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ORIGINAL ARTICLE – PANCREATIC TUMORS

Significance of ^{18}F-Fluorodeoxyglucose (FDG) Uptake in Response to Chemoradiotherapy for Pancreatic Cancer

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ABSTRACT

Background. A metabolic shift to glycolysis is reportedly involved in radioresistance. We examined whether pretreatment ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), which can detect enhanced glucose uptake, was able to predict the therapeutic response to chemoradiotherapy (CRT) in patients with pancreatic cancer (PC).

Methods. Of 125 PC patients (75 unresectable and 50 borderline resectable), 37 and 26 underwent induction chemotherapy before CRT and surgical resection after CRT, respectively. FDG-PET was performed at three different institutions.

Results. Of the 88 patients who underwent upfront CRT, 31 (35%), 34 (39%), and 23 (26%) showed a partial response (PR), stable disease, and progressive disease, respectively. The tumor PR rate was an independent factor associated with longer overall survival (OS) on multivariate analysis. We evaluated the optimal cut-off of maximum standardized uptake values (SUV_{max}) at initial diagnosis to detect the tumor PR rate at the three institutions separately. The SUV_{max} was independently associated with tumor response rate on multivariate analysis. In the low SUV_{max} group, induction chemotherapy had no significant impact on OS. In contrast, induction chemotherapy was significantly associated with longer OS in the high SUV_{max} group.

Conclusions. FDG-PET SUV_{max} was significantly associated with the therapeutic response to CRT in PC patients. Moreover, induction chemotherapy may improve the prognosis of patients with a high SUV_{max} tumor.

Pancreatic cancer (PC) shows aggressive local invasion and frequent distant metastases, with a 5-year survival rate of 7%.[1] Aggressive local invasion to surrounding vessels and organs often precludes curative surgical resection.[2] Chemoradiotherapy (CRT) is administered as a radical treatment in patients with unresectable (UR) locally advanced disease, or as neoadjuvant CRT (NACRT) in those with borderline resectable (BR) disease.[3–5] The purposes of NACRT include achieving R0 resection following local control of the primary tumor, sterilization of metastatic lymph nodes, and selection of patients who might benefit from surgical resection.[6] Among resected cases, patients with a pathologically poor response to NACRT have significantly worse survival than those with a moderate-to-good response.[7,8] We administered CRT for locally advanced PC and reported the therapeutic effect.[4] For a successful therapeutic effect, tumor radiosensitivity is critical in the use of CRT.

Cancer cells can alter their energy metabolism from oxidative phosphorylation to aerobic glycolysis, resulting in higher rates of glucose uptake and lactate production, to survive and proliferate in non-native settings under nutrient and oxygen deprivation.[9,10] This is known as the Warburg effect.[11] The metabolic shift to glycolysis is involved in

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radioresistance.[12,13] Transmembrane glucose transporter type 1 (GLUT-1) mediates the first rate-limiting step in glucose transport across the plasma membrane.[14] Several previous studies have revealed increased GLUT-1 expression in PC tissues compared with adjacent non-cancerous controls, and a significant association between increased GLUT-1 expression and poor prognosis.[15–17]

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been used to study different types of cancer,[18] and its role in the management of patients with PC has increased, not only for the diagnosis of primary tumors and distant metastases but also for antitumor therapeutic response evaluation.[19–22] The most widely used PET-derived parameter is the maximum standardized uptake value (SUV_{max}), which is designed to measure tracer accumulation in PET and quantifies the glucose metabolic uptake rate in cancer cells.[23] FDG-PET SUV_{max} was reported to be associated with GLUT-1 expression.[24,25] PC patients with high SUV_{max} or a small metabolic response during chemotherapy showed poor prognosis.[19–22]

We examined whether pretreatment FDG-PET could predict the therapeutic response to CRT in PC patients. For accurate analysis, it is important to avoid the influence of several factors, such as differences in the device used for FDG-PET, imaging protocol, and hyperglycemia in diabetic patients.[26,27] Furthermore, we evaluated the effect of induction chemotherapy before CRT according to the SUV_{max}.

MATERIALS AND METHODS

Patient and Tumor Sampling

Of 166 patients with BR or locally advanced UR PC treated at the Department of Digestive Surgery, Breast and Thyroid Surgery, Kagoshima University, from January 2006 to December 2015, 21 were excluded from the study because they did not undergo FDG-PET before treatment, and 20 were excluded because their blood glucose levels before FDG-PET/computed tomography (CT) were > 150 mg/dL. The remaining 125 patients were enrolled in our study, which was approved by the institutional Ethics Review Board of our hospital. We defined BR and UR according to the National Comprehensive Cancer Network guidelines (version 2.2017).[28] Histologic or cytologic evidence of adenocarcinoma of the pancreas was obtained before treatment. The median follow-up period was 18.2 months (mean 25.4 months).

Treatment Course

CRT regimens included hyperfractionated accelerated radiotherapy administered with S-1 (TS-1; Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) at 80 mg/m^2 for the first 21 days.[29] A total of 50–58 Gy was administered in 40 fractions over 4 weeks. At 1 month after CRT completion, S-1 was administered for 2 weeks, followed by a 2 weeks rest period. Since 2011, induction chemotherapy before CRT has been performed in 37 patients on the basis of each physician's decision. The most common induction chemotherapy regimen was gemcitabine plus S-1 (TS-1; Taiho Pharmaceutical Co., Ltd; $n = 21$), followed by S-1 ($n = 8$), gemcitabine plus nab-paclitaxel (PTX; $n = 7$), and gemcitabine ($n = 1$).

Radiological Examinations

All patients underwent whole-body FDG-PET before treatment at three different institutions (institution A: Kagoshima University; institution B: Atsuchi Memorial Clinic; and institution C: Nanpu Hospital), according to each institution's own protocol. The Discovery 600 M (GE Medical Systems, Waukesha, WI, USA), Discovery ST (GE Medical Systems), and Discovery ST Elite (GE Medical Systems) devices were used at institutions A, B, and C, respectively. Patients fasted for 5 h before intravenous administration of FDG, and FDG-PET images were acquired 120 min after FDG administration. SUV was automatically calculated as the activity concentration [^{18}F-FDG uptake divided by the injected dose of ^{18}F-FDG (dose/g body weight)]. SUV_{max} equals the organic radioactivity [(MBq/g)/^{18}F-FDG (MBq/g body weight)] and was calculated for the primary pancreatic tumor. Other imaging examinations, including contrast-enhanced CT and magnetic resonance imaging, were performed before and 1 month after CRT and every 3 months afterwards. We evaluated the tumor response rate 3 months after CRT according to the Response Evaluation Criteria in Solid Tumors (RECIST).[25]

Statistical Analysis

Associations between different categorical variables were assessed using the Chi square or Fisher's exact tests. A multivariate regression model was used to estimate the odds ratio (OR) and corresponding 95% confidence intervals (CIs), using factors found significant on univariate analysis as covariates. Analysis of variance was used to compare continuous variables. Receiver operating characteristic curve analysis of the SUV_{max} was performed to assess its ability to predict the tumor response rate. Survival curves were plotted using the Kaplan–Meier method

and analyzed using the log-rank test. Overall survival (OS) was calculated as the interval between initial treatment and death of any cause, whereas progression-free survival (PFS) was calculated as the interval between initial treatment and disease progression. The multivariate Cox proportional hazards model was used to estimate the adjusted hazard ratio (HR) and corresponding 95% CIs. A p value < 0.05 was considered statistically significant. Statistical evaluation was performed using SigmaPlot version 12.5 for Windows (HULINKS, Inc., Tokyo, Japan).

RESULTS

Patient Characteristics

Baseline demographic and clinical data for all patients are summarized in electronic supplementary Table 1. There were 50 BR and 75 UR PC patients, and 26 (21%) underwent surgical resection after CRT. There was no significant difference in the clinical profile at initial diagnosis between patients who underwent upfront CRT and those who underwent induction chemotherapy before CRT. Of the 37 patients who underwent induction chemotherapy, two did not undergo subsequent CRT because of distant metastasis during induction chemotherapy (electronic supplementary Fig. 1).

Survival Analysis in Patients Who Underwent Upfront Chemoradiotherapy (CRT)

Of the 88 patients who underwent upfront CRT, 31 (35%), 34 (39%), and 23 (26%) showed a partial response (PR), stable disease (SD), and progressive disease (PD), respectively, 3 months after CRT, according to the RECIST criteria. The most common reason for PD was distant metastasis (20/23, 87%), followed by enlargement of the primary tumor size (3/23, 13%). The tumor response rate was significantly associated with OS rates (Fig. 1). Overall median survival times (MSTs) of patients with PR, SD, and PD were 35.0 (95% CI 29.1–40.9), 16.0 (95% CI 13.1–18.9), and 9.0 (95% CI 6.1–11.9) months, respectively.

Association between FDG-PET Maximum Standardized Uptake Values (SUV_{max}) and Tumor Response Rate in Patients Who Underwent Upfront CRT

Because the three institutions used different devices for FDG-PET, we evaluated the FDG-PET SUV_{max} at initial diagnosis at each institution separately (electronic supplementary Table 2). SUV_{max} tended to differ among the three institutions, instead of similar tumor size. The mean

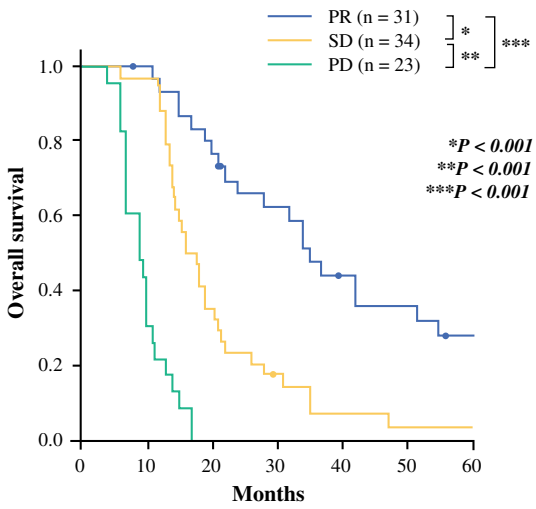

FIG. 1 Kaplan–Meier survival curves of OS rates in patients who underwent upfront CRT. There was a significant difference in OS rates according to the tumor response rate 4 months after CRT. *CRT* chemoradiotherapy, *OS* overall survival, *PD* progressive disease, *PR* partial response, *SD* stable disease

SUV_{max} at institutions *A*, *B*, and *C* was 9.6 (± 4.1), 7.4 (± 2.3), and 8.3 (± 2.8), respectively. Electronic supplementary Fig. 2 shows the SUV_{max} distribution for all patients who underwent upfront CRT, by institution. The optimal SUV_{max} cut-off values to predict tumor PR rate after upfront CRT at each institution were 9.4, 6.1, and 9.8, respectively (Fig. 2). We then evaluated the association between SUV_{max} cut-off values and tumor response rate in 88 patients (electronic supplementary Table 3). Sensitivity, specificity, and accuracy were 87%, 65%, and 73%, respectively. Furthermore, we evaluated the association between SUV_{max} cut-off values and distant metastasis (electronic supplementary Table 4). Patients with SUV_{max} more than the cut-off values exhibited a significantly higher rate of distant metastasis 3 months after upfront CRT. Table 1 shows the association between clinical factors and tumor response rate. Tumor size > 30 mm, UR status, and FDG-PET SUV_{max} more than the cut-off values were significantly associated with tumor response rate SD/PD on univariate analysis. Furthermore, SUV_{max} greater than the cut-off values was independently associated with tumor response rate SD/PD on multivariate analysis (OR 11.094, 95% CI 3.298–37.321).

Prognostic Impact of FDG-PET SUV_{max}

Tumor size > 30 mm, cN status, serum carbohydrate antigen (CA) 19-9 level > 500 U/mL, and FDG-PET SUV_{max} greater than the cut-off value were significantly associated with longer OS on univariate analysis, while cN status, serum CA19-9 level > 500 U/mL, and FDG-PET

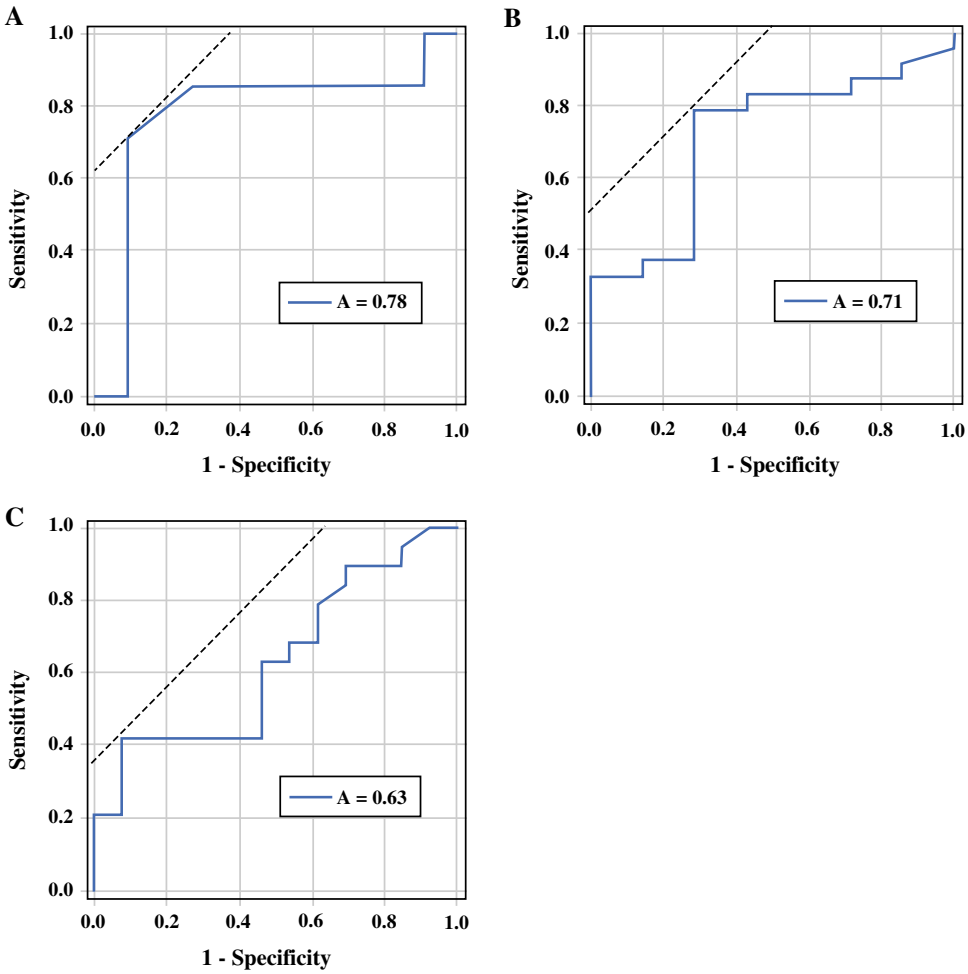

FIG. 2 The optimal cut-off values of FDG-PET SUV_{max} to predict tumor PR rate were calculated from receiver operating characteristic curves at three institutions: **a** Institution A (9.4). **b** Institution B (6.1) and **c** Institution C (9.8). *FDG-PET* ^{18}F-fluorodeoxyglucose positron emission tomography, *PR* partial response, *SUV_{max}* maximum standardized uptake value

SUV_{max} greater than the cut-off value were independent prognostic factors on multivariate analysis (Table 2).

Effect of Prognostic Improvement by Induction Chemotherapy According to FDG-PET SUV_{max}

We examined the impact of induction chemotherapy on OS rates according to the FDG-PET SUV_{max} (Fig. 3). All patients were divided into two groups according to the association between SUV_{max} and cut-off values—those with an SUV_{max} equal to or less than the cut-off values (low SUV_{max} group) and those with SUV_{max} more than the cut-off values (high SUV_{max} group). Induction chemotherapy had no significant impact on OS (Fig. 3a) in the low SUV_{max} group, but was significantly associated with longer OS in the high SUV_{max} group (Fig. 3b). The MSTs of patients who underwent upfront CRT and induction chemotherapy were 22.0 (95% CI 16.7–27.3) and 23.0 (95% CI 17.0–29.0) months, respectively, in the low SUV_{max} group, and 14.0 (95% CI 12.2–15.8) and 23.2 (95% CI 16.2–30.2) months, respectively, in the high SUV_{max} group. In addition, we examined the impact of induction chemotherapy on PFS according to the FDG-PET SUV_{max} (electronic supplementary Fig. 3). Induction chemotherapy had no significant impact on PFS in the low SUV_{max} group (electronic supplementary Fig. 3a), but was significantly associated with longer PFS in the high SUV_{max} group (electronic supplementary Fig. 3b). The MSTs of patients who underwent upfront CRT and induction chemotherapy were 14.0 (95% CI 11.3–16.7) and 19.9 (95% CI 9.8–30.0) months, respectively, in the low SUV_{max} group, and 7.0 (95% CI 5.3–8.7) and 15.0 (95% CI 10.0–20.0) months, respectively, in the high SUV_{max} group.

DISCUSSION

Although CRT for locally advanced PC has a more powerful local control effect compared with chemotherapy, the overall prognostic impact is controversial.[30] Prediction of the CRT therapeutic effect may lead to improved OS. Association between increased aggressiveness and metabolic change, which has long been recognized as a central hallmark of cancer cells, is attracting attention in

TABLE 1 Association between clinical factors and tumor response rate 4 months after CRT in patients with PC who underwent upfront CRT (n = 88)

Factors		Response rate		p value	OR (95% CI)	p value
		SD/PD	PR			
Age, years	< 70 (51)	36	15	0.265		
	≥ 70 (37)	21	16			
Sex	Male (47)	30	17	0.980		
	Female (41)	27	14			
Tumor location	Head (56)	36	20	0.916		
	Body/tail (32)	21	11			
Tumor size, mm	≤ 30 (40)	20	20	0.015	1.563	0.449
	> 30 (48)	37	11		(0.191–4.975)	
Serum	≤ 500 U/mL (67)	42	25	0.638		
CA19-9	> 500 U/mL (21)	15	6			
Resectability	BR (36)	18	18	0.029	1.806	0.311
	UR (52)	39	13		(0.575–5.669)	
FDG-PET	Less than or equal to the cut-off (47)	20	27	< 0.001	11.094	< 0.001
SUV_{max}	Greater than the cut-off (41)	37	4		(3.298–37.321)	

BR borderline resectable, *CA19-9* carbohydrate antigen 19-9, *CI* confidence interval, *CRT* chemoradiotherapy, *FDG-PET* ^{18}F-fluorodeoxyglucose positron emission tomography, *OR* odds ratio, *PC* pancreatic cancer, *PD* progressive disease, *PR* partial response, *SD* stable disease, *SUV* standardized uptake value, *UR* unresectable

TABLE 2 Association between clinical factors and OS in patients with PC (n = 125)

Factors		Univariate analysis		Multivariate analysis	
		MST, months (95% CI)	p value	HR (95% CI)	p value
Age, years	< 70 (72)	17.0 (14.3–19.7)	0.219		
	≥ 70 (53)	21.4 (16.4–26.4)			
Sex	Male (66)	18.0 (14.6–21.4)	0.971		
	Female (59)	19.5 (14.8–24.2)			
Tumor location	Head (76)	16.0 (12.4–19.6)	1.000		
	Body/tail (49)	21.0 (19.4–22.6)			
Tumor size, mm	≤ 30 (56)	23.0 (17.4–28.6)	0.015	1.386	0.164
	> 30 (69)	17.0 (13.8–20.2)		(0.875–2.196)	
cN status	0 (77)	22.0 (18.5–22.5)	0.002	2.038	< 0.001
	1 (48)	13.5 (12.1–14.9)		(1.355–3.065)	
Serum	≤ 500 U/mL (96)	21.0 (18.5–23.5)	0.017	1.920	0.005
CA 19-9	> 500 U/mL (29)	13.7 (12.1–15.3)		(1.221–3.020)	
Resectability	BR (50)	22.0 (13.1–30.9)	0.140		
	UR (75)	17.8 (15.5–20.1)			
FDG-PET	Less than or equal to the cut-off (69)	22.0 (18.4–25.6)	0.013	1.585	0.048
SUV_{max}	Greater than the cut-off (56)	14.0 (12.4–15.6)		(1.004–2.502)	

BR borderline resectable, *CA19-9* carbohydrate antigen 19-9, *CI* confidence interval, *FDG-PET* ^{18}F-fluorodeoxyglucose positron emission tomography, *HR* hazard ratio, *MST* median survival time, *OS* overall survival, *PC* pancreatic cancer, *SUV* standardized uptake value, *UR* unresectable

developing metabolism-targeted diagnosis and therapy.[9] The effects of radiotherapy, which are partly due to radiation-induced radical and oxidative stress, can reportedly be reduced in tumor cells via upregulation of their

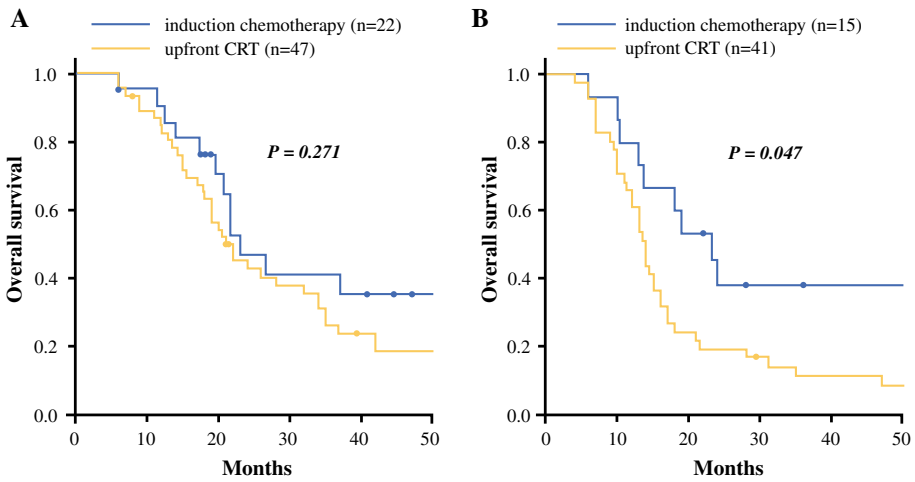

FIG. 3 Kaplan–Meier survival curves of OS rates from the initial treatment. **a** Induction chemotherapy had no significant prognostic impact in the low SUV_{max} group ($p = 0.271$). **b** Induction chemotherapy was significantly associated with longer OS in the high SUV_{max} group ($p = 0.047$). *CRT* chemoradiotherapy, *OS* overall survival, *SUV_{max}* maximum standardized uptake value

endogenous antioxidant capacity through accumulation of pyruvate and lactate caused by increased glycolysis in cancer cells.[12,13] In our study, we revealed that FDG-PET, which can detect altered glucose uptake in cancer cells, before treatment was significantly associated not only with OS but also tumor response rate after upfront CRT in patients with UR or BR PC.

Many studies reported the usefulness of FDG-PET in the diagnosis and therapeutic evaluation of patients with PC.[19–22] Mellon et al.[31] revealed that FDG-PET SUV_{max} after NACRT was significantly associated with histopathologic tumor regression. Recent studies have demonstrated that high tumor SUV_{max} was significantly associated with a high incidence of distant metastases after CRT for patients with locally advanced PC,[32] and with recurrence in the distant organs after surgical resection.[33] In our study, the most common reason for PD at 3 months after CRT was distant metastasis. PC cells with a high tumor SUV_{max} may have a high potential for developing distant metastases. FDG-PET may be useful in selecting PC patients who will benefit from upfront CRT due to high radiosensitivity and low risk of distant metastasis.

PC arises and acquires a more aggressive phenotype via various genetic mutations, including KRAS, TP53, CDKN2A/p16, and SMAD4/DPC4, leading to oncogenic activation and loss of tumor-suppressor gene function.[34] Shi et al.[35] revealed that mutations in TP53, CDKN2A/p16, and SMAD4/DPC4 caused elevation of GLUT-1 expression and aberrant glucose metabolism, while we revealed that GLUT-1 expression evaluated before treatment was significantly associated with the therapeutic response to CRT for PC.[36] GLUT-1 may be a useful predictor for the therapeutic effect of CRT; however, adequate amounts of specimens obtained through endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) biopsy are required for the accurate evaluation of GLUT-1 expression. Several studies demonstrated that GLUT-1 expression was significantly associated with FDG-PET SUV_{max}.[24,25] FDG-PET SUV_{max}, a less invasive examination than EUS-FNA, was significantly associated with the therapeutic response to CRT in our study. However, elevated serum glucose levels in diabetic patients may impair the ability of FDG-PET to detect metabolic change in cancer cells.[27] We expect FDG-PET and evaluation of GLUT-1 expression through EUS-FNA to have complementary roles in predicting the therapeutic response to CRT for PC patients.

Due to its retrospective nature, our study has several limitations. First, there were no defined criteria for induction chemotherapy before CRT or resection after CRT. Second, our study included various induction chemotherapy regimens. To confirm the prognostic impact of induction chemotherapy, further prospective studies including the same treatment regimen are required. Third, patients underwent FDG-PET at three different institutions. FDG-PET SUV_{max} is influenced by several factors, including the scanner, workstation, and imaging protocol.[26] Nevertheless, each SUV_{max} was significantly associated with the tumor response rate after CRT. Despite the absence of standardized cut-off values, FDG-PET may be useful in universally predicting the therapeutic effect of CRT. To determine standardized cut-off values of SUV_{max}, further analyses are required. Fourth, because we excluded patients who did not undergo FDG-PET before treatment, we could not analyze consecutive patients. Nevertheless, we found that FDG-PET is a useful predictor of the therapeutic response to CRT for PC patients. Furthermore, our findings suggest there are benefits of induction chemotherapy before CRT for patients with PC and high FDG-PET SUV_{max}.

CONCLUSION

Our study demonstrates that FDG-PET SUV_{max} is significantly associated with therapeutic response to CRT for PC patients. Patients with low SUV_{max} in the primary tumor showed better tumor response and prognosis than those with high SUV_{max}. Moreover, induction chemotherapy may improve the prognosis of patients with high SUV_{max} tumors.

DISCLOSURE Hiroshi Kurahara, Kosei Maemura, Yuko Mataki, Masahiko Sakoda, Satoshi Iino, Yota Kawasaki, Takaaki Arigami, Shinichiro Mori, Yuko Kijima, Shinichi Ueno, Hiroyuki Shinchi, and Shoji Natsugoe declare that they have no commercial interests.

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