Quantitative studies using positron emission tomography for the diagnosis and therapy planning of oncological patients

Abstract

Positron emission tomography (PET) has found wide-spread use in oncology due to the relatively high accuracy in staging, differential diagnosis and therapy monitoring. Most PET studies are performed as a whole body scan. In selected cases a semiquantitative analysis is performed, which is based on the calculation of standardized uptake values (SUV). The present studies were undertaken in order to evaluate the impact of dynamic PET studies in malignant diseases with respect to tumor diagnosis and therapy management. Dynamic data acquisition is superior to static images because it provides information about the tracer distribution with respect to time and space, in a region of interest. The impact of different compartmental and non-compartmental approaches for the diagnostics and therapy planning was also studied. The radiopharmaceuticals used for patient studies were: O-15-water, C-11-ethanol, F-18-fluorodeoxyglucose (FDG), F-18-fluorouracil (F-18-FU), and 6-F-18-fluoro-L-DOPA. A new evaluation strategy of dynamic PET studies based on an integrated evaluation including both compartment and non-compartment models, as well as the use of SUV, are presented. Furthermore, the parametric imaging including Fourier-analysis and regressions analysis was used. Results: PET-studies with labeled cytostatic agents provide information about the transport and elimination of a cytostatic agent and help to predict the therapeutic outcome. The retention of the radiolabeled cytostatic agent F-18-FU in liver metastases of colorectal cancer was low after systemic treatment. Lesions with retention values >3.0 SUV and <2.0 SUV correlated with negative and positive growth rates, respectively. A high F-18-FU retention (>2.96 SUV) was associated with longer survival times (>21 months). In contrast, patients with lower F-18-FU retention values (<1.2 SUV) survived no longer than one year. A higher diagnostic accuracy was obtained by using an integrated evaluation including both compartment and non-compartment models. ^{18}F-FDG studies for the diagnosis of soft tissue sarcomas showed a sensitivity and specificity of 91% and 88% for the primary tumors and 88% and 92% for the recurrences, respectively. Using a combination of SUV and transport rates, it was possible to further classify malignant soft tissue tumors with regard to tumor grading percentages as: 84% of the G III tumors, 37.5% of the G II and 80% of the G I tumors, as well as 50% of the lipomas and 14.3% of scar tissue were correctly classified using the integrated evaluation. In patients with bone tumors, integrated evaluation was also superior to SUV or visual evaluation leading to a sensitivity of 76% (for SUV: 54%), a specificity of 97% (for SUV: 91%) and an accuracy of 88% (for SUV: 75%). The diagnostic efficacy of SUV and of the fractal dimension of the time activity data of ^{18}F-FDG was evaluated in 159 patients with 200 lesions of different tumors with respect to differential diagnosis and the prognosis of the therapeutic outcome. Discriminant analysis revealed a diagnostic accuracy of 76.65% for all patients, 67.7% for the untreated group of patients and 83.44% for the pretreated patients. The advantage of parametric imaging is the visualization of one isolated parameter of the tracer's kinetics, like the phosphorylation in case of ^{18}F-FDG. Furthermore, the delineation of a tumor is better, due to the absence of background activity. The presented data also demonstrate that parametric imaging based on Fourier's transformation may be useful for the evaluation of the pharmacokinetics and the effectiveness of regional therapeutic procedures. In conclusion, a semiquantitative analysis of PET data sets based on SUV is in general helpful and should be performed under standardized conditions, concerning the time after tracer application, the blood glucose level in case of ^{18}F-FDG, partial volume correction and the choice of reconstruction parameters. The combination of two SUV, an early and a late one, is a simple and useful approach for the evaluation of a dynamic series in a clinical environment. PET studies with labeled cytostatic agents provide information about the transport and elimination of a cytostatic agent and help to predict the therapeutic outcome. Non-compartment models require further evaluation.

Hell J Nucl Med 2006; 9(1): 10-21

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Keywords: Positron emission tomography – Quantification – Modeling – Compartment – Non-compartment – Oncology

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Received:
24 November 2005

Accepted:
2 December 2005

Introduction

Positron emission tomography (PET) had found wide-spread use in oncology due to the relatively high accuracy in the staging and differential diagnosis. However, most PET studies are performed as a whole body scan 45-90 min after the injection of a radio-

pharmaceutical, which is usually, the radiotracer ^{18}F-fluorodeoxyglucose (^{18}F-FDG). FDG is a glucose analog, which is transported and phosphorylated like glucose, but then trapped. The evaluation of the ^{18}F-FDG-PET images is performed on a visual basis. Semiquantitative measurements are mostly used in particular for the evaluation of a theapeutic effect. For that purpose static images are acquired and the so called "Standardized Uptake Values" (SUV) are calculated. The SUV is a distribution value, which allows the comparison of a radioactivity concentration between different patients and different studies. A SUV of 1.0 means a homogenous tracer distribution.

A semiquantitative analysis of PET data sets based on SUV is in general helpful and should be performed under standardized conditions, concerning the time after tracer application, the blood glucose level in case of ^{18}F-FDG, partial volume correction and the choice of reconstruction parameters. The calculation of SUV has been particularly helpful for the primary tumor diagnosis and the differential diagnosis between recurrent tumor and scar tissue using FDG. SUV is recommended for the evaluation of routine ^{18}F-FDG studies in a clinical environment.

Dynamic studies are superior because they provide information about the tracer distribution with respect of time and space in a Region of Interest (ROI). A detailed analysis of the kinetic data is then possible in order to acquire the most relevant information of the tracer pharmacokinetics. The impact of different compartmental and non-compartmental approaches for the diagnostics and therapy planning will be discussed.

Materials and methods

PET studies are usually performed with full ring systems. At the German Cancer Research Center (DKFZ) an ECAT EXACT HR plus (Siemens Co., Erlangen, Germany) was used for the studies presented in this paper. The system has an axial field of view of 15.5 cm (63 transversal slices).

Radiopharmaceuticals

The radiopharmaceuticals used for the PET studies were produced in the Department of Radiochemistry and Radiopharmacology of the DKFZ as well as in the Research Center Karlsruhe (^{18}F-FDG). The cyclotron used at the DKFZ is a negative-ion-machine (MC32NI, 32 MeV, Scanditronix Co., Sweden). The isotopes used for labeling are: O-15 ($t_{1/2}$: 2.05 min), C-11 ($t_{1/2}$: 20.4 min), F-18 ($t_{1/2}$: 109.7 min) and Ga-68 ($t_{1/2}$: 68.3 min). The following radiopharmaceuticals have been used for patient studies: O-15-water, C-11-ethanol, F-18-fluorodeoxyglucose (FDG), F-18-fluorouracil (F-18-FU), Ga-68-DOTATOC.

O-15-water is an inert tracer, which provides information about the tissue perfusion. C-11-ethanol and F-18-fluorouracil provide information about the pharmacokinetics of the non-labeled form, which is identical to the labeled one. FDG is a glucose analogue, that is transported and phosphorylated, as mentioned above. Ga-68-DOTATOC is a peptide, which provides information of the SSTR II receptor expression.

Data processing

A prerequisite for an accurate quantification of radioactivity concentrations is the use of appropriate reconstruction algorithms [1-6]. Iterative image reconstruction algorithms have been used in all these studies, because they are superior to the filtered backprojection (FB). All studies were performed using a dynamic data acquisition. The acquisition time varied from 5 min (e.g. for O-15-water studies) to two hours (e.g. for F-18-fluorouracil studies) dependent on the radiopharmaceutical used.

Data evaluation

After the data reconstruction PET images were evaluated using different methods. A semiquantitative evaluation is generally performed based on the calculation of the SUV.
SUV (Standardized Uptake Value) = Tissue concentration (MBq/g) / (injected dose (MBq) / body weight (g)).

The evaluation of the dynamic data was performed using dedicated compartment and non-compartment models depending on the tracer used. The software package PMod (PMod Technologies Ltd., Adliswil, Switzerland) was applied to the data. The software allows the implementation of new models for the pharmacokinetic analysis of the data [7].
Compartment models: A more detailed quantification of the dynamic PET data was performed using compartment models, which originate from the pharmacology and were first used for brain studies, in order to study the FDG kinetics.

Input function

All compartmental approaches require an accurate measurement of the input function. The input function can be estimated by using arterial or venous blood samples. A noninvasive method consists in the direct measurement of the arterial concentration from the early phase PET images (e.g. of the first frame) by placing a Volume of Interest (VOI) in a large arterial vessel, like the descending aorta. Ohtake et al (1991) report a good correlation between the input function as measured in a VOI over the descending aorta (consisting of at least seven sequential ROIs) and the input function based on arterial or venous blood sampling [8]. Keiding et al (2000) report a good relation between the transport rates based on an input function derived from the PET data and the ones based on arterial blood sampling [9]. We used an input function derived from the PET data for all studies. If possible, a VOI placed in the descending aorta was used, which is advantageous in comparison to the one from the heart due to the low spillover.

One-tissue-compartment model

This model is appropriate for tracers, which are pure transport markers or which are not further metabolized. The model allows the calculation of the influx rate (k1), the efflux rate (k2), as well as the fractional blood volume (VB). The one-tissue-compartment model is used for the pharmacokinetic analysis of transport tracers, like C-11-aminoisobutyric acid (AIB), a tracer of the alanin-like (A-type) amino acid transport,

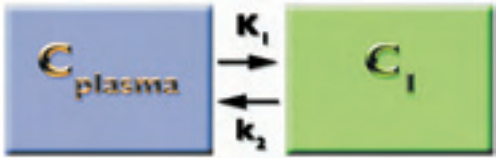

Figure 1. One-tissue-compartment model with one input function: In this case the whole radiotracer activity is transported into one tissue compartment (C_1)

Figure 2. Two-tissue-compartment model with one input function: Compartment C_1 represents the free and non-metabolized part of the applied tracer in tissue, compartment C_2 the metabolized part of the tracer in the tissue. In case of FDG the metabolized part is the phosphorylated FDG

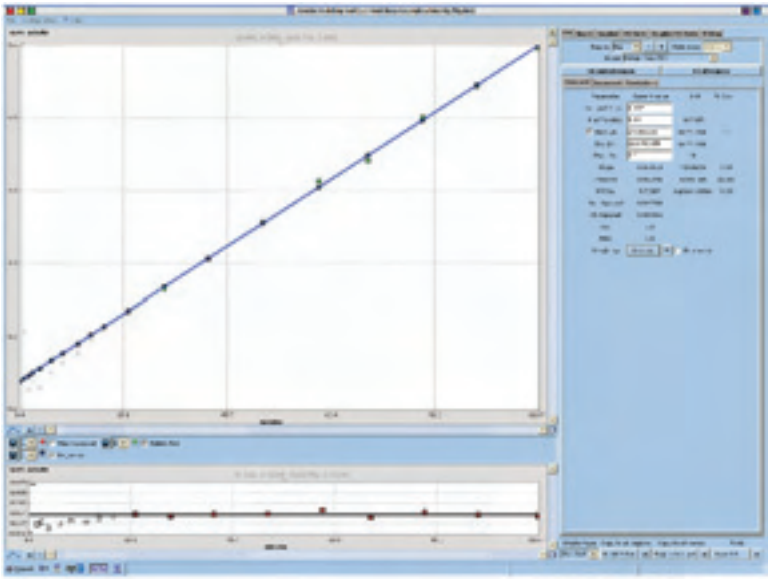

Figure 3. Patlak plot: Prerequisite for a Patlak-plot is an irreversible trapping. In this case, a so called influx constant Ki can be graphically determined. The model consists, comparable to the two-tissue compartment model of a blood/plasma compartment, which is a reversible compartment and a non-reversible compartment. The metabolic rate of ^{18}F-FDG (MRFDG) is calculated by using the formula: MRFDG=Ki x plasma glucose level

as well as for inert tracers like the perfusion tracer O-15-water, which is free diffusable (Fig. 1).

Two-tissue-compartment model

This model is appropriate for tracers, which are transported, and after the first metabolic step trapped, like in case of FDG. A two-tissue compartment model first described by Sokoloff et al. and was used for the quantification of brain studies [10-11].

As demonstrated in Figure 2, four transport rates (k1, k2, k3, k4) describe the exchange of the tracer between blood and tissue. In case of ^{18}F-FDG, k1 reflects the influx, k2 the efflux, k3 the phosphorylation rate and k4 the dephosphorylation rate of the glucose analogue. A simplification of the model consists of the summary of the interstitial and cellular space. A modification of the two-tissue compartment model consists of the calculation of the fractional blood volume, which is a parameter that correlates to the blood volume and is called VB. This model is different than the one proposed by Sokoloff et al., which does not take into k4 and VB. The lack of k4 and VB of the model proposed by Sokoloff leads to different k1 and k3 values, since k1 is dependent on VB and k3 on k4. The dephosphorylation rate (k4) of ^{18}F-FDG was in all these oncological studies low, but not negligible.

Patlak plot

Prerequisite for the use of a Patlak-plot is an irreversible trapping of the tracer, like in case of ^{18}F-FDG [12]. The model demonstrates if the major metabolic step fits to an unidirectional transfer of the tracer. If this assumption is confirmed, an influx constant (Ki) can be calculated graphically. The model consists of a blood/plasma compartment, a reversible and a non-reversible compartment. The influx rate can also be calculated using the rate constants of the two-tissue-compartment and the formula:

$$Ki = (k1 \times k3/k2+k3)$$

k4 is zero. The influx rate Ki presents the slope of the curve, which is linear if the metabolic step of a tracer is irreversible. The interval in the y-axis correlates to the fractional blood volume (VB). The metabolic rate of FDG can then be calculated using the formula:

$$MRFDG = Ki \times plasma\ glucose\ (Fig.\ 3).$$

Non-compartmental models

Fractal dimension

A new approach is based on the calculation of the fractal dimension, a procedure that was initially used for the evaluation of arrythmia of the heart. The calculation of fractal dimension (FD) of the time-activity curves was based on the box-counting procedure [13]. FD describes the heterogeneity of tracer kinetics. A high FD means a chaotic tracer distribution and correlates to a more heterogenous tissue. The calculation is performed by placing a matrix with increasing number of boxes over the time-activity curve, which is handled like an image and simply count the number of boxes containing some of the structures. The model variables used for the calculation of FD were fixed for all our studies. The maximal number of boxes was 7×7 and the maximum SUV was 20. The values for FD varied between 0 and 2 when using these parameters. Furthermore, pixelwise-parametric images of FD were calculated.

Fourier-analysis

Another non-compartment model based on the Fourier-analysis was applied to the dynamic data to analyze the local distribution of radiopharmaceuticals. The applied model allows the visualization of the amplitude and phase images for the first harmonic. Parametric images of the amplitude provide information about the maximum local uptake, whereas images of the phase demonstrate the point in time of the appearance of the maximum tracer uptake. The major impact of this procedure is the measurement of the local redistribution of radiopharmaceuticals during a dynamic data acquisition.

Parametric imaging

Nuclear medicine images are functional images, which represent the average tracer activity concentration at a defined time after tracer injection. However, using dedicated mathematical models it is possible to visualize a specific parameter of the tracer kinetics. The idea of parametric imaging is the visualization of a specific parameter of the tracer kinetics. Using e.g. a regression model it is possible to visualize separately the perfusion-dependent part (intercept-images) as well as the phosphorylated part (slope-images) of the tracer F-18-fluorodeoxyglucose (^{18}F-FDG) in a tumor lesion. A prerequisite for the calculation of parametric images is the acquisition of a dynamic series.

Evaluation based on the SUV

SUV is a robust parameter, which is helpful for both diagnosis and therapy monitoring studies, if it is used under standardized conditions. SUV is useful, in particular for radiopharmaceuticals, which have a simple metabolic pathway, like transport tracers (e.g. C-11-aminoisobutyric acid). However, SUV has found widespread use for the evaluation of ^{18}F-FDG studies, because ^{18}F-FDG has a known pathway, consisting of transport and phosphorylation. SUV's are comparable only for the same time points following tracer application, because they reflect a dynamic pharmacokinetic process, which is time-dependent and different for each radiotracer. For the presented ^{18}F-FDG-studies, the 55-60 min SUV was used by glucose blood levels within normal range. Inspite the fact, that the SUV are time-dependent, they can be used even for radiopharmaceuticals with a complex metabolic pathway, like F-18-fluorouracil (F-18-FU), which has a catabolic (main catabolite F-18-fluoro-beta-alanin) and an anabolic pathway (F-18-FUMP). In case of radiopharmaceuticals with a more complex metabolic pathway, the SUV of standardized time points post injection (p.i.) should be used for quantification. In case of F-18-FU, we used the early, 20 min p.i. and late, 120 min p.i. SUV for quantification. The 20 min SUV reflect the transported and non-metabolized part of the labeled cytostatic agent, whereas the 120 min SUV correlate to the amount of the trapped FU. For the evaluation of dynamic studies with C-11-ethanol, we used the SUV 5 min and 45 min after the intratumoral injection of the tracer, in order to evaluate the tracer dilution and redistribution.

Systemic application of F-18-FU and O-15-water:

We used a double tracer protocol, consisting of O-15-water and F-18-FU in patients with liver metastases of colorectal carcinoma to study the FU pharmacokinetics after the systemic tracer administration using a dynamic acquisition protocol (5 min for the perfusion studies and two hours for the F-18-FU studies). F-18-FU has identical properties with the non-labeled substance. The evaluation included 78 liver metastases of 50 patients with colorectal tumors. Perfusion data were available in 53 metastases for comparison.

For the semiquantitative data evaluation, we used the following parameters: 5 min SUV for O-15-water (parameter for the tissue perfusion), 20 min SUV for F-18-FU (parameter for the FU-transport) and 120 min SUV for F-18-FU (parameter for the FU-retention).

Results

The results demonstrated, that the retention of the radiolabeled cytostatic agent in liver metastases was low. The average 120 min SUV was 1.3 SUV in the metastases with a strong variation for different metastases even in the same patient. The comparison with the perfusion data did not reveal a statistical significant correlation neither between perfusion and F-18-FU transport nor between perfusion and F-18-FU retention. Using Cluster analysis two groups of liver metastases could be identified. Most of them (n=75) demonstrated a significant linear correlation between F-18-FU transport and retention ($r=0.89$, $P<0.01$). Further three metastases were classified to another Cluster, and revealed no correlation between F-18-FU transport and retention. The analysis of the perfusion data and the FU-transport showed again two groups of lesions. Most of the liver metastases (n=43) were classified to a Cluster with a significant correlation ($r=0.61$, $P<0.01$) between perfusion and FU-transport. In contrast, 10 metastases of another Cluster did not show a correlation between perfusion and FU-transport [14].

Comparison of CT volumetric data to growth rate and survival

In order to evaluate the impact of the F-18-FU retention values, we compared the 120 min SUV for F-18-FU prior ot onset to chemotherapy with the growth rate of the metastases, based on CT volumetric data, following therapy (17 patients, 25 metastases). The comparison between the F-18-FU retention values and the growth rate of the metastases revealed a correlation of $r=0.86$ ($P<0.001$). Only lesions with retention values >3.0 SUV correlated with negative growth rates. Lesions with retention values <2.0 SUV were associated with a positive growth rate [15]. The data demonstrated, that one F-18-FU study prior to onset to chemotherapy can be used for prediction of therapy outcome. Furthermore, the F-18-FU retention was compared to the survival rate of 14 patients, scheduled for FU-chemotherapy. A high F-18-FU retention (>2.96 SUV) was associated with longer survival times (>21 months). In contrast, patients with lower F-18-FU retention values (<1.2 SUV) survived no longer than one year [16].

Diagnosis of soft tissue sarcomas

^{18}F-FDG studies were performed in patients with primary (n=11) and recurrent soft tissue (n=24) sarcomas as well as in 13 benign soft tissue lesions to evaluate the impact of ^{18}F-FDG studies based evaluation of the 55-60 min SUV. The sensitivity was 91% for the primary tumors and 88% for the recurrences, the specificity was 88% for the primary tumors and 92% for the recurrences. The differentiation of GII and GIII tumors was not a problem due to the enhanced ^{18}F-FDG-uptake. However, the differentiation between GI tumors and benign lesions (e.g. lipomas, leiomyomas, scars) was difficult due to the low ^{18}F-FDG-uptake. Furthermore, inflammatory lesions could not be differentiated from high grade sarcomas [17].

Combined evaluation: SUV, Patlak Diagnostic of bone tumors

In patients with histologically confirmed bone lesions (21 malignant, 19 benign) we evaluated the impact of different evaluation parameters: the average and maximal SUV, as well as the ratio tumor SUV/muscle SUV (T/M), the ratio average 60 min tumor SUV /average 30 min tumor SUV (averSUV60/30) as well as the ratio of the maximum tumor SUV 60 min /maximum tumor SUV 30 min (maxSUV 60/30).

Furthermore, the metabolic rate (MRFDG) was calculated according to Patlak. Both parameters, the 60 min SUV and the MRFDG were enhanced in tumors in comparison to bening lesions.The average 60 min SUV correlated to the MRFDG (r=0.67, P<0.05).

Using a cutoff of 1.8 SUV, the sensitivity was 85% and the specificity 82.4%. MRFDG demonstrated a sensitivity of 82.4% and a specificity of 92.9%. The combination of both parameters, an average SUV 60>1.8 and averSUV 60/30 >1.1 revealed an improvement of specificity (93.3%) and a decrease in sensitivity (81.3%) in comparison to a single SUV evaluation [18].

Integrated evaluation based on SUV, compartment modeling, influx according to Patlak and the fractal dimension

Differential diagnosis and biological grading of soft tissue sarcomas

The impact of compartment and non-compartment models was evaluated with respect to the preoperative diagnosis in 56 patients with soft tissue sarcomas. 43 patients had histologically confirmed soft tissue sarcomas and 13 patients benign lesions.The dynamic ^{18}F-FDG series were evaluated with a two-tissue-compartment model and the non-compartmental calculation of the fractal dimension. Furthermore, the global influx according to Patlak and the 55-60 min SUV were used for evaluation. Based on the data of the visual analysis alone, sensitivity was 76.2%, specificity 42.9% and the accuracy 67.9%. The fractional blood volume VB and the SUV were higher in tumors than in benign lesions (t-test, P<0.05). Based on the fractal dimension and kinetic parameters, GI and G III tumors could be correctly diagnosed. In contrast, the differential diagnosis between G I sarcomas and lipomas was difficult. Best results were obtained using 6 kinetic parameters (SUV, VB, k1, k3, influx, fractal dimension) as an input for the discriminant analysis (DA). 84% of the G III, 37.5% of the G II, 80% of the G I tumors, as well as 50% of the lipomas and 14.3% of the scars could be correctly classified using DA and the kinetic parameters mentioned above. In comparison, based solely on the 55-60 min SUV data, only two groups could be correctly classified, namely 92% of the G III tumors and 50% of the G I tumors. The results of this study demonstrate, that only the detailed kinetic analysis of the ^{18}F-FDG kinetics allows a differentiation according to the histological grading with a sensitivity exceeding 80% for G I and G III tumors [19].

Differential diagnosis of bone tumors

Comparable results were obtained in 83 patients with bone lesions, including 37 histologically confirmed bone tumors (osteosarcomas, Ewing sarcomas, giant cell tumors, multiple myelomas, bone metastases and others) and 46 benign lesions, like enchondromas, osteomyelitis, scars, bone cysts, fibromas, osteitis. Malignant tumors demonstrated significant higher values for SUV, VB, k1 and k3.

Discriminant analysis revealed the highest diagnostic accuracy for the combined analysis of the ^{18}F-FDG kinetics. Based on SUV, FD, VB, k1-k4 and global influx the sensitivity increased to 75.86% (for SUV: 54.05%), specificity increased to 97.22% (for SUV: 91.30%) and the accuracy to 87.69% (for SUV: 74.70%). The Bayes-analysis demonstrated even for a relatively low prevalence of disease (P=0.235) a diagnostic accuracy of 80 % for a positive finding [20].

Evaluation of therapeutic effects: application of mathematical models for the evaluation of the kinetic PET-data with respect to the prognosis of therapeutic outcome

The impact of the use of mathematical models for the early prognosis of a therapeutic effect was studied in patients with colorectal carcinomas, who received FOLFOX chemotherapy (5-FU, folinic acid, oxaliplatin). This study included 55 metastases in 28 patients. ^{18}F-FDG studies were performed immediately prior to onset to chemotherapy, after one cycle and after the end of the fourth cycle. The quantification was performed using a two-tissue-compartment model and the non-compartmental model of the fractal dimension. As reference for the PET data served the restaging data (three groups according to WHO-criteria: partial remission (PR), stable disease (SD), and progressive disease (PD) as well as the survival time. Median SUV prior to onset to chemotherapy was 3.15 SUV, after completion of the first cycle 2.68 SUV and after the fourth cycle 2.61 SUV. Using discriminant analysis and the initial SUV and/or the initial FD was possible to select patients with progressive disease in more than 90% of the patients. In contrast to SUV, using FD it was possible to predict stable disease in 75% of the patients [21].

Furthermore, we assessed the impact of different quantitative parameters of the ^{18}F-FDG kinetics on individual survival rates. The evaluation was based on data of 25 patients with 43 metastases. Discriminant analysis and a multiple linear regression model was used for the evaluation. A classification into two groups was used based on a cutoff value of one year survival time (364 days). Based solely on the SUV the correct classification rate (CCR) was 62 to 69%. Best results were obtained by using different kinetic parameters (k1, k3, VB, FD) of the first and third study with a correct classification rate (CCR) of 78% in comparison to 69% for the combination of the SUV of the first and third study.

A multiple linear correlation was used to assess the relation between the individual survival time and the PET data. Best subset analysis was used and a correlation of 0.850 was found for the combination of kinetic data of the first study (k3, k4, VB, FD) and of the third ^{18}F-FDG study (k1, k2, k4, VB) and the survival [22]. The data demonstrated that the most accurate prognosis of the individual survival time was possible based on kinetic data of the first and third study (Fig. 4). The change in SUV between the first and the follow-up ^{18}F-FDG studies was not accurate for the prediction of the individual survival.

Fractal dimension as a single parameter for the differential diagnosis of tumors

The impact of the fractal dimension was evaluated in 159 patients with 200 lesions. In order to validate the different quantification methods we evaluated tumors with several histologies as well as benign lesions. 101/200 of the malignant lesions were pretreated with chemotherapy, whereas 99/200 lesions and all 57 benign lesions did not have any therapy at least 6 months prior to PET. The visual evaluation of the conventional PET images and the parametric fractal images revealed different distribution patterns (Fig. 5). The absolute values of FD were dependent on the number of boxes and the cutoff value used for the calculation. The average and median FD value were different, depending on the tumor type. The highest FD was measured in melanoma metastases with a value of 1.4 and the lowest FD in benign bone lesions with 1.02. The variability of the FD values was generally low in comparison to other parameters, like SUV. The highest variability was measured in patients with malignant soft tissue sarcomas. Discriminant analysis revealed a diagnostic accuracy of 76.65% for all patients, 67.7% for the untreated group of patients and 83.44 % for the pretreated patients. The cutoff value of FD for the differential diagnosis between benign and malignant lesions was 1.13 (input variables; 7 x 7 boxes, maximum: 20 SUV). The data demonstrate a 14 % increase of the sensitivity, 20 % increase of specificity and 15.7% of accuracy for the group of pretreated lesions [23].

Fourier-analysis

The impact of the Fourier-analysis was assessed in patients (n=8) with primary and inoperable liver tumors after the intratumoral application of C-11-ethanol together with the therapeutic dose of non-labeled ethanol.The effect of ethanol in each patient depends on the intratumoral ethanol concentration and its redistribution. The intratumoral application of the tracer was performed via a puncture needle positioned under sonographic guidance. A dynamic data acquisition was performed for 45 min immediately after the tracer injection. Five of eight tumors demonstrated almost constant uptake values after the initial distribution phase. In contrast, a rapid elimination was measured in three of eight tumors. The relative median tracer concentration 45 min p.i. was 56% of the initial concentration values 5 min p.i. Parametric images based on the Fourier analysis were applied to the dynamic data to visualize the local distribution of the tracer. Phase and amplitude images were calculated. The Fourier analysis was focused on the spatial change of the C-11 activity in the tumors. The amplitude images reflect the local maximum of the time activity curve for each pixel, while the phase images represent the time interval when the local maximum was achieved. Seven out of eight tumors demonstrated highly inhomogenous parts on the amplitude images and six tumors showed a redistribution on the phase images [24]. Patients with a more homogenous distribution of the tracer and lack of redistribution survived longer than 7 months, whereas the remaining patients demonstrated an average survival time of 3 months.

Parametric imaging

Parametric imaging was applied in different tracers to visualize a specific parameter of tracer's pharmacokinetics. Regression based images (slope and intercept based) were applied on dynamic ^{18}F-FDG data sets. Figure 6 demonstrates a parametric image of the ^{18}F-FDG-uptake (slope-based), which shows only the phosphorylated part of FDG. The advantage of this method is the visualisation of the first metabolic step (phosphorylation) of ^{18}F-FDG and furthermore, the better delineation of a tumor due to the absence of background activity. Intercept-based images allow the visualisation of the perfusion-dependent part of a radiopharmaceutical.

Discussion

Evaluation based on Standardized Uptake Values

Besides the visual evaluation of PET images, a semiquantitative evaluation based on the SUV is widely used. SUV is a dimensionless value, which represents the global uptake of a radiopharmaceutical at a defined time point after tracer application. The impact of SUV was examined in different tumors and by several authors. Strauss et al. report for the first time in 1989 the results obtained in colorectal recurrences and found that based on SUV 29/30 tumors and 13 scars were correctly classified [25]. In 2001, Gambhir et al. published an overview as a tabulated summary about the diagnostic impact of ^{18}F-FDG in all studies published up to that time [26]. The authors report a patient-based sensitivity of 94%, a specificity of 87% and an accuracy of 94% in 1387 patients with colorectal recurrences. The results were comparable for patients with recurrent lung tumors with a sensitivity of 98%, a specificity of 92% and an accuracy of 96% (in 417 patients). In con-

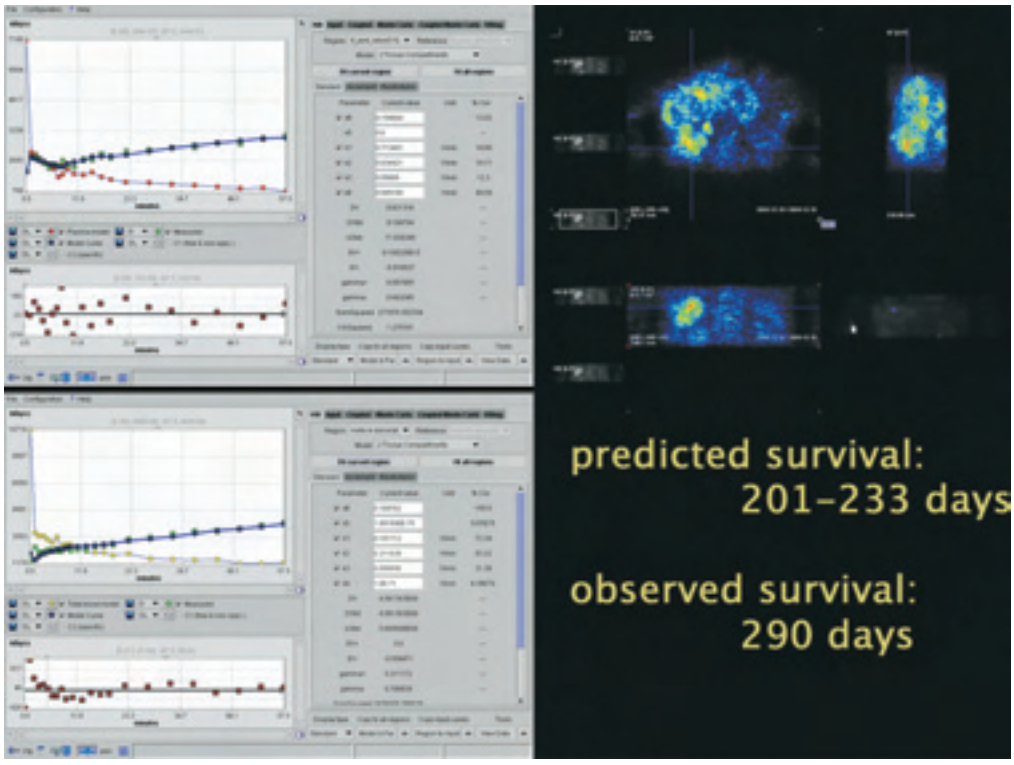

Figure 4. ^{18}F-FDG follow-up studies in a patient with multiple liver metastases of a colorectal carcinoma, who received FOLFOX chemotherapy. The first ^{18}F-FDG study was performed prior to onset to FOLFOX and the third study after the completion of the fourth cycle. Based on the kinetic data of the first (upper left row) and the third ^{18}F-FDG study (lower left row) the predicted survival time was 201-233 days. The observed survival was 290 days

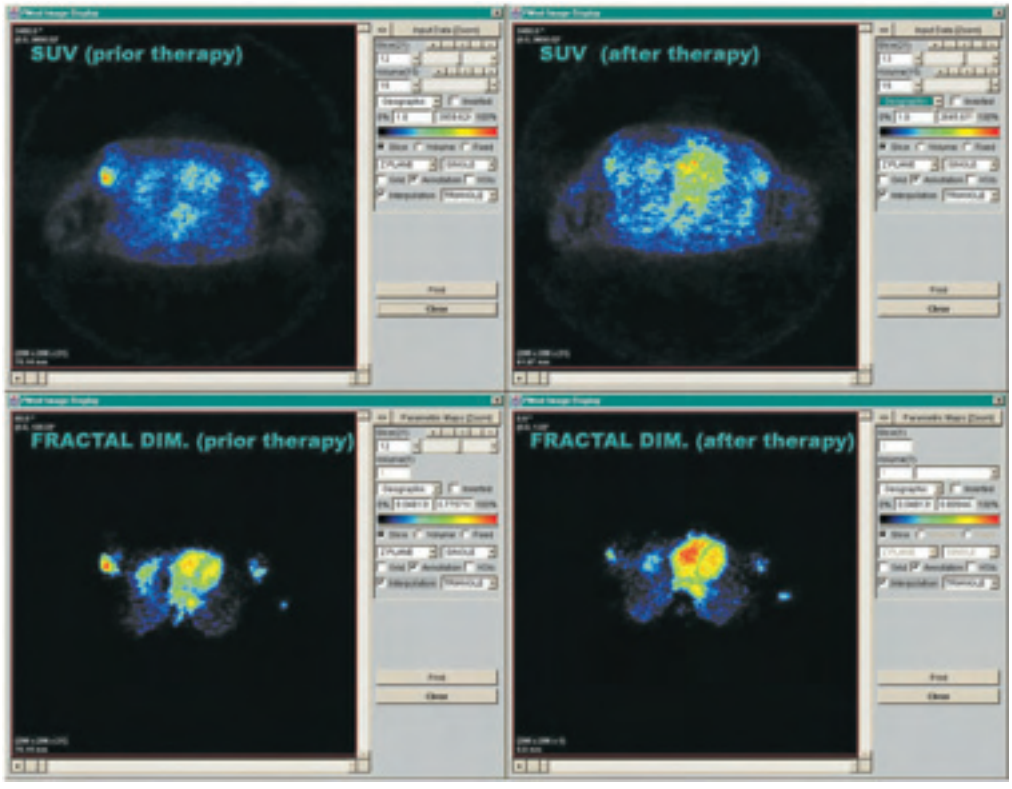

Figure 5. Parametric ^{18}F-FDG images based on the calculation of the fractal dimension in a patient with breast carcinomas on both sides prior and after one chemotherapeutic cycle. The delineation of the breast carcinomas is superior on the parametric images (lower row) in comparison to the SUV images (upper row)

trast, in 1255 patients with primary lung tumors, the specificity was lower (73%), but the sensitivity comparable high (96%) and the accuracy 90%. A high sensitivity (87%) was reported in 516 patients with recurrent lymphomas, with a specificity of 93% and an accuracy of 88%. The reported data are in accordance to our data obtained in 114 lesions of 46 patients with lymphoma recurrences [27]. All malignant lesions revealed an enhanced ^{18}F-FDG-uptake and were correctly diagnosed. In 90.4% of the malignant lesions the 55-60 min SUV was higher than the residual activity in an arterial vessel. Normal sized lymph nodes could cause diagnostic problems depending on the location. If the surrounding tissue is hypometabolic, like fat tissue, the identification of a malignancy is not a problem. The reported study included however,

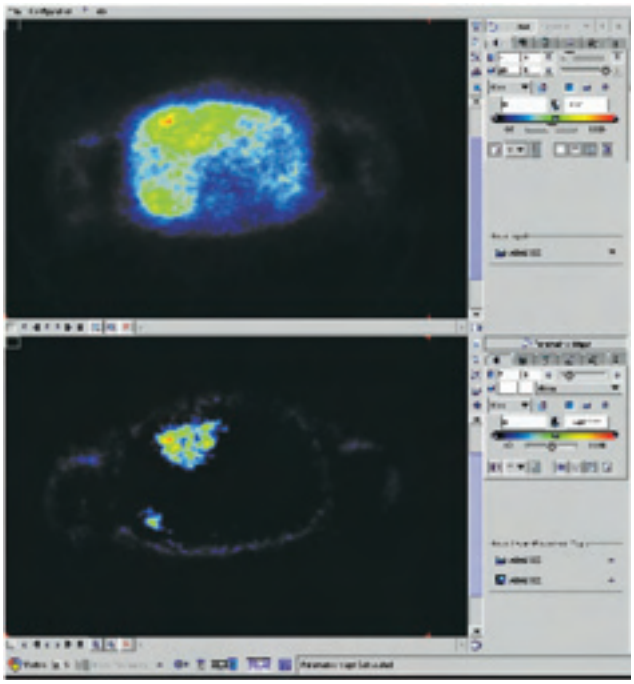

Figure 6. SUV image (upper row) and parametric image of the ^{18}F-FDG metabolism (lower row) in a patient with multiple liver metastases of a carcinoid. The delineation of the liver metastases is clearly superior in the parametric image as compared to the SUV image. The parametric image represents primarily the phosphorylated part of ^{18}F-FDG in the dorsolateral part of the right liver lobe.

highly malignant recurrent lymphomas, which are hypermetabolic in most cases. Problems may be caused in low grade primary lymphomas, which could be negative in ^{18}F-FDG. We noted two false positive results in patients with histologically confirmed abscesses. Not only inflammatory processes, but also a symmetric supraclavicular ^{18}F-FDG-uptake in the brown fat tissue has been reported, which can lead to diagnostic problems [28].

False negative results can generally occur in patients with low grade tumors. Delbeke et al (1995) report on a low ^{18}F-FDG-uptake in patients with G I brain tumors [29]. The authors found an association between the ^{18}F-FDG-uptake and the tumor grading. The results are in accordance to our results obtained in patients with soft tissue sarcomas. Schwarzbach et al (2003) report on a sensitivity of 91% and a specificity of 88% in patients with primary sarcomas [17]. The corresponding data for sarcoma reccurences were 88% (sensitivity) and 92% (specificity). Furthermore, the authors found an association between tumor grading and the 55-60 min SUV for ^{18}F-FDG. Diagnostic problems existed for the differentiation between benign soft tissue processes, like lipomas and myomas and low grade sarcomas [19]. SUV is a parameter, which is in particular helpful for the diagnostics of GII and GIII soft tissue tumors. Twelve of 13 lesions, which could not be correctly classified using MRT, were clearly diagnosed as malignant or benign using ^{18}F-FDG-PET and the 55-60 min SUV. It is known, that SUV is a parameter, that is dependent on the time point of measurement and on the tumor type. Whereas G III tumors demonstrated an almost continuous increase over the 60 min acquisition time, G I tumors and scars reached a plateau phase after the initial distribution phase. Lodge et al. (1999) examined high grade sarcomas up to 6 h p.i. and measured the maximum activity concentration 4 h p.i.. In contrast, benign lesions demonstrated the maximum uptake 30 min p.i. [30]. However, there are also other factors, that have an influence on the SUV, like the plasma glucose level, partial volume effects as well as reconstruction parameters. We measured the glucose blood level, immediately prior to the ^{18}F-FDG study and excluded patients with diabetes. A partial volume correction was performed, if required. Furthermore, the reconstruction parameters were kept constant for all evaluated data sets.

SUV was helpful not only for diagnostic purposes, but also for therapy monitoring. Weber et al. (2001) studied the prognostic value of ^{18}F-FDG in 40 patients with adenocarcinoma of the gastroesophageal junction, who received preoperative chemotherapy [31]. All patients were examined prior therapy and 14 days after onset to cisplatin-based therapy. The authors found a correlation between the reduction of the ^{18}F-FDG-uptake in tumors and the response to preoperative chemotherapy. As reference for PET served the restaging data three months after onset to therapy as well as histopathological data of patients, who underwent surgery. For a 35% reduction of the ^{18}F-FDG-uptake, the sensitivity was 93% and the specificity 95% for the response to preoperative chemotherapy. It is open, if these data can be transferred to other tumors and chemotherapeutic protocols. We also noted a correlation between the change in ^{18}F-FDG-uptake following one chemotherapeutic cycle and the restaging data in 14 patients with recurrent lymphomas. In contrast, it was difficult to assess the long term effects following second line chemotherapy based on only one follow-up ^{18}F-FDG study. For that purpose, we performed at least three ^{18}F-FDG studies in the therapy-free interval.The evaluation of the dynamic PET data was performed on the base of the Standardized Integral Uptake (SIU). The slope of the SIU-curves correlated to the restaging data, namely a negative slope was indicative for a complete remission, whereas a positive slope was associated for progressive disease [27]. In contrast to the data published by Okada et al (1991), the initial ^{18}F-FGD-uptake was not predictive for therapy outcome [32].

Based on the SUV evaluation, studies with F-18-FU have been performed. Two SUV have been used for data analysis. The 20 min SUV was used as a parameter, which reflects the influx or transport of F-18-FU and the 120 min SUV as a parameter for the F-18-FU retention. The choice of these points in time was based on literature data [33,34]. The kinetic F-18-FU data after the systemic administration of the tracer revealed a relatively high 20 min SUV (FU-transport) in 53% of the metastases. However, the 120 min SUV (FU-retention) was low. In only 14.1% of the metastatic lesions the FU retention exceeded 2.0 SUV. The data give evidence for a high efflux of FU. Cluster analysis revealed two groups of metastases with different transport systems for FU, namely a “passive”, perfu-

sion-dependent one and an "active", non-perfusion-dependent transport system [14]. FU trapping was higher in metastases with an "active" transport system. Because the efflux of FU is high, a blockade of the FU catabolism was propagated to enhance the retention of FU in tumors. Such a substance is eniluracil, which inactivates the enzyme dihydropyrimidin-dehydrogenase (DHPDH). DHPDH is responsible for the production of a-fluoro-b-alanin (FBAL). Bading et al. (2003) examined the pharmacokinetic of the combined administration of FU and eniluracil in colon tumor bearing rats up to 120 min p.i. The authors found an enhanced retention of F-18-FU following the eniluracil application [35]. Saleem et al. (2000) performed F-18-FU studies with and without eniluracil application in 6 patients with metastasized gastrointestinal tumors [36]. They found a reduction of the F-18-FU retention in normal liver parenchyma as well as an increase of non-metabolized F-18-FU in plasma. These data demonstrate, that F-18-FU PET studies can be used for monitoring of different FU-based chemotherapeutic protocols in patients.

The 120 min SUV for F-18-FU as measured with PET prior to onset to chemotherapy correlated to the growth rate of the liver metastases (r=0.86, P<0.001). Only metastases, with a high F-18-FU retention (>3.0 SUV) showed a response to chemotherapy. A low F-18-FU retention with SUV <2.0 SUV was associated with non-response. The data demonstrate, that one F-18-FU SUV measurement prior to onset to therapy can be used for prediction of therapy outcome [15]. Similar results were obtained for the comparison of the 120 min SUV for F-18-FU and the survival data. Patients with retention values >2.96 SUV survived longer than 21 months. In contrast, patients with retention values <1.2 SUV lived shorter than one year [16]. The advantage of this method in comparison to FDG, is that just one measurement prior to onset to therapy is needed for the prediction of outcome and the identification of non-responders. However, the value of F-18-FU PET in case of combined protocols, like FOLFOX or FOLFIRI is open at the moment. One possibility, which has to be evaluated is the combined administration of F-18-labeled FU and the therapeutic dose of non-labeled cytostatic agents according to the protocols used for therapy in order to predict therapy outcome.

Combined evaluation: SUV, Patlak

The quantification of ^{18}F-FDG-studies based on two measurements, one in the early and one in the late phase was evaluated by Matthies et al. (2002) in solitary lung nodules [37]. The authors examined 26 patients 70 and 123 min after the ^{18}F-FDG injection. The sensitivity was 80% and the specificity 94% for a cutoff-value of 2.5 SUV 70 min p.i. In contrast, sensitivity increased to 100% and specificity was 89%, for a 10% increase of the ratio SUV 70 to SUV 123. The data indicate, that malignant lesions demonstrate an increase of the ^{18}F-FDG-uptake within time, whereas benign lesions are often associated with a decrease of ^{18}F-FDG. Zhuang et al. (2001) performed ^{18}F-FDG dual point measurements, 45 and 90 min p.i. in cell lines, animals and also in patients with comparable results [38]. The data are in accordance to our data in patients with bone lesions. The combination of the 57-60 min SUV (>1.8) and of the ratio averSUV60 min/averSUV30 min (>1.1) led to better results in comparison to the SUV as a single parameter.

SUV and metabolic rate of ^{18}F-FDG (MRFDG) were evaluated with respect to accuracy. Hubner et al. (1996) performed dynamic ^{18}F-FDG studies in patients with lung lesions and found a sensitivity of 100% and a specificity of 73% based on a single SUV [39]. Using a cutoff value of 3.8 for SUV and 0.025 (1/min) for the influx according to Patlak, specificity increased to 81% and 85% accordingly. Our results in patients with bone lesions demonstrated an overlap between SUV and MRFDG, while tumors revealed higher values than benign lesions [18]. Sensitivity and specificity dependent on the cutoff value. For MRFDG values exceeding 9.0 mmol/min/100g, sensitivity was 82.4% and specificity 92.9%. For SUV's higher than 1.8, sensitivity was 85% and specificity 60%. There was a correlation between the maximum SUV and the MRFDG of r= 0.84 (P<0.001).

SUV and MRFDG or influx according to Patlak (Ki) was helpful not only for the diagnostics but also for therapy management. Römer et al. (1998) examined 11 patients with primary non-Hodgkin lymphomas prior to chemotherapy, as well as one and six weeks after onset to therapy and compared the PET data to the restaging data obtained 16 months after onset to therapy [40]. The authors found a larger change between the MRFDG of the first and third study as well as between the MRFDG of the second and third study as compared to the change in SUV. Best parameter for prediction of therapy outcome was the ^{18}F-FDG-uptake of the third study. Weber et al. (2003) performed ^{18}F-FDG studies prior and after the completion of one cisplatin-based chemotherapy in patients with progressive non-small-cell-lung-cancer (NSCLC) [41]. They found a high correlation between the change in SUV and the change in Ki and the response to chemotherapy. The overall survival time as well as the progression-free interval was longer for patients, who demonstrated a decrease in the ^{18}F-FDG-uptake after one cycle. SUV and Ki provided comparable results. In contrast, Freedman et al. (2003) examined patients with renal cell carcinomas and found a different prognostic impact for the change in SUV and in Ki [42]. In 4/6 cases the results were even divergent for SUV and Ki. The results of Freedman et al. (2003) are in agreement to our results in patients with colorectal carcinomas, who received FOLFOX chemotherapy. We found that the change of one parameter of the ^{18}F-FDG kinetic following one cycle was not predictive with respect to overall survival [21].

Integrated evaluation based on SUV, compartment-modeling, influx according to Patlak and fractal dimension

Tracer kinetics can best be described by using a combination of compartment and non-compartment modeling. Influx, efflux as well as trapping of a tracer can be quantified by using the calculation of transport rates. The choice of an appropri-

ate model is crucial and depends on the metabolic pathway of the tracer.

A two tissue compartment is the appropriate model for the quantification of ^{18}F-FDG. The global ^{18}F-FDG uptake, expressed in SUV, reflects the tissue viability [43]. The ^{18}F-FDG-kinetics is modulated via the glucose transporters (Glut1-4), which are related to the ^{18}F-FDG transport and via the hexokinases (HK1-3), which are related to the phosphorylation of ^{18}F-FDG. Experimental data give evidence of an increase of GLUT-1 and hexokinase 1 (HK1) in different tumor types [44].

Limited literature data exist about the impact of the ^{18}F-FDG transport rates for differential diagnosis and therapy management. Sugawara et al. (1999) performed dynamic measurements in patients with treated and untreated germ cell tumors and used a two-tissue-compartment model for data evaluation [45]. Goal of the study was the differentiation between viable tumor tissue and scar tissue, necrosis or teratoma. In particular, the differentiation between a teratoma and scar tissue or necrosis was not possible based on SUV. In contrast, the authors found significant differences for k1 and influx according to Patlak (Ki). Teratomas revealed higher k1 and ki values as compared to scar tissue and necrotic tissue. The data are in accordance to our results in musculosceletal lesions. Based on the 57-60 min SUV it was possible to correctly classify 92% of the G III and 50% of the G I tumors using discriminant analysis (DA). A differentiation between lipomas and G I liposarcomas was not possible based on SUV. Kinetic analysis revealed higher values for the fractional blood volume VB in liposarcomas as compared to lipomas. Best results were obtained by using six different parameters of the ^{18}F-FDG-kinetics (SUV, k1, k3, ki, fractal dimension) as an input for DA. Using the combination of 6 kinetic parameters it was possible to correctly classify 84% of the G III, 37.5% of the G II, 80% of the G I, 50% of the lipomas and 14.3% of the scar tissue. Inflammatory lesions were misclassified [19]. The data demonstrate, that dynamic quantitative measuremets are superior to a static acquisition and should be preferentially used for the differential diagnostics.

Similar problems exist in the differentiation of bone lesions, which include different histologies for both benign and malignant processes. Semimalignant lesions, like giant cell tumors represent another category with certain features. The evaluation of the ^{18}F-FDG-metabolism in 83 patients with 37 histologically confirmed malignant bone lesions and 46 patientes with bening bone processes revealed a sensitivity of 54% and a specificity of 91% based on discriminant analysis. False positive results were observed not only in inflammatory lesions, like osteomylitis and osteitis, but also in fibrous dysplasias or eosinophilic granulomas. Low grade osteosarcomas and Ewing sarcomas, as well as multiple myelomas and neuroectodermal tumors were false negative in ^{18}F-FDG. Kinetic analysis revealed however in a subgroup of patients typical patterns. Giant cell tumors revealed a high fractional blood volume VB. Best results were obtained when using all kinetic parameters (SUV, VB, k1-k4, influx Ki, fractal dimension) for discrimination leading to a sensitivity of 75.86%, a specificity of 97.22% and an accuracy of 87.69% [20]. The data demonstrate, that the use of ^{18}F-FDG kinetics is more accurate for the diffferential diagnosis and improve the accuracy.

An integrated evaluation of the ^{18}F-FDG data improves not only the diagnostics but also the therapy monitoring. However, limited data exist in the literature on this topic. Our data in patients with metastases of a colorectal carcinoma, who received a second-line FOLFOX therapy demonstrated an FDG decrease in the majority of the metastases following chemotherapy. Median SUV was 3.15 SUV prior to therapy, 2.68 after completion of the first cycle and 2.61 after completion of the fourth cycle. Based on the SUV and/or the FD prior to therapy and discriminant analysis it was possible to identify 90% of the patients with progressive disease. In contrast to SUV, based on FD alone, it was possible to identify 75% patients with stable disease [21].

The change in ^{18}F-FDG did not correlate to the overall survival. The global ^{18}F-FDG uptake, as expressed in SUV, is not accurate for prediction of long term therapy outcome. We therefore evaluated the impact of each kinetic parameter of the ^{18}F-FDG kinetics for prediction of the individual survival rates in a subgroup of 20 patients, who received FOLFOX. We dichotomized the patients according to the one-year survival rate. Based on the SUV as single parameter, 62%-69% of the patients could be correctly classified. In general, SUV was superior for the classification of the group of patients who survived longer. By adding the model parameters VB, k1, k3, FD for the first and third study, it was possible to correctly classify 78% of the patients. The most accurate results for the prediction of individual prognosis was achieved by using kinetic parameters of the first and third study [22]. The data demonstrated, that a detailed data analysis provides more accurate results for the prediction of individual survival rates. A further improvement of the prognosis would be possible for a new generation scanners which provide a larger field of view, like a dynamic whole body.

Fractal dimension as a single parameter for the differential diagnostics of tumors

Non-compartment models have several advantages in comparison to compartmental ones for the evaluation of dynamic studies. One advantage is that no input function is needed and that the data evaluation is not operator-dependent. The calculation of the fractal dimension is a non-compartmental approach based on the chaos theory. Fractal geometry is a new language that describes, models and analyzes complex forms, like a cloud, a tree, a mountain or a coast line [13]. In comparison to the euclid geometry, which describes lines and circles, fractal geometry provides algorithms that describe visible forms and structures. The fractal dimension can be used to describe not only natural forms, but even a bacterium or a dynamic PET sequence.

The visual evaluation of conventional PET-images and the parametric images of the fractal dimension revealed different distribution patterns (Fig. 4). Figure 4 demonstrates parametric

images of a patient with breast carcinomas prior and after chemotherapy. Fractal images demonstrate the highest FD for the heart and the breast tumors. It is known, that blood flow is chaotic and reveals a higher FD. Tumor lesions also demonstrate a higher FD than benign lesions. FD is a robust parameter for the evaluation of dynamic PET data and provides valuable information about the heterogeneity of tumors [23].

Fourier-analysis

The Fourier-transformation is a method which transforms the time/location signals into amplitude, phase and frequency. Fourier transformation can be used for the visualization of the spatial and time-dependent redistribution of radiotracer kinetics. This can be in patricular helpful for the evaluation of high local tracer concentrations, e.g. after the intratumoral application of a tracer. In this case, an evaluation of tracer redistribution is not possible due to the extremely high locally tracer concentrations. In patients with small hepatocellular carcinomas a percutaneous US or CT-guided ethanol injection is often used for therapeutic reasons. We used the Fourier-transformation to study the intratumoral distribution as well as the elimination of the ethanol in the tumor as a predictor of therapy outcome. The evaluation of the intratumoral ethanol distribution revealed an inhomogenous intratumoral tracer distribution with local maxima and minima as well as a redistribution towards the peripheral parts of the tumor. The inhomogenous intratumoral tracer distribution as well as the slow redistribution of ethanol may be the cause for the low therapy response. Furthermore, we found a correlation between the ethanol distribution and the survival time. Patients with a more homogenous ethanol distribution survived longer [24].

The presented data demonstrate that parametric imaging based on Fourier transformation may be useful for the evaluation of the pharmacokinetics and effectiveness of regional therapeutic procedures. The calculation of amplitude and phase images is in particular helpful, for the evaluation of distribution and redistribution patterns in regions with high local radiotracer concentrations.

Conclusive remarks

A semiquantitative analysis of PET data sets based on SUV is in general helpful and should be performed under standardized conditions, concerning the time after tracer application, the blood glucose level in case of ^{18}F-FDG, partial volume correction and the choice of reconstruction parameters. The calculation of SUV has been particularly helpful for the primary tumor diagnosis and the differential diagnosis between recurrent tumor and scar tissue using ^{18}F-FDG. SUV is recommended for the evaluation of routine ^{18}F-FDG studies in a clinical environment.

However, a higher diagnostic accuracy can be obtained by using an integrated evaluation including both compartment and non-compartment models. The noninvasive evaluation of tumor grading or the differential diagnosis between a low grade soft tissue sarcoma and a benign process can be done more accurately by using the transport rates and the FD of the tracer kinetics, than the SUV alone. Therapy monitoring is another topic, which requires an integrated tracer evaluation. The change in the SUV for ^{18}F-FDG was associated with the short term therapeutic effect and this can be helpful in the evaluation of rapid growing tumors. In this case, the nonresponders can be identified quite fast. However, for the prediction of long term therapy outcome the evalution of the ^{18}F-FDG kinetics using transport rates and FD is superior. By using the appropriate combination of kinetic parameters and the combination of more than two follow-up studies, it is possible to predict long term therapy outcome and even the individual survival time.

PET-studies with labeled cytostatic agents provide informations about the transport and elimination of a cytostatic agent and help to predict the therapeutic outcome. The combination of two SUV, an early and a late one can be used for tracer evaluation. Non-compartment models are not operator-dependent and do not require an input function. Fractal dimension is a parameter that primarily reflects the heterogeneity of a tracer in a lesion. Fourier analysis is helpful for the assessment of tracer distribution and redistribution at high local tracer concentrations. However, non-compartment models require a further evaluation and can only be recommended for the evaluation of scientific studies at the moment.

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