ORIGINAL ARTICLE

Diffusion-weighted MRI predicts the histologic response for neoadjuvant therapy in patients with pancreatic cancer: a prospective study (DIFFERENT trial)

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Abstract

Purpose Pre-operative prediction of histological response to neoadjuvant therapy aids decisions regarding surgical management of borderline resectable pancreatic cancer (BRPC). We elucidate correlation between pre-/post-treatment whole-tumor apparent diffusion coefficient (ADC) value and rate of tumor cell destruction. We newly verify whether post-treatment ADC value at the site of vascular contact predicts R0 resectability of BRPC.

Methods We prospectively reviewed 28 patients with BRPC who underwent diffusion-weighted magnetic resonance imaging before neoadjuvant chemotherapy and surgery. Correlation between the percentage of tumor cell destruction and various parameters was analyzed. Strong parameters were assessed for their ability to predict therapeutic histological response and R0 resectability.

Results Pre-/post-treatment whole-tumor ADC value correlated with tumor cell destruction rate by all parameters ($R = 0.630/0.714$, $P < 0.001/< 0.0001$). The post-treatment cutoff value of ADC at the site of vascular contact for discriminating histological response of tumor destruction of $\leq 50\%$ and tumor destruction of $> 50\%$ was determined at 1.42×10^{-3} mm^2/s. It predicts R0 with 88% sensitivity, 50% specificity, and 61% accuracy. For histological response, the post-treatment whole-tumor ADC cutoff value for discriminating between tumor destruction of $\leq 50\%$ and tumor destruction of $> 50\%$ was determined at 1.40×10^{-3} mm^2/s. It predicts histological response with 100% sensitivity, 81% specificity, and 89% accuracy. It predicts R0 with 88% sensitivity, 70% specificity, and 75% accuracy.

Conclusions Post-treatment whole-tumor ADC value may be a predictor of R0 resectability in patients with BRPC. Tumor cell destruction rate is indicated by the difference between pre-/post-treatment ADC values. This difference is strongly affected by the pre-treatment ADC value. The cutoff value of ADC at the site of vascular contact could not discriminate R0 resectability.

Keywords Apparent diffusion coefficient · R0 resectability · Borderline resectable

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Introduction

Studies investigating the multimodality management of pancreatic ductal adenocarcinoma (PDAC) have reported a 5-year survival rate of 40% if complete surgical tumor resection (R0) is performed, and the surgery is followed by adjuvant chemotherapy. Even for borderline resectable pancreatic cancer (BRPC), neoadjuvant therapy has reported resectability rates of 60–68% [1, 2]. BRPC has been defined as superior mesenteric vein (SMV) or portal vein (PV) with distortion, narrowing, or occlusion, but with remaining anatomic options for resection and reconstruction. It has gastroduodenal artery encasement up to the hepatic artery with short segment

encasement or abutment of the hepatic artery, but without involvement of the celiac axis. There are no metastases, and tumor abutment of the superior mesenteric artery is < 180° [3]. Pre-operative treatment is therefore an essential initial therapy for such patients [1]. In previous studies, differences in radiographic findings have rarely been apparent after neoadjuvant therapy with multidetector row computed tomography (MDCT). RECIST response has not been an effective treatment scale for patients who undergo pre-operative therapy [4, 5]. Although histological response to the pre-operative therapy is a local factor critical to favorable survival, until recently, there have been few tools able to predict it. Diffusion-weighted magnetic resonance imaging (DW-MRI) is increasingly playing a role in evaluation of the therapeutic effect in patients with cancer of various organs [6–9]. We previously demonstrated a correlation between the pre-/post-treatment whole-tumor apparent diffusion coefficient (ADC) value on DW-MRI and rate of histological tumor cell destruction in BRPC [10]. Owing to the desmoplastic change in invasion, however, the character of PDAC makes it unsuitable for evaluation of the therapeutic effect by CT [11]. Many clinicians have become interested in adopting the recent stronger regimen not only for tumor cell destruction in microscopic metastases but also for site of vascular contact as a neoadjuvant therapy [12, 13]. Prospective studies have not yet investigated the usefulness of DW-MRI focusing on the site of vascular contact in order to predict histological response to neoadjuvant therapy in patients with BRPC.

The present prospective trial aims to confirm whether the tumor cell destruction rate or R0 resectability with uniform regimen of neoadjuvant therapy can be predicted by ADC value of whole-tumor and by the ADC value at the site of vascular contact. We aim to clarify the correlation between pre-/post-treatment whole-tumor ADC value and tumor cell destruction rate. Moreover, we investigate whether the post-treatment ADC value at the site of vascular contact can predict R0 resectability of BRPC. This trial is registered at UMIN Clinical Trials Registry, UMIN000022010, 000028030 and at ClinicalTrials.gov, NCT02777463.

Material and methods

Patients and study design

This study was approved by the Wakayama Medical University Hospital (WMUH) Institutional Review Board (Nos. 1813, 2092). It is a prospective study defining its protocol treatment to complete neoadjuvant chemotherapy and following pancreatectomy. Between June 2016 and November 2018, 34 patients with borderline resectable pancreatic cancer (BRPC) were scheduled for neoadjuvant therapy and subsequent surgical resection (Fig. 1). Resectability

status was defined in this study according to National Comprehensive Cancer Network (NCCN) criteria, version 2.2015 [3]. As previously reported [10], all patients underwent imaging studies including staging and restaging by enhanced MDCT (abdominal, chest), enhanced magnetic resonance imaging (MRI), DW-MRI, ^{18}F-fluorodeoxyglucose positron emission tomography ([18F]-FDG PET/CT), and all underwent staging laparoscopy prior to and after neoadjuvant therapy to evaluate resectability. Demographic characteristics were collected from electronic records, including sex, age, tumor location, carbohydrate antigen (CA) 19-9 value as tumor marker, ADC value, maximum standardized uptake (SUVmax) value, surgical procedure, and pathologic response [10].
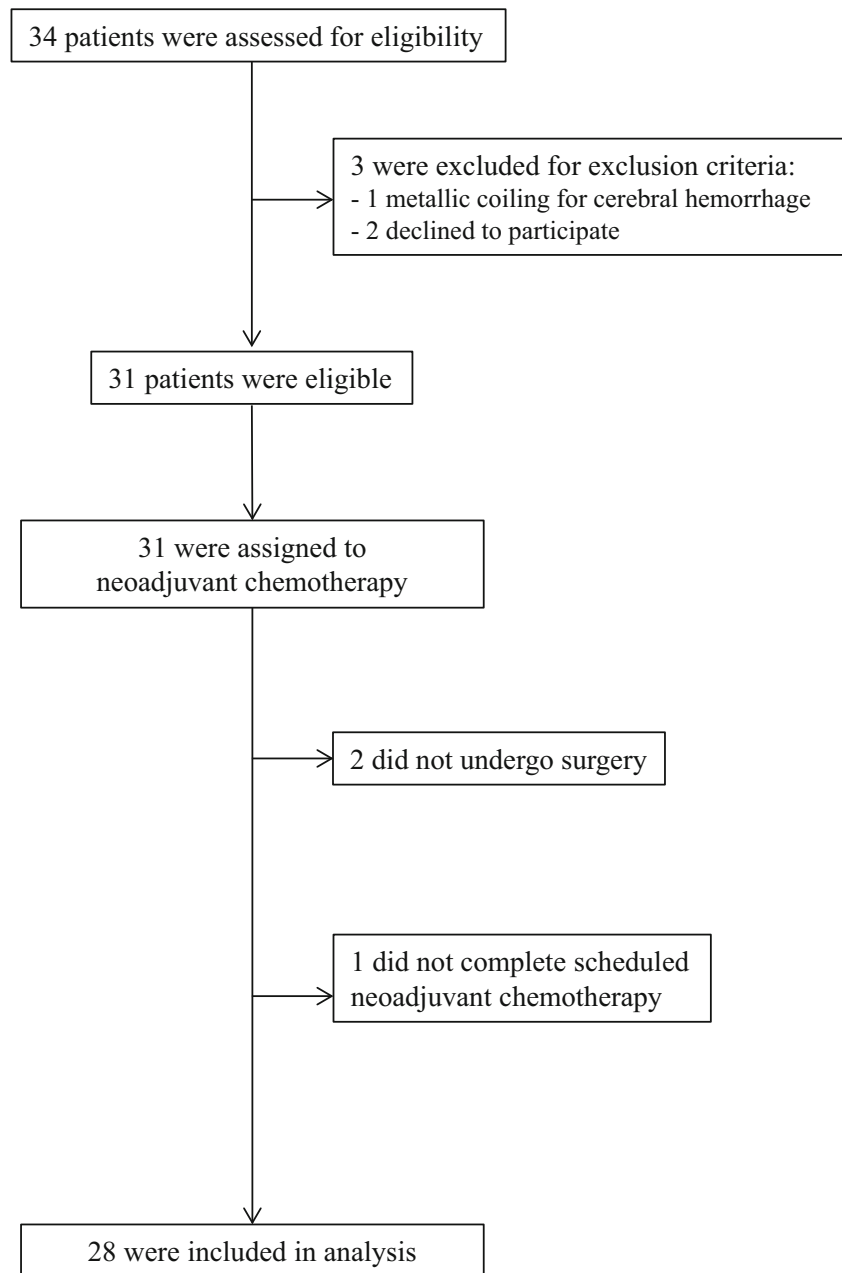
Pathological assessment

The grading of the extent of residual carcinoma in specimens was performed by integration of two different grading schemes [4]: the grading protocol recommended by the College of American Pathologists (CAP), which is based on the ratio of residual tumor cells and the stroma [14], and the grading scheme reported by Evans et al., which is based on the percentage of residual tumor cells [15]. Tumor cell destruction rate was defined using the pathological response grading system developed by Evans et al. and was also converted to numerical values as previously reported: grade I to 5%, grade IIa to 30%, grade IIb to 70%, and grade III to 95% [9, 15]. At least two of three fixed experienced pathologists (F.K., Y.I., S.M.) reviewed all post-treatment slides of the tumor tissue. Inter-observer agreement for the Evans grading among the three pathologists was confirmed by pathological conference. Assessment of tumor cell destruction rate was based on the degree of presence of sizable mucin pools or fibrous tissue replacement to confirm the therapeutic effect against pancreatic carcinoma. No pathologists had access to results of DW-MRI or other clinical data, and the radiologist could not access the pathological data. Based on the pathological diagnosis of the resected specimen, microscopic surgical margin status (R0 or R1) was examined. R0 resectability (R0-status) was defined as the absence of tumor cell infiltration within 1 mm of the resection margin, and R1 status was defined as the presence of tumor cell infiltration within 1 mm of the resection margin.

Neoadjuvant therapy

During the study period, all enrolled patients were scheduled for neoadjuvant nab-paclitaxel plus gemcitabine therapy as participants in a multicenter phase II trial [16, 17]. Similar to that previously reported, one cycle of regimen includes the following: on days 1, 8, and 15 over a 4-week period, enrolled patients are administered a 30-min intravenous infusion of nab-paclitaxel at a dose of 125 mg/m^2. This is followed by a

Fig. 1 Consort diagram

34 patients were assessed for eligibility

3 were excluded for exclusion criteria:
- 1 metallic coiling for cerebral hemorrhage
- 2 declined to participate

31 patients were eligible

31 were assigned to
neoadjuvant chemotherapy

2 did not undergo surgery

1 did not complete scheduled
neoadjuvant chemotherapy

28 were included in analysis

30-min intravenous infusion of gemcitabine at a dose of 1000 mg/m^2 [16]. This regimen was repeated twice based on the result of a previous study that reported the median time to response was 6 weeks [18]. There is 1 week of rest between each cycle. Criteria for restart, dose reduction, and discontinuation of chemotherapy are also as previously reported [16]. Planned pancreatectomy was performed on patients with no progression of disease.

Quality of surgery

To guarantee the quality of the pancreatectomy with/without vascular combined resection and systemic lymphadenectomy,

board-certified surgeons from the Japanese Society of Hepato-Biliary-Pancreatic Surgery performed or supervised all surgery. WMUH is one of the high volume institutions in Japan at which more than 50 pancreatectomies for pancreatic cancer are performed per year. We adhere to the Japanese Pancreatic Cancer Treatment Guidelines, but a central review was not performed.
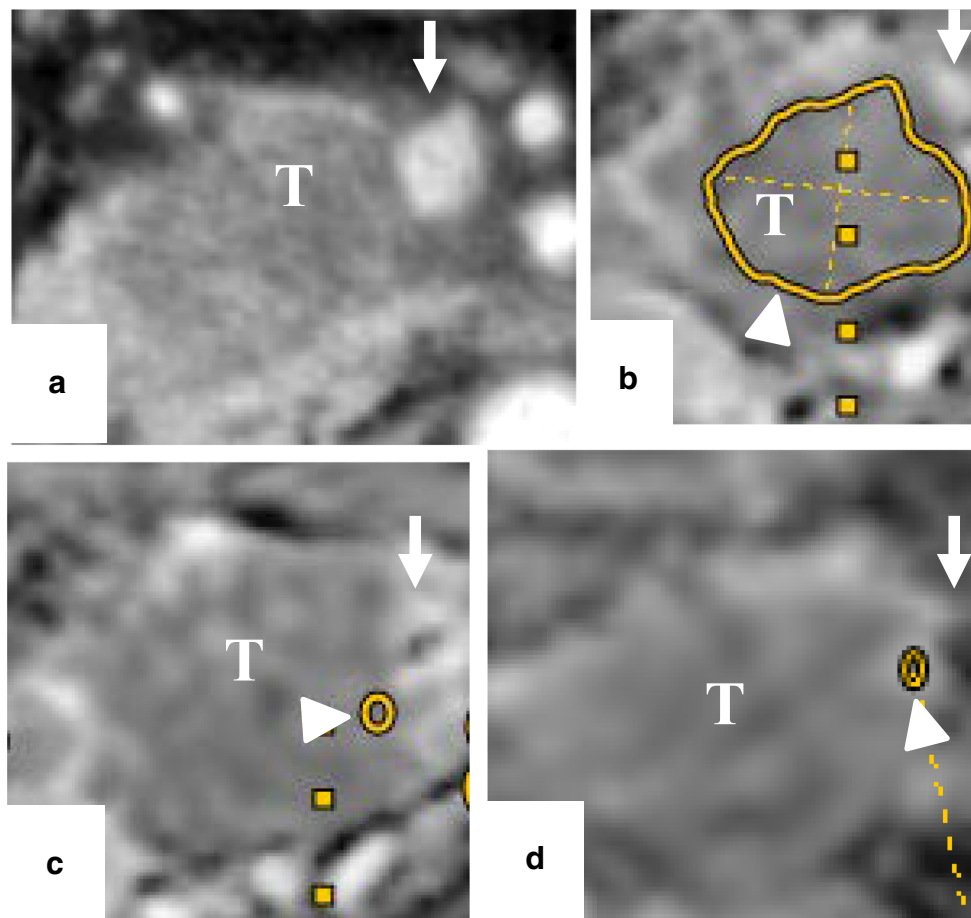
Diffusion MRI

Diffusion MRI procedures were the same as those we previously reported [10]. Patients underwent MRI within 3 weeks before the start of neoadjuvant therapy and again 3 weeks after the last

administration. The ADC map was made using diffusion-weighted images at $b = 0$, 50, and 1000 s/mm^2. Mean ADC values for each tumor were automatically calculated on the ADC map image. The same MRI system/scanner (Intera Achieva 3.0T, Philips Medical Systems) was used for all patients analyzed in this study. Region of interest (ROI) was determined by a single experienced MR radiologist (M.T.) as 3–4 small cross-sectional areas at the site of vascular contact based on abdominal CT scan images, excluding the vascular area on the ADC map image (Fig. 2), and as 3–4 largest cross-sectional areas representing a whole-tumor, as previously reported [10]. The site of vascular contact of a tumor was defined as a marginal part of tumor with short segment encasement or abutment to vessels that categorized the case as BRPC. Mean values of these data were treated as two values (site of vascular contact and whole tumor) in one study. All images were obtained with multiple slices in the axial phase, at least three slices to cover the entire tumor volume.

FDG PET/CT

Patients underwent PET/CT and MRI on the same day. PET studies and calculation of the tumor SUVmax were performed as previously reported [10].

Statistical analysis

For the purpose of the present study, to select a predictor for histological response, statistical analysis (per protocol analysis) was performed for each correlation between tumor size, ADC value (mean), SUVmax value, CA19-9 value, and their change ratios/difference and percentage of tumor cell destruction. We also compared overall survival (OS) and recurrence-free survival (RFS) between the groups divided by cutoff value. The cutoff value for the identified parameter was determined to maximize the difference between histologically poor responders (< grade IIb) and good responders (≥ grade IIb) by receiver-operator characteristic (ROC) curve. Sample size was calculated according to the correlation coefficient of our previous retrospective study on the prediction of the histopathological treatment effect before pre-operative chemotherapy: average ADC value of DW-MRI was $r = 0.625$ (Pearson's $r = 0.625$) [10]. In the present study, reproducibility is judged to be poor if the result is < 10% than that of our previous retrospective study, if the correlation coefficient threshold is ≥ 0.56, if the alternative hypothesis is 0.6, if the α error 0.05, if the detection power $(1 - \beta)$ is 0.8, or if the 95% confidence interval is 0.10 (group 0.05) in a single group of 28 cases. Taking into account the approximately 10% excluded from

Fig. 2 Computed tomography (CT) imaging and apparent diffusion coefficient (ADC) maps obtained from pancreatic head carcinoma. **a** Pre-treatment CT of a borderline resectable pancreatic cancer patient showing tumor abuts to portal vein (arrow). **b** Pre-treatment magnetic resonance imaging (MRI) showing the region of interest (ROI) (arrow head) of whole tumor is outlined. The mean ADC value for the tumor was automatically calculated avoiding the vascular area on the image of ADC map using a tomographic software. **c** Pre-treatment MRI showing the ROI (arrow head) determined by a radiologist in 3–4 small cross-sectional areas as site of vascular contact. **d** Post-treatment MRI showing the ROI (arrow head) determined by a radiologist in 3–4 small cross-sectional areas as site of vascular contact. T tumor

analysis, to allow for cases that do not lead to resection, we planned registration of 30 cases. The relationship between the two groups divided by ADC cutoff value was analyzed by means of the χ^2 test for categorical variables. Mean ADC values on imaging prior to and after neoadjuvant therapy were compared by paired T tests. Cumulative overall survival was calculated by Kaplan–Meier method, and a comparison of the survival curves was analyzed using log-rank test. All survival times were evaluated from the day of diagnosis. P value of $\le$ 0.05 was considered to be statistically significant. All analyses were performed using the statistical software package RStudio: Integrated Development Environment for R version 1.1.463.

Results

Patient characteristics

Table 1 shows the characteristics of the 28 analyzed patients with BRPC. A consort flow diagram of this study is shown in Fig. 1. During the study period, 31 patients were enrolled for this study, two did not undergo surgery for disease progress on restaging imaging studies, and one did not complete neoadjuvant therapy for repeated cholecystitis. Finally, 28 patients were included in per protocol analysis, all of whom completed two cycles of scheduled neoadjuvant therapy within 8–12 weeks. They underwent surgery 3–8 weeks after the final administration of chemotherapy. Eight patients required metal biliary stent insertion prior to neoadjuvant therapy. The presence of a metal biliary stent did not have any effect on the data, and no patients required metal biliary stent insertion during the period of neoadjuvant chemotherapy. Table 2 shows the data on inter-observer agreement about tumor cell destruction rate. Except for one case with R1 at the pancreatic cut margin, the sites of R1 were identified at the dissection surface of neural plexuses around artery that categorized these cases as BRPC. There was no mortality of registered patients.

Parameters

Table 3 shows the observed changes in parameters during neoadjuvant treatment. The reduction percentage of tumor maximum diameter was $21.1 \pm 17.8\%$ (-7 to 55%). Mean ratio of whole-tumor and ADC value on site of vascular contact (pre-/post-treatment ADC) was 1.15 ± 0.1 (1.0–1.4) and 1.28 ± 0.2 (1.0–1.7). The rate of normalization of CA19-9 was 54% including the data of one patient with Lewis[a-b-] type. The ratio of pre-/post-treatment CA19-9 value was 0.42 ± 0.59 (0.01–3.06). The ratio of pre-/post-treatment SUVmax value was 0.6 ± 0.2 (0.1–1.3). Table 4 shows the result of comparison of correlation between each parameter and tumor cell destruction rate of pre and post-treatment phase. Analysis

Table 1 Demographics and characteristics of patients with pancreatic carcinoma

Baseline	$N = 28$ (100%)
Sex (male/female)	
Male	15 (54%)
Female	13 (46%)
Age (years)	69 ± 7
Location of pancreatic cancer	
Body-Tail	9 (32%)
Head	19 (68%)
Diabetes mellitus	8 (29%)
Biliary stent	12 (43%)
SEMS	8 (29%)
Plastic	4 (14%)
Abutment vessel (with overlap)	
Portal vein	13 (46%)
Artery	16 (57%)
SMA	6 (21%)
CA	6 (21%)
CHA	4 (14%)
UICC-Stage	
IA	6 (21%)
IB	2 (7%)
IIA	5 (18%)
IIB	5 (18%)
III	10 (36%)
Regimen of neoadjuvant therapy	
nab-Paclitaxel plus gemcitabine	28 (100%)
Response evaluation	
PR	8 (29%)
SD	20 (71%)
Operative procedure	
Pancreaticoduodenectomy	19 (68%)
DP-CAR	6 (21%)
PD-CHAR	2 (7%)
Distal pancreatectomy	1 (4%)
Combined resection (with overlap)	
Portal vein	18 (64%)
SMV	4 (14%)
PV	1 (4%)
SPC	13 (46%)
Artery*	9 (32%)
CA	6 (21%)
CHA	2 (7%)
Replaced RHA	1 (4%)
Histologic response (Evans grade)	
Grade I	6 (21%)
Grade IIa	10 (36%)
Grade IIb	11 (39%)
Grade III	1 (4%)
Residual tumor	
R0	20 (71%)
R1	8 (29%)
Site of vascular contact	7 (25%)
Pancreatic cut margin	1 (4%)

Values are mean ± standard deviation or number, unless otherwise stated. Radiological tumor response was defined according to the Response Evaluation Criteria In Solid Tumors (RECIST, version 1.0). Tumor staging was performed based on the TNM classification proposed by the Union for International Cancer Control (UICC)

SMA superior mesenteric artery, *CA* celiac axis, *CHA* common hepatic artery, *SEMS* self-expandable metallic stent, *PR* partial response, *SD* stable disease, *DP-CAR* distal pancreatectomy with en bloc celiac axis resection, *PD-CHAR* pancreaticoduodenectomy with en bloc common hepatic artery resection, *SMV* superior mesenteric vein, *PV* portal vein, *SPC* splenoportal confluence, *RHA* right hepatic artery

*We did not perform pancreatectomy combined with superior mesenteric artery in this study

Table 2 The data on inter-observer agreement about tumor cell destruction rate

Observer B	Observer A				
	Evans grade I CAP grade 3	Evans grade IIa CAP grade 3	Evans grade IIb CAP grade 2	Evans grade III CAP grade 1	Totals
Evans grade I CAP grade 3	6	2	0	0	8
Evans grade IIa CAP grade 3	0	8	0	0	8
Evans grade IIb CAP grade 2	0	0	11	0	11
Evans grade III CAP grade 1	0	0	0	1	1
Totals	6	10	11	1	28

Inter-observer agreement about the Evans grading among the pathologists was confirmed as Table 1 at pathological conference

revealed pre-/post-treatment whole-tumor ADC value correlated with tumor cell destruction rate among all parameters ($R = 0.630/0.714$, 95% confidential interval (CI) 0.336–0.812/0.465–0.858, $P < 0.001/< 0.0001$) (Fig. 3a, b). Representative micrographs for the extent of residual carcinoma in post-treatment specimens are shown in Fig. 3c, d.

Post-treatment ADC value on site of vascular contact for prediction of R0 resectability

For prediction of discrimination between histologically poor responder (< grade IIb) and good responder (≥ grade IIb), we used receiver operating characteristic (ROC) analysis to calculate the cutoff value of post-treatment ADC at the site of vascular contact. The post-treatment area under the curve (AUC) for ADC value at the site of vascular contact discriminating < grade IIb and ≥ grade IIb was 0.750 (95% confidential interval 0.594–0.947). The post-treatment cutoff value of ADC at the site of vascular contact for discriminating between grade < IIb and ≥ grade IIb was determined at 1.42×10^{-3} mm^2/s, and it predicts R0 resectability with 88% sensitivity, 50% specificity, and 61% accuracy (Odds ratio 7, 95% CI [0.722–67.839, $P = 0.098$, χ^2 test]).

Whole-tumor ADC value for prediction of pathological response and R0 resectability

ROC analysis was used to calculate the cutoff value of whole-tumor ADC for prediction of discrimination between histologically poor responder (< grade IIb) and good responder (≥ grade IIb). The pre-/post-treatment AUC for whole-tumor ADC value of discrimination between < grade IIb and ≥ grade IIb was 0.807/0.911 (95% confidential interval 0.648–0.967/0.804–1.000) (Fig. 4a, b). The pre-treatment cutoff value of whole-tumor ADC for discriminating between grade < IIb and ≥ grade IIb after treatment was determined at 1.20×10^{-3} mm^2/s. It predicts histological response with 92% sensitivity, 63% specificity, and 75% accuracy. It predicts R0 resectability with 63% sensitivity, 70% specificity, and 68% accuracy. The post-treatment cutoff value of whole-tumor ADC for discriminating between grade < IIb and ≥ grade IIb after treatment was determined at 1.40×10^{-3} mm^2/s. It predicts histological response with 100% sensitivity, 81% specificity, and 89% accuracy. It predicts R0 curability with 88% sensitivity, 70% specificity, and 75% accuracy. Histological response > grade IIb and its R0 resectability ($P < 0.001$, $P = 0.011$, χ^2 test) (Table 5) were detected more frequently in patients with cutoff value and higher post-treatment whole-tumor ADC.

Table 3 The observed changes in parameters during neoadjuvant treatment

Values of predictive factors	Before treatment	After treatment	P
Mean whole tumor ADC value ($\times 10^{-3}$ mm^2/s)	1.24 ± 0.20 (0.84–1.93)	1.42 ± 0.22 (1.04–2.15)	< 0.001
Mean ADC value on site of vascular contact ($\times 10^{-3}$ mm^2/s)	1.12 ± 0.22 (0.77–1.77)	1.40 ± 0.22 (1.02–1.91)	< 0.001
Median CA19-9 value* (U/ml)	122.3 (0.6–7994.1)	28.6 (0.6–4324.0)	0.037
Mean SUVmax value	6.0 ± 2.2 (2.4–10.1)	3.2 ± 1.5 (1.0–7.9)	< 0.001
Tumor diameter (mm)	27.8 ± 9.36 (16–50)	22.3 ± 9.8 (10–46)	< 0.001

ADC apparent diffusion coefficient (mean values), *CA* carbohydrate antigen, *SUVmax* maximum of standardized uptake value

*The data includes one patient with Lewis[a-b-] type

Table 4 Comparison of correlation between parameters and tumor cell destruction rate

Values of predictive factors	Coefficient of correlation*	95% CI	P
Pre-treatment whole tumor ADC	0.630	[0.336, 0.812]	0.00032
Post-treatment whole tumor ADC	0.714	[0.465, 0.858]	0.00002
Ratio of pre-/post whole tumor ADC	0.093	[− 0.290, 0.450]	0.63855
Difference of pre-/post whole tumor ADC	0.287	[− 0.096, 0.596]	0.13799
Pre-treatment ADC on site of vascular contact	0.524	[0.188, 0.750]	0.004
Post-treatment ADC on site of vascular contact	0.564	[0.242, 0.774]	0.002
Ratio of pre-/post ADC on site of vascular contact	− 0.037	[− 0.404, 0.341]	0.853
Difference of pre-/post ADC on site of vascular contact	0.0465	[− 0.332, 0.413]	0.8141
Pre-treatment CA19-9	0.024	[− 0.352, 0.394]	0.90205
Post-treatment CA19-9	− 0.140	[− 0.488, 0.246]	0.47788
Ratio of pre-/post CA19-9	0.119	[− 0.266, 0.471]	0.54669
Pre-treatment SUVmax	− 0.109	[− 0.463, 0.275]	0.58125
Post-treatment SUVmax	− 0.242	[− 0.564, 0.144]	0.21552
Ratio of pre-/post SUVmax	− 0.102	[− 0.458, 0.282]	0.60693
Difference of SUV max	− 0.059	[− 0.423, 0.321]	0.76481
Pre-treatment tumor diameter	0.027	[− 0.350, 0.396]	0.89242
Post-treatment tumor diameter	− 0.009	[− 0.381, 0.365]	0.96199
Reduction rate of pre-/post-tumor diameter	0.061	[− 0.319, 0.424]	0.75605
Difference of the pre-/post-tumor diameter	− 0.073	[− 0.434, 0.308]	0.7128

ADC apparent diffusion coefficient (mean values), *CA* carbohydrate antigen, *SUVmax* maximum of standardized uptake value, *CI* confidence interval

*Pearson correlation was calculated to describe the relationship between each predictor and percent tumor cell destruction

Tumor cell destruction rate and the difference between pre-/post-ADC values

Both the difference of pre-/post whole-tumor ADC and the cutoff value of pre-treatment whole-tumor ADC for discriminating between < grade IIb and ≥ grade IIb were set as explanatory variables, and tumor cell destruction rate was set as the outcome. As a result, P values of the difference and the pre-treatment whole-tumor ADC were 0.043 and < 0.001, respectively. Tumor cell destruction rate is indicated by the difference between pre- and post-treatment ADC values. This difference is strongly affected by the pre-treatment ADC value.

Survival

Median follow-up time was 16 (7–36) months, and estimated median survival time (MST) was 16 months for all patients. Estimated RFS was 16 (5–36) months. According to the two groups divided by whole-tumor ADC cutoff value after treatment, the estimated OS was greater in patients with high ADC value ($≥ 1.40 × 10^{-3}$ mm^2/s; $n = 13$) than in patients with low ADC value ($< 1.40 × 10^{-3}$ mm^2/s; $n = 15$; log-rank $P = 0.015$; not reached to median time vs 30 months; Fig. 5a), although there was no difference in survival between the groups in RFS ($P = 0.172$, log-rank test; 21 vs 12 months; Fig. 5b).

Discussion

The diagnostic ability of MRI to evaluate therapeutic response is controversial because quantitative diagnosis by MRI is rarely used in clinical settings [5, 19]. The primary endpoint of this prospective study was met. We reproduced significant correlation between whole-tumor ADC value prior to neoadjuvant therapy and histological tumor cell destruction rate. In addition, we demonstrated that there was also significant correlation between ADC value after neoadjuvant therapy and tumor cell destruction rate. Post-treatment whole-tumor ADC value higher than cutoff appeared to be a predictor of increased tumor cell destruction rate and R0 resectability in patients with BRPC. There were obvious patients whose resectability could not be sufficiently predicted via this method, however, because the sensitivity was not 100%. DW-MRI is highly sensitive to cellularity, viscosity, and extracellular fluid. ADC value is thought to be affected by multiple factors, such as tissue components, edema, necrosis, fibrosis, tumor structure, and cell density. We can therefore speculate that ADC value may be affected by these factors directly during neoadjuvant treatment. In the present study, we hypothesized the change of ADC value was the therapeutic effect of neoadjuvant therapy on tumor stroma. In our cohort of patients, however, we could not confirm apparent histological evidence for depleted stroma. The change of ADC value might be influenced, not only by depleted stroma, but also other factors, such as increased presence of sizable mucin

Fig. 3 *Y*-axes represent tumor cell destruction rate, and *x*-axes represent apparent diffusion coefficient (ADC) value on diffusion-weighted magnetic resonance imaging. **a** Pre-treatment whole-tumor ADC value correlated with tumor cell destruction rate ($R = 0.630$, 95% confidential interval (CI) 0.336–0.812, $P < 0.001$); **b** Post-treatment whole-tumor ADC value correlated with tumor cell destruction rate ($R = 0.714$, 95% confidential interval (CI) 0.465–0.858, $P < 0.0001$). **c** Representative micrographs show poorly differentiated adenocarcinoma with minimal treatment effect, more than 90% of the tumor cells are viable (CAP grade 3 and Evans grade I). **d** Post-treatment tumor bed with residual tumor cells outgrown by edematous stroma, nuclear decay (arrow), vacuolar degeneration (arrow head), and mucin pools (approximately 25% of viable residual tumor cells, CAP grade 2, and Evans grade IIb)
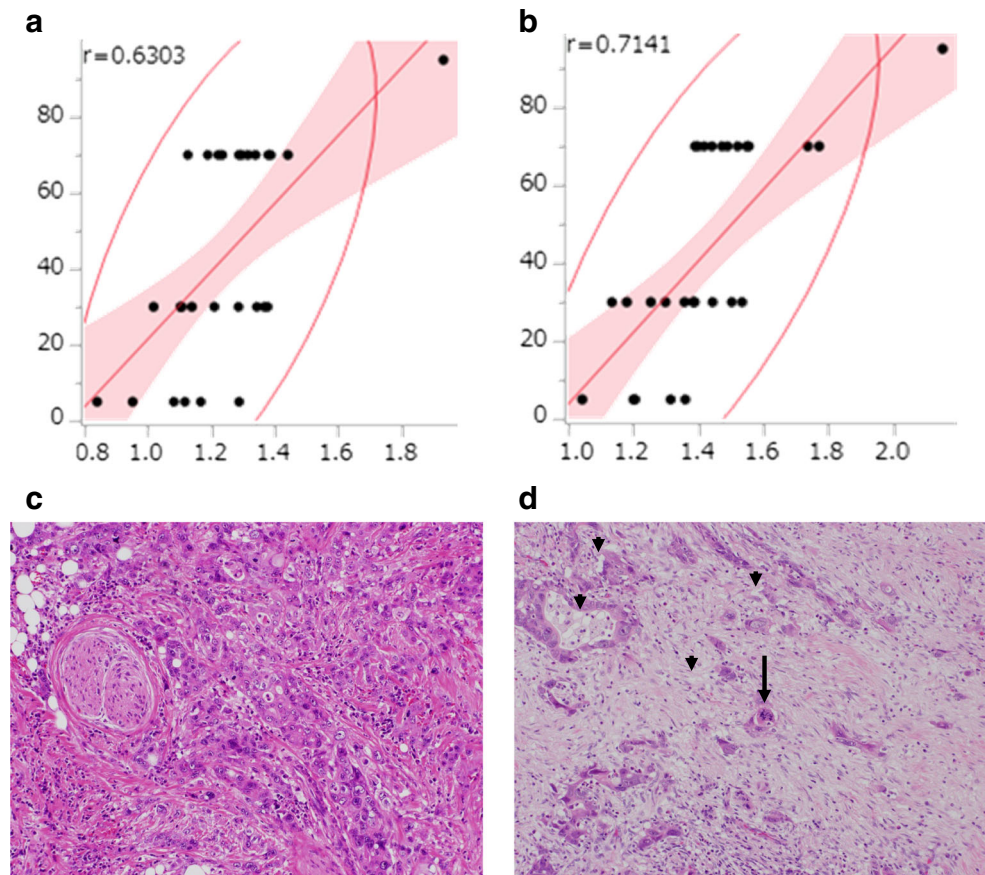
pools or fibrous tissue replacement. Previous histological studies that analyzed stromal materials from breast cancer or that investigated the association between gemcitabine delivery and tumor response may support this phenomenon [20, 21]. Ko et al. (2014) demonstrated that ADC values have significant differences according to the tumor-stroma ratio and dominant stroma type. Stroma-poor tumors reportedly represent a collagen-dominant or fibroblast-dominant stroma, and stroma-
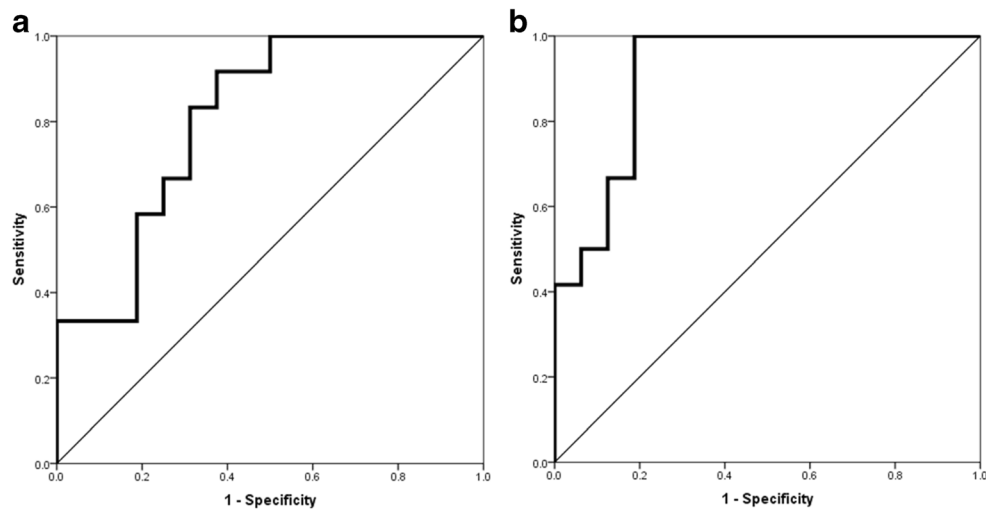
Fig. 4 Receiver operating characteristic curve used to determine the optimal ADC cutoff values of the pancreatic tumor obtained by ADC mapping image of diffusion MRI. **a** The area under the curve for the pre-treatment whole-tumor ADC values 0.807 (95% confidential interval 0.648–0.967), and the determined cutoff value for discriminating < grade IIb and ≥ grade IIb was 1.20×10^{-3} mm²/s. **b** The area under the curve for the post-treatment whole-tumor ADC values. 0.911 (95% confidential interval 0.804–1.000), and the determined cutoff value for discriminating < grade IIb and ≥ grade IIb was 1.40×10^{-3} mm²/s

Table 5 Correlation between pre-/post treatment ADC value and histological result

Pre-treatment ADC value ($\times 10^{-3}$ mm^2/s)	< Grade IIb* CAP grade 3	≥ Grade IIb CAP grades 1, 2	P value	Residual tumor R0	R1	P value
< 1.20	10	1	0.006	6	5	0.200
≥ 1.20	6	11		14	3	
Post-treatment ADC value ($\times 10^{-3}$ mm^2/s)	**< Grade IIb CAP grade 3**	**≥ Grade IIb CAP grades 1, 2**	**P value**	**Residual tumor R0**	**R1**	**P value**
< 1.40	13	0	< 0.001	6	7	0.011
≥ 1.40	3	12		14	1	

*The grading of the extent of residual carcinoma in specimens was performed integrating two different grading schemes: the grading protocol recommended by the College of American Pathologists (CAP) and the grading scheme reported by Evans et al.

rich tumors represent a lymphocyte-dominant stroma [20]. Koay et al. (2014) reported that gemcitabine incorporation into tumor DNA is highly variable and correlates with multiscale transport properties [21].

In this study, we also investigated the correlation between ADC value at the site of vascular contact and the tumor cell destruction rate. Interestingly, there was a pattern of increased incidence of R0 resectability after neoadjuvant therapy in patients with post-treatment ADC value at the site of vascular contact more than the cutoff value. Although there was significant correlation between the ADC value at the site of vascular contact and tumor cell destruction rate, the cutoff value of ADC at the site of vascular contact could not discriminate the tumor cell destruction rate or R0 resectability. We speculate that the lower predictability was an effect of the heterogeneity of cancer cell distribution and measurement error due to small ROI. Regarding heterogeneity of tumor margins, a recent study demonstrated tumor margin similar to the site of vascular contact had more aggressive histologic tumor grades, less frequent remaining acini, and more frequent necrosis within the tumor compared with the non-margin area [22]. Although the tumor margin has greater possibility of exposure

to penetrated chemo-agents than the non-margin area, the sensitivity, specificity, and accuracy are less predictable than those of the whole-tumor ADC value.

There was no histological response correlation with values regarding CA19-9, SUVmax value, or CT response in any of the investigated surrogate markers, which is similar to in previous studies [23–28]. As studies have recently demonstrated, these predictors might be not only local major response predictors but also systemic metastatic predictors. Regarding CA19-9, in particular, normalization of CA19-9, rather than the magnitude of change, might be the strongest prognostic marker for long-term survival following neoadjuvant therapy [24–26]. Conversely, ADC value could be a parameter used to predict local histological response to neoadjuvant therapy. From this point of view, patients whose tumor cell destruction is expected to be more than 50% could be considered as higher priority in decision making for optimal timing of surgery or additional neoadjuvant therapy [29]. In this context, when R0 resectability cannot be reassessed after treatment by MDCT only, post-treatment whole-tumor on DW-MRI might assist in making a decision regarding additional treatment before surgical resection in selected patients with not only BRPC, but in
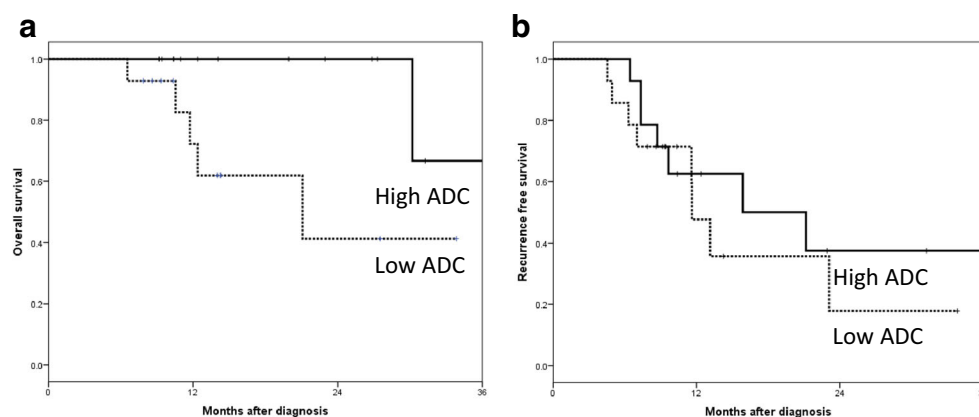
Fig. 5 According to the two groups divided by whole-tumor ADC cutoff value after treatment, **a** the estimated overall survival in all patients was greater in patients with higher ADC group (whole-tumor ADC value after treatment ≥ 1.40×10^{-3} mm^2/s; $n = 13$) than with lower ADC group (whole-tumor ADC value after treatment < 1.40×10^{-3} mm^2/s; $n = 15$; log-rank $P = 0.015$); **b** there were no differences in survival between the groups in recurrence-free survival time ($P = 0.172$, log-rank test)

the future, patients with locally advanced pancreatic cancer [30].

Our results may be limited, however, by the small sample size, this study being a single institution-based retrospective study, and the short follow-up period. The low number of patients whose treatment response ≥ grade III might be considered a bias in the present study [4]. It is problematic because studies that have examined the association between pathologic responses using the Evans grade and have not found an association between Evans grade IIb response and outcomes [4, 31]. There are still concerns that the findings suggesting a significant decrease in size either highlights the potential for type I error in our work or, alternatively, is representative of a treatment/enrollment bias. Otherwise, our results may be limited by being based on single regimen of neoadjuvant therapy. Validation of this study with FOLFIRINOX or chemoradiation therapy is needed.

Conclusion

In conclusion, we found significant correlation between the pre-/post-treatment whole-tumor ADC value and histological tumor cell destruction rate after neoadjuvant therapy. Post-treatment whole-tumor ADC value may be a predictor of R0 resectability in patients with BRPC. The predictive role of ADC values may be useful in individual therapeutic approach in neoadjuvant therapy for BRPC patients.

Compliance with ethical standards

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