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Background: To evaluate the clinical usefulness of [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) compared with histopathological grading, clinical stage and serum prostatic specific antigen (PSA) level in the detection and characterization of prostate cancer.
Methods: Forty-four patients with histologically proven prostate cancer and five control subjects with benign prostatic hyperplasia (BPH) were prospectively investigated with FDG-PET prior to treatment.
Results: By visual inspection, FDG accumulation was positive in 28 patients with prostate cancer (sensitivity 64%), whereas all were negative in the control group. FDG-PET in three patients with lymph node metastases did not show any high intrapelvic accumulations corresponding to metastatic sites. Among 12 patients with multiple bone metastases which were detected with 99m-HMDP bone scintigraphy, nine (75%) showed moderate to high FDG accumulation at the sites of bone metastases. Quantitatively, FDG accumulation in prostate cancer was significantly higher than in BPH and there was a tendency for FDG uptake of tumors to be higher with higher histological Gleason grades. Furthermore, FDG uptake in tumors with lymph node and/or bone metastasis was significantly higher than that of localized stages. However, the correlation between PSA and FDG uptake in the prostate cancer was very weak for clinical relevance.
Conclusions: Although FDG-PET was not sensitive enough to detect prostate cancer in clinical use, it is suggested that glucose metabolism in prostate cancer tended to be higher in patients with tumors of advanced stages.

Key words: FDG-PET – prostate cancer – cancer detection

INTRODUCTION

Prostate cancer is the most common neoplasm in men in the USA and its incidence has also been increasing in Japan. Since the usefulness of serum prostate specific antigen (PSA) for screening prostate cancer has been established (1,2), it plays a major role in detecting prostate cancer, combined with digital rectal examination (DRE) and transrectal ultrasonography (TRUS).

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Abbreviations: FDG-PET, [^{18}F]fluorodeoxyglucose positron emission tomography; PSA, prostate specific antigen; BPH, benign prostatic hyperplasia; DRE, digital rectal examination; TRUS, transrectal ultrasonography; USG, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; ROI, region of interest; *Kc*, K complex; ANOVA, analysis of variance

Conventional imaging modalities such as ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging (MRI) are used for the anatomical evaluation of prostate cancer.

FDG-PET for malignancy has been introduced as a technique for metabolic imaging, based on the facts that cancer tissue consumes a large amount of glucose as an energy source and [^{18}F]fluorodeoxyglucose enters cancer cells by the same transport route as glucose. FDG-PET has already been applied for metabolic imaging of cerebral tumor, head and neck cancer, mediastinal cancer, pancreatic cancer, hepatocellular carcinoma and rectal cancer (3–8). In the field of brain tumors, the malignancy of glioma has been found to be positively correlated with the glucose utilization measured by FDG-PET (6). In pelvic tumors, FDG-PET was valuable in distinguishing between surgical scars and the relapse of rectal cancer (7).

There are some published reports, including three abstracts, of clinical studies on FDG-PET for prostate cancer. The first clinical study of FDG-PET for primary prostate cancer diagnosis was reported by Effert et al. in 1996 (9). They performed FDG-PET on 48 patients with untreated prostate cancer and

concluded that it was not useful for differentiating prostate cancer from benign prostatic hyperplasia (BPH). FDG accumulation in the prostate was visually positive in only nine of 48 (19%) patients with prostate cancer. Furthermore, they reported that FDG accumulation was not related to clinical stage or histological grade. In a study by Laubenbacher et al., differentiation between prostate cancer and benign prostatic hyperplasia was difficult with FDG-PET (10). They also reported that differentiation between local recurrence after radical prostatectomy and scar tissue was not possible with FDG-PET. Shreve et al. demonstrated a sensitivity of 65% with FDG-PET for the detection of bone metastases (11). In a study by Yeh et al., only 20% of patients with bone metastases could be identified by FDG uptake (12). In a study by Hoh et al., patients with advanced metastatic lesions were monitored with PET during suramin therapy. Clinical effects of suramin on prostate cancer were not related to the changes in FDG-PET estimation (13). There seems to be a consensus that FDG–PET is not useful for the detection or metabolic grading of prostate cancer, which suggested that prostate cancer, contrary to other malignant neoplasms, is a peculiar neoplasm with glucose consumption not being associated with its malignancy.

Before the publication of these reports, we had already begun to assess the efficacy of FDG-PET in detecting malignant tissue in the prostate gland and had been trying to establish whether or not glucose utilization of prostate cancer had any association with the malignancy. Our results are partly in accordance with previous studies, that is, FDG-PET is not useful for detecting prostate cancer. However, the accumulation of FDG in the prostate is higher with a statistical significance in prostate cancer than in BPH and is also higher in prostate cancer in advanced stages than in early stages. We report here increased glucose consumption, i.e. increased FDG accumulation of prostate cancer associated with tumor progression.

MATERIALS AND METHODS

The subjects were 44 consecutive patients (aged 52–84 years) with histologically proven adenocarcinoma of the prostate who were diagnosed at Fukui Medical University between January 1996 and September 1998 (Table 1) and five patients (aged 62–81 years) with benign prostatic hyperplasia (Table 2). Histological diagnosis was accomplished with specimens obtained by transrectal systematic sextant prostate biopsy. Clinical staging was done according to the fifth edition of the TNM classification (14). PET studies were performed before any treatment, hence the patients who required immediate treatment due to extensive bone metastasis were excluded from this study. T stage was T1 in two, T2 in 18, T3 in 16 and T4 in eight patients. Twelve patients with T3 or T4 had bone metastases. Seventeen of 44 patients with prostate cancer underwent radical prostatectomy. Three out of these seventeen patients received hormonal therapy as neoadjuvant therapy. Lymph node metastases were detected in three patients by histopathological examination of surgically removed pelvic lymph nodes; hence, they received postoperative hormonal therapy. Twenty patients received only hormonal therapy. Two received radiotherapy and another was followed up without treatment. The protocol was approved by the Ethical Committee of Fukui Medical University. In both oral and written forms, all patients were adequately informed of the purpose of this study, the method of scanning, the time required and necessary pretreatment and gave their informed consent.

Patient Preparation

Each patient underwent FDG-PET after fasting for at least 4 h. Small plastic catheters were placed in the left anterior cubital veins for FDG injection and in the right radial artery for intermittent arterial samplings. During scanning, the bladder was irrigated continuously with a large amount of physiological saline through a 20 Fr. three-way balloon catheter indwelt to prevent retention of FDG in the bladder, permitting accurate evaluation of FDG accumulation in the prostate.

FDG-PET Imaging Procedure

FDG was produced by the method of Hamacher et al. (15). with an automated FDG synthesis system (NKK, Tokyo, Japan) with a small cyclotron (OSCAR3, Oxford Instruments, Oxford, UK). PET scanning was performed with a GE Advance system (GE, Milwaukee, WI). The physical characteristics of this scanner have been described in detail by DeGrado et al. (16). This system permits the simultaneous acquisition of 35 transverse slices with interslice spacing of 4.25 mm with septa (two-dimensional mode). Images were reconstructed to a full width at half maximum (FWHM) of 4.2 mm in both the transaxial and axial directions. The field of view and pixel size of the reconstructed images were 256 mm and 2 mm, respectively. Two transmission scans covering the prostate and adjacent lower abdominal regions were obtained for 10 min each using a standard pin source of $^{68}Ge/^{68}Ga$ for attenuation correction of the emission images.

A 350 MBq dose of FDG was administered via cubital vein over 10 s. Dynamic scans covering the prostate gland were obtained up to 60 min after the injection, with intermittent arterial sampling. The mode of dynamic data acquisition consisted of four 30 s frames, eight 60 s frames and five 600 s frames. Subsequently, the lower abdominal region was scanned for 20 min. Plasma glucose concentrations were measured in all patients. From the time of injection, 2 ml of arterial blood were sampled every 15 s in the first 2 min and then at 3, 5, 7, 10, 15, 20, 30, 45, 60 and 85 min after the injection. The plasma radioactivity was measured by a scintillation counter, against which the PET camera was cross-calibrated, using a cylindrical phantom filled with the ^{18}F-labeled solution.

Data Analysis

Images were visually evaluated by nuclear medicine physicians and urologists with consensus on the interpretation with clinical data blinded. The accumulation of FDG was catego-

Table 1. Patients with prostate cancer

Pt.No.	Age	PSA	Gleason Score	Clinical stage	Treatment	Visual inspection	K-complex
1	62	41.2	4+2	T2cN0M0	R.P.	high	16.947
2	70	33.2	4+3	T4aN0M0	R.P.	high	33.031
3	74	773.4	2+3	T3N0M1	H.T.	high	39.906
4	66	59.7	2+3	T3aN0M0	R.P.	int	11.977
5	52	54.4	2+3	T2cN0M0	H.T.	low	15.563
6	69	80.9	3+4	T2N0M0	H.T.	low	23.166
7	78	6.4	1+2	T1cN0M0	FOLLOW	low	9.916
8	72	43.8	3+4	T2aN0M0	R.P.	low	10.591
9	66	12.2	1+2	T2aN0M0	R.P.	int	12.224
10	61	6.1	2+4	T3cN0M0	R.P.	low	13.296
11	57	10.9	3+2	T2aN0M0	R.P.	low	16.286
12	60	12	3+4	T3cN0M0	H.P. to R.P.	int	18.906
13	64	43.8	3+4	T2cN0M0	R.P.	int	11.881
14	78	17	1+2	T2cN0M0	H.T.	int	11.521
15	76	49.1	3+2	T4aN0M0	H.T. to R.P.	int	10.927
16	56	189.7	3+4	T3aN0M1	H.T.	high	52.535
17	71	38.5	3+2	T2cN0M0	R.P.	low	11.358
18	68	23.4	1+2	T2aN0M0	R.T.	int	14.241
19	69	1836	2+3	T4aN0M1	H.T.	high	39.286
20	67	150	3+4	T3cN0M0	H.T. to R.P.	high	22.764
21	70	2300	3+4	T3bN0M1	H.T.	low	16.623
22	81	220	1+1	T3bN0M1	H.T.	int	18.245
23	80	3000	1+2	T4aN2M1	H.T.	high	34.403
24	84	78	1+2	T2cN0M0	H.T.	low	20.334
25	71	30	4+4	T3aN0M0	R.P.	low	10.932
26	75	17	1+1	T3aN0M0	R.P.	low	14.689
27	61	1200	3+2	T4aN0M1	H.T.	int	15.022
28	68	170	4+5	T4aN0M1	H.T.	high	44.804
29	74	4.9	1+2	T2aN0M0	R.P.	low	7.512
30	73	75	4+3	T3bN0M0	H.T.	high	5.834
31	69	15	2+3	T3aN1M0	H.T.	int	14.283
32	67	15	2+3	T2aN0M0	R.P.	int	13.708
33	67	16	4+5	T2bN0M0	H.T.	int	17.56
34	73	57.1	3+3	T3bN1M0	H.T.	int	21.075
35	69	69.5	3+3	T3cN0M0	H.T.	high	79.586
36	71	8.4	1+1	T2aN0M0	R.P.	low	11.131
37	66	20.8	2+3	T2bN0M0	H.T.	int	27.833
38	73	92.8	4+3	T3cN2M1	H.T.	low	14.821
39	77	13.2	3+3	T2aN0M0	R.T.	low	10.625
40	74	84.4	4+4	T4aN1M1	H.T.	high	25.424
41	74	24	4+4	T4aN0M1	H.T.	high	22.453
42	75	10.3	1+1	T1aN0M0	prostatectomy	low	13.818
43	52	36.8	2+3	T2bN0M0	H.T.	int	32.401
44	72	42.1	3+4	T3aN0M1	H.T.	int	27.332

R.P.; radical prostatectomy, H.T.; hormonal therapy, int; intermediate

rized into three classes: high, intermediate and low accumulation. High accumulation was designated as a prominent accumulation, similar to various substances rapidly entering the urine, low accumulation was similar to that of a normal prostate gland and intermediate accumulation was between high and low accumulation. Quantitative analysis was done as follows: the region of interest (ROI) was selected in the prostate and the graphical analysis was performed on pixel-by-pixel. The K complex (*Kc*) value was determined using the linear fitting of the time–activity curve of FDG accumulation based on a Gjedde–Patlak plot (17,18). If there was an area with a high accumulation of FDG in the prostate, this area was

Table 2. Patients without prostate cancer

Patient No.	Age (years)	Visual inspection	*Kc* (μl/min/ml)
1	81	Low	12.021
2	66	Low	9.484
3	62	Low	11.299
4	69	Low	12.422
5	79	Low	8.734

selected as the ROI, and if the accumulation was low, the ROI was placed with anatomical reference to MRI or CT. To minimize the effect of ROI size on *Kc*, we utilized the maximum value of *Kc* within an ROI to represent FDG uptake in that particular region (Kc_{max}).

FDG-PET images of the prostate were compared with TRUS, CT and MRI results. Relationships between the accumulation of FDG and histological grading, clinical staging and serum PSA value were evaluated. The PSA value was determined with a double monoclonal antibody radioimmunoassay [Tandem-R (Hybritech, San Diego, CA)]. When evaluating the histological grade, we used Gleason grading (19) and chose the less differentiation grade in either primary or secondary dominant histological pattern as the representative grade, which, we considered, might be a more accurate indicator of the prognosis in patients with prostate cancer than the Gleason sum. Indeed, Bostwick et al. reported that the percentage of poorly differentiated adenocarcinoma in biopsies and prostatectomies was predictive of the local invasion of prostate cancer (20), suggesting that less differentiation grade might be valid for one of the prognostic factors.

Statistical Evaluation

Analysis of variance (ANOVA) was used to compare FDG uptake with the parameters of the prostate cancer. The correlation between FDG data and PSA value was done with Pearson's correlation coefficient. Significance was set at $p < 0.05$.

RESULTS

The retention of FDG in the urinary bladder was successfully minimized by continuous irrigation of the bladder.

Five patients with benign prostatic hyperplasia (control group) showed low accumulation of FDG, about the same as that for striate muscle. On the other hand, 28 of 44 patients (sensitivity 64%) were visually positive (Fig. 1). Specificity and positive or negative predictive value were 100, 100 or 25%, respectively.

FDG-PET in three patients with lymph node metastases did not show any high intrapelvic accumulations corresponding to metastatic sites. Among 12 patients with multiple bone metastases which were detected with 99m-HMDP bone scintigraphy, nine patients (75%) showed moderate to high FDG accumulation at the sites of bone metastases.

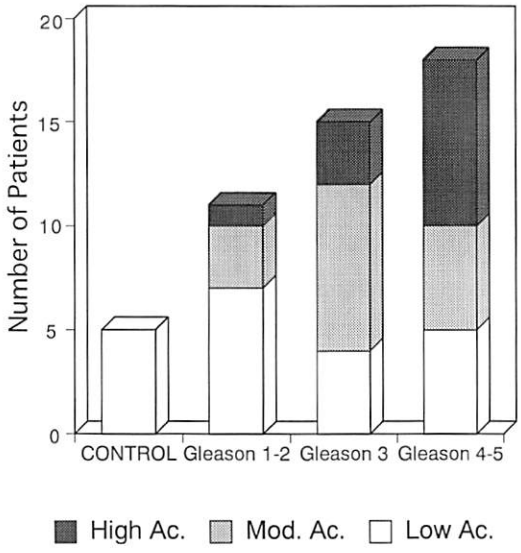


Figure 1. FDG-PET showed higher FDG accumulation in prostate cancer of higher Gleason grades.

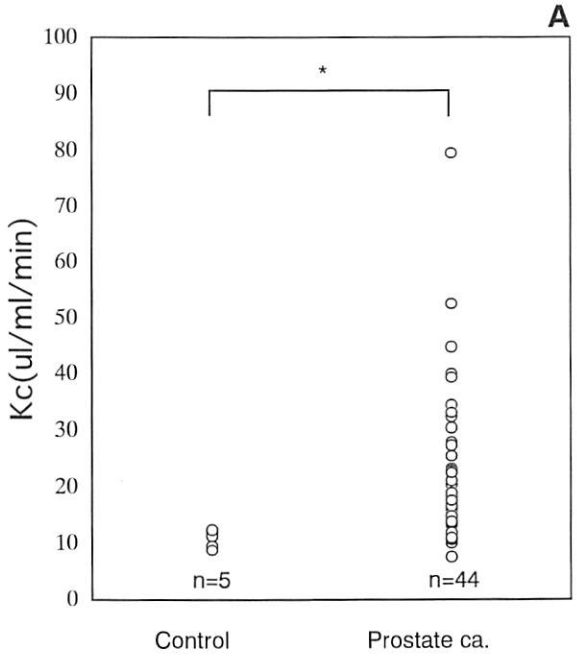
The *Kc* values in the prostates in patients with prostate cancer were significantly higher than in the control group (21.394 ± 13.693 μl/min/ml (mean ± standard deviation) in cancer patients and 10.792 ± 1.610 in the control group, ($p = 0.01$, Mann–Whitney *U*-test, Fig. 2). *Kc* tended to be higher in tumors of Gleason grade 3 or 4–5 than in those of Gleason grade 1–2 or in BPH (15.276 ± 7.303, 23.989 ± 18.393 and 22.970 ± 11.469 μl/min/ml in patients with tumors of Gleason grade 1–2, 3 and 4–5, respectively), although there was no significant difference among each group ($p = 0.11$, ANOVA, Fig. 3).

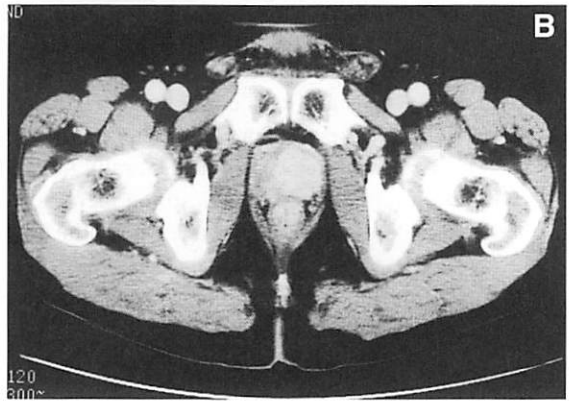
Kc of advanced clinical stages was significantly higher than that of earlier stages (15.431 ± 6.296 μl/min/ml in T1/T2, 24.651 ± 20.878 μl/min/ml in T3/T4 and 27.587 ± 12.505 μl/min/ml in N+/M+ ($p = 0.01$, ANOVA, Fig. 4). However, the correlation between *Kc* and PSA values was very weak ($r = 0.426$, Pearson's correlation coefficient, Fig. 5).

Among patients who underwent radical prostatectomy, *Kc* of the primary lesion was compared between patients with lymph node metastases ($n = 3$) and those without metastases ($n = 14$). *Kc* of the former (24.247 ± 8.144 μl/min/ml) was higher than that of the latter (12.530 ± 2.768 μl/min/ml).

DISCUSSION

When considering the clinical PET for malignancy, there are two important respects in which PET can play a highly efficient role: metabolic diagnosis of malignant lesions and *in vivo* detection of metabolic changes occurring in malignant tissues. For the diagnosis of prostate cancer, FDG-PET was of no value in comparison with the conventional diagnostic modalities





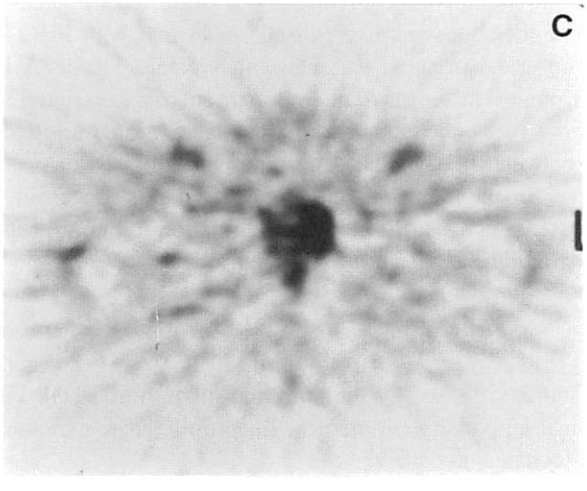


Figure 2. (A) There was a significant difference in *Kc* values in the prostate between control group and cancer group ($p = 0.01$, Mann–Whitney *U*-test). (B) CT revealed a mass with contrast enhancement in the left peripheral and transition zone. (C) FDG-PET showed a high accumulation in the same region.

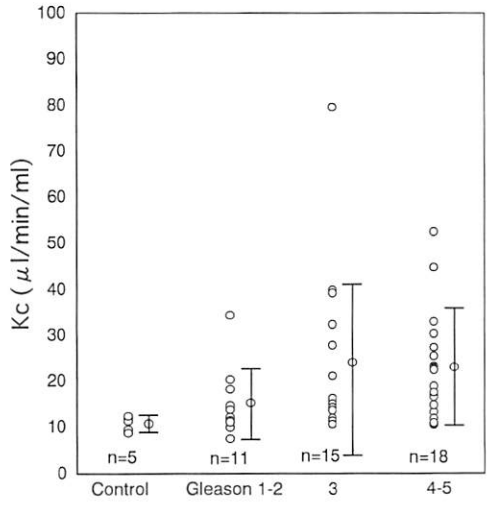


Figure 3. Stepwise increases of Kc_{max} in the prostate were observed in relation to Gleason grading although there were no significant differences.

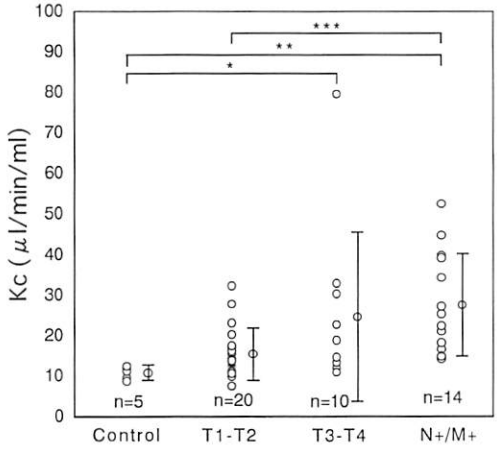


Figure 4. *Kc* in prostate cancer in advanced clinical stages was significantly higher than that in earlier stages (15.431 ± 6.296 μl/min/ml in T1/T2, 24.651 ± 20.878 in T3/T4 and 27.587 ± 12.505 in N+/M+. $*p = 0.04$, $**p = 0.01$, $***p = 0.006$, ANOVA).

such as PSA, CT scan, MRI and bone scintigraphy. The sensitivity of 64% for cancer detection was not high enough and did not seem a sufficient value to justify the clinical application of FDG-PET for the detection of prostate cancer, considering that FDG-PET is much more expensive and invasive (requiring continuous bladder irrigation) than is the accepted method of PSA. Especially for early-stage prostate cancer (T1/T2), the sensitivity was 50% and also there was no difference in FDG accumulation (*Kc* value) between benign prostatic hyperplasia and highly differentiated prostate cancer. FDG-PET is of no use for the detection of early-stage prostate cancer. Similarly, FDG-PET may not be the method of choice for the evaluation of lymph node metastasis as no surgically proven lymph node metastasis was detected by FDG-PET.

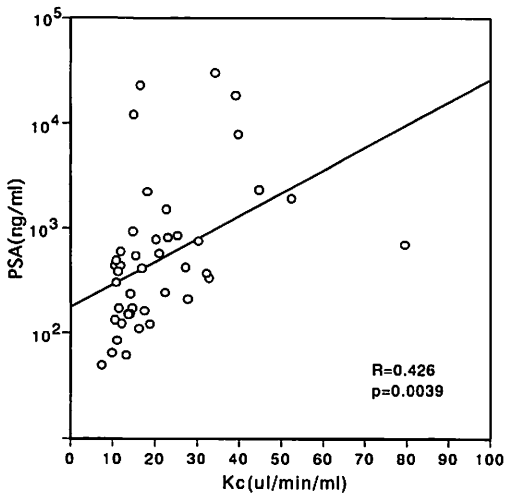


Figure 5. *Kc* values in the prostate were weakly correlated with serum PSA values ($r = 0.426$, Pearson's correlation coefficient).

In the study concerning the *in vivo* detection of metabolic changes occurring in malignant tissues, the present study showed that the FDG accumulation in primary prostate cancer was higher in advanced clinical stages, which may be consistent with the fact that invasive prostate cancer has a higher proliferation activity than localized cancer (21). Furthermore, although Pearson's correlation coefficient was relatively low, FDG accumulation was correlated with serum PSA levels. These findings might indicate that glucose utilization, demonstrated by FDG-PET, was associated with tumor progression of the prostate cancer. Our results were contrary to those of the previous report that FDG accumulation in the prostate was not different between BPH and prostate cancer and no association was observed between FDG uptake and clinical stage of prostate cancer (9).

This discrepancy might be explained by several technical factors such as a different spatial resolution of the PET scanner or a difference in the injected doses. The method of quantification of FDG uptake also differs. Effert et al. used the standardized uptake value (SUV) in the ROI. This is calculated by tissue radioactivity divided by injected dose per body weight. Because of its simplicity without any dynamic scan or plasma input function, SUV has been widely used in FDG-PET oncology. On the other hand, SUV has been criticized as being subject to many sources of variability (22). The main factors affecting the variability of SUV are body frame and weight, uptake period, plasma glucose concentration and partial volume effect. To minimize these confounding factors, we analyzed our data using the *Kc* value calculated with dynamic data and plasma input function. The discrepancy between previous reports and ours might be ascribed to the different methods of data analysis.

Since both the *Kc* value and SUV could be affected by the partial volume effect, one might criticize our data as merely representing the tumor size, that is, the larger the size of the tumor, the smaller is the partial volume effect and hence the larger is *Kc*. It was not possible in this study to correlate FDG accumulation with tumor volume because of the small number of patients treated with radical prostatectomy. However, *Kc* values for prostate cancer were widely distributed even in patients with the same T stages (Fig. 4). Hence the partial volume effects on *Kc* values are not likely to be significant although not correlating *Kc* values with tumor size.

Another explanation for the discrepancy between our results and the previous study may be the racial differences between Japanese and Caucasians. A racial difference in the frequency of *ras* gene mutations in prostate cancer was observed between Japanese and American men (23). Also, a racial difference in the type of *p53* gene mutations (transition versus transversion) has been reported in prostate cancer (24). Such genetic alterations might be attributed to the difference in FDG uptake in the prostate between our study and the previous reports. Indeed, a possible link has been suggested between the mutations of *ras* gene and *p53* gene and high glycolytic phenotype in malignancy (25,26). Further studies should be performed on the gene alterations linked with glucose metabolism in prostate cancer and the genetic differences between races.

FDG-PET for prostate cancer failed to detect cancerous lesions precisely but was associated with tumor progression. However, the clinical significance of the increased FDG uptake in individual patients with prostate cancer remains to be determined. High glucose metabolism is generally linked with a high proliferation rate of cancer cells so the increased FDG uptake might indicate the high malignancy potential and also aid in predicting the outcome of the patients. We are now investigating the correlation between FDG-PET and the prognosis of patients with prostate cancer.

In conclusion, although FDG-PET was not sensitive enough to detect prostate cancer in clinical use and was not useful for detecting lymph node metastases, a significant increase in glucose metabolism in the prostate measured with FDG-PET was observed in some patients with prostate cancer. A high FDG uptake in the prostate was particularly associated with tumors in advanced stages. The results suggested an association between FDG uptake and tumor progression of prostate cancer. Biochemical and genetic investigations concerning the increased glucose utilization and its relation to tumor progression should be carried out in the future.

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References

1. Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6630 men. *J Urol* 1994;151:1283–90.

2. Stone NN, DeAntoni EP, Crawford ED, Prostate Cancer Education Council. Screening for prostate cancer by digital rectal examination and prostate-specific antigen: results of prostate cancer awareness week. *Urology* 1994;44:1989–92.
3. Pantronas NJ, Chiro GD, Kufta C, Bairamian D, Kornblith PL, Simon R, et al. Prediction of survival in glioma patients by means of positron emission tomography. *J Neurosurg* 1985;62:816–22.
4. Rege S, Maass A, Chaiken L, Hoe CK, Lufkin R, Anzai Y, et al. Use of positron emission tomography with fluorodeoxyglucose in patients with extracranial head and neck cancers.*Cancer* 1994;73:3047–58.
5. Jabour BA, Choi Y, Hoh CK, Rege SD, Soong JC, Lufkin RB, et al. Extracranial head and neck: PET imaging with 2-[F-18]fluoro-2-deoxy-D-glucose and MRI imaging correlation. *Radiology* 1993;186:27–35.
6. Di Chiro G, DeLaPaz RL, Brooks RA, Sokoloff L, Korniblith PL, Smith BH, et al. Glucose utilization of cerebral gliomas measured by 18F-fluorodeoxyglucose and positron emission tomography. *Neurology* 1982;32:1323–9.
7. Strauss LG, Clorius JH, Schlag P, Lehner B, Kimmig B, Engenhrat R, et al. Recurrence of colorectal tumors: PET evaluation. *Radiology* 1989;170:329–32.
8. Rasey JS, Koh WJ, Evans ML, Peterson LM, Lewellen TK. Quantifying regional hypoxia in human tumors with positron emission tomography of [18F]fluoromisonidazole: a pretherapy study of 37 patients. *Int J Radiat Oncol Biol Phys* 1996;36:417–28.
9. Effert PJ, Bares R, Handt S, Wolff JM, Bull D, Jakse G. Metabolic imaging of untreated prostate cancer by positron emission tomography with 18-fluorine-labeled deoxyglucose. *J Urol* 1996;155:994–8.
10. Laubenbacher C, Hofer C, Avril N, Block T, Ziegler S, Herz M, et al. F-18 FDG PET for differentiation of local recurrent prostate cancer and scar. *J Nucl Med* 1995;36(Suppl 1):198.
11. Shreve PD, Grossman HB, Gross MD, Wahl RL. Metastatic prostate cancer: initial findings of PET with 2-deoxy-2-[F-18]fluoro-D-glucose. *Radiology* 1996;199:751–6.
12. Yeh SDJ, Imbriaco M, Garza D, Kalaigian H, Reddy D, Zhang JJ, et al. Twenty percent of bony metastases of hormone resistant prostate cancer are detected by FDG-PET whole body scanning. *J Nucl Med* 1995;36(Suppl 1):198.
13. Hoh CK, Rosen PJ, Belldegrun A, Moon DH, Maddahi J, Phelps ME. Quantitative and whole body FDG PET in the evaluation of suramin therapy in patients with metastatic prostate cancer. *J Nucl Med* 1996;37(Suppl 1):267.
14. Sobin LH, Wittekind Ch, editors. TNM Classification of Malignant Tumors, 5th ed. New York: Wiley-Liss 1997.
15. Hamacher K, Coenen HH, Stocklin G. Efficient stereospecific synthesis of no-carried-added 2-[18F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. *J Nucl Med* 1986;27:235–8.
16. DeGrado TR, Turkington TG, Williams JJ, Stearns CW, Hoffman JM, Coleman RE. Performance characteristics of whole-body PET scanner. *J Nucl Med* 1994;35:1398–406.
17. Patlak C, Blasberg R, Fenstermacher J. Graphical evaluation of blood to brain transfer constants from multiple-time uptake data. *J Cereb Blood Flow Metab* 1983;3:1–7.
18. Gjedde A. High- and low-affinity transport of D-glucose from blood to brain. *J Neurochem* 1981;36:1463–71.
19. Gleason DF, Veterans Administration Cooperative Urological Research Group. Histologic grading and clinical staging of carcinoma of the prostate in urologic pathology. In: Tannenbaum M, editor. The Prostate. Philadelphia: Lea & Febiger 1977:171–97.
20. Bostwick DG, Quian J, Bergstralh E, Dundore P, Dugan J, Myers RP, et al. Prediction of capsular perforation and seminal vesicle invasion in prostate cancer. *J Urol* 1996;155:1361–7.
21. Coetzee LJ, Layfield LJ, Hars V, Paulson DF. Proliferative index determination in prostate carcinoma tissue: is there any additional prognostic value greater than that of Gleason score, ploidy and pathological stage? *J Urol* 1997;157:214–8.
22. Keyes JW. SUV: standard uptake or silly useless value. *J Nucl Med* 1995;36:1836–9.
23. Konishi N, Hiasa Y, Tsuzuki T, Enomoto T, Miller GJ. Comparison of ras activation in prostate carcinoma in Japanese and American men. *Prostate* 1997;30:53–7.
24. Watanabe M, Fukutome K, Shiraishi T, Murata M, Kawamura J, Shimazaki J, et al. Differences in the p53 gene mutational spectra of prostate cancers between Japan and Western countries. *Carcinogenesis* 1997;18:1355–8.
25. Biaglow JE, Cerniglia G, Tuttle S, Bakanauskas V, Stevens C, McKenna G. Effect of oncogene transformation of rat embryo cells on cellular oxygen consumption and glycolysis. *Biochem Biophys Res Commun* 1997;235:739–42.
26. Mathupala SP, Heese C, Pedersen PL. Glucose catabolism in cancer cells. The type 2 hexokinase promoter contains functionally active response elements for the tumor suppressor. *J Biol Chem* 1997;272:22776–80.