# Usefulness of $^{18}$F-fluorodeoxyglucose Positron Emission Tomography as Predictor of Distant Metastasis in Preoperative Carbon-ion Radiotherapy for Pancreatic Cancer

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**Abstract.** *Aim: The purpose of this study was to evaluate the role of FDG-PET regarding the indication of preoperative carbon-ion radiotherapy (CIRT) for pancreatic cancer patients. Patients and Methods: Patients with resectable pancreatic cancer underwent preoperative CIRT. The impact of baseline $SUV_{max}$ on prognosis for patients was assessed by analyzing correlations with distant metastasis-free survival (DMFS) and overall survival (OS). Results: Out of 21 patients, local recurrence was observed in no patient and distant metastasis was found in 13 patients (62%). 1-year DMFS and OS in low-$SUV_{max}$ group were significantly higher than those in high-$SUV_{max}$ group (91% vs. 20% and 91% vs. 56%). $SUV_{max}$ was significantly correlated with DMFS and OS. Conclusion: Our data indicated a significant correlation between $SUV_{max}$ and DMFS. FDG-PET might be useful for determining the indication of preoperative short-course CIRT for patients with resectable pancreatic cancer.*

Pancreatic cancer is a malignant tumor with an extremely poor prognosis. Complete surgical resection has traditionally been considered as the only curative treatment. However, even if a curative resection is performed, the expectation of long-term survival is low, because local and distant recurrences during the post-surgery period is most common.

Currently, multimodality treatment of resectable pancreatic cancer is used to improve a prognosis, while moderately improved results have been obtained by new preoperative strategies using chemotherapy or chemoradiotherapy (1-3). This procedure may increase the R0 resection rate and reduce the risk of local tumor recurrence.

Since 2003, we have been performing preoperative short-course carbon-ion radiotherapy (CIRT) for patients with potentially resectable pancreatic cancer (4). This study suggested that powerful local control with a combination of CIRT and surgery provided good results: local control rate was 100% and 5-year overall survival was 52%. On the other hand, 52% of the patients who had undergone resection experienced distant metastases, and most of the metastases appeared within one year after surgery. The patients who developed distant metastases after surgery had very poor prognosis, and surgery is unlikely to provide any benefit to them. Considering that distant metastases became evident in the early post-operative period, it can be assumed that the majority of these patients already had microscopic metastases before treatment. In order to avoid unnecessary surgery, it is important to identify patients with microscopic metastases, which were undetectable by existing diagnostic modalities at pre-treatment staging.

Recently, positron emission tomography using $^{18}$F-fluorodeoxyglucose (FDG-PET) has been reported to be of prognostic value for pancreatic cancer (5-7). However, no previous studies have shown the relationship between evaluation of FDG-PET and risk of distant metastasis after CIRT and surgery in patients with potentially resectable pancreatic cancer. If we could predict for patients at high risk for distant metastases before treatment, those who would benefit from preoperative CIRT and radical surgery could be selected. In the present study, we evaluated the usefulness of FDG-PET as a predictor of distant metastasis in patients with resectable pancreatic cancer and a more adequate modality to select patients for preoperative CIRT and surgery.

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## Patients and Methods

*Patients.* This study was a retrospective analysis of a prospectively-maintained database from consecutive patients treated in the National Institute of Radiological Sciences from April 2003 to December 2010 with preoperative CIRT for resectable pancreatic cancer. All patients were treated in a prospective dose-escalation clinical trial for evaluating the efficacy and safety of preoperative short-course CIRT. All patients were assessed radiographically as having radically-resectable pancreatic cancer without involvement of the hepatic artery, celiac trunk, or superior mesenteric artery and without evidence of metastatic disease by CT, PET, and/or MRI imaging. Other criteria have been previously published but included age ≤80, Eastern Cooperative Oncology Group performance status (PS) <2, and adequate organ function to tolerate surgery (4).

*Treatment*

*Carbon-ion radiotherapy.* All patients were positioned in customized cradles (Moldcare; Alcare, Tokyo, Japan) and immobilized with a low-temperature thermoplastic shell (Shellfitter; Kuraray, Osaka, Japan). A set of 2.5- or 5-mm-thick computed tomography (CT) images was obtained for treatment planning with the immobilization devices under respiratory gating. Three-dimensional treatment planning of CIRT was performed using the HIPLAN software program (National Institute of Radiological Sciences, Chiba, Japan). Irradiation was carried-out with a carbon-ion beam once a day, four days a week (Tuesday-Friday). CIRT was administered in 8 fractions within 2 weeks. Radiation treatment planning has been described previously (4). In this protocol, patients were treated with preoperative CIRT alone without concurrent chemotherapy.

*Surgery.* All patients underwent CT scans to evaluate resectability before surgery. Resectable disease was defined as the absence of distant metastasis and no infiltration of major arteries, for example, the common hepatic, celiac, and superior mesenteric arteries. Invasion of the portal vein, superior mesenteric vein, or splenic vein was not a contraindication to resection, and such vessels were resected and reconstructed if necessary. Surgical resection was to be performed 2 to 4 weeks after the completion of CIRT. Overall treatment duration was approximately 4 to 8 weeks. After surgery, no treatment was permitted until disease failure.

*PET and PET/CT study.* In the PET study, whole-body scanners (ECAT EXACT HR+ and ECAT EXACT 47; Siemens CTI, Knoxville, TN, USA) were used. Emission data corrected for random events, dead time, and attenuation were reconstructed by filtered back-projection using a Ramp filter with a cut-off frequency of 0.4, followed by decay correction. In the PET/CT study, whole-body PET/CT scanners (Biograph duo and Biograph 16; Siemens CTI, Knoxville, TN and Aquiduo; Toshiba Medical Systems Corporation, Otawara-shi, Tochigi-ken) were used. With Biograph duo, emission data corrected for random events, dead time, and attenuation were reconstructed by filtered backprojection using a Ramp filter with a cut-off frequency of 0.4, followed by decay correction. With Biograph 16 and Aquiduo, emission data with the corrections were reconstructed by Ordered Subsets Expectation Maximization (OSEM) using 16 subsets, 4 iterations, and Gaussian filter Full Width at Half Maximum (FWHM) of 8.0 mm, followed by decay correction.

PET or PET/CT studies were carried-out prior to the start of CIRT (6.9±2.6 days). The patients fasted from at least 6 hours or more prior to the study. For the emission data, on average, 515±56 MBq (8.5±1.5 mCi) of FDG was administered intravenously and collection started after 60 min. Regarding the difference in sensitivities of PET scanners, static emission scans were performed for 30 min in ECAT EXACT HR+ and for 15 min in ECAT EXACT 47 for each bed position. For the PET/CT study, prior to a PET emission scan, a CT scan was performed and the μ-map data for attenuation correction was calculated from the CT data. The CT scan was performed on the calvarium to the femoral regions, and the PET emission data were collected for these regions. The emission scan was performed for 3 min per bed and was performed for 7 to 9 beds. The images were analyzed semi-quantitatively using the maximum standardized uptake value ($SUV_{max}$). For quantitative analysis of the uptake of FDG by the tumor, regions of interest were drawn on the attenuation-corrected FDG-PET images around the primary tumor, and $SUV_{max}$ was calculated using the following formula:

$$SUV_{max} = C(kBq/kg)/ID(kBq)/bodyweight(kg),$$ where C is the activity at a pixel within the tissue defined by a region of interest measured by PET, and ID is the injected dose per kilogram of the patient's body weight. All PET scans were re-reviewed by two radiologists.

*Follow-up.* Patients were followed-up by CT, MRI, or PET scans every 3-6 months. Local recurrence and disease progression were scored at the time of the first site of progression documented radiographically and biopsy confirmation was no required.

*Statistical analysis.* The $SUV_{max}$ was compared between two groups, patients with and without distant recurrence after CIRT by the Wilcoxon test. Patients were also sub-categorized into the low-$SUV_{max}$ group (below the median) or high-$SUV_{max}$ group (median or above). In addition, patients were sub-categorized by the following factors: age (≥67 years old *vs.* <67 years old), PS (0 *vs.* 1), pre-treatment carbohydrate antigen (CA)19-9 (≥180 *vs.* <180), tumor volume (≥5 ml *vs.* <5 ml), and clinical stage (IIA *vs.* IIB). Overall survival (OS), local control (LC), and distant metastasis-free survival (DMFS) were estimated for the entire population along with each subgroup using the Kaplan-Meier method, and the differences were evaluated by the log-rank test. Survival estimates were calculated from the first day of CIRT. All patients who undergone preoperative CIRT were included in the present analysis, even if surgery was not performed for some reason, such as disease progression.

Statistical significance was defined as a value of *p*<0.05 in the present study. All statistical calculations were performed using statistical analysis software (JMP, version 8.0.2, SAS, Cary, NC, and Prism, version 5.0, GraphPad, San Diego, CA, USA).

## Results

From April 2003 to December 2010, we treated 26 patients with resectable pancreatic cancer. Out of these 26 patients, 21 who underwent assessable FDG-PET before preoperative CIRT were included in the present study. Patients' characteristics are listed in Table I. The median age of our
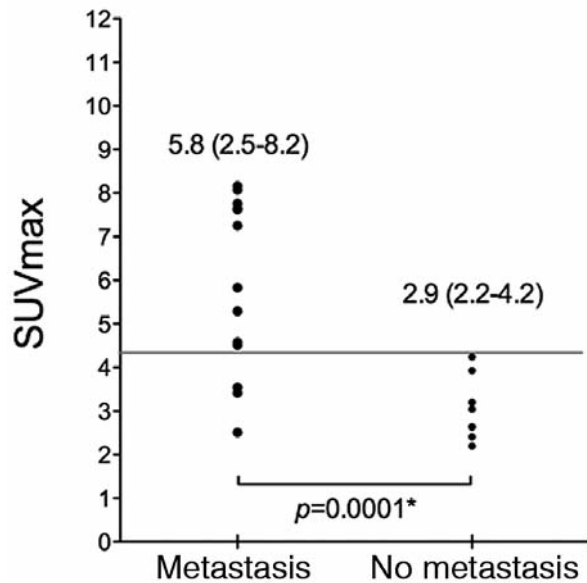
Figure 1. *Maximum standardized uptake value ($SUV_{max}$) of distant recurrence (metastasis) and no distant recurrence (no metastasis). The $SUV_{max}$ with metastasis was statistically significant higher than the $SUV_{max}$ with no metastasis (p=0.0001).*

Table I. Patients' characteristics at baseline.

| | | |
|---|---|---|
| Number of patients | | 21 |
| Gender (male/female) | | 13/8 |
| Median Age (range) | | 67 (47-79) |
| ECOG PS (0/1) | | 14/7 |
| CA19-9 (range) | | 181.2 (1.1-9090) |
| $SUV_{max}$ (≥4.3 /<4.3) | | 10/11 |
| Tumor Location | Head | 12 |
| | Body-tail | 9 |
| Clinical stage (UICC 6th) | IIA | 9 |
| | IIB | 12 |
| Surgery | PD | 10 |
| | DP | 5 |
| | TP | 1 |
| | Bypass | 2 |
| | No surgery | 3 |

PD, Pancreatoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy.

population was 67 years (range: 47-79 years). PS was 0 in 16 patients and 1 in 5 patients. Median pre-treatment serum CA19-9 was 181.2 U/mL (range: 1.1-9090). Clinical stages were IIA in 9 patients and IIB in 12 patients. The median dose of CIRT was 35.2 GyE (range: 30-36.8 GyE). All 21 patients completed planned preoperative CIRT. Sixteen patients underwent tumor resection, and pancreatic ductal adenocarcinoma was confirmed in all resected patients. Five
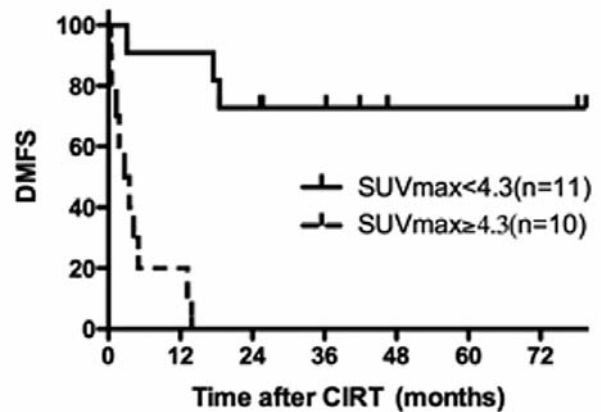


Figure 2. *Relationship of distant metastasis free survival (DMFS) to the $SUV_{max}$ of the primary tumor. DMFS of the low-$SUV_{max}$ group and the high-$SUV_{max}$ group were 91% and 20% for 1 year, and 71% and 0% for 3 years, respectively (p<0.001).*

patients did not undergo tumor resection due to metastatic progression in 4 patients and refusal to undergo surgery by 1 patient. No patient was found to have unresectable disease based on local tumor extension.

At the final analysis, 13 patients had died. Median follow-up among survivors was 48.9 months (range: 36.8-79.6 months). No patient was lost to follow-up, and overall median survival for all patients was 18.7 months. Out of the 21 patients enclosing 5 patients who did not undergo surgery, 13 patients experienced distant failure and no patient experienced local recurrence. The one patient who refused resection experienced distant metastasis after 13 months without local recurrence. The 13 patients who experienced distant metastases were treated with systemic chemotherapy such as gemcitabine or TS-1 after recurrence. The initial distant failure pattern was as follows: liver in eight cases, lung in three cases, bone in one case, and lymph nodes in one case.

$SUV_{max}$ of the patients with distant recurrence was significantly higher than that of patients without distant recurrence (Figure 1). The median $SUV_{max}$ was 4.3 (range: 2.2-8.2) in all patients. $SUV_{max}$ of patients who did not experience distant metastases was below the median. $SUV_{max}$ of 5 patients who were not resected for primary tumor was higher than median $SUV_{max}$. DMFS in the low-$SUV_{max}$ group and that in the high-$SUV_{max}$ group were 91% and 20% at 1 year and 73% and 0% at 5 years, respectively (p<0.001) (Figure 2). OS in the low-$SUV_{max}$ group and that in the high-$SUV_{max}$ group were 91% and 56% at 1 year and 72% and 0% at 5 years, respectively (p<0.001) (Figure 3A). In the high-$SUV_{max}$ group, median survival time of the patients who were not resected and who were resected were 11.5 months and 15.3 months, respectively (Figure 3B). There was no significantly difference (p=0.77).
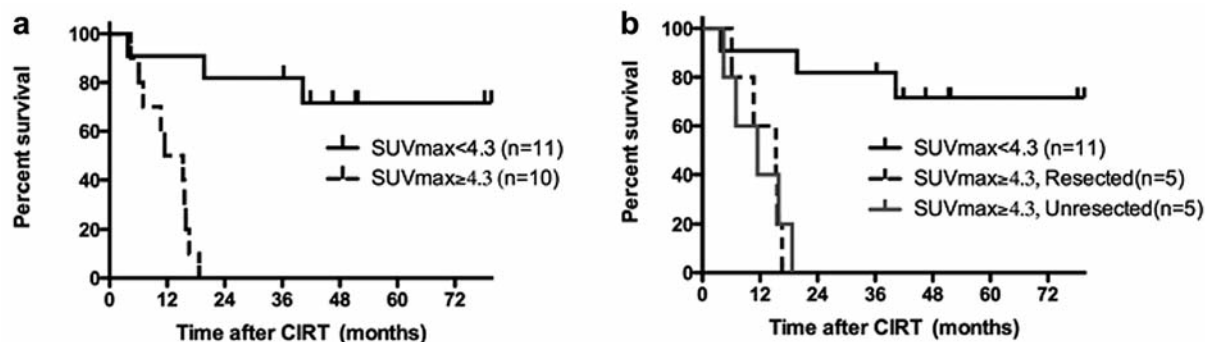
Figure 3. *(A) Relationship of overall survival (OS) to the $SUV_{max}$ of the primary tumor. OS of the low-$SUV_{max}$ group and the high-$SUV_{max}$ group were 91% and 50% for 1 year, and 81% and 0% for 3 years, respectively (p<0.001). (B) In the high-$SUV_{max}$ group, all patients died of distant metastasis within 2 years. The median survival time of patients who were not resected and of those resected were 11.5 months and 15.3 months, respectively. There was no significant difference between the two groups.*

Table II. *Univariate analysis of the risk factors for distant metastasis and overall survival.*

| Factor | | Patients | 1-year-DMFS | p-Value | 1-year-OS | p-Value |
|---|---|---|---|---|---|---|
| Age | ≥67 | 12 | 50% | | 75% | |
| | <67 | 9 | 67% | 0.66 | 67% | 0.39 |
| PS | 0 | 16 | 56% | | 69% | |
| | 1 | 5 | 60% | 0.80 | 80% | 0.81 |
| CA19-9 | ≥180 | 11 | 45% | | 64% | |
| | <180 | 10 | 70% | 0.45 | 80% | 0.29 |
| Tumor Volume | ≥5 mL | 11 | 45% | | 64% | |
| | <5 mL | 10 | 70% | 0.32 | 90% | 0.13 |
| Stage | IIA | 9 | 56% | | 78% | |
| | IIB | 12 | 58% | 0.73 | 67% | 0.92 |
| $SUV_{max}$ | ≥4.3 | 10 | 20% | | 50% | |
| | <4.3 | 11 | 91% | <0.001 | 91% | <0.001 |

The results of univariate analysis for DMFS and OS are summarized in Table II. $SUV_{max}$ was significantly correlated with DMFS and OS. Age, PS, pre-treatment CA19-9, tumor volume, and clinical stage were not prognostic factors for DMFS or OS.

## Discussion

Preoperative short-course CIRT has been performed for patients with resectable pancreatic cancer at our institution since 2003. This study showed that powerful local control with a combination of CIRT and surgery might decrease postoperative local recurrence and contribute to an increase in the number of long-term survivors. On the other hand, patients in whom distant recurrence appeared early after treatment accounted for over half of the patients evaluated for localized pancreatic cancer at pre-treatment diagnosis.

These patients seemed to have already microscopic metastases, which were undetectable by existing imaging modalities at the time of initial diagnosis. Prior studies have shown that preoperative chemoradiation might identify for patients presenting with rapidly progressive or disseminated disease at re-staging before surgery. In those studies, 26-37% of the patients were precluded from indication of surgery because of disease progression or decline in performance status (2, 3, 8). Therefore, the establishment of a novel diagnostic procedure to predict for probability of distant metastasis before treatment is needed.

Higashi *et al.* reported that pancreatic cancer cells overexpressed glucose transporters (GLUT). They concluded that GLUT has a significant role in malignant glucose metabolism and may contribute to increased uptake of FDG in PET imaging in pancreatic cancer patients (9). The accumulation of FDG reflects the rate of carbohydrate metabolism, which is more active in malignant cells, and is believed to indicate the malignancy of the cancer (10).

Many studies have suggested that $SUV_{max}$ is a prognostic indicator in other areas such as lung cancer and esophageal cancer (11-14). Some studies have proven similar utility of FDG-PET in pancreatic cancer (10, 15). It was shown that patients with high-$SUV_{max}$ experienced early disease failure on local and distant lesions and that their prognosis was poor. However, these reports evaluated not only distant failure but also local failure. These included patients whose primary tumor showed progression and then distant metastasis developed during the follow-up period. A distinctive stand-point of this study is that $SUV_{max}$ was correlated with distant failure but not with local failure because there was no local recurrence in our series. It is also interesting that FDG accumulation in the primary pancreatic tumor represented the tumor cell potential for extra pancreatic spread. Furthermore, the fact that no local

recurrence was observed for a long period in the patients who experienced distant metastases indicated that all distant metastasis occurred before the treatment. The existence of this occult distant disease may be predicted to by FDG-PET. In the high-$SUV_{max}$ group, there was no significance in survival outcome between the patients with and without surgery. All patients in the high-$SUV_{max}$ group died within 2 years because of distant metastasis. The results indicate that for patients with high $SUV_{max}$, it might be better to switch the strategy from preoperative CIRT to definitive CIRT with concurrent chemotherapy to avoid unnecessary surgery. We treated the patients for locally advanced pancreatic cancer with CIRT and concurrent gemcitabine. In patients, to whom the total dose of ≥45.6 GyE in 12 fractions with concomitant use of gemcitabine (1000 mg/m$^2$) was given, the 2-year OS was 66% (16).

Our study has several limitations. First, this study encompassed a relatively small number of patients. Furthermore, $SUV_{max}$ values were obtained from 3 different PET or PET/CT scanners. Therefore, there is some variability in quantification of PET measurement. Such a limitation could endanger our statistical reliability. The conclusions revealed here are hypothesis-generating and should be verified by larger prospective studies. In addition, pathological findings were not analyzed in the present study, being important factors related to possible metastases. There is need to discuss about the correlation between SUV accumulation and pathological status such as tumor size, nodal status, or surgical margin and so on. Although future studies will be necessary to investigate the impact of the association between SUV and pathological findings on outcome, the most important point of this investigation is to identify a prognostic factor among pre-treatment parameters because we have to predict the prognosis before starting the treatment.

## Conclusion

FDG-PET is useful for predicting prognosis in pancreatic cancer patients who underwent preoperative CIRT and surgery. Pre-treatment of FDG-PET is required in this group of patients.

## Conflicts of Interest

The Authors have no conflicts of interest to disclose.

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