

BMJ Open Neoadjuvant S-1 with concurrent radiotherapy followed by surgery for borderline resectable pancreatic cancer: study protocol for an open-label, multicentre, prospective phase II trial (JASPAC05)

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ABSTRACT

Introduction Borderline resectable pancreatic cancer (BRPC) can involve the portal vein, superior mesenteric vein, superior mesenteric artery, coeliac axis or hepatic artery, and has a high probability of positive surgical margins and poor prognosis after resection. Neoadjuvant chemoradiation is expected to provide substantial local control and prolong survival in patients with BRPC.

Methods and analysis This open-label, multicentre, prospective phase II trial will assess S-1 with concurrent radiotherapy as preoperative treatment for BRPC. Participants will receive S-1 (40 mg/m² twice daily) and concurrent radiotherapy (50.4 Gy in 28 fractions), with restaging and surgery after 3–8 weeks. Recruitment will be for a 36-month period with a minimum 24-month follow-up. The primary endpoint is the R0 resection rate for BRPC confirmed with central review. The secondary endpoints are overall survival, disease-free survival, response rate to neoadjuvant chemoradiation, pathological response rate, 2-year survival rate, surgical morbidity rate and acute and late toxicity rates. Objectives include quantifying the number of participants per year to evaluate whether randomised trials can be performed for this rare tumour.

Ethics and dissemination This trial has been approved by the National Cancer Center Institutional Review Board. Written informed consent will be obtained from all participants. Serious adverse events will be reported to the safety desk of the trial, the Data and Safety Monitoring Board and trial sites. Trial results will be submitted for peer-reviewed publication.

Trial registration number Pre-results, UMIN000009172.

INTRODUCTION

Borderline resectable pancreatic cancer (BRPC), which has emerged as a new category, is a pancreatic cancer that involves major vessels such as the portal vein, superior mesenteric vein, superior mesenteric artery (SMA), coeliac axis or hepatic artery.^{1 2 3 4} BRPC is

Strengths and limitations of this study

- This is one of the first multicentre phase II trials to evaluate neoadjuvant treatment for borderline resectable pancreatic cancer (BRPC).
- The study design is appropriate for neoadjuvant treatment in BRPC, including refined BRPC criteria, central review to determine BRPC eligibility, determination of standard procedures for pathological examination and determination of surgical indications after neoadjuvant treatment.
- This study will quantify the number of participants per year to assess the feasibility of future randomised trials in patients with BRPC.
- Standard treatment for BRPC has not been established and fundamental data that can be used for statistical analysis are limited.

frequently associated with positive surgical margins and poor prognosis after resection. Postsurgical adjuvant therapy, which is effective in patients with resectable PC, may not be effective in treating BRPC⁵ because frequent positive surgical margins are expected with upfront resection. Neoadjuvant chemoradiation (CRT) is therefore expected to provide substantial local control and to prolong the survival of patients with BRPC, which is associated with a high risk of early local and systemic failure.^{6 7} However, standard therapy for patients with BRPC has not been established.

S-1 is an oral fluorinated pyrimidine that contains tegafur (a prodrug of 5-FU (fluorouracil)), 5-chloro-2,4-dihydropyrimidine and potassium oxonate, which are effective for gastric and other cancers.^{8 9 10} S-1 is effective in treating pancreatic cancer^{11 12} and is not inferior to gemcitabine for overall survival in

patients with metastatic or unresectable locally advanced pancreatic cancer (LAPC). S-1 therapy with concurrent radiation therapy (RT) achieves favourable results, with an overall tumour response rate of 27%, and is associated with mild toxicity in patients with unresectable LAPC.¹³ The median survival time and 2-year survival rate for patients with unresectable LAPC treated with combined S-1 and RT are 16.2 months and 26%, respectively. Considering the treatment profile of excellent antitumour effect with mild toxicity, S-1/RT seems suitable for neoadjuvant therapy of BRPC, followed by major intensive surgery.

However, the number of patients with BRPC may be insufficient for a large trial.⁵ Moreover, obstacles such as the need for central diagnosis of BRPC and lack of consensus on standard criteria of BRPC and surgical indications after neoadjuvant therapy make conducting a multicentre prospective study of BRPC challenging.¹⁴ Therefore, it is important to determine whether a clinical study of BRPC alone is feasible. To evaluate the efficacy and safety of neoadjuvant S-1 with concurrent RT for BRPC and also to verify the feasibility of a clinical study for BRPC, neoadjuvant S-1 with concurrent RT will be explored in a single-arm, phase II study that includes only patients with BRPC.

METHODS AND ANALYSIS

Study objectives

The primary objective of the study is to assess S-1 with concurrent RT as neoadjuvant therapy to determine whether it increases the R0 resection rate for BRPC diagnosed according to diagnostic radiology central review. The following are the secondary study objectives:

- ▶ to assess prognosis of patients with BRPC undergoing CRT
- ▶ to assess the safety of preoperative CRT and subsequent pancreatic resection
- ▶ to evaluate the potential correlation between radiological (multidetector CT (MDCT)) and histopathological assessment of tumour response to the neoadjuvant CRT
- ▶ to test the appropriateness of diagnosis of BRPC at local institutions by comparison with diagnosis by central review
- ▶ to quantify the number of participants per year to evaluate whether randomised trials can be performed for this rare tumour.

R0 resection in this trial is defined as tumour resection with pathologically negative margins without distant metastasis, para-aortic lymph node metastasis or positive peritoneal washing cytology.

Study outline

This is a multi-institutional, single-arm, open-label, phase II trial under the auspices of the Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC). Patients with BRPC will receive S-1 (40 mg/m² twice daily) and concurrent RT (50.4 Gy in 28 fractions) before surgery.

Box Major inclusion and exclusion criteria of the trial

Inclusion criteria

- ▶ Cytological or histological proof of pancreatic ductal carcinoma or adenosquamous carcinoma prior to study entry
- ▶ Disease assessment with multidetector CT scan within 2 weeks of study entry
- ▶ Diagnosis of borderline resectable pancreatic cancer
- ▶ No evidence of metastatic disease as determined with chest CT scan, abdominal CT scan and laparoscopy
- ▶ Para-aortic lymph node metastasis is considered metastatic
- ▶ Age ≥20 years, ≤75 years
- ▶ Eastern Cooperative Oncology Group performance status 0 or 1
- ▶ No prior chemotherapy or radiotherapy for pancreatic cancer
- ▶ All pancreatic lesions and lymph node metastases could fit within a 10×10 cm radiation field
- ▶ Adequate oral intake
- ▶ Appropriate biliary drainage for obstructive jaundice
- ▶ Adequate organ system function
- ▶ Written informed consent

Exclusion criteria

- ▶ Tumour invasion of the alimentary tract determined with abdominal CT scan or endoscopic examination
- ▶ Prior chemotherapy using fluoropyrimidine
- ▶ Prior radiation therapy to the abdomen
- ▶ Watery diarrhoea
- ▶ Concurrent phenytoin, warfarin potassium or flucytosine treatment
- ▶ Presence of contrast medium allergy
- ▶ Pulmonary fibrosis or interstitial pneumonia
- ▶ Pleural effusion or ascites
- ▶ Active infection
- ▶ Uncontrolled diabetes mellitus (FBS (fasting blood sugar) ≥200 mg/dL or HbA1c ≥10.0%)
- ▶ Active concomitant malignancy
- ▶ Active gastroduodenal ulcer
- ▶ Severe complications such as cardiac or renal disease
- ▶ Regular administration of systemic corticosteroid
- ▶ Psychiatric disorder
- ▶ History of drug hypersensitivity
- ▶ Pregnant and lactating women and women of childbearing age not using effective contraception

Site selection

The phase II trial will take place in hepatobiliary-pancreatic units that have a high volume of pancreatic cancer cases and that belong to the JASPAC group. Sites will be eligible to participate based on current case volume, surgical quality, adequate experience with clinical oncology and RT, and ability to perform MDCT and histopathology to the protocol's standards.

Patient selection

The study population will be identified by the pancreatic cancer multidisciplinary team. Diagnosis of BRPC will be made with MDCT in accordance with the protocol. The inclusion and exclusion criteria are listed in the [Box](#).

If eligible, participants will receive study information from the surgeon and oncologist, reinforced with a patient information sheet. Participants will be offered a minimum of 24 hours to consider enrolment before

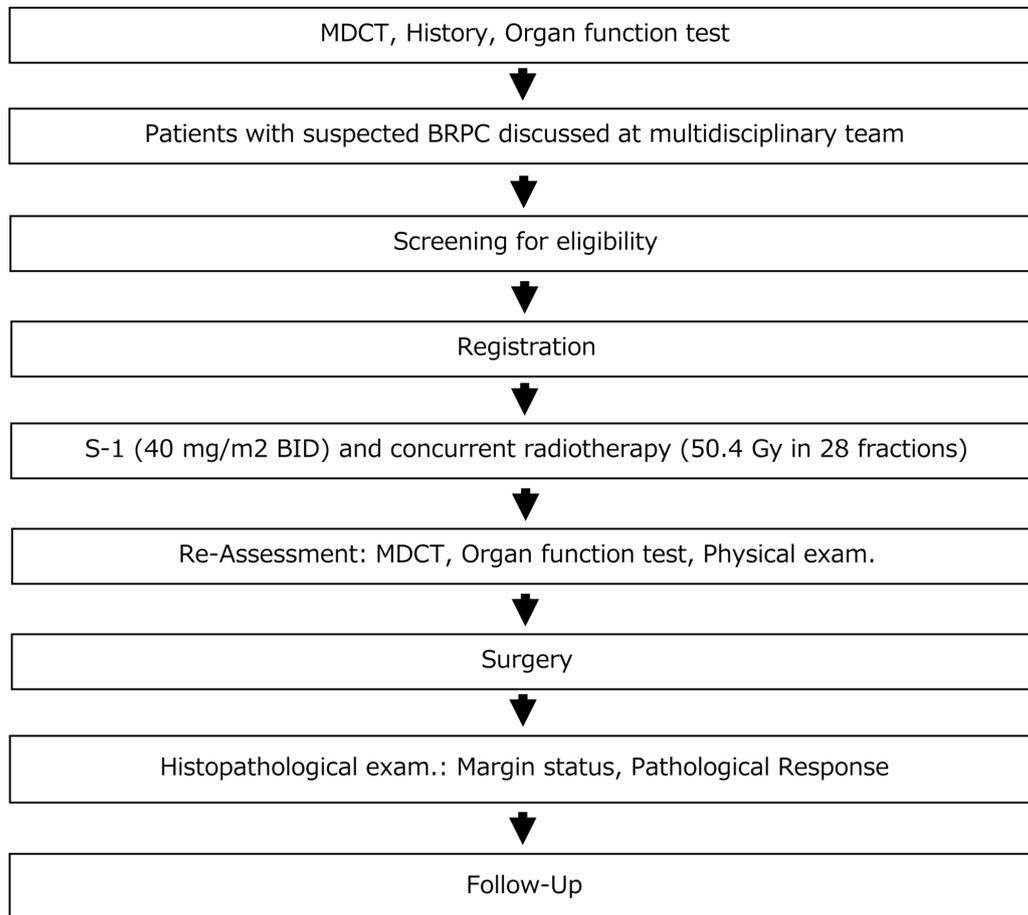


Figure 1 Study flow chart. BRPC, borderline resectable pancreatic cancer; MDCT, multidetector CT.

providing written informed consent. Informed consent will be obtained before trial-specific procedures are performed. A study flow chart is included in [figure 1](#).

Definition of BRPC

BRPC is defined in this study according to the definition of the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines 2009,³ with several modifications made according to group consensus to clarify eligibility.

1. reconstructible bilateral impingement of the superior mesenteric vein or portal vein, except occlusion by tumour thrombus
2. tumour contact with the SMA of $\leq 180^\circ$; tumour contact with the second or further jejunal SMA branches is considered unresectable
3. tumour contact with the common hepatic artery (CHA) of $\leq 180^\circ$ without extension to the coeliac axis or bifurcation of the hepatic artery
4. tumour contact with the coeliac axis of $\leq 180^\circ$.

Distal pancreatectomy with en bloc coeliac axis resection (DP-CAR) is commonly performed for advanced cancer of the pancreatic body or tail in contact with the coeliac axis or CHA in high-volume pancreas centres in Japan. However, DP-CAR that accompanies resection of the relevant vessel makes unclear the significance of the R0 resection rate in this clinical trial. Thus, tumours that

contact the CHA or coeliac axis by $\leq 180^\circ$, thereby meeting the above criteria (3) or (4), but that can be resected with DP-CAR, are considered ineligible.

Tumours in contact with the aorta, those with extensive infiltration of the retroperitoneum, those with $>180^\circ$ of contact with the SMA and those with $>180^\circ$ of contact with the CHA or coeliac axis are considered unresectable.

Registration

After confirmation of eligibility, registration will be sent via fax to the J-CRSU (Japan Clinical Research Support Unit) Data Center (J-CRSU, Tokyo, Japan).

S-1 and concurrent RT

S-1 will be administered orally at 40 mg/m^2 twice daily on the day of irradiation (Monday through Friday) during RT. RT is delivered with >6 -megavolt photons, using a multiple field technique; 50.4 Gy will be delivered in 28 fractions over a 5.5-week period. Primary tumour and metastatic lymph nodes $>1 \text{ cm}$ identified with CT will be contoured as gross tumour volumes.

Schedule modifications for S-1 and RT are considered separately to avoid prolonged interruption of RT as much as possible. S-1 administration will be suspended in case of neutrophils $<1000/\text{mm}^3$, platelets $<70\ 000/\text{mm}^3$, serum bilirubin level $\geq 3.1 \text{ mg/dL}$, AST (aspartate transaminase) /ALT (alanine transaminase) $\geq 200 \text{ U/L}$,

serum creatinine ≥ 1.5 mg/dL, diarrhoea greater than or equal to Common Terminology Criteria for Adverse Events (CTCAE) grade 2, stomatitis greater than or equal to CTCAE grade 2, febrile neutropaenia greater than or equal to CTCAE grade 3 or other non-haematological toxicity greater than or equal to CTCAE grade 3. S-1 administration will be discontinued until all of the following conditions are met: neutrophils $\geq 2.5 \times 10^9/L$, platelets $\geq 75 \times 10^9/L$, serum bilirubin level ≤ 3.0 mg/dL, AST/ALT ≤ 150 U/L, serum creatinine ≤ 1.2 mg/dL, diarrhoea less than or equal to CTCAE grade 1, stomatitis less than or equal to CTCAE grade 1, no febrile neutropaenia and other non-haematological toxicity less than or equal to CTCAE grade 2. If withdrawal of S-1 administration exceeds 14 days because of an adverse effect correlated with chemoradiation, the S-1 dose will be reduced to level 1 at restart.

RT will be interrupted in case of neutrophils $< 500/mm^3$, platelets $< 25\,000/mm^3$, serum bilirubin level ≥ 3.1 mg/dL, AST ≥ 200 U/L, serum creatinine ≥ 1.5 mg/dL, diarrhoea greater than or equal to CTCAE grade 3, febrile neutropaenia greater than or equal to CTCAE grade 3 or other non-haematological toxicity greater than or equal to CTCAE grade 3. RT must be delayed until all of the following conditions are met: neutrophils $\geq 500/mm^3$, platelets $\geq 25\,000/mm^3$, serum bilirubin level ≤ 3.0 mg/dL, AST/ALT ≤ 150 U/L, serum creatinine ≤ 1.2 mg/dL, diarrhoea less than or equal to CTCAE grade 2, no febrile neutropaenia and other non-haematological toxicity less than or equal to CTCAE grade 2.

If the total treatment period will be more than 60 days, the treatment will be ended at 60 days, with surgery performed subsequently.

When R0 resection is considered difficult because of distant metastasis, local progression, or deterioration of blood biochemistry values or physical status, surgical resection will be abandoned and protocol treatment will be terminated.

Surgery

Patients fulfilling surgery-entry criteria, which consist of no distant metastasis or retroperitoneal invasion that precludes R0 or R1 resection, good performance status (0/1), no massive ascites, no massive pleural effusion, no serious infection, no serious adverse CRT events and adequate organ system function, will undergo surgery 15–56 days after the end of neoadjuvant CRT. The interval will be determined with consideration of recovery from CRT.

The below-mentioned procedures are chosen to minimise the potential risk of surgical complications and also to secure the possibility of R0 resection. Surgical resection of the pancreas should be performed via laparotomy. Laparoscopic or laparoscopically assisted pancreatic resection is not allowed. After laparotomy, peritoneal washing cytology and sampling of para-aortic lymph nodes will be conducted to check residual tumour status. When tumour exists in the head of the pancreas,

pancreaticoduodenectomy (PD), pylorus-preserving PD or subtotal stomach-preserving PD will be performed. For tumours of the body or tail of the pancreas, distal pancreatectomy will be performed. For tumours extending throughout the entire pancreas, total pancreatectomy will be performed. Dissection of regional lymph nodes will be performed; however, neither extended lymphadenectomy including para-aortic lymph nodes nor complete dissection of the SMA nerve plexus is recommended. Portal vein resection is allowed when needed for R0 resection. Reconstruction of the portal vein using an autograft is also allowed. Resection of the SMA is not allowed; however, short-segment CHA resection and both CHA and coeliac axis resection by DP-CAR are allowed at the surgeon's discretion when the concomitant arterial resection is inevitable for R0 resection and can be performed safely. Reconstruction after PD, pylorus-preserving PD, subtotal stomach-preserving PD or total pancreatectomy depends on physician's choice. Protocol treatment will be discontinued if any of the following events occurs:

- ▶ distant metastasis or retroperitoneal invasion that precludes R0 or R1 resection
- ▶ para-aortic lymph node metastasis confirmed by pathological diagnosis during surgery
- ▶ positive peritoneal washing cytology.

Study completion/postoperative treatment

Patients will be considered to have been treated according to protocol if they have received both preoperative CRT and subsequent R0 or R1 pancreas resection in the absence of disease recurrence or severe adverse effect leading to discontinuation of the protocol treatment. Additional treatments, including adjuvant treatment after completion or termination of protocol treatment, are not defined in the protocol and depend on the oncologist's discretion or the practice in use at the institution.

Evaluation, laboratory tests and follow-up

A signed, written informed consent form will be obtained from patients prior to any study-specific procedures or assessments. Procedures conducted as part of routine clinical management and obtained prior to signing of informed consent may be used for screening or baseline purposes provided these procedures are conducted as specified in the protocol. The study assessment schedules are summarised in [table 1](#).

Multidetector CT

For screening, all patients require an MDCT with a pancreas CT protocol including triphasic (ie, pancreatic parenchymal phase, portal venous phase and equilibrium phase) cross-sectional imaging with thin slices. CT scans will be performed with 16-slice or 64-slice MDCT. Non-ionic iodinated contrast agent with high concentration (> 300 mgI/mL) will be injected intravenously at a volume ranging from 100 to 150 mL and a rate of 2.5–3.5/s. The triphasic scans will be initiated 35–45 s (pancreatic parenchymal phase), 70–90 s (portal venous

Table 1 Time and events table

Required measurements	Screening (before registration)	During treatment	7days before operation	8 weeks after operation
Informed consent	◆			
Subjective/objective symptom, toxicity/compliance	◆*		◆	
Physical assessment (including weight, height)	◆*			
ECOG PS	◆*		◆	
Blood count	◆*		◆	
Bilirubin, AST, ALT, alkaline phosphatase, albumin, amylase, creatinine, sodium, potassium	◆*		◆	
Blood urea nitrogen, C reactive protein, fasting blood glucose	◆*		◆	
History	◆*			
Creatinine clearance	◆*			
12-lead ECG	◆†		◆	
CEA, CA19-9	◆†		◆§	◆
HBs-Ag, HCV-Ab	◆‡			
Chest X-ray	◆†			
Upper gastrointestinal endoscopy	◆†			
MDCT with a pancreas CT protocol involving triphasic (ie, arterial, late arterial, and venous phases) cross-sectional imaging with thin slices	◆‡		◆§	
Chest-abdominopelvic CT+contrast				◆
FDG-PET	◆†		◆§	

◆ A single measurement is required on the corresponding day.

<<<NO ENTITY>>> Weekly measurements are required in the corresponding period.

*A measurement should be taken ≤ 7 days before registration.

†A measurement should be taken ≤ 14 days before registration.

‡A measurement should be taken ≤ 28 days before registration.

§A measurement should be taken ≤ 28 days after end of chemoradiation.

ECOG: Eastern Cooperative Oncology Group; PS: performance status; AST: aspartate transaminase; ALT: alanine transaminase;

CEA: carcinoembryonic antigen; HBs-Ag: hepatitis B surface antigen; HCV-Ab: hepatitis C virus antibody; FDG-PET: Fluorodeoxyglucose-positron emission tomography; MDCT: multidetector CT.

phase) and 180 s (equilibrium phase) after injection. Triphasic scans corresponding to the aforementioned scans using bolus tracking will also be allowed. Slice thickness is 5 mm, gantry rotation speed is 0.5–1.0 s, beam pitch is 1 and kVp is 120. Axial images at 1 mm to 2 mm interval reconstruction and multiplanar reconstructions on the coronal and sagittal planes are required for vascular evaluation. Chest, lower abdominal and pelvic images in the portal venous or equilibrium phases are also needed for evaluation of metastasis.

Study design and statistical analysis

Study design and sample size

This is an open-label, multicentre, single-arm, phase II trial evaluating the efficacy and safety of neoadjuvant S-1 with concurrent RT for BRPC. The primary endpoint of this study is the R0 resection rate of BRPC confirmed through diagnostic radiology central review. The R0 resection rate after neoadjuvant therapy of BRPC alone has not been fully elucidated; the reported rates after neoadjuvant therapy for both resectable and BRPC

combined are 40%–60%.¹⁵⁻¹⁷ Thus, we presume that the R0 resection rate for BRPC after neoadjuvant therapy will be 10%–30%. Our null hypothesis is that the R0 resection rate for BRPC confirmed through diagnostic radiology central review is <10%. In the present trial, the planned sample size is 40 patients, which was calculated according to an expected R0 resection rate of 30%, threshold of 10%, alpha error of 0.05 and beta error of 0.05. Diagnostic radiology central review is planned after patient registration to confirm BRPC. We anticipate that 80% of registered patients will be diagnosed with BRPC through central review and that the actual sample size will be 50 patients.

Analysis plan

The primary endpoint is the R0 resection rate for BRPC diagnosed with diagnostic radiology central review. The main analyses, including that of the primary endpoint and those of the secondary endpoints with respect to tumour response and safety, are as follows: response rate measured with the Response Evaluation Criteria in Solid

Tumors (RECIST) V.1.1 within 4 weeks after completion of neoadjuvant therapy; pathological response rate using the classification of Evans *et al*¹⁵; R0 resection rate of enrolled patients; surgical morbidity rate measured with CTCAE V.4.0 and the Clavien-Dindo classification¹⁸; and acute and late toxicity rates measured with CTCAE V.4.0. These evaluations will be performed 6 months after completion of enrolment. Analyses of the secondary endpoints regarding prognosis will include overall survival, 2-year survival and progression-free survival. These analyses will be performed 2 years after completion of enrolment. No interim analysis is planned. Monitoring will be performed every 6 months by the staff of the Data Center, clinical trial secretariats and the principal investigator.

Evaluation criteria

R0 resection

R0 resection is defined as tumour resection with pathologically negative margins without distant metastasis, para-aortic lymph node metastasis or positive peritoneal washing cytology.

Overall survival

Overall survival is defined as the time interval between the date of registration and the date of death. Patients who are still alive when last traced will be censored at the date of last follow-up.

Progression-free survival

Progression-free survival is defined as the time interval between the date of registration and the date of progression or date of death, or the last day when the patient was known to be disease-free. The date of diagnosis of progression is defined as the first day when the below-mentioned criteria for progression are met.

1. imaging diagnosis of progressive disease according to RECIST V.1.1
2. clinical diagnosis of evident progressive disease
3. protocol termination resulting from adverse effects or patients' refusal is not regarded as progressive disease.

Safety measures

Serious adverse events including death within 30 days from the end of protocol treatment or unexpected grade 4 toxicity must be reported to the safety desk of the trial within 72 hours. Death occurring more than 30 days after the end of protocol treatment, expected non-haematological grade 4 toxicity and unexpected grade 3 toxicity will be reported to the safety desk of the trial within 15 days.

Quality assurance

Radiotherapy

All RT treatment plans for the enrolled patients will be reviewed centrally by an independent radiation committee. To assess RT protocol compliance, the following parameters will be reviewed: fraction size; prescribed dose to the reference point; energy; relationships between gross tumour volume, clinical target volume, planning target volume and radiation field;

overall treatment time; and isodose distributions at the transverse section of the reference points and doses to organs at risk.

Pathology

A standardised protocol based on the sixth edition of General Rules for the Study of Pancreatic Cancer will be used. For accurate diagnosis of R0 resection, lymph node harvest from the specimen is prohibited. Inking of SMA margin, posterior margin, portal vein groove margin and anterior surface is recommended for accurate analysis of margin positivity.

Withdrawal from study

Patients will be able to withdraw from the study at any point. Data collected up to point of withdrawal will be retained for use within analyses.

ETHICS AND DISSEMINATION

The trial will be performed in accordance with the principles of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects. The National Cancer Center Institutional Review Board approved this protocol on 9 March 2012. Approval by the institutional review board of each institution was acquired before initiating patient accrual. Patient enrolment began on 28 December 2012. This trial has been registered in the UMIN (University Hospital Medical Information Network) Clinical Trial Registry (UMIN000009172) since 23 October 2012. Written informed consent will be obtained from all participants. All serious adverse events will be reported to the safety desk of the trial, the ethics committee and all participating sites.

The protocol treatment of this trial consists of preoperative CRT and subsequent radical pancreatic resection for advanced pancreatic cancer. To minimise the risk and impact of adverse effects and surgical morbidity caused by the protocol treatment and to secure patients' safety, patient selection criteria, dose and schedule modification, concomitant medications and surgical indication after chemoradiation are defined appropriately.

The originals of all central study documents will be archived at the principal study site for at least 5 years after preparation of the final report.

The participants, healthcare professionals, the public and other relevant groups will be informed of the study results. We aim to publish results from this study in the form of one or several manuscripts in international medical journals. The principal investigator will review all manuscripts to prevent forfeiture of patient rights to data not in the public domain. Publication of the first manuscript reporting study results is planned to take place as soon as possible after analysis of the primary endpoint.

Registration ended on 13 May 2016, when the number of enrolled patients reached the planned sample size. The study and data collection are ongoing.

TIME SCALE

The date of the trial registration was 23 October 2012. The date of the first patient enrolment was 28 December 2012. The registration ended on 13 May 2016. This study is ongoing, but not recruiting participants. Estimated completion date is September 2018.

DISCUSSION

BRPC is an advanced tumour in contact with the surrounding major vessels, making R0 resection difficult to achieve. Thus, BRPC has a poorer prognosis with more local failure than resectable PC when treated with post-operative adjuvant chemotherapy.⁵ Therefore, neoadjuvant strategy is deemed more appropriate for patients with BRPC, as recommended in the AHPBA (Americas Hepato-Pancreato-Biliary Association) /SSO (Society of Surgical Oncology)/SSAT (Society for Surgery of the Alimentary Tract) Consensus Conference recommendation and NCCN guideline.^{2, 3, 19} However, few clinical trials have investigated the efficacy of neoadjuvant treatment in BRPC alone,²⁰ whereas studies of locally advanced tumours that included both BRPC and unresectable locally advanced PC have been reported.^{6, 7} The standard treatment for BRPC has not yet been defined.

Delay in the development of neoadjuvant treatment for BRPC has resulted partly from lack of standardisation of clinical trial design optimised for BRPC.¹⁴ There are several obstacles to conducting clinical trials limited to BRPC. In this trial, those obstacles are dealt with as appropriately as possible. First, BRPC is rare, accounting for 10% of non-metastasised PC. The feasibility of clinical trials needs to be proven. This trial will be conducted in the JASPAC group, a nationwide pancreas surgery group composed of 23 high-volume hepatobiliary-pancreatic units, to quantify the number of participants per year to evaluate whether randomised trials can be performed in BRPC.

Second, the definition of BRPC is not standardised and differs among guidelines. In particular, the definition of BRPC related to tumour–portal vein contact varies enough to influence the results of the trial. Therefore, definitions of BRPC should be stated clearly and precisely in the protocol. In this trial, the criteria of BRPC are based on the NCCN Clinical Practice Guideline from 2009. However, several modifications and additions have been made to avoid ambiguity and misunderstanding by investigators and third parties. Furthermore, interinstitutional variation exists in the interpretation of MDCT findings, and this variation influences diagnosis of BRPC even with the precise criteria defined in our protocol. Accordingly, all MDCTs used for registration will be collected and diagnosed centrally by the central diagnosis committee after registration. Eighty per cent of registered patients are anticipated to be diagnosed with BRPC according to central review, which increases the actual sample size to 50 patients. The need for additional increases in sample size will be considered in an interim

analysis examining the ratio of centrally diagnosed BRPC at that time.

Third, the indications for surgical resection after neoadjuvant treatment have not been standardised. Tumour–vessel interaction in BRPC rarely improves to that of resectable PC after only 1–2 months of preoperative treatment. Most BRPC remains borderline resectable. Moreover, some cases of BRPC appear to be unresectable, locally advanced PC after neoadjuvant therapy. However, the pathological response of the main tumour and R status do not correlate with the radiological resectability after neoadjuvant treatment. Considering the discrepancy between radiological resectability after neoadjuvant treatment and pathological status, all patients without progressive disease according to RECIST V.1.1 are considered to be candidates for surgical resection in this trial, regardless of radiological resectability. Furthermore, the protocol defines the standard procedure for pathological examination, R0 status and surgical indications from the point of organ function considering patient safety. Devising the study design for clinical trials of neoadjuvant treatment in BRPC and verifying the appropriateness of the clinical design is an important element of this trial.

An Alliance trial evaluated the feasibility of preoperative modified FOLFIRINOX followed by capecitabine-based chemoradiation in patients with BRPC.²¹ Comparatively high efficacy with an R0 resection rate of 64% was shown in the first intergroup feasibility study for BRPC. However, because 64% of participants experienced a grade 3 or higher adverse event during the preoperative treatment, the modified protocol of FOLFIRINOX followed by capecitabine-based chemoradiation might be relatively hard for patients who will undergo subsequent radical resection and adjuvant chemotherapy.

S-1 is effective for pancreatic cancer.^{11, 12} S-1 therapy with concurrent RT achieves favourable activity and mild toxicity in patients with unresectable LAPC and seems suitable for neoadjuvant therapy of BRPC, followed by major intensive surgery. The efficacy and safety of neoadjuvant S-1 with concurrent RT and subsequent pancreatic resection for BRPC will be evaluated in this multi-institutional phase II trial. Similar trials have rarely been performed in a pure BRPC population.

In summary, this trial will provide initial evidence regarding neoadjuvant S-1 with concurrent radiation for BRPC. If efficacy and safety can be demonstrated, this study will lead to further trials. Moreover, this study explores clinical trial design optimised for BRPC for future standardisation.

Participating institutions (from North to South)

Asahikawa Medical University, Hokkaido University Hospital, Hirosaki University Hospital, Yamagata University Hospital, Jichi Medical University Hospital, Tochigi Cancer Center, Gunma Prefectural Cancer Center, National Cancer Center Hospital East, Chiba Cancer Center, Saitama Cancer Center, Tokyo Women's Medical University Hospital, St. Marianna University School of

Medicine Hospital, Kanagawa Cancer Center, Shizuoka Cancer Center, Seirei Mikatahara General Hospital, Aichi Cancer Center, Nagoya University Hospital, National Hospital Organization Osaka National Hospital, Kobe University Hospital, Fukuyama City Hospital, National Hospital Organization Kure Medical Center, Shikoku Cancer Center and National Hospital Organization Kyusyu Cancer Center.

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Contributors ST and MI conceived of and planned the trial. IO, MI and ST drafted the trial protocol and edited its final version. TK wrote the protocol relating to MDCT. MK and KU provided advice on the parts of the protocol relating to surgical treatment. TA advised regarding radiation treatment. MK advised on the protocol relating to pathological examination. All of the authors read and approved the final version of the protocol and of the manuscript. The J-CRSU Data Center was in charge of data management and registration.

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Competing interests MI has received payment for lectures and research funding from Taiho Pharmaceutical.

Ethics approval The National Cancer Center Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

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