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Difference between carbohydrate antigen 19-9 and fluorine-18 fluorodeoxyglucose positron emission tomography in evaluating the treatment efficacy of neoadjuvant treatment in patients with resectable and borderline resectable pancreatic ductal adenocarcinoma: Results of a dual-center study

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Abstract

Background: An accurate evaluation of neoadjuvant treatment is important to maximize the prognostic benefit of this strategy in each individual patient. The main aim of the present study is to investigate the difference between carbohydrate antigen 19-9 and fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) in evaluating the response to neoadjuvant treatment for resectable and borderline resectable pancreatic ductal adenocarcinoma (PDAC) patients.

Methods: Pancreatic ductal adenocarcinoma patients with positive standard uptake values (SUV) on FDG-PET before neoadjuvant chemoradiotherapy (NACRT) were enrolled (n = 141). In all patients, CA19-9 and FDG-PET were evaluated before the initiation of and after the completion of NACRT. The statuses of CA19-9 and FDG uptake alterations during NACRT were assessed in association with survival and tumor recurrence profiles.

Results: A favorable response in each CA19-9 and FDG-PET was significantly related to better survival, respectively, than the unfavorable response (44.3% vs 19.5%, $P < .001$ and 45.8% vs 24.6%, $P < .001$). The status of CA19-9 was significantly associated with the incidence of distant recurrence whereas the status of FDG-PET was significantly associated with the incidence of local recurrence, and only patients with a favorable response in both CA19-9 and PET statuses showed a significantly better survival than the others (5-year survival: 56% vs 24%, $P < .001$), and those with

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unfavorable response in either of CA19-9 or PET status showed similar poor survival to those with unfavorable in both ($P = .164$).

Conclusion: CA19-9 and PET evaluation provided oncologically different risk assessments in terms of tumor recurrence profile, and favorable response in both CA19-9 and FDG-PET were necessary to achieve prognostic benefit from NACRT.

KEYWORDS

CA19-9, chemoradiotherapy, FDG-PET, neoadjuvant, pancreatic cancer

1 | INTRODUCTION

A trend toward a multidisciplinary treatment strategy is emerging in various malignant diseases. Neoadjuvant treatment with subsequent surgery for pancreatic ductal adenocarcinoma (PDAC) is being actively investigated, with reported favorable survival (5-year survival rates of 36% to 53%).[1-3] One theoretical advantage of a neoadjuvant treatment strategy for PDAC is accurate identification of patients with unresectable factors who are unlikely to benefit from surgery.[4,5] However, a substantial number of patients still experienced postoperative tumor recurrence after subsequent surgery.[1,6,7] For this reason, maximizing the therapeutic benefit of neoadjuvant treatment for each individual patient requires meticulous discrimination of who would truly benefit from the subsequent surgery and who would not.

Carbohydrate antigen 19-9 (CA19-9) is the most widely used serum marker for PDAC detection. Preoperative serum CA19-9 is positively associated with tumor burden and serum CA19-9 levels are prognostic in pancreatic cancer.[8] In addition, changes in serum CA19-9 during preoperative treatment are reported to be useful indicators of treatment response. In particular, many previous reports have suggested that normalization of CA19-9 during preoperative treatment is a robust, significant predictor of improved survival after subsequent resection, reflecting a favorable treatment response and significantly reduced tumor burden.[9-11] However, even with successful CA19-9 normalization during preoperative treatment, 5-year survival remains approximately 50%;[9-12] hence, a single evaluation of successful CA19-9 normalization after preoperative treatment remains unsatisfactory for identifying optimal candidates for subsequent pancreatectomy.

Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/ computed tomography (CT) is a functional imaging modality that can detect changes in tissue metabolism. Carbohydrate metabolism is more active in malignant cells, resulting in significant accumulation of FDG.[13] FDG-PET/CT has been thoroughly investigated in esophageal, rectal, and other cancers for detecting residual viable cancer or response after anticancer treatment.[14,15] An early decrease in FDG uptake in the primary tumor during preoperative therapy can predict not only the pathological response but also survival among patients with esophageal or breast cancer, among others.[16,17] We previously reported that a change in FDG uptake during neoadjuvant chemoradiotherapy (NACRT) is significantly associated with surgical outcomes among patients with PDAC.[18] Our findings indicated that a > 50% decrease in the maximum standard uptake value (SUV-max) during preoperative chemoradiotherapy (CRT) is significantly related to favorable outcomes after radical resection, reflecting a favorable response to neoadjuvant treatment and significant attenuation of locoregional tumor activity.

These observations may indicate that FDG uptake evaluation assesses a different aspect of tumor pathophysiology and response to neoadjuvant treatment from the CA19-9 evaluation. In this context, assessment of the response per FDG-PET in combination with CA19-9 evaluation might enhance the prognostic significance of CA19-9 changes in patients with PDAC treated preoperatively; however, evidence for this effect is scarce. Truty et al assessed the significance of CA19-9 alterations and pathological response of the resected specimen in patients with unresectable and borderline resectable pancreatic cancer receiving neoadjuvant chemotherapy. In their patient population, FDG-PET alterations were highly correlated with pathological response,[19] but these authors could evaluate changes in FDG uptake during preoperative treatment in only 67 (35%) of 194 patients enrolled. In addition, they found no additional impact of FDG-PET in predicting surgical outcome, primarily because of the small number of patients for whom information about preoperative FDG changes was available.

In the current two-center study of 141 patients with resectable and borderline resectable PDAC, we examined the prognostic significance of changes in CA19-9 and in FDG uptake during preoperative treatment. In addition to evaluating the association of these two predictive factors with response to neoadjuvant treatment for PDAC, we investigated any further predictive significance of FDG-PET evaluation in patients with successful CA19-9 normalization during NACRT.

2 | METHODS

2.1 | Patients

Between 2008 and 2016, a total of 401 patients with pancreatic cancer received NACRT at Osaka International Cancer Institute (OICI) or Osaka University Hospital (OUH). Either histological or cytological

evidence of adenocarcinoma of the pancreas was obtained before initiation of preoperative treatment. Of this group, 32 patients did not undergo radical surgery after NACRT mainly because of the detection of distant metastasis, and FDG-PET was not carried out before NACRT in 101 patients although they underwent radical surgery; all of these patients were excluded from this study. Another 65 patients with a negative FDG-PET SUV before NACRT and 62 who did not receive FDG-PET after NACRT were also excluded. Patients additionally were excluded if they had pancreatitis, cholangitis, or uncontrolled diabetes before the preoperative treatment. Finally, a total of 141 patients with PDAC-R (n = 102) or PDAC-BR (n = 39), according to NCCN guideline Ver. 2.2018 resectability criteria, were enrolled in the study (Figure S1).

All patients underwent FDG-PET/CT using the same protocol before NACRT initiation and after its completion but before surgical laparotomy (ie, at least 3 weeks after completion of the radiation component). They also all had routine radiographic imaging, such as CT, magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS). Serum CA19-9 was examined before and after NACRT. All patients were followed until disease recurrence and/or death with a median follow-up period of 31.0 months (range, 4.9-112.9 months).

2.2 | Preoperative chemoradiation therapy

Patients received preoperative CRT according to the regimen of a prospective phase II clinical trial in each hospital (UMIN-CTR: UMIN000037142). Written informed consent was granted under an approved procedure. Details of the regimens for NACRT have been described previously.[6,20] Briefly, three-dimensional radiation was targeted to the following fields, given at a total dose of 40-60 Gy with a daily fraction of 1.8-2.0 Gy for 5 days/week: the primary pancreatic tumor, celiac and superior mesenteric arteries, retroperitoneal soft tissue, and para-aortic region. The gastrointestinal tract, including the stomach and duodenum, was excluded from the field of irradiation. At OICI, gemcitabine alone was given with radiotherapy; i.v. gemcitabine (1000 mg/m^2) was initiated concurrently on days 1, 8, and 15 during each 4-week cycle for three cycles. This preoperative CRT was completed within 3 months.[6] In OUH, gemcitabine and S-1 were given with radiotherapy; i.v. gemcitabine (1000 mg/m^2) was initiated concurrently on days 1 and 8 and S-1 orally on days 1-5 and 8-12 during each 3-week cycle for two cycles. This preoperative CRT was completed within 2 months.[20] The pathological response of the primary pancreatic tumor to preoperative CRT was evaluated using the histological grading schema described by Evans et al.[21]

2.3 | Protocol for FDG-PET/CT

Whole-body FDG-PET/CT was carried out using the Gemini GXL (Phillips, Eindhoven, the Netherlands) or Biograph Duo (Siemens, Munich, Germany). Prior to imaging, all patients fasted for 5 hours before i.v. administration of FDG at a dose of 3.7 MBq/kg weight (mean dose 200 MBq). Whole-body PET/CT images were acquired 120 minutes after FDG administration. SUV-max was calculated for the primary pancreatic tumor. The SUV-max obtained before initiating preoperative CRT was defined as the pre-CRT SUV, and the SUV-max obtained after completion of preoperative CRT was defined as the post-CRT SUV. The decrease ratio of SUV-max was defined as follows; decrease ratio = (1 − post-CRT SUV/pre-CRT SUV) × 100. In this study, the SUV-max of the tumor before initiating CRT was positive in all patients.

2.4 | Statistical analysis and ethical concerns

All data are expressed as mean ± standard deviation or median and range. Differences in continuous values were evaluated using the Student' *t* test or Mann-Whitney *U* test. Categorical data were compared using Fisher's exact probability test or Pearson's chi-squared test, as appropriate. Overall survival rates were estimated using the Kaplan-Meier method and compared by log-rank test. To analyze independent prognostic factors, we used a Cox proportional hazards regression model with stepwise comparisons. All analyses were carried out in IBM SPSS statistics version 21.0 (IBM Japan Business Logistics), and $P < .05$ was considered significant. The statistical expert in our laboratory performed all statistical analyses.

The study protocol was approved by the Human Ethics Review Committee of Osaka International Cancer Institute and Osaka University Hospital. Signed consent was obtained from each participant.

3 | RESULTS

3.1 | Patient characteristics

Patient characteristics are summarized in Table 1. Most patients had R0 resection, but one patient had an R1 resection (residual microscopic cancer). The pathological T factor (pT) from the UICC-TNM classification, 7th edition, was determined in patients with pathologically complete response (pCR), and pT1, pT2, pT3, or lymph node metastasis was observed in 40 patients (28.4%). The 5-year survival rate for the complete cohort was 34.1%, and recurrence was observed in 85 patients. We found no difference between the OICI and OHU groups for gender, tumor location, resectability status, CA19-9 level, or SUV-max before NACRT, but the groups did differ for age, chemotherapy regimen, total irradiation dose, and rate of recurrence (data not shown).

3.2 | Prognostic significance of CA19-9 status and FDG-PET after NACRT

Median CA19-9 value after NACRT was 31.0 (0.0-16 460) U/mL, which was significantly lower than the CA19-9 value before NACRT

TABLE 1 Characteristics of enrolled patients

	Total (n = 141)
Institute (OICI/OUH)	83/58
Age (years)	67.5 ± 9.1
Gender (male/female)	87/54
Tumor location (head/body-tail)	83/58
Tumor size (mm)	24.6 ± 9.6
Resectability status (Resectable/Borderline resectable)	102/39
CA19-9 (U/mL)	165 (0-14 795)
SUV-max	5.41 ± 3.62
Chemotherapy (Gem/Gem + S-1)	101/40
Irradiation dose (Gy) (40/50/60)	14/58/69
Operation (PD/DP/TP)	80/56/5
Surgical margin (R0/R1/R2)	140/1/0
Histology (poor/mod/well/pCR)	22/75/40/4
pT (pCR/T1/T2/T3)	4/23/7/107
pN (negative/positive)	101/40
Evans classification (I/IIA/IIB/III/IV)	14/65/45/13/4
Recurrence (no/yes)	56/85

Abbreviations: DP, distal pancreatectomy; OICI, Osaka International Cancer Institute; OUH, Osaka University Hospital; PD, pancreatoduodenectomy; SUV, standard uptake value; TP, total pancreatectomy.

(165.0 [0-14 795] U/mL; $P < .001$, Figure S2A). We divided the patients into two groups: those with normalized CA19-9 (≤37 U/mL) after NACRT (potentially normalized CA19-9 group, n = 82) and those without CA19-9 normalization after NACRT (CA19-9–elevated group, n = 59). The 82 patients in the potentially normalized CA19-9 group were further analyzed as two subgroups; those with elevated CA19-9 (>37 U/mL) before NACRT and normalized CA19-9 (≤37 U/mL) after NACRT (true normalized CA19-9 group, n = 46) and those with negative CA19-9 (≤37 U/mL) before NACRT (negative CA19-9 group, n = 36). Because survival in the negative CA19-9 group did not differ significantly from that of the other CA19-9 group (Figure S3), we defined the 82 patients with CA19-9 < 37 U/mL after NACRT as CA19-9 good responders and the remaining 59 patients in the CA19-9–elevated group as CA19-9 poor responders. Figure 1 shows disease-free and overall survival curves. The 5-year disease-free survival rate among CA19-9 good responders was 49.5%, which was significantly higher than in the poor responders subgroup (17.2%, $P < .001$; Figure 1A). The 5-year overall survival rate was 44.3% among the CA19-9 good responders, which was also significantly higher than among poor responders (19.5%, $P < .001$; Figure 1B).

Average SUV-max was significantly lower after NACRT (2.55 ± 1.29) than before NACRT (5.41 ± 3.62, $P < .001$; Figure S2B). Based on our previous study, we defined patients whose decrease ratio of SUV-max was ≥ 50% as PET good responders, and patients with a < 50% decrease ratio as PET poor responders.[18] Figure 1C,D shows the survival curve for each group, indicating that PET good responders had a significantly better prognosis than the poor responder group for both disease-free and overall survival (5-year disease-free survival rate: 48.5% vs 26.6%, $P = .001$; 5-year overall survival rate: 45.8% vs 24.6%, $P < .001$).

In the 82 patients in the CA19-9 good responder subgroup, 45 were PET good responders, and 37 were PET poor responders. The latter had significantly worse survival compared to those in the PET good responder group, despite also being in the CA19-9 good responder subgroup (Figure 2). These findings indicated the additional prognostic significance of PET status added to CA19-9 status in the evaluation of NACRT response.

3.3 | Relationship between CA19-9/PET status and patterns of recurrence

Figure 3A,B shows the cumulative incidence of distant and local recurrence according to CA19-9 status. As shown in Figure 3A, the CA19-9 good responder subgroup had a significantly lower incidence of distant recurrence, without a significant difference in local site recurrence between the CA19-9 good and poor responders (Figure 3B). This result indicated that an absence of CA19-9 normalization after NACRT suggests a residual systemic tumor burden after preoperative treatment and subsequent surgery.

Figure 3C,D shows the pattern of recurrence according to PET status. In contrast to CA19-9 status, PET good responders had a significantly lower incidence of local and distant recurrence compared to PET poor responders (Figure 3C,D). These observations indicated that an unfavorable PET status may indicate a more aggressive tumor biology and resistance to NACRT in local and systemic diseases.

3.4 | Relationship between CA19-9/PET status and histological response and nodal status

For this part of the analysis, we divided patients into histological poor responders, grade I/IIA (n = 79), and histological good responders, grade IIA/III/IV (n = 62), based on histological response per Evans et al[21]. As shown in Table 2, PET status was significantly related to histological response status ($P = .003$), but CA19-9 status was not ($P = .175$). PET and CA19-9 status both showed significant associations with lymph node status ($P = .021$ and 0.002, respectively), with CA19-9 status showing the stronger association (Table 2).

3.5 | Prognostic impact of combining CA19-9 status and SUV-max (combination status)

Of the 141 patients enrolled in this study, 45 were classified as both CA19-9 and PET good responders, 37 as CA19-9 good responders but PET poor responders, 19 as CA19-9 poor responders and PET good responders, and the remaining 40 as poor responders for

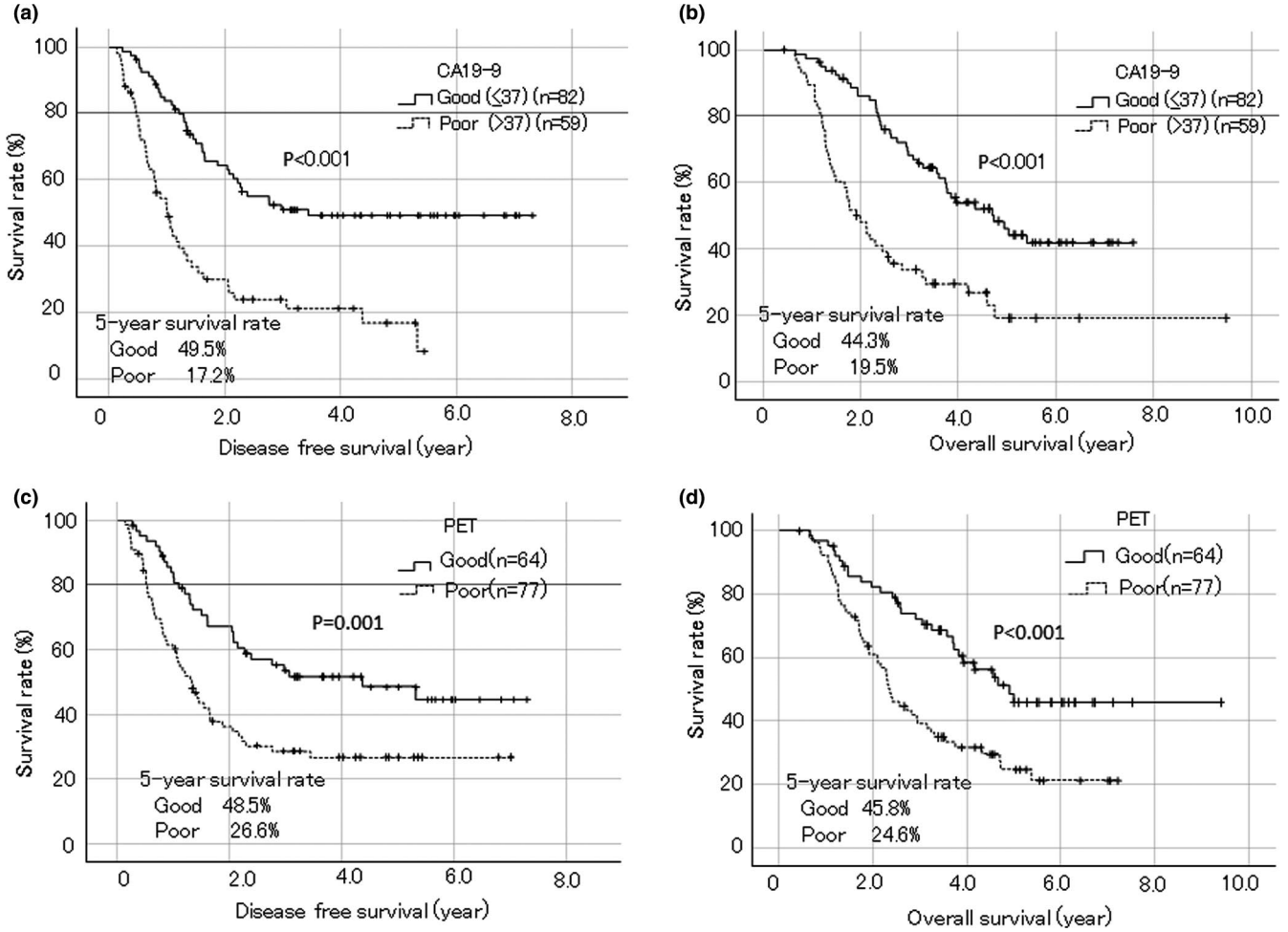

FIGURE 1 Disease-free survival (A) and overall survival (B) of CA19-9 good responder group (patients with CA19-9 normalization after NACRT, n = 82) were significantly better than those of CA19-9 poor responder group (patients without CA19-9 normalization after NACRT, n = 59). Disease-free survival (C) and overall survival (D) of PET good responder group (patients with > 50% SUV-max decrease after NACRT, n = 64) were significantly better than those of SUV-max poor responder group (patients with < 50% SUV-max decrease, n = 77)

both CA19-9 and PET. As shown in Figure 4A, the group of good responders on both measures had better survival than the other three groups, with a 5-year survival rate of 56.0%, which was significantly higher than the other groups combined (23.8%, $P < .001$; Figure 4B).

On univariate analysis, tumor size before NACRT, tumor size after NACRT, CA19-9 value before NACRT, CA19-9 value after NACRT, combination status, and resectability status were significant prognostic factors (Table 3). On multivariate analysis using these six factors, however, only the combination status and resectability status were independent prognostic factors, with the combination status emerging as the more powerful of the two (Table 3).

4 | DISCUSSION

An appropriate evaluation of the response to neoadjuvant treatment and accurate identification of optimal candidates for subsequent surgery are key to improving outcomes for patients with PDAC treated using a neoadjuvant treatment strategy.[7,22,23] Several approaches are possible for evaluating the response to neoadjuvant treatment before subsequent surgery. An alteration of tumor markers is a standard method in various malignant diseases, and increasing clinical evidence highlights the prognostic implications of CA19-9 normalization during this treatment for PDAC, as shown in the current study.[9-12] We also found that changes in FDG uptake during neoadjuvant treatment were significantly associated with pancreatectomy outcomes. More important, even in the CA19-9 good responders, an unfavorable PET status was associated with impaired survival. The 5-year survival was 44% in patients with a CA19-9 favorable status only (normalized CA19-9), but increased to 56% in patients who had good response based on both CA19-9 and PET. These findings indicate an additional impact of PET status on CA19-9 measures in evaluating response to neoadjuvant treatment. Evaluation of the combination status allowed for more accurate identification of patients who would likely benefit from the subsequent surgery.

We also note that only patients with a favorable response in terms of both CA19-9 (normalization) and PET status (>50% decrease in SUV-max) after NACRT gained the optimal prognostic benefit from our treatment strategy. Survival of patients with favorable status for only one of these measures was not significantly improved

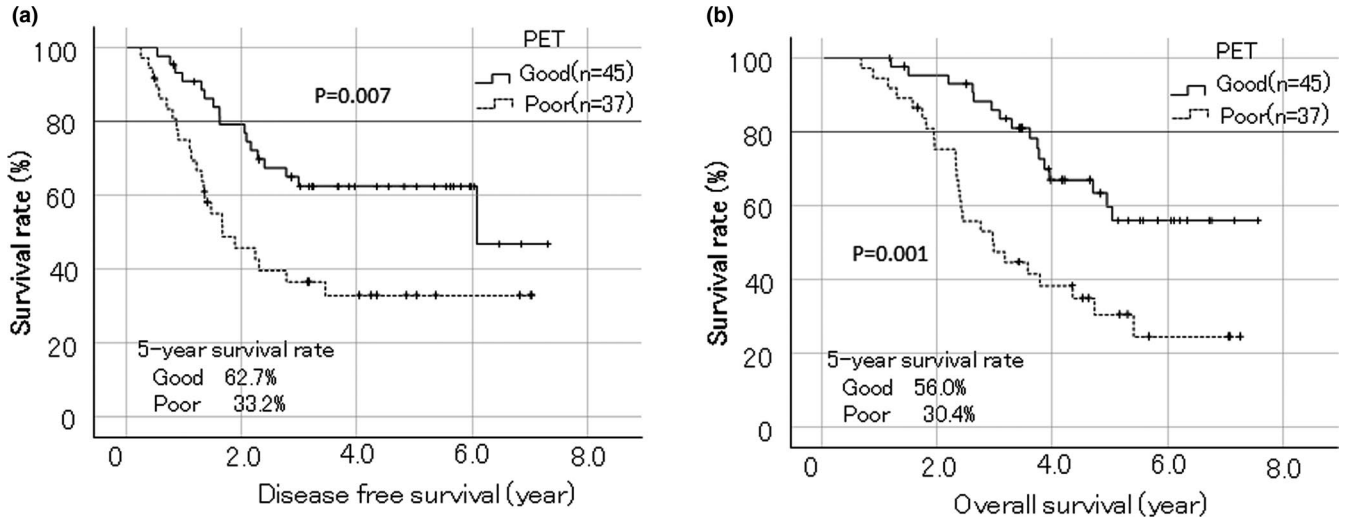

FIGURE 2 In the 82 patients in the CA19-9 good responder subgroup, 45 were PET good responders, and 37 were PET poor responders. The latter had significantly worse disease-free survival (A) and overall survival (B) compared to those in the PET good responder group, despite also being in the CA19-9 good responder subgroup

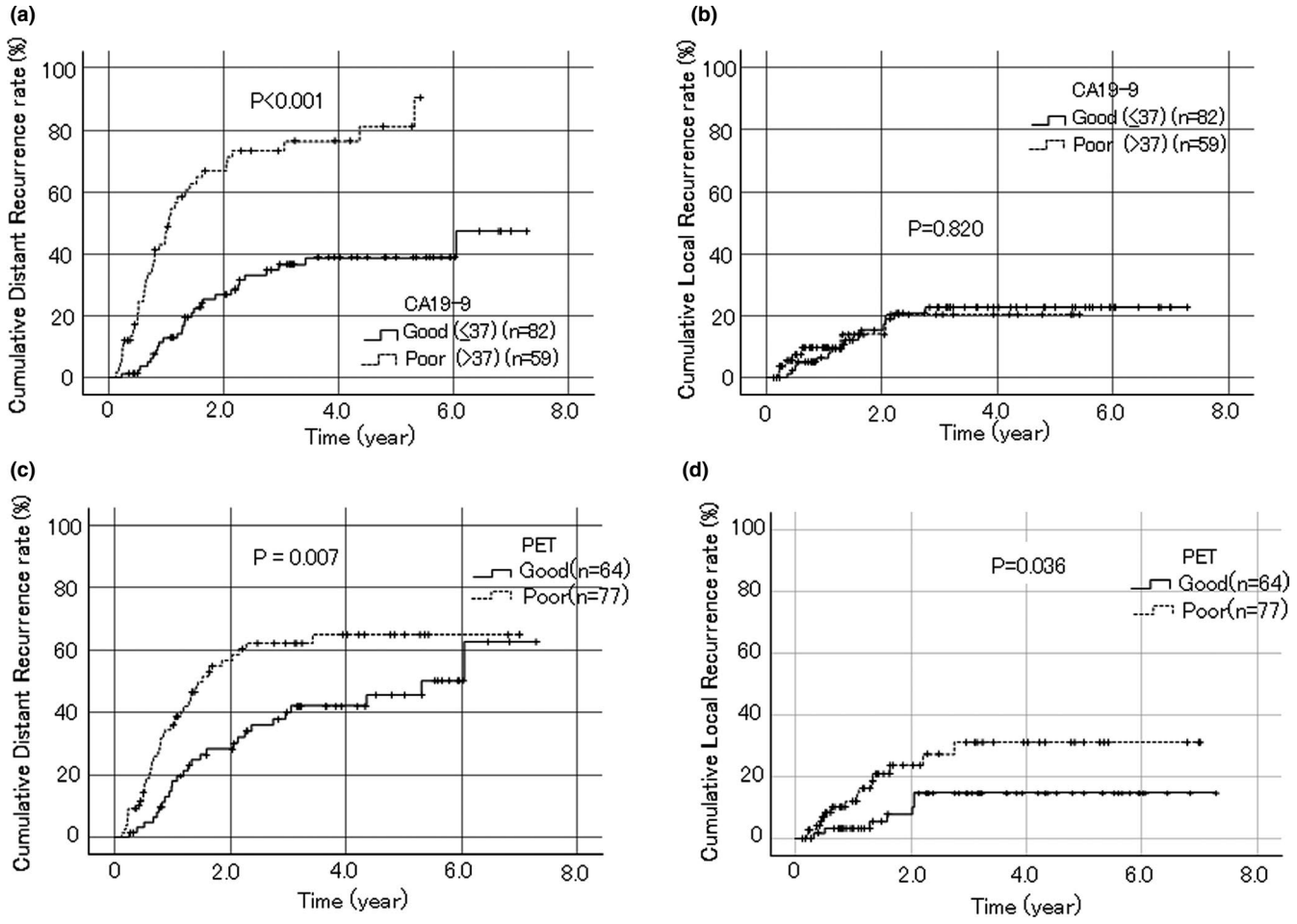

FIGURE 3 CA19-9 good responders had a significantly lower incidence of distant recurrence, without a significant difference in local site recurrence between the CA19-9 good and poor responders (A, B). PET good responders had a significantly lower incidence of local and distant recurrence compared to PET poor responders (C, D)

compared to having an unfavorable status on both. Although an unfavorable status for either CA19-9 or PET after NACRT does not necessarily preclude surgical intervention, care is necessary for proceeding to surgery because these patients are at high risk for early tumor recurrence after pancreatectomy. Thus, patients without a favorable response per CA19-9 or PET status might fare better with additional chemotherapy using more effective agents (eg, FOLFIRINOX and Gem+nab-PTX) and re-evaluation of CA19-9 and PET status instead of immediate radical surgery after NACRT.[24,25]

We also carried out a detailed comparative analysis regarding patterns of recurrence according to CA19-9 and PET status. Our results showed that an unfavorable status on CA19-9 and PET was associated with different profiles of tumor recurrence depending on whether it involved one of the measures alone or both. For identifying patients at high risk for local recurrence, FDG-PET was more useful than CA19-9 in our patient group. FDG-PET is a functional imaging modality that can detect changes in tissue metabolism, and FDG uptake is strongly associated with tumor aggressiveness. Yamamoto et al reported that a high SUV (SUV-max ≥ 6.0) was significantly associated with microscopic locoregional tumor extension in PDAC and that survival after resection with high SUV was notably poor.[26] This observation indicated a profound local aggressiveness of high SUV PDAC, which is in agreement with our findings of a significant association of an insufficient decrease in FDG uptake with impaired histological response and unfavorable local control.

In identifying patients at high risk for distant recurrence, CA19-9 status was more significant than PET status, although an unfavorable status with either was associated with a higher incidence of distant recurrence. Previous reports indicated that a lack of CA19-9 normalization after pancreatectomy is significantly associated with distant metastasis in a surgery-first approach for PDAC.[27] Motoi et al found a significantly higher incidence of liver metastasis in patients with sustained elevation of postoperative CA19-9 compared to those with normalized postoperative CA19-9.[27] Our findings of a significantly high risk for distant recurrence in patients without normalized CA19-9 after presurgical neoadjuvant treatment can be considered a counterpart of these previous results in the surgery-first approach. Certainly, it is not surprising that

TABLE 2 Relationship between each status and pathological findings

	Evans classification		LN metastasis	
	Good/Poor	*P* value	Negative/Positive	*P* value
PET status				
Good (n = 64)	37/27	.003	52/12	.021
Poor (n = 77)	25/52		49/28	
CA19-9 status				
Good (n = 82)	40/42	.175	67/15	.002
Poor (n = 59)	22/37		34/25	

Note: Evans classification good: Evans grade IIA/III/IV, Evans classification poor: Evans grade I/IIA. PET status good: Patients with a ≥ 50% decrease ratio of SUV-max after NACRT; PET status poor: Patients with a < 50% decrease ratio of SUV-max after NACRT; CA19-9 status good: patients with normalized CA19-9 after NACRT; CA19-9 status poor: patients without CA19-9 normalization after NACRT.
Abbreviation: LN, lymph node.

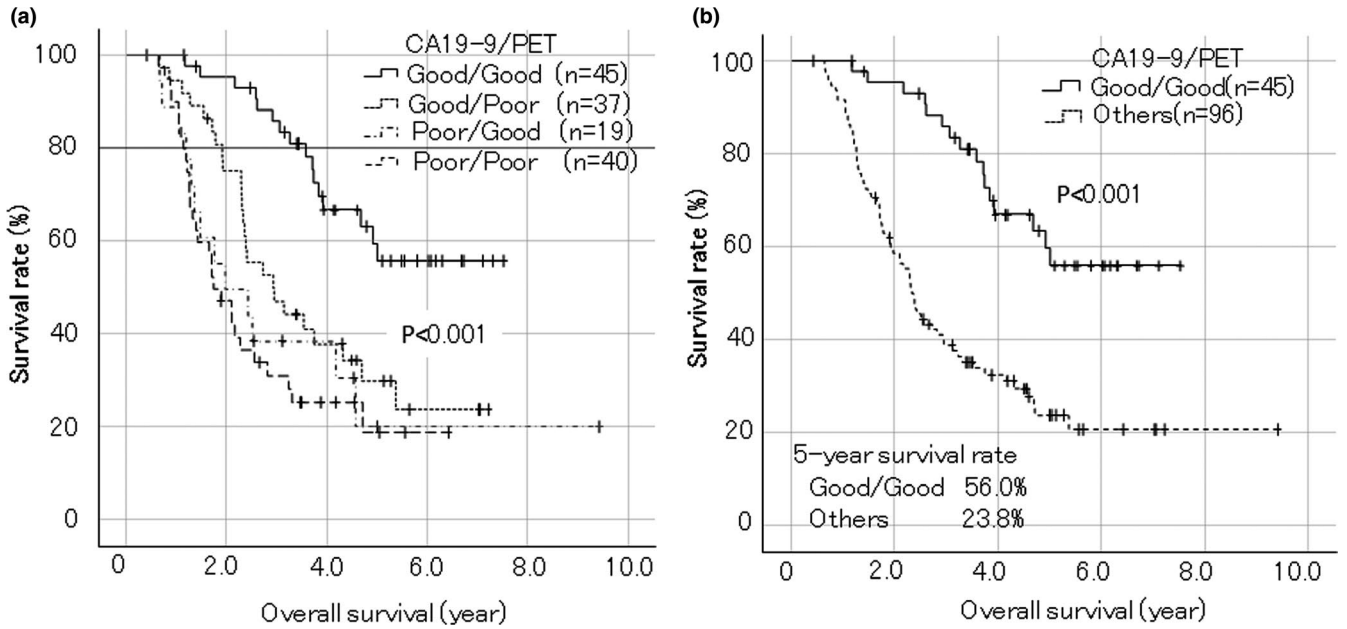

FIGURE 4 The group of good responders on both CA19-9 and PET had better survival than the other three groups ($P < .001$) with a 5-year survival rate of 56.0%, which was significantly higher than the other groups combined (23.8%, $P < .001$; B). In four groups according to the combination of CA19-9 and SUV-max status, only the CA19-9 good/PET good group (n = 45) showed a significantly better survival curve than the other three groups (A). The 5-year survival rate was 56.0% in the CA19-9 good/PET good group, which was significantly higher than that of the others (23.8%, $P < .001$)

TABLE 3 Analysis of prognostic factor by Cox hazard model

	Univariate analysis		Multivariate analysis	
	Hazard ratio	*P* value	Hazard ratio	*P* value
Gender (Female/Male)	1.149 (0.741-1.782)	0.534		
Age (years) (≥70/<70)	0.930 (0.603-1.433)	0.742		
Pre-tumor size (mm) (>20/≤20)	1.630 (1.025-2.591)	0.039	1.075 (0.601-1.927)	0.806
Post-tumor size (mm) (>20/≤20)	1.899 (1.231-2.928)	0.004	1.111 (0.638-1.934)	0.709
Decrease ratio of tumor size (%) (<30/≥30)	1.322 (0.840-2.083)	0.228		
Pre-CA19-9 (U/mL) (≥500/<500)	1.996 (1.224-3.247)	0.006	1.261 (0.707-2.248)	0.432
Post-CA19-9 (U/mL) (≥500/<500)	3.165 (1.269-7.874)	0.013	1.963 (0.683-5.643)	0.210
Pre-SUV-max	1.005 (0.943-1.071)	0.872		
Post-SUV-max	1.302 (1.122-1.510)	0.001	1.086 (0.903-1.306)	0.383
Combination status (Other/Good-Good)	3.371 (1.946-5.837)	<0.001	2.765 (1.553-4.922)	0.001
Resectability status (BR/R)	2.420 (1.540-3.803)	<0.001	2.162 (1.321-3.540)	0.002

Abbreviations: BR, borderline resectable; R, resectable.

sustained elevation of CA19-9 after the eradication of locoregional tumor burden, such as with pancreatectomy or CRT, indicates the presence of occult systemic disease. In the setting of NACRT in this study, the improved eradication of local tumor burden because of CRT followed by pancreatectomy minimized the difference in local control regardless of CA19-9 status after NACRT. In this way, the difference in occult residual systemic tumor burden was maximized and became more evident for patients with normalized CA19-9 versus those without.

The current study has several limitations. First, it is retrospective, so significant selection bias was inevitable. Furthermore, the regimen of preoperative CRT differed between the two institutes, with a variety of chemotherapy agents and dose of irradiation, so the response to treatment and outcome after radical surgery could be different. In addition, the regimen of postoperative treatment was also different. In OICI, we usually performed liver perfusion chemotherapy (LPC) for the prevention of postoperative liver metastasis followed by systemic chemotherapy, whereas in OUH, only systemic chemotherapy was performed postoperatively. Certainly, the recurrence rate after radical surgery at OUH was significantly higher than at OICC, although the significance with CA19-9 and FDG-PET was similar at each institute, which adds strength to our results. Second, our conclusion is based on patients with PDAC receiving NACRT as preoperative therapy, and patients receiving neoadjuvant chemotherapy (NAC) were not included. Radiotherapy can have a strong locoregional anticancer effect, and we think that this effect might explain the relevance of PET status in adding to the prognostic significance of CA19-9 status, which is a good indicator of systemic effect. Further analysis is necessary to evaluate the utility of FDG-PET in combination with CA19-9 for the assessment of preoperative chemotherapy in PDAC patients.

In conclusion, we have identified the additional utility of FDG-PET in combination with CA19-9 in evaluating the efficacy of NACRT for PDAC. An unfavorable CA19-9 status indicated a high risk for distant recurrence, and an unfavorable PET status was associated with a high risk for local recurrence. Neoadjuvant treatment efficacy was maximized only in patients with a favorable status with both CA19-9 and PET. The response evaluation of neoadjuvant treatment using multiple methods enables more accurate risk assessment for treatment failure and potentially contributes to the optimization of treatment strategy in each patient with PDAC.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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