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Role of positron emission tomography with 2-deoxy-2-[^{18}F]fluoro-D-glucose in evaluating the effects of arterial infusion chemotherapy and radiotherapy on pancreatic cancer

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Background. This study evaluated the usefulness of positron emission tomography with 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG-PET) in monitoring the response to continuous arterial infusion chemotherapy (CAI) combined with external radiation therapy (ERT) for unresectable pancreatic carcinomas. ***Methods.*** Ten patients with unresectable pancreatic cancer were enrolled in this study. Computed tomography (CT) and FDG-PET were done before and after CAI (5-fluorouracil [FU], 500 mg/body per day) combined with ERT (50.4 Gy total dose). Tumor regression was evaluated by standardized uptake value (SUV) with FDG-PET, tumor size on CT, and changes in blood levels of carbohydrate antigen (CA) 19-9. The three methods of evaluation were compared. ***Results.*** The ten patients were classified in three categories. In category I, tumor changes evident on CT and FDG-PET were consistent. In category II, CT could not accurately detect the area of the tumor. However, tumor uptake on FDG-PET decreased markedly after the treatment in category II patients. In category III, both CT and FDG-PET detected the tumor, as in category I. Although there was no definite change in tumor size on CT, FDG-PET uptake was markedly reduced immediately after the treatment. Reduction in tumor size did not appear on CT until 2 months later. ***Conclusions.*** FDG-PET aids in analysis of the effectiveness of chemotherapy and/or radiotherapy.

Key words: FDG-PET, pancreatic cancer, treatment response, arterial infusion chemotherapy, radiotherapy

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Introduction

At the present time, despite progress in diagnostic imaging, the majority of patients with pancreatic cancer present with either locally advanced disease or metastases, making cure impossible. For such patients, treatment choices include continuous arterial infusion chemotherapy (CAI) or external radiation therapy (ERT) to prolong survival by inducing tumor regression, or to relieve symptoms caused by the tumor.[1,2] The effects of the chemotherapy or radiotherapy are usually evaluated by computed tomography (CT) and tumor markers. However, CT scanning cannot always detect tumor progression, especially when the tumor is not large enough to be identified accurately. In many cases, there are discrepancies between the tumor size apparent on CT scans and that indicated by serum levels of tumor markers, because the viability of tumor cells cannot be evaluated by CT scan.

Positron emission tomography with 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG-PET) is a new, noninvasive imaging procedure based on cellular glucose metabolism.[3] It is, reportedly, a valuable measure for diagnosing and staging certain kinds of malignancy, including pancreatic carcinoma.[4,5] In this study, FDG-PET was used to monitor the responses of unresectable pancreatic carcinomas to CAI and ERT. The usefulness of FDG-PET in this field was compared with that of CT and tumor markers in sera.

Patients and methods

Patients

Ten patients with unresectable pancreatic cancer, six men and four women, ranging in age, from 56 to 74 years, were the subjects of the study (Table 1). Tumors were located in the pancreatic head in five patients and

Table 1. Patient data, and evaluation of treatment by examination of tumor marker, size change on CT, and SUV on FDG-PET

Patient No.	Category	Age (years)	Sex	Tumor location	Pre- or post-treatment	CA 19-9 (U/ml)	CT (cm^2)	SUV	BG level (mg/dl)[a]	Outcome[b]
1	I	61	M	Body	Pre	253.0	26.83	3.12	133	7.5 Months, died
					Post	361.1	15.21	1.85	151	with LM
					R/R(%)		43.30	40.70		
2	I	67	M	Body	Pre	181.1	12.30	4.34	99	12 Months, died
					Post	39.4	8.53	1.77	110	without LM
					R/R(%)		30.70	59.20		
3	I	74	M	Body–tail	Pre	38.4	12.36	5.02	115	17 Months, alive
					Post	581.6	8.31	2.64	130	with LM
					R/R(%)		34.20	47.40		
4	I	68	F	Head	Pre	59.6	6.21	6.02	107	18 Months, alive
					Post	29.5	3.18	2.63	92	without LM
					R/R(%)		48.80	56.30		
5	I	57	M	Head	Pre	153.9	8.54	6.67	88	6 Months, alive
					Post	48.8	5.78	3.41	105	without LM
					R/R(%)		32.30	48.80		
6	I	66	M	Head	Pre	455.4	11.89	4.03	85	6 Months, alive
					Post	520.7	6.73	2.99	102	with LM
					R/R(%)		43.40	25.80		
7	II	64	F	Head	Pre	69.7	Impossible	3.62	82	4.5 Months, died
					Post	12.5	to evaluate	1.96	101	without LM[c]
					R/R(%)			45.80		
8	II	64	M	Body	Pre	273.2	Impossible	4.27	135	4 Months, alive
					Post	140.2	to evaluate	2.26	175	with LM
					R/R(%)			47.00		
9	III	56	F	Head	Pre	702.6	7.92	3.25	128	17 Months, alive
					Post	1293.7	7.82	1.53	109	with LM
					R/R(%)		1.30	52.90		
10	III	61	M	Body–tail	Pre	2963.1	28.02	3.35	210	6 Months, alive
					Post	575.5	26.87	2.59	103	without LM
					R/R(%)		4.10	22.60		

R/R, reduction rate; LM, liver metastasis; BG, blood glucose; CT, computed tomography; SUV, standardized uptake value; FDG-PET, 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography
[a] Blood glucose level at time of FDG-PET study
[b] Time period from the onset of pancreatic cancer
[c] Died of cerebral hemorrhage

in the pancreatic body or tail in the other five patients. Tumors in all patients were unresectable because of local tumor progression; all patients showed extensive invasion to the superior mesenteric artery (SMA), the superior mesenteric vein (SMV), or both. During the follow-up period of 4 to 18 months, two patients died of cancer and one died of cerebral hemorrhage. The other seven patients are alive with or without liver metastasis (Table 1).

After they had given their informed consent, the patients received CAI and ERT. ERT consisted of a total dose of 50.4 Gy, administered in daily fractions of 1.8 Gy for 5 weeks. In combination with ERT, CAI was administered, using 5-fluorouracil (5-FU) at a dose of 500 mg/body per day, continuously infused for 24 h. Flow from the arterial infusion catheter was directed toward the pancreas by placing the catheter in the common hepatic artery, gastroduodenal artery, dorsal pancreatic artery, or celiac artery.

Measurement of tumor size

Tumor size was measured on the CT scan slice where maximal tumor area could be imaged. This area was measured by computerized image analysis on a Macintosh computer, using the United States National Institutes of Health (NIH) Image program (public domain, version 1.62). Changes in tumor size associated with ERT and CAI were evaluated within 2 weeks after the treatment ended. The same coronal slice was used to measure the area before and after treatment, and the reduction rate was calculated according to the following formula, and was expressed as a percentage.

$$\text{Reduction rate} = \frac{\text{Pretreatment area} - \text{posttreatment area}\left(cm^2\right)}{\text{Pretreatment area}\left(cm^2\right)}$$

FDG-PET methods

FDG-PET was performed at 2-week intervals between CT examinations. We used an FDG-PET scanner with a 15-cm axial field of view (Headtome V; Shimadzu, Kyoto, Japan) 40 min after ^{18}FDG injection. The ^{18}FDG dose administered was approximately 370 MBq. Prior to the study, the patients fasted for 5 to 6 h. Acquisition time was 10 min for one table position. All emission data were corrected for tissue attenuation by transmission scan. With the aid of CT imaging, a region of interest (ROI) was designated at the site of maximum accumulation in the tumor. The mean radioactivity of the ROI was determined. FDG uptake was measured by the standardized uptake value (SUV) calculated according to the following formula:

$$\mathrm{SUV} = \frac{\text{Tissue concentration (millicuries/g)}}{\text{Injection dose (millicuries)/body weight (g)}}$$

Tumor marker measurement

The serum level of carbohydrate antigen (CA) 19-9 was measured in each patient by sandwich enzyme immunoassay (EIA) before and after the period of treatment.

Results

Changes in tumor size and SUVs in the ten patients are summarized in Table 1. The ten patients were classified into three categories according to the CT scan and FDG-PET findings. Category I comprised six patients (patients 1, 2, 3, 4, 5, and 6) in whom CT and FDG-PET were both of diagnostic value in the pretreatment and posttreatment stages. In this category, changes measured by CT and FDG-PET were consistent in spite of some differences in the reduction rate. Figure 1A,B shows CT and FDG-PET images before and after CAI and ERT in a representative patient in category I. The tumor-reduction rate of the six patients in category I was 38.8% ± 7.4% (mean ± SD), as measured by CT, and 46.4% ± 4.9% as measured by FDG-PET.

In category II (patients 7 and 8), CT scanning did not have sufficient power to detect the area of the tumor accurately, even though the tumor's presence was ascertained by an accompanying finding of dilatation of the distal pancreatic duct. Accordingly, any change in tumor size could not be tracked by CT scan (Fig. 2A). However, the FDG-PET image showed high uptake in the pancreatic head before treatment (Fig. 2B), clearly indicating the presence of the tumor. Uptake was significantly reduced after treatment; the SUV decreased from 3.62 to 1.96 in patient 7 (reduction rate, 45.8%).

In category III (patients 9 and 10), both CT and FDG-PET could detect the tumor, as in category I. However, CT scans showed no definite change in tumor size after treatment, whereas FDG-PET showed a marked decrease in uptake (Fig. 3A,B); the SUV decreased from 3.25 to 1.53 after treatment in patient 9 (reduction rate, 52.9%). A CT scan taken 2 months after the posttreatment examinations (Fig. 4) showed a reduction in tumor size (reduction rates in patients 9 and 10 were 53.7% and 36.3%). These findings confirmed that, in category III patients, the FDG-PET image showed the therapeutic effect 2 months before changes appeared on the CT image.

Levels of serum CA19-9 in six patients (patients 2, 4, 5, 7, 8, and 10) decreased in response to treatment. However, the increased levels of serum CA 19-9 in the other four patients (patients 1, 3, 6, and 9) were inconsistent with the decreasing FDG uptake observed as the result of treatment. These four patients suffered multiple liver metastases after the treatment.

Discussion

FDG-PET detects acceleration in cellular glucose metabolism, and it has been used to detect various kinds of malignancies, including pancreatic cancer.[6–9] In principle, FDG-PET is superior to conventional diagnostic tools such as CT scan or ultrasonography because it alone can indicate the cellular viability of a tumor. Therefore, FDG-PET could be useful to assess the therapeutic effects of chemotherapy and/or radiotherapy. It has been used to measure such therapeutic responses in breast cancer,[10] head and neck cancer,[11,12] and colorectal cancer.[13] In these reports, FDG uptake decreased after treatment when the treatment was effective, and the change was generally proportional to the change in tumor volume. It has been suggested that FDG-PET could be an early indicator of treatment responses. However, there have been few reported assessments of the efficacy of chemotherapy or radiotherapy for pancreatic cancer using FDG-PET.[14,15]

The superiority of FDG-PET compared with CT or tumor markers as a measure of treatment efficacy has been reported. One study of pancreatic adenocarcinoma evaluation reported that FDG-PET sensitivity ranged from 85% to 95%,[5] the highest sensitivity among the diagnostic measures studied. In our study, the tumor in two patients (patients 7 and 8) could only be seen clearly on FDG-PET. FDG-PET was also the only marker of the therapeutic effects of CAI and ERT in our category II patients. Consequently, we concluded that FDG-PET can reflect the effects of chemotherapy or radiotherapy even when CT or tumor markers cannot detect them.

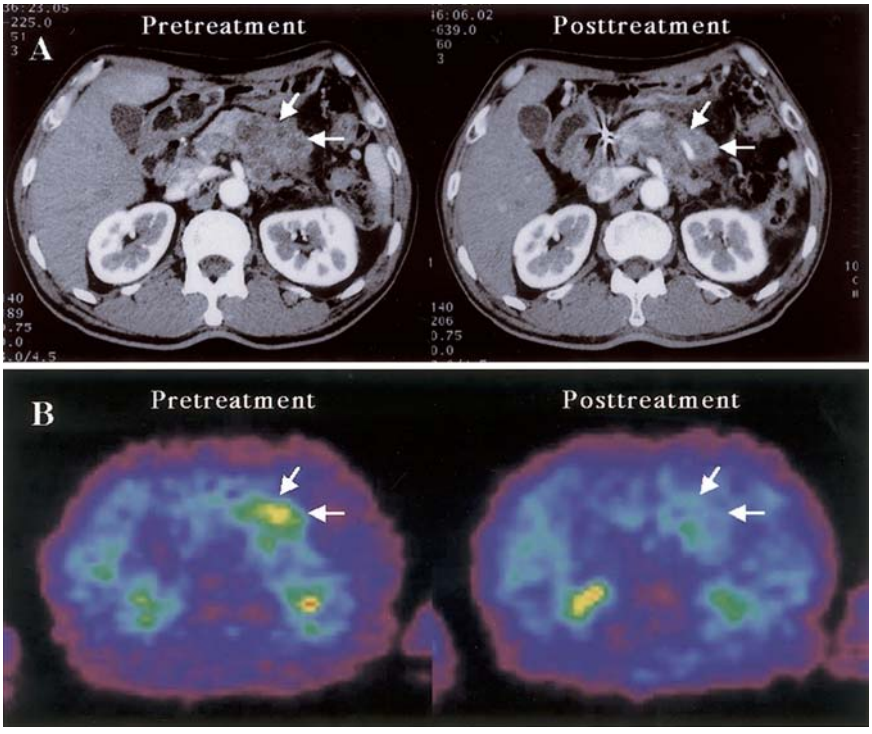

Fig. 1A,B. Diagnostic images of patient 1, as a representative of category I. **A** The size of the tumor in the pancreatic body (*arrows*) is visibly reduced in the posttreatment stage. **B** Pretreatment 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography (FDG-PET) image shows increased FDG uptake in the pancreatic body (*arrows*); the uptake is clearly reduced in the posttreatment stage

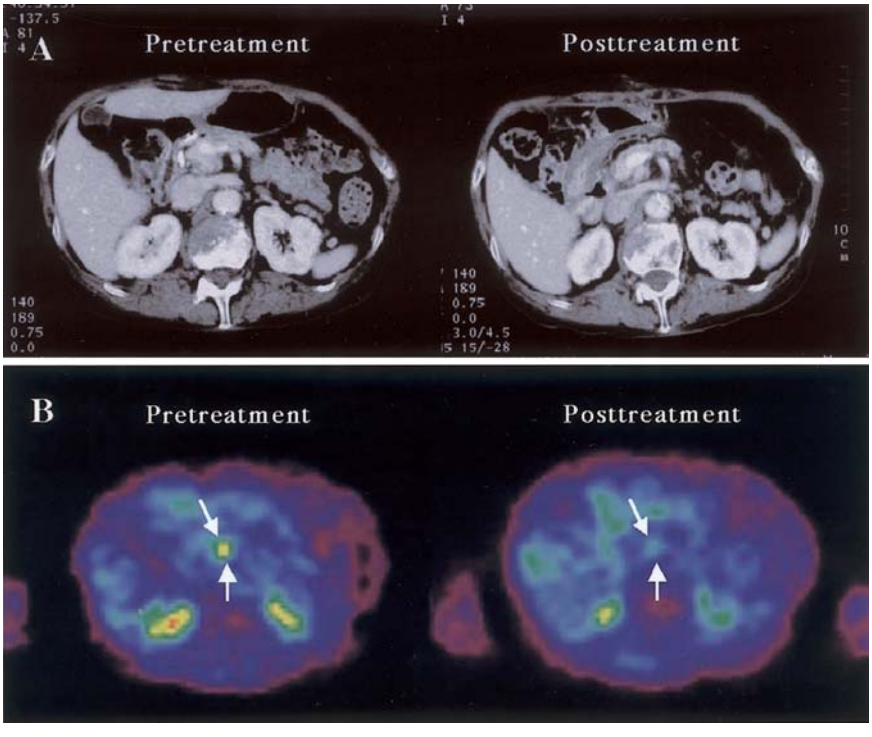

Fig. 2A,B. Diagnostic images of patient 7, as a representative of category II. **A** Computed tomography (CT) scan does not show the tumor in the pancreatic head accurately, so changes in tumor size cannot be tracked in the posttreatment stage. **B** Pretreatment PET image shows increased FDG uptake in the pancreatic head (*arrows*); uptake is clearly reduced in the posttreatment stage

This was further confirmed by our results with the category III patients. In these patients, the change in tumor uptake on the FDG-PET image preceded tumor size change on the CT scan. Maisey et al.[14] reported a pilot study of FDG-PET capability as a predictor of survival after chemotherapy. In seven of eight patients, reduction in FDG uptake was observed 1 month before treatment response could be assessed by CT and tumor markers. Higashi et al.[15] also reported that FDG-PET could detect treatment response earlier than a CT scan

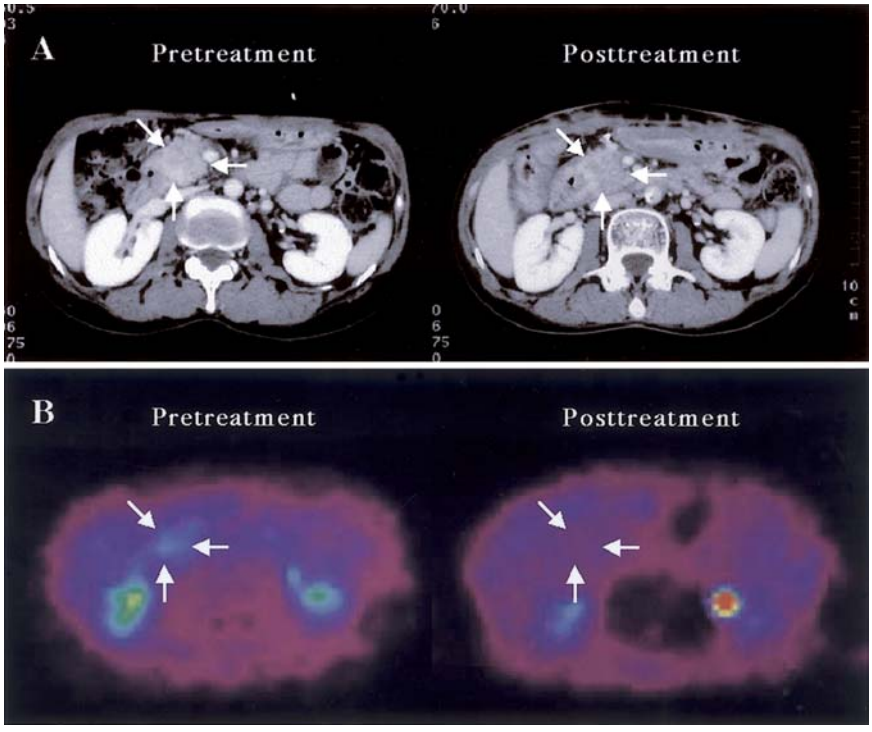

Fig. 3A,B. Diagnostic images of patient 9, as a representative of category III. **A** The size of the tumor in the pancreatic head (*arrows*) is not visibly reduced in the posttreatment stage. **B** Pretreatment PET image shows increased FDG uptake in the pancreatic head (*arrows*); uptake is clearly reduced in the posttreatment stage

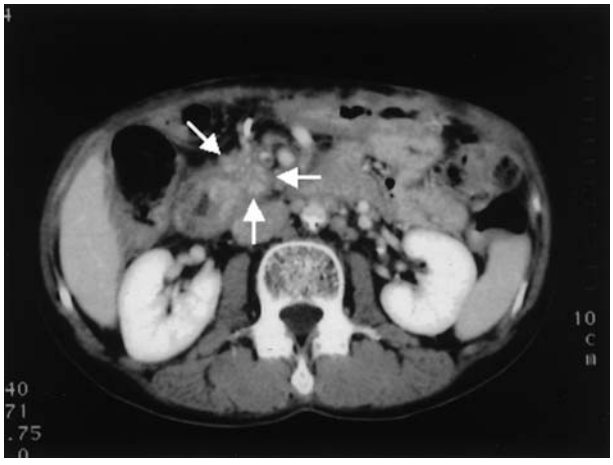

Fig. 4. CT scan of patient 9, taken 2 months after the posttreatment examinations, shows a reduction in tumor size (*arrows*)

could indicate a decrease in tumor size after intraoperative radiation therapy. Rapid FDG-PET detection of treatment response could greatly improve treatment plans, because it would enable the timely discontinuation of ineffective therapies and support the continuous use of effective therapies.

The high incidence of liver metastases in advanced pancreatic cancer reduces the usefulness of tumor markers as a measure of treatment efficacy in primary lesions. Serum levels of tumor markers are significantly elevated when liver metastases occur. Therefore, it is difficult to evaluate the effects of treatment on the primary lesion because these effects may not be reflected in the tumor marker levels.

There are also problems with the use of the SUV as a measure of FDG accumulation, because the SUV varies depending not only on the purity and dose of ^{18}FDG but also on blood glucose levels, especially when FDG-PET targets a pancreatic lesion. Zimny et al.[16] reported that the SUVs in patients treated for diabetes (insulin/glibenclamide) were lower than those in euglycemic controls or untreated diabetic patients. In that report, there were eight treated diabetic patients among ten false-negative (SUV $\leqq$ 3.10) hyperglycemic patients. In our study, four patients (patients 1, 8, 9, and 10) with diabetes were treated with insulin. Although the SUVs of these patients were lower than those of the other (euglycemic) patients, the SUVs of these patients were not less than a threshold SUV of 3.10. Furthermore, diabetes did not become more severe after treatment and the insulin quantity was not increased. Therefore, the decrease in SUV after treatment was not due to the aggravation of diabetes in these patients. The establishment of a standardized quantitative parameter is needed for FDG-PET to ensure the reproducibility and universality of FDG-PET findings.

In conclusion, in ten patients with unresectable pancreatic carcinoma, FDG-PET was used to monitor re-

sponses to chemotherapy and radiotherapy. In six patients, FDG-PET results were consistent with the CT findings. However, in two patients, only FDG-PET could detect a therapeutic response, and in the two other patients, FDG-PET showed a therapeutic response before the CT scan showed a change in tumor size. Therefore, we conclude that FDG-PET is a useful modality to indicate the effectiveness of chemotherapy and/or radiotherapy.

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