6 (1.5–13.7)	4.1 (1.0–59.0)	0.439			
CA19–9 level after CRT	**92.0 (9.7–1315.6)**	**25.6 (1.0–2406.3)**	**0.002**	1.00	0.999–1.002	0.444
CEA level after CRT	**4.9 (1.0–369.0)**	**3.5 (1.6–11.0)**	**0.025**	0.99	0.961–1.029	0.752
RECIST (PD/SD/PR)	3/17/2	16/43/3	0.428			
PV patency rate before CRT	**0.35 ± 0.34**	**0.51 ± 0.29**	**0.037**	0.466	0.73–79.00	0.699
PV patency ratio after CRT	**0.31 ± 0.29**	**0.52 ± 0.31**	**0.004**	0.647	0.013–1.585	0.774
Improvement of PV patency ratio (yes/no)	**6/16**	**36/26**	**0.024**	5.195	0.999–1.021	0.065
Degree of PV contact before CRT	**277.52 ± 93.71**	**205.73 ± 94.97**	**0.005**	1.010	0.997–1.020	0.141
Degree of PV contact after CRT	**265.64 ± 102.44**	**216.01 ± 96.25**	**0.029**	0.996	0.987–1.005	0.339
Improvement of degree of PV contact after CRT	6/16	26/36	0.308			
SMA contact (absent/present)	17/5	42/20	0.368			
Celiac axis contact (absent/present)	20/2	56/6	0.829			
CHA contact (absent/present)	16/6	49/13	0.821			
UICC T classification (=<T3/T4)	17/5	37/25	0.258			
UICC N classification (N0/N1)	17/5	43/19	0.481			

CA19-9: carbohydrate antigen 19–9, CEA carcinoembryonic antigen, RECIST: Response evaluation criteria in solid tumors, PD: progressive disease, SD: suppressive disease, PR: partial response, PV: portal vein, CRT: chemoradiotherapy, SMA: superior mesenteric artery, CHA: common hepatic artery, UICC: Union for International Cancer Control.

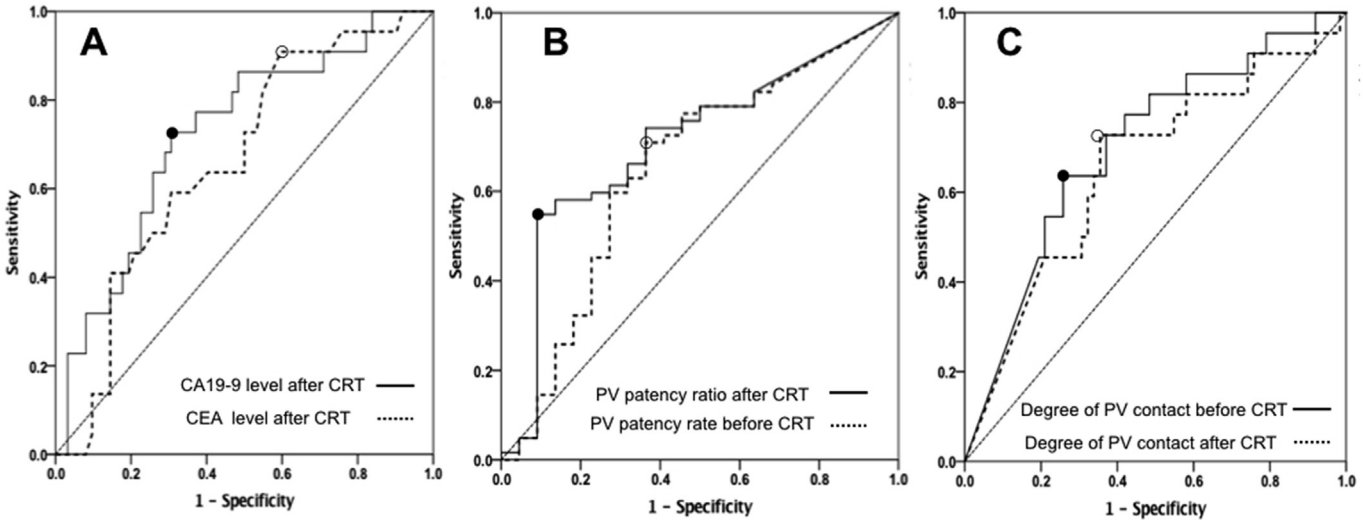

Fig. 3. ROC curves for evaluating the optimal cut-off values of clinical risk factors for pPV. **A**. ROC curves for CEA and CA19-9. **B**. ROC curves for PV patency ratios. **C.** ROC curves for degree of PV contacts.

Table 3
Optimal cut off values for predicting PV invasion.

Variables	Optimal cut off for predicting PV invasion	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC	p-value
CA19-9 level after CRT	45.2	72.7	69.4	70.3	0.72	**0.002**
CEA level after CRT	3.10	90.7	40.3	53.6	0.66	**0.025**
PV patency rate before CRT	0.39	71.0	63.6	65.6	0.65	**0.038**
PV patency ratio after CRT	0.62	54.8	91.9	**81.5**	0.71	**0.004**
Degree of PV contact before CRT	260.0	63.6	74.2	71.4	0.70	**0.005**
Degree of PV contact after CRT	227.0	72.7	64.5	66.7	0.65	**0.031**

CA19-9: carbohydrate antigen 19–9, CEA carcinoembryonic antigen, PV: portal vein, CRT: chemoradiotherapy, AUC: area under the curve.

the initiation of CRT. The 3- and 5-year DSS of patients in the improved group were significantly better than that of non-improved group (61% and 51% vs. 24% and 16%, $p < 0.0001$, Fig. 6A). In the 51 patients whose PV patency ratio before CRT was less than 0.6 which is considered to be moderate stricture, the 3- and 5-year DSS of patients in the improved group, were significantly better than that of non-improved group (50% and 44% vs. 16% and 8%, $p = 0.0021$, Fig. 6B). In the 33 patients whose PV patency ratio before CRT was less than 0.4 which is considered to be severe PV stricture, the 3- and 5-year DSS of patients in the improved

Table 4
Uni and multivariate analysis for identifying preoperative prognostic factors for survivals of patients who underwent concurrent PV resection.

Preoperative variables	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.01	0.975–1.039	0.684			
Sex (male/female)	0.95	0.537–1.796	0.952			
Performance status 2 or 3 vs 0 or 1	2.19	0.667–7.246	0.184			
Tumor size (mm)	0.99	0.966–1.016	0.460			
SMA contact (present vs absent)	0.85	0.567–1.998	0.845			
Celiac axis contact (present vs absent)	1.01	0.363–2.823	0.982			
CHA contact (present vs absent)	1.56	0.821–2.972	0.174			
UICC T classification (T4< vs =<T3)	0.95	0.512–1.714	0.866			
UICC N classification (N1 vs N0)	1.14	0.590–2.204	0.697			
CA19-9 before the initiation of CRT	1.00	0.9998–1.0001	0.814			
CEA before the initiation of CRT	1.00	0.950–1.043	0.846			
CA19-9 after CRT	1.00	0.999–1.001	0.524			
CEA after CRT	1.00	0.996–1.007	0.685			
RECIST (PD/SD vs. PR)	2.21	0.988–4.945	0.053			
PV patency rate before CRT	**0.33**	**0.128–0.859**	**0.023**	0.177	0.023–1.392	0.100
PV patency ratio after CRT	**0.31**	**0.167–0.585**	**<0.001**	**0.166**	**0.035–0.790**	**0.024**
Improvement of PV patency ratio (no/yes)	**2.780**	**1.529–5.051**	**0.001**	**3.059**	**1.243–7.527**	**0.015**
Degree of PV contact before CRT	**1.004**	**1.001–1.007**	**0.019**	0.999	0.995–1.005	0.184
Degree of PV contact after CRT	**1.004**	**1.001–1.007**	**0.008**	0.999	0.995–1.003	0.988
Improvement of degree of PV contact (no/yes)	0.67	0.367–1.003	1.229			

Gem: gemcitabine, CA19-9: carbohydrate antigen 19–9, CEA carcinoembryonic antigen, RECIST: response evaluation criteria in solid tumors, PD: progressive disease, SD: suppressive disease, PR: partial response, PV: portal vein, SMA: superior mesenteric artery, CHA: common hepatic artery, UICC: Union for International Cancer Control, HR: hazard ratio, CI: confidential interval.

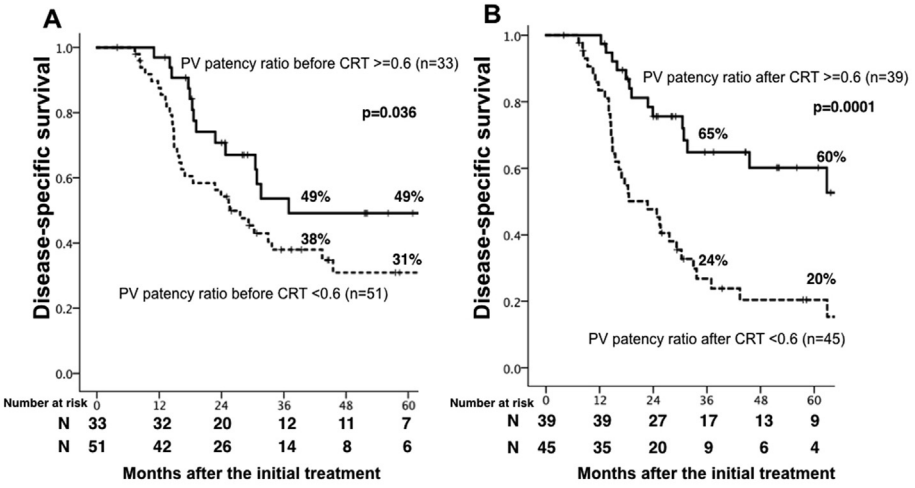

Fig. 4. Comparison of disease-specific survival curves according to the PV patency ratio before (A) and after CRT ≥ 0.6 or <0.6 (B), CRT: chemoradiotherapy.

group were significantly better than that of non-improved group (42% and 28% vs. 17% and 0%, p = 0.004, Fig. 6C). Surprisingly, the 3- and 5-year DSS were 75 and 70% in the 25 patients of improved group whose PV patency ratio is > 0.6 after CRT (Fig. 6D).

Discussion

In this study, we newly revealed the following insights; **1)** Our protocol using Gemcitabine based CRT followed by pancreatectomy with combined PV resection allowed the patient to obtain a favorable prognosis (Median survival time:30.9months). **2)** PV patency ratio after CRT, rather than degree of PV contact, reflected the patient prognosis and the incidence of pathological PV invasion. **3)** The prognosis of the patients whose post-CRT PV patency ratio was more than 0.6 was excellent regardless of preoperative severity of PV stricture. **4)** This prolongation of survival was evidenced by a lower incidence of pathological PV invasion, better tumor response for CRT and better R0 resection rate. **5)** Even if severe PV stricture was seen prior to CRT, favorable surgical outcome could be obtained when PV patency ratio had recovered at the time of reevaluation.

Recently, a role of chemoradiotherapy followed by surgery for PDAC has been commonly accepted as the initial step in the management in order to improve R0 resection rate [4,5,15,16]. This concept has provided an early treatment for micro-metastatic disease, allowing us to identify the patients with unrecognized distant metastasis prior to surgery, controlling local tumor progression and reducing the risk of postoperative recurrence. Since February 2005, our institution has conducted neoadjuvant CRT using gemcitabine, and reported that the 3- and 5-year survival rates of 11 R-PDAC patients with resection were 69% and 69%, and those of 81 BR-PDAC patients with resection were 38% and 29% [17], showing better clinical outcome with compared to the result from multi-institutional survey by the Japanese Society of Pancreatic Surgery; the 3- and 5-year survival rates of 506 resected BR-PDAC

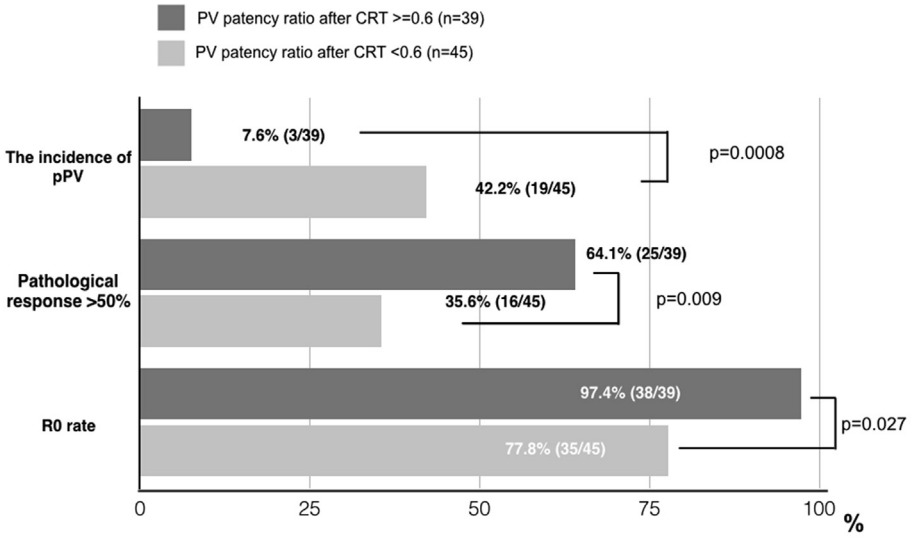

Fig. 5. Significance of postoperative PV patency ratio on pathological PV invasion (pPV), pathological response and R0 resection rate. pPV: pathological portal venous invasion.

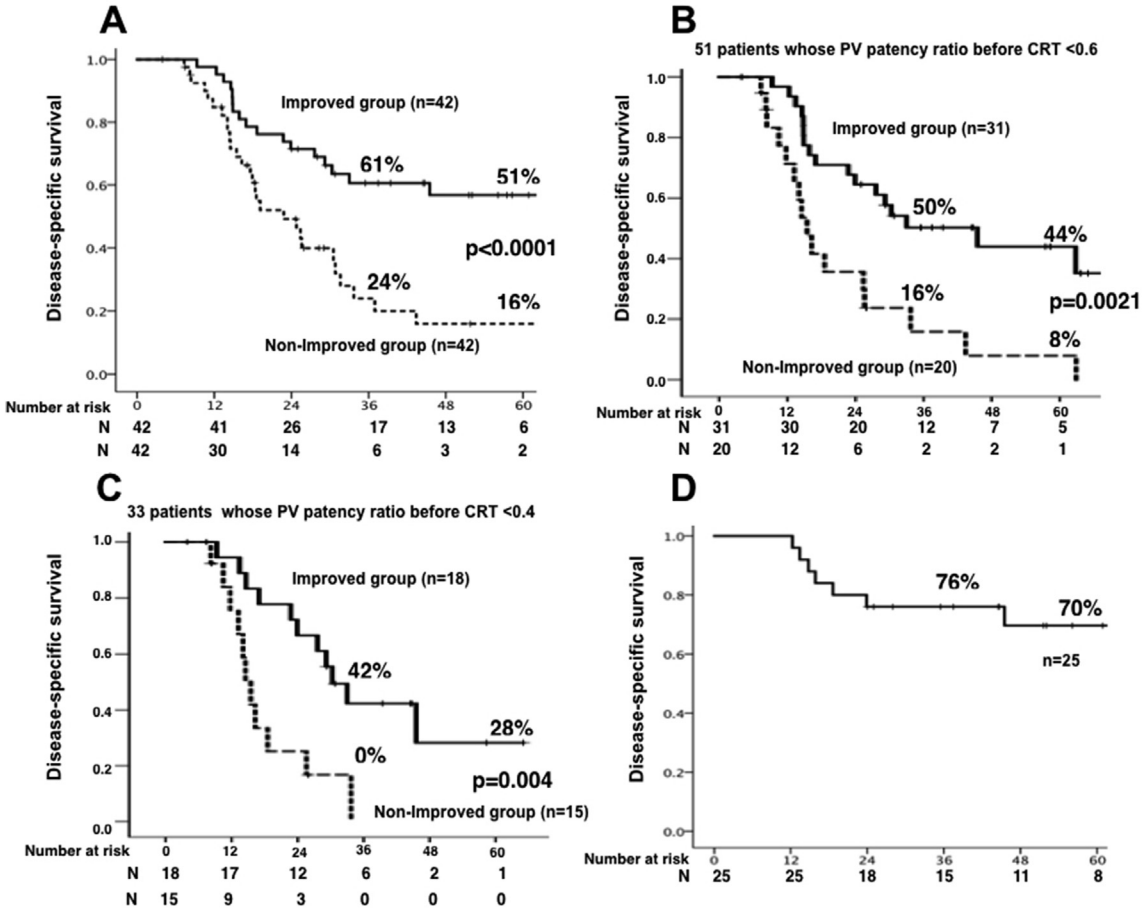

Fig. 6. Disease-specific survival (DSS) with or without improvement of PV patency ratio. A. Comparison of DSS between the patients with and without improvement of PV patency ratio. The prognosis of patients in improved group (n = 42) is significantly better than that of patients in non-improved group (n = 42). B. Comparison of DSS between the patients with or without improvement of PV patency ratio in the 51 patients whose PV patency ratio before CRT was less than 0.6. The prognosis of patients with improved group (n = 31) was significantly better than that of non-improved group (n = 20). C. Comparison of DSS between the patients with and without improvement of PV patency ratio in the 33 patients whose PV patency ratio before CRT was less than 0.4. The prognosis of patients with improved group (n = 18) was significantly better than that of non-improved group (n = 15). D DSS of the 25 patients of improved group whose PV patency ratio is > 0.6 after CRT.

were 22.8% and 12.5% [18]. To obtain further improvement of prognosis, we converted the protocol of chemotherapy from gemcitabine alone to gemcitabine and S-1 combined therapy from November 2011 to now. S-1 is an oral agent that contains tegafur, gimeracil, and oteracil, and the agent appears at least equivalent to or even more active than Fluorouracil (5-FU) when combined with radiotherapy for locally advanced PDAC [10,11,16,19]. Tegafur is converted to the active 5-FU by the CYP2A6 enzyme in the liver, while gimiracil inhibit the activity of dihydropyrimidine-dehydrogenase and, thus, leads to a prolonged exposure to 5-FU. Oteracil potassium inhibits the conversion of 5-FU to the active metabolite, fluorouridine monophosphate in the intestine. This inhibition leads to a lower concentration of FU in the gut, thereby at least reducing gastrointestinal adverse effects. Thus, S-1 has been widely accepted for adjuvant treatment of several gastro-intestinal malignancies such as gastric, colorectal, biliary tract and pancreatic cancer in Japan. Recently, a randomized phase III study of GEM plus S-1, S-1 alone, or GEM alone in patients with locally advanced and metastatic PDAC (GEST Study) showed that monotherapy with S-1 demonstrated noninferiority to GEM in overall survival with good tolerability and that GEM plus S-1 combined therapy significantly improved progression-free survival as compared with GEM alone [20]. In addition to these excellent outcomes with clinical meaningful benefit in randomized Asian studies, S-1, so called Teysuno in Europian countries, had been approved by the European Medicines Agency (EMA) in 2010 and launched in many European countries with the indication for the treatment of advanced gastric adenocarcinoma in combination with cisplatin based on the international FLAGS study [21]. Furthermore, Winther SB et al. prospectively analyzed the efficacy and toxicity of Gemcitabine + S1 therapy in the 64 Caucasian patients with unresectable pancreatic adenocarcinoma and revealed that Gemcitabine + S1 therapy is safe and associated with promising efficacy in a Caucasian population, based on low incidence of adverse events (Grade3 fatigue in 3%, febrile neutropenia in 8%)[22].

As of the prognosis of PDAC patients receiving concurrent PV resection, the PV resection during pancreatectomy is considered to be safe and potentially beneficial for accomplishing R0 resection and better survival, based on the fact that survival outcomes are comparable to standard pancreatectomy without PV resection [23–26], but better than those of patients treated with only palliative surgery [23]. In fact, multi-center study from the 9 high volume centers from United Kingdom showed that median survivals of the patients with BR-PDAC (T3 tumors based on the American Joint Commission on Cancer Staging System 6th edition) was 18 months for PD without PV resection, 18.2 months for PD with PV resection, and 8 months for surgical bypass [24]. The multi-center study from Italy showed 5-year survival rate of the 406 BR-PDAC patients with PV resection was 24.4% with median survival of 24 months and the presence of pathological PV invasion was most important negative prognostic factor [23]. In the present study, we evaluated the prognosis of 84 PDAC patients whose preoperative CT scan showed PV contact and received pancreatectomy with combined PV resection and the 3- and 5-year disease-specific survival rates of these patients were 44% and 39% respectively, proving the evidence that our protocols allow to obtain the favorable survival outcomes for the patients with PDAC having PV contact.

As of the preoperative PV configuration for PDAC, NCCN Clinical Practice Guidelines has focused on it influenced by tumor. For example, in 2009, BR-PDAC related to PV factors was defined as the tumor showing severe unilateral or bilateral PV/SMV or SMV occlusion, if it involved a short segment and was reconstructible. And then, NCCN 2016 announced the new definition focusing on whether PV is $>180^\circ$ or $\leq 180^\circ$ [6]. However, there has been no evidence-based background to show the adequacy of these criteria, and whether degree of PV contact was really associated with the prognosis has yet to be assessed. Thus, we analyzed the objective finding of PV configuration affected by tumor, such as PV patency ratio, degree of PV contact and these serial difference affected by CRT. As for the results of our current study, the degree of PV contact, which has been recognized as the most important factor associated with PV invasion in NCCN, has not been selected as the prognostic factor by the multivariate analysis. Instead, PV patency ratio after CRT, rather than degree of PV contact, was selected as a more valid predictor because of its simple way to measure and its better prediction of surgical outcome, efficacy of CRT and patient prognosis. Especially when this value was more than 0.6 after CRT, the patients significantly achieved a long-term survival regardless of the preoperative severity of PV constriction; the 3 and 5-year DSS were 65% and 60% respectively in these cases. Furthermore, this cut-off value of 0.6 was also regarded as the optimal cut-off value whether pPV is present or not by postoperative pathological examination. Pathological PV invasion is already reported to be a dismal prognostic factor by previous reports [7,8]. And there has been several reports regarding the preoperative prediction for positive PV invasion [8,9]. Whereas, these reports focused on the patients undergoing up-front surgery, to the best of our knowledge, this is the first report focusing on prediction of PV invasion after CRT for PDAC.

Among the peripancreatic vessels, the wall of PV could be much more flexible than that of other arteries, and because of this reason, it is considered that PV patency is easily lost when adjacent tumor invades it, and direct regression of its patency might occur as soon as CRT becomes effective and tumor shrinks. On the other hands, the degree of PV contact before or after neoadjuvant CRT does not provide useful information for the prediction of prognosis. Since preoperative CRT results in necrotic, fibrous, or inflammatory response in PDAC, standard evaluation of CT is of limited value in differentiating residual tumor from inflammatory or fibrotic tissue replacement secondary to preoperative treatment. Degree of PV contact might not be affected on CT scan if the PV is still surrounded by this kind of replaced tissue even when neoadjuvant therapy is effective. This probably explains why PV patency ratio strongly influences the surgical outcome, the oncologic response and patient's prognosis, rather than degree of PV contact. Moreover, our study also revealed that the patients whose PV patency ratio was improved at the timing of reevaluation, had favorable prognosis with compared to the patients without improvement. Moreover, we conducted further analysis using the selected patients whose PV had severe stricture before CRT, revealing the new fact that even if severe PV stricture was seen before the CRT, favorable prognosis could be obtained when PV patency ratio was recovered after CRT. According to the change of peripancreatic vascular configuration, previous paper demonstrated that partial regression of the extent of tumor contact with the SMV/portal vein was associated with R0 resection and partial regression of tumor contact with any peripancreatic vascular axis (SMV/portal vein, SMA, hepatic artery, or celiac trunk) was associated with high R0 resection rate [8], but it did not mention its association with patient prognosis. To the best of our knowledge, this is the first report elucidating the significant association between change of PV configuration and prognoses of the patients with PDAC showing PV contact, treated with preoperative CRT.

In conclusion, our data consolidated the efficacy of Gem based CRT prior to pancreatectomy with combined PV resection in PDAC. PV patency ratio and its improvement during CRT, rather than degree of PV contact, were feasible marker for predicting portal venous invasion, R0 resection, tumor oncologic response and prognosis. PV patency ratio helps patient's selection regarding who obtain the surgical benefit after CRT.

Data availability statement

The all data generated or analyzed during this study are included within the article.

References

[1] Xu CP, Xue XJ, Liang N, Xu DG, Liu FJ, Yu XS, et al. Effect of chemoradiotherapy and neoadjuvant chemoradiotherapy in resectable pancreatic cancer: a systematic review and meta-analysis. J Canc Res Clin Oncol 2014;140:549–59.

[2] Varadhachary GR, Tamm EP, Abbruzzese JL, Xiong HQ, Crane CH, Wang H, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. Ann Surg Oncol 2006;13:1035–46.

[3] Cassinotto C, Cortade J, Belleannée G, Lapuyade B, Terrebonne E, Vendrely V, et al. An evaluation of the accuracy of CT when determining resectability of pancreatic head adenocarcinoma after neoadjuvant treatment. Eur J Radiol 2013;82:589–93.

[4] Katz MH, Fleming JB, Bhosale P, Varadhachary G, Lee JE, Wolff R, et al. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. Cancer 2012;118:5749–56.

[5] Cassinotto C, Mouries A, Lafourcade JP, Terrebonne E, Belleannée G, Blanc JF, et al. Locally advanced pancreatic adenocarcinoma: reassessment of response with CT after neoadjuvant chemotherapy and radiation therapy. Radiology 2014;273:108–16.

[6] Network NCC. NCCN clinical practice guidelines in oncology. Pancreatic adenocarcinoma, version 2. 2016 edn. 2016.

[7] Okabayashi T, Shima Y, Iwata J, Morita S, Sumiyoshi T, Kozuki A, et al. Reconsideration about the aggressive surgery for resectable pancreatic cancer: a focus on real pathological portosplenomesenteric venous invasion. Langenbeck's Arch Surg 2015;400:487–94.

[8] Teramura K, Noji T, Nakamura T, Asano T, Tanaka K, Nakanishi Y, et al. Preoperative diagnosis of portal vein invasion in pancreatic head cancer: appropriate indications for concomitant portal vein resection. J Hepatobiliary Pancreat Sci 2016;23:643–9.

[9] Klauss M, Mohr A, von Tengg-Kobligk H, Friess H, Singer R, Seidensticker P, et al. A new invasion score for determining the resectability of pancreatic carcinomas with contrast-enhanced multidetector computed tomography. Pancreatology 2008;8:204–10.

[10] Kobayashi M, Mizuno S, Murata Y, Kishiwada M, Usui M, Sakurai H, et al. Gemcitabine-based chemoradiotherapy followed by surgery for borderline resectable and locally unresectable pancreatic ductal adenocarcinoma: significance of the CA19-9 reduction rate and intratumoral human equilibrative nucleoside transporter 1 expression. Pancreas 2014;43:350–60.

[11] Murata Y, Mizuno S, Kishiwada M, Hamada T, Usui M, Sakurai H, et al. Impact of histological response after neoadjuvant chemoradiotherapy on recurrence-free survival in UICC-T3 pancreatic adenocarcinoma but not in UICC-T4. Pancreas 2012;41:130–6.

[12] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.

[13] Mizuno S, Isaji S, Tanemura A, Kishiwada M, Murata Y, Azumi Y, et al. Anterior approach to the superior mesenteric artery by using nerve plexus hanging maneuver for borderline resectable pancreatic head carcinoma. J Gastrointest Surg 2014;18:1209–15.

[14] Evans DB, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. Arch Surg 1992;127:1335–9.

[15] McClaine RJ, Lowy AM, Sussman JJ, Schmulewitz N, Grisell DL, Ahmad SA. Neoadjuvant therapy may lead to successful surgical resection and improved survival in patients with borderline resectable pancreatic cancer. HPB 2010;12:73–9.

[16] Ohigashi H, Ishikawa O, Eguchi H, Takahashi H, Gotoh K, Yamada T, et al. Feasibility and efficacy of combination therapy with preoperative full-dose gemcitabine, concurrent three-dimensional conformal radiation, surgery, and postoperative liver perfusion chemotherapy for T3-pancreatic cancer. Ann Surg 2009;250:88–95.

[17] Isaji S, Kishiwada M, Kato H. Surgery for borderline resectable pancreatic cancer: the Japanese experience. In: Multimodality management of borderline resectable pancreatic cancer. Springer; 2016. p. 265–87.

[18] Kato H, Usui M, Isaji S, Nagakawa T, Wada K, Unno M, et al. Clinical features and treatment outcome of borderline resectable pancreatic head/body cancer: a multi-institutional survey by the Japanese Society of Pancreatic Surgery. J Hepatobiliary Pancreat Sci 2013;20:601–10.

[19] Ikeda M, Ioka T, Ito Y, Yonemoto N, Yonemoto N, Nagase M, Yamao K, et al. A multicenter phase II trial of S-1 with concurrent radiation therapy for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2013;85:163–9.

[20] Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Boku N, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol 2013;31:1640–8.

[21] Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol 2010;28:1547–53.

[22] Winther SB, Bjerregaard JK, Schonnemann KR, Ejlsmark MW, Krogh M, Jensen HA, et al. S-1 (Teysuno) and gemcitabine in Caucasian patients with unresectable pancreatic adenocarcinoma. Cancer Chemother Pharmacol 2018;81:573–8.

[23] Elberm H, Ravikumar R, Sabin C, Abu Hilal M, Al-Hilli A, Aroori S, et al. Outcome after pancreaticoduodenectomy for T3 adenocarcinoma: a multivariable analysis from the UK vascular resection for pancreatic cancer study group. Eur J Surg Oncol 2015;41:1500–7.

[24] Dumitrascu T, Dima S, Brasoveanu V, Stroescu C, Herlea V, Moldovan S, et al. Impact of a portal/superior mesenteric vein resection during pancreaticoduodenectomy for pancreatic head adenocarcinoma. Minerva Chir 2014;69:301–13.

[25] Yu XZ, Li J, Fu DL, Di Y, Yang F, Hao SJ, et al. Benefit from synchronous portal-superior mesenteric vein resection during pancreaticoduodenectomy for cancer: a meta-analysis. Eur J Surg Oncol 2014;40:371–8.

[26] Ramacciato G, Nigri G, Petrucciani N, Pinna AD, Ravaioli M, Jovine E, et al. Pancreatectomy with mesenteric and portal vein resection for borderline resectable pancreatic cancer: multicenter study of 406 patients. Ann Surg Oncol 2016;23:2028–37.