Quantitative, dynamic 18F-FDG-PET for the evaluation of soft tissue sarcomas: Relation to differential diagnosis, tumor grading and prediction of prognosis

Shinichi Okazumi[1,2] MD,
Antonia Dimitrakopoulou-Strauss[1] MD,
Matthias H. M. Schwarzbach[3] MD,
Ludwig G. Strauss[1] MD

1. *Clinical Cooperation Unit Nuclear Medicine, German Cancer Research Center, INF 280, 69120 Heidelberg, Germany*
2. *Department of Surgery, Toho University, Sakura Medical Center, Shimoshizu 564-1 Sakura, 285-8741 Japan*
3. *Department of Surgery, University of Mannheim, Theodor-Kutzer Ufer 1-3, 68135 Mannheim, Germany*

Keywords: ^{18}F-FDG-PET – Dynamic study – Soft tissue sarcoma – Quantitation -Differential diagnosis

Correspondence address:
Professor Antonia Dimitrakopoulou-Strauss,
Clinical Cooperation Unit Nuclear Medicine, German Cancer Research Center,
Im Neuenheimer Feld 280
69120 Heidelberg, Germany
e-mail: ads@ads-lgs.de or a.dimitrakooulou-strauss@dkfz.de

Received:
22 June 2009
Accepted-revised:
10 July 2009

Abstract

The purpose of this study was to evaluate soft tissue sarcomas by dynamic ^{18}F-FDG-PET studies, and to establish an index of kinetic parameters for evaluation of their malignancy, histological grade and prognosis, after surgical resection. *One hundred and seventeen* patients including 79 with histologically proven soft tissue malignancies, 14 with primary benign soft tissue tumors and 24 with postoperative scar tissues were examined. The ^{18}F-FDG studies were accomplished as a dynamic series for 60min. The evaluation of the ^{18}F -FDG kinetics was performed using the following parameters: standardized uptake value (SUV), global influx (Ki), computation of transport constants (k1-k4) with consideration of the vascular fraction (VB) according to a two tissue compartment model, and fractal dimension (FD) based on the box-counting procedure (non-compartmental model). Discriminant analysis (DA) was used for data evaluation. Multivariate analysis was performed to assess the predictive value of each kinetic parameter on survival. *Our results showed that* in the primary cases (n=46), SUV, k1, Ki and FD were higher in sarcomas than benign tumors. The diagnostic sensitivity of 62.50%, a specificity of 92.86%, and an accuracy of 71.74% were achieved by using the combination of k1 and SUV as input variables for DA. In the postoperative cases (n=71), SUV, VB, k3, Ki, and FD were higher in recurrent lesions than in scar tissues. DA revealed a sensitivity of 80.85%, a specificity of 87.50%, and an accuracy of 83.10% by using the combination of SUV, Ki and FD. In liposarcoma patients (n=32), SUV and FD were higher in GII,III tumors as compared with GI. DA led to a sensitivity of 86.96%, a specificity of 55.56%, and an accuracy of 78.13% by using the combination of SUV and FD. By multivariate analysis of primary soft tissue sarcomas (n=26) after surgical resection, groups with k3>0.025 (P<0.0026) or FD>1.25 (P<0.0162) had significantly poor prognosis. *In conclusion,* the evaluation of full ^{18}F-FDG kinetics provides important information for the diagnosis of malignant lesions, histological grading and prognosis of soft tissue sarcomas.

Hell J Nucl Med 2009; 12(3) : 223-228 • Published on line: 23 October 2009

Introduction

Soft tissue sarcomas tend to be recurrent or metastasize even after resection, and it is necessary to diagnose and start treatment earlier for both primary and recurrent lesions. Therefore, differential diagnosis between malignant and benign tumors, grading and prediction of prognosis are of major diagnostic importance. However, clinically there are some problems. In small size tumors, differential diagnosis is difficult due to the imaging system's resolution. Even in a large size tumor, the biopsy for histological decisive diagnosis is often difficult because of the heterogeneity of the tumor.

Recently, the usefulness of fluorine-18 fluorodeoxyglucose-positron emission tomography (^{18}F-FDG-PET) as a functional diagnostic imaging modality for soft-tissue sarcoma treatment planning has been reported. Most studies are focused on the differential diagnosis between tumor and benign lesions [1-3], on the detection of highly active parts in large size tumors [4] and on the prediction of recurrence rate after surgery [5]. Most of these reports evaluated ^{18}F-FDG uptake by standardized uptake value (SUV) based on static data of ^{18}F-FDG-PET.

The aim of this study was to evaluate soft-tissue sarcomas by dynamic ^{18}F-FDG-PET using clinically useful parameters for the differential diagnosis, tumor grading or prediction of prognosis on soft-tissue sarcomas. Kinetic parameters of the compartment model of ^{18}F-FDG [6] and the value of fractal dimension (FD), which expresses the inhomogeneity of ^{18}F-FDG uptake of tissue were obtained by the dynamic study. We have previously reported on the use of dynamic ^{18}F-FDG-PET studies for differential diagnosis in 56 patients with soft tissue sarcomas [7].

Patients and methods

Patients

Our evaluation study included 117 patients with soft-tissue lesions suggestive of malignan-

cy. All patients were referred with the preliminary diagnosis of a primary or recurrent soft-tissue malignancy based on clinical symptoms and radiological examinations, either computerized tomography (CT) or magnetic resonance imaging (MRI). The final diagnosis was based on the histological data obtained from specimens of surgical resection or biopsy. Most masses were located in the extremities (n=69), but masses were also found in the abdomen (n=40) and the thoracic region (n=8). The final histological examination revealed 79 malignant soft-tissue tumors and 38 benign lesions. Among the primary malignant tumors, there were 14 liposarcomas, 7 malignant fibrous histiocytomas, 4 leiomyosarcomas, 2 hemangiosarcomas, 2 chondrosarcomas, 2 synovial sarcomas, and 1 malignant schwannoma. Recurrent lesions comprised 18 liposarcomas, 9 malignant fibrous histiocytomas, 9 leiomyosarcomas, 6 malignant schwannomas, 3 chondrosarcomas, and 2 haemangiosarcomas. Benign lesions comprised 24 scars, 6 lipomas, 4 haemangiomas, 2 schwannomas, 1 ganglioneuroma and 1 inflammatory lesion.

None of the 117 patients had received chemotherapy before ^{18}F-FDG-PET examination. All patients with suspected local recurrence (71/117) had a documented history of surgery for a sarcoma. Among the 32 patients with primary or recurrent liposarcomas, there were 9 GI, 9 GII, and 14 GIII liposarcomas. 26 primary cases of soft-tissue sarcomas (13 liposarcomas, 5 malignant fibrous histiocytomas, 3 leiomyosarcomas, 2 synovial sarcomas, 2 hemangiosarcomas and 1 chondrosarcoma) underwent surgical resection and were followed up. Twelve of 26 patients died up to 47 months after surgery related to malignancy and 14 patients were alive.

Informed consent was obtained from each patient. The study was performed in accordance with the institutional review board requirements.

Data acquisition

Dynamic PET studies were performed after intravenous injection of 300-370MBq ^{18}F-FDG for 60 min. For the first eight patients, we used 15 frames (5 frames of 2 min followed by 10 frames of 5min) for the dynamic ^{18}F-FDG studies. The other 109 patients were examined with a 23-frame protocol (10 frames of 1min, 5 frames of 2min, and 8 frames of 5 min). ^{18}F-FDG was prepared according to the method described by Toorongian et al. (1990) [8].

A dedicated PET system (ECAT EXACT HR+; Siemens, Erlangen, Germany) based on the block detector technology with a craniocaudal field of view of 15.3cm, operated with septa extended (two-dimensional mode), was used for the patients' studies. The system allows the simultaneous acquisition of 63 transverse slices with a theoretic slice thickness of 2.4mm. The system consists of four rings and each of the rings has 72 bismuth germanate detector (BGO) blocks. A single block detector is divided into an 8×8 matrix. The crystal size of a single detector element is 4.39×4.05×30mm. The evaluation of spatial linearity revealed that the maximum displacement from the ideal source position was <0.4mm in the whole field of view. Transmission scans for a total of 10min were obtained with three rotating germanium pin sources before the first radionuclide application for the attenuation correction of the acquired emission tomographic images.

Data analysis

The evaluation of the dynamic PET was performed using the software package partial mode (PMod) (PMod Ltd., Zurich, Switzerland*). Visual analysis was performed by evaluating the hypermetabolic areas on transaxial, coronal, and sagittal images. Time-activity curves were created using volumes of interest (VOI). A VOI consists of several regions of interest (ROI) over the target area. Irregular ROI were drawn manually. To compensate for possible patient motion during the acquisition time, the original ROI were repositioned visually but not redrawn. In general, a detailed quantitative evaluation of tracer kinetics requires the use of compartment modeling. Patlak analysis as well as a two-tissue-compartment model is standard methodology for the quantification of dynamic ^{18}F-FDG studies [6]. We used for the basic analysis the semiquantitative approach based of the calculation of a distribution value, for which the term "SUV" was introduced by Strauss and Conti (2001) [9]: *SUV= tissue concentration(MBq/g)/(injected dose [MBq]/body weight[g])*. The 55 to 60min uptake values served for the quantification of the ^{18}F-FDG SUV data.

The input function was retrieved from the image data. For input function, the mean value of the VOI data obtained from a large arterial vessel was used [7]. A vessel VOI consisted of at least seven ROIs in sequential PET images. In patients with an abdominal or a thoracic mass, the descending aorta was used for this purpose because the spillover from other organs is low and the descending aorta extends from the upper chest to the lower abdomen. The recovery coefficient is 0.85 for a diameter of 8mm and for the system described above. Partial-volume correction was used for small vessels with a diameter <8mm but not for the aorta.

Furthermore, we used a preprocessing tool, available in PMod software, which allows a fit of the input curve namely by a sum of up to three decaying exponentials to reduce noise. The transport constant k1 as well as the rate constants k2, k3, and k4 were calculated using a two-tissue-compartment model implemented in the PMod software taking into account the vascular fraction (VB) in a VOI. The ^{18}F-FDG influx (Ki) was calculated using the transport rates from the two-tissue-compartment model according to the following formula: $Ki = ([k1 \times k3]/[k2+k3])$.

Besides the compartment analysis, we used a noncompartment model based on the FD. As shown by other investigators [10], the FD is a parameter for the heterogeneity. We implemented a Java-based module in the PMod software to calculate the FD for the time-activity data. Fractal dimension was calculated for the time-activity-data in each individual voxel of a VOI. The program is based on the box-counting method [7]. The values of the FD vary from 0 to 2 and are a parameter for a deterministic or more chaotic distribution of the tracer activity.

The statistical evaluation of the data was performed using the Statistica™ software package (version 6.0; StatSoft Co.) on a personal computer running with Windows XP (Microsoft). Mann-Whitney's U-test for variances was applied to all evaluated parameters (SUV, k1, k2, k3, k4, Ki, VB, FD) to find out,

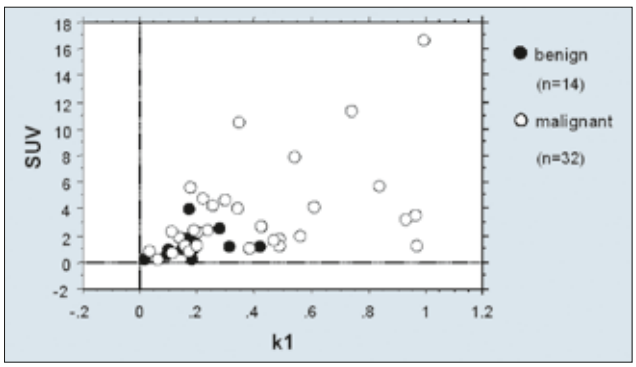

Figure 1. The relationship between k1 and SUV in primary lesions (n=46). The data demonstrate an overlap between malignant and benign disease in the low k1 and SUV area.

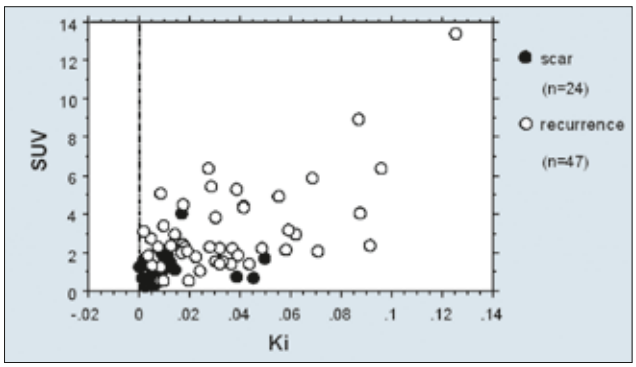

Figure 2. The relationship between Ki and SUV in postoperative lesions (n=71). The data demonstrate an overlap between recurrent and scar lesions in the low Ki and SUV area.

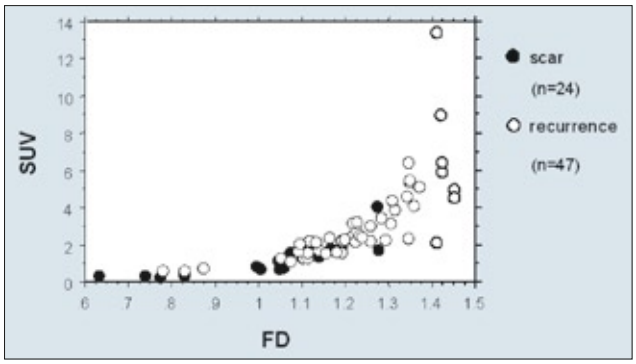

Figure 3. The relationship between fractal dimension (FD) and SUV in postoperative lesions (n=71). The data demonstrate an overlap between recurrent and scar lesions in the low FD and SUV area.

which parameter was most significant for the differential diagnosis and discriminant analysis (DA) was applied to obtain diagnostic accuracy. Differences were considered significant for P<0.05. Overall survival was defined as the time interval from the date of operation until death. Multi-variate analysis was performed with the proportional hazards model to assess the predictive value of each kinetic parameter of a dynamic PET study on overall survival in 29 cases. Then, a multiple linear regression model was applied to examine the relationship between the individual survival time (dependent variable) in 12 patients and the selected kinetic parameters. Scatterplots of individually predicted and observed values for survival time were used to assess the appropriateness of the fit.

Results

Differential diagnosis between malignant and benign lesions

In primary cases (n=46), soft tissue sarcomas (n=32) showed significantly higher SUV (P=0026), k1 (P=0.0045), Ki (P=0.0122) and FD (P=0.0401) than primary benign lesions (n=14). Accuracy of 56.52% (sensitivity 43.75%, specificity 85.71%) as malignant was obtained by DA with SUV as an input variables (Table 1). By using k1 as an index of malignancy, accuracy was 63.04% (sensitivity 53.13%, specificity 85.71%). By using Ki as an index, accuracy was 54.35% (sensitivity 43.75%, specificity 78.57%). By using FD as an index, accuracy was 67.39% (sensitivity 75.00%, specificity 50.00%). The combination of SUV and k1 led to the best accuracy of 71.74% (sensitivity 62.50%, specificity 92.86%). The scatterplot of SUV and k1 showed that the false diagnosis tended to occur in low k1 and SUV area (Fig. 1). In patients with a suspicious recurrent disease (n=71), recurrent lesions (n=47) showed significantly higher SUV (P<0.0001), VB (P=0.0449), k3 (P=0.0166), Ki (P=0.0002) and FD (P<0.0001) than scar lesions (n=24). Accuracy of 70.42% (sensitivity 57.47%, specificity 95.83%) was obtained by using SUV as an index of malignancy (Table 2). Using VB, k3,Ki or FD, accuracy were 59.15%, 53.52%, 67.60% or 74.65%, respectively. The combination of SUV, Ki and FD resulted in the best accuracy of 83.10% (sensitivity 80.85%, specificity 87.50%). The scatterplots showed that the false diagnosis tended to occur in low SUV, Ki and FD area (Fig. 2 and Fig. 3).

Table 1. *Results of the discriminant analysis using kinetic parameters as independent variables for the prediction of 2 groups in primary lesions (n=46)*

Variable	CCR malignant	CCR benign	CCR both groups
SUV	43.75 (14/32)	85.71 (12/14)	56.52 (26/46)
k1	53.13 (17/32)	85.71 (12/14)	63.04 (29/46)
Ki	43.75 (14/32)	78.57 (11/14)	54.35 (25/46)
FD	75.00 (24/32)	50.00 (7/14)	67.39 (31/46)
SUV, k1	62.50 (20/32)	92.86(13/14)	71.74 (33/46)
SUV, Ki	46.86 (15/32)	92.86(13/14)	60.87 (28/46)
SUV, FD	53.13 (17/32)	85.71(12/14)	63.04 (29/46)

CCR: correct classification rate (%), FD: fractal dimension

Table 2. *Results of the discriminant analysis using kinetic parameters as independent variables for the prediction of 2 groups in postoperative lesions (n=71)*

Variable	CCR recurrence	CCR scar	CCR both groups
SUV	57.47 (27/47)	95.83 (23/24)	70.42 (50/71)
VB	51/06 (24/47)	75.00 (18/24)	59.15(42/71)
k3	38.30 (18/47)	83.33 (20/24)	53.52 (38/71)
Ki	59.57 (28/47)	83.33 (20/24)	67.60 (53/71))
FD	76.60 (36/47)	70.83 (17/24)	74.65 (53/71)
SUV,Ki,FD	80.85 (38/47)	87.50 (21/24)	83.10 (59/71)

CCR: correct classification rate (%), FD: fractal dimension

Evaluation of the grade of differentiation

In 32 cases with primary or recurrent liposarcomas (9 GI, 9 GII liposarcoma, and 14 GIII tumors), GII or GIII tumors (n=23) showed significantly higher SUV (P=0.0021) and FD (P=0.0069) than GI (n=9). Accuracy of 71.86% (sensitivity 60.87%, specificity 100.0%) was obtained by using SUV as an index for the lower grade of differentiation (GII or GIII) (Table 3). Using FD or the combination of SUV and FD, the best accuracy was 78.13% (sensitivity 86.96%, specificity 55.56%). The scatterplot of SUV and FD showed the increase of both parameters according to the grade (Fig. 4). Grade II cases were overlapped between GI and GIII cases.

Table 3. *Results of the discriminant analysis using kinetic parameters as independent variables for the prediction of 2 groups according to grading in liposarcoma patients (n=32).*

Variable	CCR GI	CCR GII, GIII	CCR both groups
SUV	100.0 (9/9)	60.8714/23)	71.86 (23/32)
FD	55.56 (5/9)	86.96 (20/23)	78.13 (25/32)
SUV, FD	55.56 (5/9)	86.96 (20/23)	78.13 (25/32)

CCR: correct classification rate (%), FD: fractal dimension

Prediction of prognosis

Patients with primary soft tissue sarcoma who underwent surgical resection were examined (n=26) to clarify the prognostic value of ^{18}F-FDG with respect to overall survival. Every parameter of the ^{18}F-FDG-kinetics (SUV, k1-k4, Ki, FD) was evaluated by a univariate analysis. As a result, SUV, k3, Ki and FD demonstrated a significant relationship to overall survival (Table 4). Furthermore, multivariate analysis revealed k3 and FD to be independently significant parameters for the prediction of prognosis (Table 5). A multiple linear regression model was applied to the data to assess the relationship between individual survival times and these selected parameters. The most significant results were obtained by the use of the combination of k3 and FD (Table 6). The scatterplot of Figure 5 demonstrates the correlation between the observed survival time and the predicted survival time (Table 7).

Table 4. *Uni-variate analysis of the prognostic value of kinetic parameters of ^{18}F-FDG-PET (n=26)*

Variable		HR	P value
SUV	4.0<	3.649	0.0268 *
VB	0.2<	1.510	0.4822
k1	0.3<	1.443	0.5323
k2	0.3<	1.502	0.5075
k3	0.025<	15.121	0.0008 *
k4	0.025<	1.431	0.5432
Ki	0.03<	3.839	0.0267 *
FD	1.25<	5.764	0.0093 *

FD: fractal dimension, * statistically significant

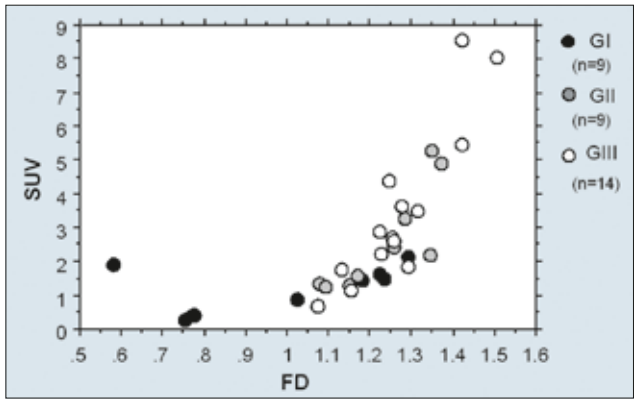

Figure 4. The relationship between fractal dimension (FD) and SUV in liposarcomas (n=32). The data demonstrate an overlap of Grade I and GII - GIII. G: grade.

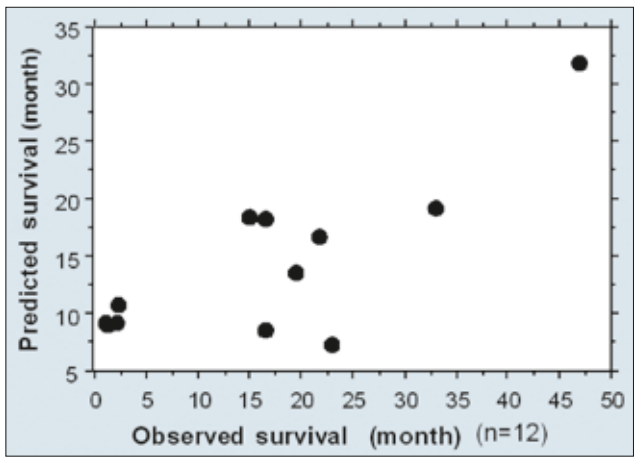

Figure 5. The relationship between observed and individually predicted survival times in months using kinetic data (k3 and FD) in 12 patients.

Table 5. *Multivariate analysis of the prognostic value of kinetic parameters of ^{18}F-FDG-PET (n=26)*

Variable		HR	P value
SUV	4.0<	0.198	0.1469
k3	0.025<	31.442	0.0026 *
Ki	0.03<	3.861	0.1102
FD	1.25<	15.428	0.0162 *

FD: fractal dimension, * statistically significant

Table 6. *Correlation coefficient of observed survival times (dependent valuable) and predicted survival times as calculated by multiple linear regression function*

Subset	Regression	P value
SUV, k3, Ki, FD	0.872	0.0244 *
k3, FD	0.860	0.00236 *

FD: fractal dimension, * statistically significant

Table 7. *Observed versus predicted survival time for each patient*

Patient no.	Observed survival (month)	Predicted survival (month)
1	1.0	9.2
2	1.2	9.0
3	2.2	9.2
4	2.3	10.8
5	14.9	18.5
6	16.5	8.6
7	16.6	18.3
8	19.5	13.6
9	21.8	16.7
10	23.0	7.3
11	33.1	19.2
12	47.0	31.8

Predicted survival is based on the kinetic data of k3 and FD.

Discussion

The increase of glucose metabolism in malignant tumors is known, as well as the clinical usefulness of ^{18}F-FDG-PET to visualize and to evaluate the metabolism of various malignant tumors. Soft tissue sarcoma is one of the difficult tumor to treat because of its diagnostic problems and of recurrent tendency. Conventional imaging modalities are important, but they are not adequate for the differential diagnosis of small sarcomas from a benign tumor as well as for early diagnosis of postoperative recurrence, the evaluation of tumor grading and the prediction of prognosis. Recently, several authors reported on ^{18}F-FDG-PET results and usefulness on these concerns [11-15]. They generally evaluate ^{18}F-FDG uptakes using SUV obtained by static ^{18}F-FDG-PET images. In this study, soft tissue sarcomas were evaluated on the concerns mentioned above by kinetic parameters derived by dynamic PET studies. The rate constants of the compartment model of ^{18}F-FDG (k1, k2, k3, k4), the Ki, VB, FD and SUV.

According to the result of this study, concerning the differential diagnosis of primary tumors, SUV, k1, Ki and FD proved to be useful. The accuracy using SUV was 56.52%, however the combination of SUV and k1 resulted in the highest accuracy of 71.74%. k1 is the rate constant for the transport of ^{18}F-FDG from the serum into the tumor cell and it is supposed to reflect the activity of the glucose transporters (GLUT), which are cell membranous proteins. The GLUT was recently noticed because of its increase in malignant tumors [16, 17].

In the diagnosis of postoperative lesions SUV, VB, k3, Ki, and also FD proved to be useful. The best accuracy of 83.10% for malignancy was obtained by the combination of SUV, Ki and FD while that of SUV alone was 70.4%. Ki, FD, k3 and VB reflected ^{18}F-FDG turnover, heterogeneity, hexokinase activity and fractional volume of the blood in tumor respectively [7]. The result suggested the significantly higher tendency of these factors in the recurrent tissues than in the scar tissues.

In the diagnosis of tumor grading in liposarcomas, SUV and FD proved to be useful. The better accuracy of 78.13% between lower and high grade was obtained by FD in comparison to 71.86% by SUV. Fractal dimension reflects the heterogeneity of ^{18}F-FDG uptake in the tumor [10, 18]. It is known that sarcomas have a heterogenic tissue structure according to the differentiation grade [19-21]. The result suggested a higher FD tumor in low differentiated tumors.

In the prediction of prognosis, k3 and FD also proved to be useful. Multivariate analysis revealed them as significant independent prognostic parameters. k3 is the rate constant of phophorylation of ^{18}F-FDG by hexokinases. It has been reported that the hexokinase activity in malignant tumor increases according to its proliferative tendency and correlates to the prognosis [22, 23]. On the other hand, the k3 values obtained by dynamic ^{18}F-FDG-PET studies were reported to be correlated with the actual hexokinase activities and with prognosis on esophageal cancers [24]. The result of this study showed the usefulness of k3 as a prognostic parameter in soft tissue sarcoma, too. FD is the index for the heterogeneous uptake of ^{18}F-FDG in the tumor tissue. As mentioned above, the heterogeneity of sarcoma tissue reflects its differential grade. It was also reported that sarcomas with high malignancy had necrotizing tendency and this fact influences prognosis [25]. Therefore, as the index for heterogeneity and necrosis of sarcoma tissue, FD is a useful prognostic parameter.

It is hopeful to currently perform kinetic evaluation by dynamic ^{18}F-FDG-PET for tumor evaluation to optimize and individualize the diagnosis and treatment planning.

In conclusion, using kinetic parameters of dynamic ^{18}F-FDG-PET, several indices, which were clinically useful in the treatment of soft-tissue sarcomas were obtained. The diagnostic accuracies were superior to the results of SUV alone. The input function used in this study has been less invasive using large arterial vessels from the image data, and the data analysis has been easier using dedicated software. Moreover, examination time also can be shortened by a newly introduced method [26].

Bibliography

1. Schwarzbach MH, Dimitrakopoulou-Strauss A, Mechtersheimer G et al. Assessment of soft tissue lesions suspicious for liposarcoma by ^{18}F-deoxyglucose (^{18}F-FDG) positron emission tomography (PET). *Anticancer Res* 2001; 21: 3609-3614.
2. Cardona S, Schwarzbach M, Hinz U et al. Evaluation of ^{18}F-deoxyglucose positron emission tomography (^{18}F-FDG-PET) to assess the nature of neurogenic tumours *Eur J Surg Oncol* 2003; 29: 536-541.
3. Feldman F, van Heertum R, Manos C. ^{18}F-FDG-PET scanning of benign and malignant musculoskeletal lesions. *Skeletal Radiol* 2003; 32: 201-208.
4. Hain SF, O'Doherty MJ, Bingham J et al. Can ^{18}F-FDG PET be used to successfully direct preoperative biopsy of soft tissue tumours? *Nucl Med Commun* 2003; 24: 1139-1143.
5. Schwarzbach M, Willeke F, Dimitrakopoulou-Strauss A et al. Functional imaging and detection of local recurrence in soft tissue sarcomas by positron emission tomography. *Anticancer Res* 1999; 19: 1343-1349.
6. Phelps ME, Huang SC, Hoffman EJ et al. Tomographic measure-

ments of local cerebral glucose metabolic rate in humans with [18F]2-fluoro-2-deoxy D-glucose: validation of method. *Ann Neurol* 1979: 6; 371-388.
7. Dimitrakopoulou-Strauss A, Strauss LG, Schwarzbach M et al. Dynamic PET ^{18}F-FDG studies in patients with primary and recurrent soft-tissue sarcomas: impact on diagnosis and correlation with grading. *J Nucl Med* 2001; 42: 713-720.
8. Toorongian SA, Mullholland GK, Jewet DM et al. Routine production of 2-deoxy -fluoro-D-glucose by direct nucleophilic exchange on a quanternary 4-aminopyridinium resin. *Nucl Med Biol* 1990; 3: 273-279.
9. Strauss LG, Conti PS. The applications of PET in clinical oncology. *J Nucl Med* 1991; 32: 623-648
10. Kalliokoski KK, Kuusela TA, Nuutila P et al. Perfusion heterogeneity in human skeletal muscle: fractal analysis of PET data. *Eur J Nucl Med* 2001; 28: 450-456.
11. Williams HT, Gossage JR Jr, Allred TJ et al. ^{18}F-FDG Positron Emission Tomography Imaging of Rare Soft Tissue Sarcomas: Low-Grade Fibromyxoid Sarcoma and Malignant Hemangiopericytoma. *Clin Nucl Med* 2004; 29: 581-584.
12. Johnson GR, Zhuang H, Khan J et al. Roles of positron emission tomography with fluorine-18-deoxyglucose in the detection of local recurrent and distant metastatic sarcoma. *Clin Nucl Med* 2003; 28: 815-820.
13. Schwarzbach MH, Dimitrakopoulou-Strauss A, Willeke F et al. Clinical value of ^{18}F-fluorodeoxyglucose positron emission tomography imaging in soft tissue sarcomas. *Ann Surg* 2000; 231: 380-386.
14. Folpe AL, Lyles RH, Sprouse JT et al. ^{18}F-fluorodeoxyglucose positron emission tomography as a predictor of pathologic grade and other prognostic variables in bone and soft tissue sarcoma. *Clin Cancer Res* 2000; 6: 1279-1287.
15. Eary JF, O'Sullivan F, Powitan Y et al. Sarcoma tumor ^{18}F-FDG uptake measured by PET and patient outcome: a retrospective analysis. *Eur J Nucl Med Mol Imaging* 2002; 29: 1149-1154.
16. Strauss LG, Dimitrakopoulou-Strauss A, Koczan D et al. ^{18}F-FDG Kinetics and Gene Expression in Giant Cell Tumors. *J Nucl Med* 2004; 45: 1528-1535.
17. Armoni M, Quon MJ, Maor G et al. PAX3/forkhead homolog in rhabdomyosarcoma oncoprotein activates glucose transporter 4 gene expression in vivo and in vitro. *J Clin Endocrinol Metab* 2002; 87: 5312-5324.
18. Dimitrakopoulou-Strauss A, Strauss LG, Heichel T et al. The role of quantitative ^{18}F-FDG-PET studies for the differentiation of malignant and benign bone lesions. *J Nucl Med* 2002; 43: 510-518
19. Waligore MP, Stephens DH, Soule EH, McLeod RA. Lipomatous tumors of the abdominal cavity: CT appearance and pathologic correlation. *Am J Roentgenol* 1981; 137: 539-545.
20. Kim T, Murakami T, Oi H et al. CT and MR imaging of abdominal liposarcoma. *Am J Roentgenol* 1996; 166: 829-833.
21. Takao H, Yamahira K, Watanabe T. Encapsulated fat necrosis mimicking abdominal liposarcoma: computed tomography findings. *J Comput Assist Tomogr* 2004; 28: 193-194.
22. Greengard O, Head JF, Goldberg SL, Kirschner PA. Enzyme pathology and the histologic categorization of human lung tumors: the continuum of quantitative biochemical indices of neoplasticity. *Cancer* 1982; 49: 460-467.
23. Paggi MG, Fanculli M, Del Carlo C et al. The membrane-bound hexokinase as a potential marker for malignancy in human gliomas. *J Neurosurg Sci* 1990; 34: 209-213.
24. Fukunaga T, Okazumi S, Koide Y et al. Evaluation of esophageal cancers using fluorine-18-fluorodeoxyglucose PET. *J Nucl Med* 1998; 39: 1002-1007.
25. Engellau J, Anderson H, Rydholm A et al. Time dependence of prognostic factors for patients with soft tissue sarcoma: a Scandinavian Sarcoma Group Study of 338 malignant fibrous histiocytomas. *Cancer* 2004; 100: 2233-2239.
26. Strauss LG, Dimitrakopoulou-Strauss A, Haberkorn U. Shortened PET data acquisition protocol for the quantification of ^{18}F-FDG kinetics. *J Nucl Med* 2003; 44: 1933-1939.