Parametric imaging: a promising approach for the evaluation of dynamic PET-^{18}F-FDG studies - the DKFZ experience

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Keywords:
– Dynamic PET
– Oncology
– Parametric imaging
– Feature extraction

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Received:
5 March 2010

Accepted:
15 March 2010

Abstract

Dynamic positron emission studies (dPET) with fluorine-18-fluoro-deoxyglucose (^{18}F-FDG) were performed in oncologic patients. *The primary aim was* to evaluate the impact of parametric imaging and assess its feasibility with regard to diagnostics and treatment management. *Parametric PET images based on different algorithms have been calculated*. Regression-based images, influx images according to Patlak, two-tissue compartment images as well as non-compartmental approaches, based on the fractal dimension, principal component images, and similarity mapping have been used. *Our results showed that t*he use of parametric images is helpful to visualize quantitative parameters of the tracer kinetics and adds a new dimension to the existing conventional PET or PET/computerized tomography (CT) images. Especially, non-compartment models are computationally fast and can be applied in daily routine to gain more detailed information about the distribution of a tracer over time and space. *In conclusion,* it is our opinion that parametric images will gain increasing importance and find their way into clinical routine due to the improvement of the technical equipment, like computer power, faster data acquisition by new generations of PET/CT scanners and more sophisticated software for data evaluation.

Hell J Nucl Med 2010; 13(1): 18-22 • Published on line: 10 April 2010

Introduction

Positron emission tomography (PET) as well as PET/computerized tomography (CT) are increasingly used in oncologic patients for primary diagnostics, staging and treatment monitoring. Dynamic imaging with PET (dPET) or PET/CT (dPET/CT) is currently primarily used for scientific purposes because it is more time-consuming and requires more sophisticated evaluation software as compared to simple static imaging. However, the rapid progress of computer power, the introduction of PET/CT and the development of more sophisticated software for data analysis are facilitating a more widespread application of dPET or dPET/CT also within clinical environments. The advantages of parametric imaging are the visualization of dedicated parameters of the radiopharmaceuticals' kinetics, e.g. like perfusion, transport or phosphorylation in case of fluorine-18-fluoro-deoxyglucose (^{18}F-FDG). In particular for ^{18}F-FDG, the calculation of parametric images for the phosphorylated part of ^{18}F-FDG may facilitate diagnostics by delineating small lesions with high contrast, which are not clearly seen in conventional images due to the high amount of ^{18}F-FDG in the surrounding tissue, like in the normal liver parenchyma and/or a high fractional blood volume in the target area. However, because the phosphorylation rate is higher in a metastatic liver lesion than in the normal liver parenchyma, it is easier to detect small metastases using parametric images. Furthermore, parametric images of the perfusion-dependent part of ^{18}F-FDG may be helpful in delineating metastatic lesions, which are not ^{18}F-FDG-avid, e.g. due to several chemotherapeutic treatments or because they are primarily cystic, like in patients with gastrointestinal stromal tumors (GIST).

Prerequisite for the calculation of parametric images is a dynamic data acquisition, which is easily possible in particular with the new generation of PET/CT scanners, which provide the possibility to acquire the data in a list mode and then choose a frame mode, depending on the applied radiopharmaceutical and the method used for parametric imaging. There are several approaches available for parametric imaging. Some of them are compartment based and require an input function, while others are non-compartment based and do not require input data for the calculation. We developed several methods for parametric imaging and dPET studies in oncologic patients, which are presented in this paper.

Dynamic PET studies

Dynamic PET studies at our institution are performed over the primary, recurrent or metastatic tumor for 60min following the intravenous application of ^{18}F-FDG using a 28-frame protocol (10 frames of 30sec, 5 frames of 60sec, 5 frames of 120sec and 8 frames of 300sec). Additional static images are acquired in all patients by moving the table in cranial and caudal position in relation to the initial position. The gap used for each repositioning was 13.5cm. A dedicated PET system (ECAT EXACT HR+, Siemens Co, Erlangen, Germany) with an axial field of view of 15.3cm, operated in septa extended (two-dimensional mode) was used for patient studies. The system allows the simultaneous acquisition of 63 transversal slices with a theoretical slice thickness of 2.4mm. A transmission scan for a total of 10min was obtained prior to the radionuclide application for the attenuation correction of the acquired dynamic emission tomographic images. A transmission scan of 3min followed by an emission scan of 7min was performed for each additional static acquisition. All PET images were attenuation corrected and an image matrix of 256x256 pixels was used for iterative image reconstruction. The reconstructed images were converted to SUV images [1].

The calculation of the parametric images as well as the evaluation of the dPET data were performed using the software package PMod (PMOD Technologies Ltd., Zuerich, Switzerland) [2]. Visual analysis was performed by evaluating the hypermetabolic areas on transaxial, coronal and sagittal images by two experienced nuclear medicine physicians (ADS, LGS).

Parametric imaging

Regression based analysis

Parametric images were calculated based on the dPET data, by fitting a linear regression function to the time activity data and for each pixel. Images of the slope and the intercept of the time-activity data were calculated using the PMod software. Parametric images of the slope reflect primarily the trapping of ^{18}F-FDG and may be used for the delineation of the malignant lesions and the volume of interest (VOI) placement due to the high contrast to the surrounding tissue. Parametric images of the intercept reflect the distribution volume of ^{18}F-FDG and may be used for the better anatomic localization of the lesions due to the delineation of the vessels. Details of this method have been described elsewhere [3]. Parametric images of the distribution volume have been used for better anatomic delineation of the vessels.

Figure 1 demonstrates an example of a patient with liver metastases from colorectal carcinoma after several chemotherapeutic cycles. The ^{18}F-FDG standardized uptake value (SUV) image (55-60min p.i) clearly demonstrates an enhanced ^{18}F-FDG-uptake in one liver metastasis in the ventral part of the right liver lobe. Interestingly, viability was shown in the regression-based slope images, which are related to the phosphorylation, in a second small metastatic lesion in the dorsolateral part of the right liver lobe. The regression-based intercept images, which are related to the blood-volume, show a high homogenous distribution of the ^{18}F-FDG in the liver. Restaging data confirmed this result.

Figure 2 demonstrates another example of an ^{18}F-FDG study in a patient with a tumor marker elevation following a resection of a primary ovary carcinoma. In particular, the regression-based slope images demonstrate a circumscribed enhanced area, dorsal of the bladder, which is suspicious of recurrent disease. This finding was confirmed by surgery.

Influx images based on Patlak

Prerequisite for the use of a Patlak-plot is an irreversible trapping compartment of the tracer, like in the case of ^{18}F-FDG [4]. This model demonstrates whether the major metabolic step fits to an unidirectional transfer of the tracer. If this assumption is valid, an influx constant (Ki) can be calculated graphically. The model is based on a blood/plasma compartment, a reversible and a non-reversible compartment.

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 ^{18}F-FDG can then be calculated using the formula:

$$MR^{18}F\text{-}FDG = Ki \times plasma\ glucose$$

If a two-tissue compartment was fitted to the data, the influx rate can also be calculated using the rate constants of the two-tissue-compartment and the formula:

$$Ki = (k1 \times k3 / k2 + k3)\ k4\ is\ set\ to\ zero$$

Figure 3 presents an example of an ^{18}F-FDG study in a patient with an osteosarcoma of the femur. The 55-60min SUV image clearly demonstrates an enhanced ^{18}F-FDG uptake in particular in the dorsal part of the tumor. This finding is in accordance to the influx-image according to Patlak.

Input function

One problem in patient studies is the accurate measurement of the input function, which theoretically requires arterial blood sampling. However, the input function can be retrieved from the image data with good accuracy [5]. For the input function the mean value of the VOI data obtained from a large arterial vessel was used. A vessel VOI consisted of at least seven ROI in sequential PET images. The recovery coefficient is 0.85 for a diameter of 8mm and for the system described above. Partial volume correction was performed in selected cases for small vessels or lesions of diameter < 8mm on the basis of phantom measurements of the recovery function using the Pmod software. Noise in the input curve has an effect on the parameter estimates. Therefore, we used a preprocessing tool, available in the PMod software, which allows a fit of the input curve, namely by a sum of up to three decaying exponentials to reduce noise [6, 7].

Two-tissue compartment model

This model is appropriate for tracers, which are transported, and after the first metabolic step trapped, like in case of ^{18}F-FDG. A two-tissue compartment model first described by Sokoloff et al. (1983) and was used for the quantification of

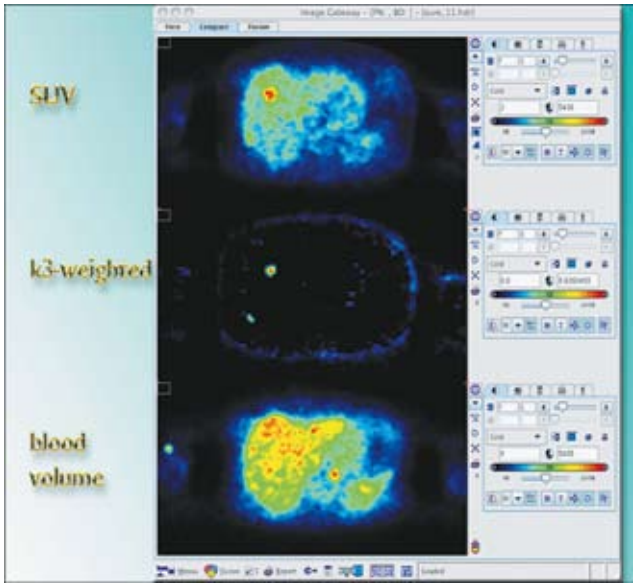

Figure 1. ^{18}F-FDG-PET study, in a patient with liver metastases from colorectal carcinoma. for treatment monitoring following several therapies. Upper row: 55-60min SUV image of the liver demonstrating an enhanced uptake in one liver metastasis in the ventral part of the right liver lobe. Middle row: parametric image of the slope (related to phosphorylation) demonstrating two lesions with enhanced phosphorylation. Lower row: parametric image of the intercept (related to blood volume) showing an enhanced but homogenous blood volume distribution.

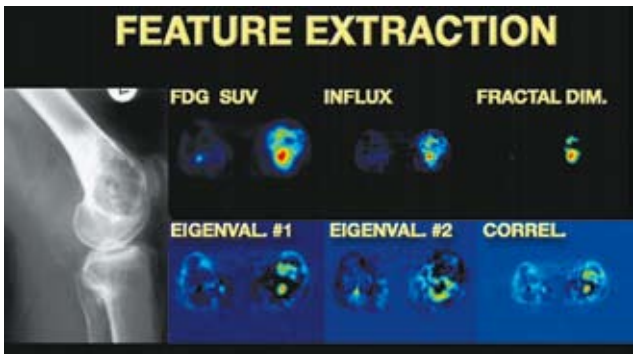

Figure 3. Left: x-ray of the femur in a patient with an osteosarcoma. Upper row left: conventional ^{18}F-FDG SUV image 55-60min p.i. Clearly enhanced ^{18}F-FDG uptake in the tumor area. Upper row middle: parametric image of the influx according to Patlak indicating an enhanced metabolic rate of ^{18}F-FDG. Upper row right: parametric image of the fractal dimension indicating an enhanced heterogeneity. Lower row left: parametric image of the first component according to PCA. Lower middle: parametric image of the second component according to PCA. Lower right: parametric image of the correlation based on PCA.

brain studies [7]. 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

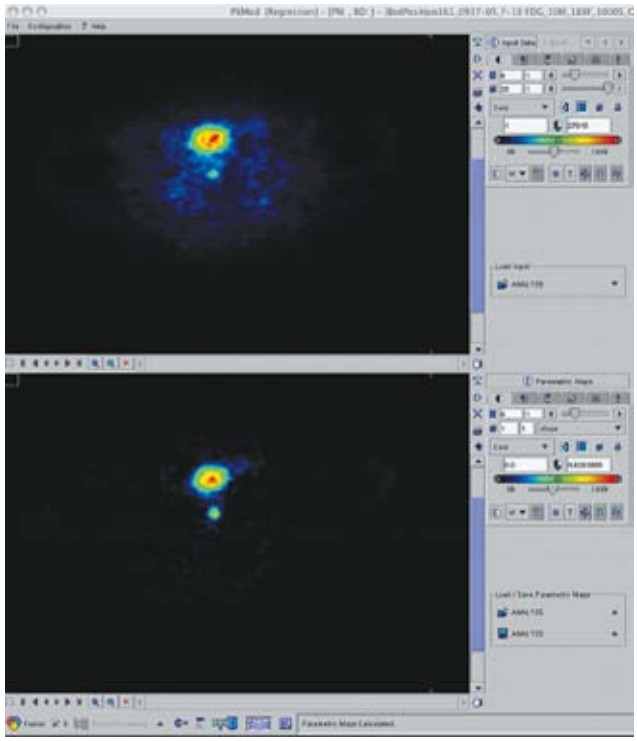

Figure 2. Upper row: Transversal image of the ^{18}F-FDG-uptake, 55-60min p.i. demonstrating an enhanced uptake dorsal of the bladder. Lower row: parametric image of the slope clearly demonstrating the retrovesical finding with high contrast. Histology revealed ovarian cancer recurrence.

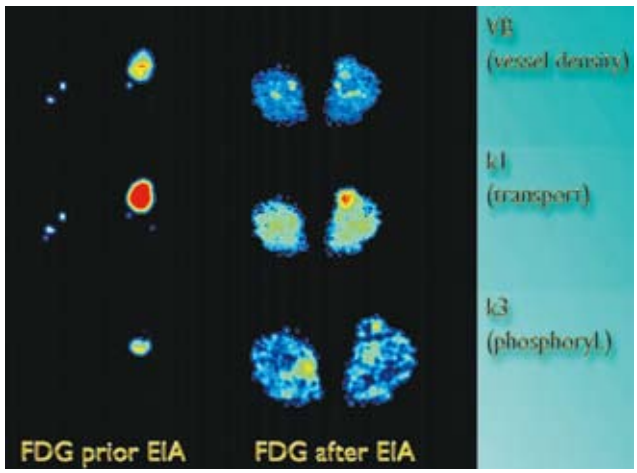

Figure 4. Parametric images based on a two-tissue compartment model in a patient with a soft tissue sarcoma in the left upper leg prior and after neoadjuvant chemotherapy (NAC). Upper left: parametric image of the vessel density VB prior to NAC. Upper right: the corresponding images after 2 cycles of NAC. Middle left: parametric images of the transport (k1 images) prior NAC. Middle right: the corresponding images after 2 cycles of NAC. Lower left: parametric images of the phosphorylation rated (k3 images) prior NAC. Lower right: the corresponding images after 2 cycles of NAC.

that correlates to the blood volume and is called VB. This model is different than the one proposed by Sokoloff et al. (1983) which does not take into account k4 and VB. The lack of k4 and VB of the model proposed by Sokoloff et al (1983) 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 oncologic studies low, but not negligible. Details about the applied compartment model are described by Burger and Buck [8, 3]. Details about the use of the two-tissue compartment model in oncologic patients have been described elsewhere in detail [3]. The model parameters were accepted when VB and k1-k4 were less than one and the VB values exceeded zero. The unit for the rate constants k1 to k4 is 1/min, while VB reflects the fraction of blood within the evaluated volume.

Figure 4 presents an example of an ^{18}F-FDG follow-up study in a patient with a liposarcoma grade 2 of the left upper leg, who received neoadjuvant chemotherapy with etoposide/ifosfamide/adriamycin. Parametric images based on a two-tissue compartment demonstrate a high decrease in the vessel density (VB), a moderate decrease in the transport rate k1 and a moderate decrease in the phosphorylation rate k3 after two cycles. The second study demonstrates residual viability primarily due to the enhanced transport rate k1. Restaging data according to RECIST revealed stable disease, and histopathology data showed a high amount of viable tumor tissue within the excised tumor.

Fractal dimension

Besides the compartment analysis a non-compartment model based on the fractal dimension was used. The fractal dimension (FD) is a parameter for the heterogeneity and was calculated for the time activity data in each individual voxel of a VOI. The values of the fractal dimension vary from 0 to 2 showing the deterministic or chaotic distribution of the tracer activity. We used a subdivision of 7x7 and a maximal SUV of 20 for the calculation of FD [9]. The example of Figure 3 clearly demonstrates an enhancement of the fractal dimension within the tumor of the femur on the parametric image of the fractal dimension, which is indicative for an enhanced heterogeneity in the tumor area.

Principal component analysis (PCA)

Besides the compartment analysis a non-compartment model based on the PCA was used. Details about this method have been described elsewhere [10]. In general, PCA is concerned with explaining the variance-covariance structure of a set of variables through a few linear combinations of these variables. Its general objectives are data reduction and interpretation. Principal component analysis visualizes regions with different kinetics in a dynamic sequence by explaining the variance-covariance structure of the data set. It optimizes the signals by simultaneously considering the complete set of images in the dynamic sequence. It does not require the manual selection of ROI and does not include any model-based restrictions, since it is independent of any kinetic model.

The parametric PCA images of Figure 3 demonstrate the enhanced perfusion in the first component (labeled as "EIGENVAL.#1" for eigenvalue 1, which is the first component) and an enhanced rim-like uptake within the tumor in the second component (labeled as "EIGENVAL.#2 for eigenvalue 2, which is the second component). All images indicate an enhanced viability, heterogeneity and enhanced fractional blood volume in the tumor area.

Similarity mapping (SM)

In SM, the similarity between the time activity curve (TAC) of each pixel and the TAC of a reference ROI is calculated and displayed as an image. Similarity Maps segment images into regions according to their temporal rather than spatial properties. Similarity mapping images therefore provide spatially differentiated quantitative information describing the physiological behavior of the image structures, which sometimes may not be easily extracted from the visual inspection of dPET image sequences. Details about this method have been described elsewhere [11].

Discussion

Imaging with ^{18}F-FDG has a great impact on the diagnostics and management of oncologic patients and gains increasing use worldwide. Most studies are performed as whole body studies based on static images acquired mostly one hour after tracer injection. However, the major advantage of PET is the quantitative aspect, which is neglected when using only whole body protocols and visual evaluation as primary diagnostic tool. Even with whole body protocols a semiquantitative data evaluation based e.g. on the calculation of SUV is often performed at least for treatment monitoring purposes. In order to gain more quantitative data and use the whole spectrum of possibilities offered by this method, the use of dynamic scanning is needed. This approach is more time consuming but has the major advantage of full utilization of the PET or PET/CT technique. Dynamic PET provides the possibility of absolute quantification of the data based on compartment and non-compartment methods and furthermore, allows the calculation of parametric images.

Parametric images are some kind of feature extraction, it means that based on dedicated algorithms it is possible to visualize one isolated parameter of the tracer kinetics. Concerning ^{18}F-FDG, it is possible to visualize only the perfusion-dependent part of the tracer or only the phosphorylated part. For this purpose different methods are available with specific advantages and limitations. One method which is operator friendly and robust due to the lack of any data preprocessing is the calculation of regression-based images of the intercept and the slope. Intercept images reflect the perfusion-dependent part of ^{18}F-FDG, whereas slope images are related to the phosphorylated part of ^{18}F-FDG. These images can be easily calculated and they do not need any input data. Figures 1 and 2 demonstrate two representative examples of this approach.

Another approach is the use of a two-tissue compartment model for the calculation of parametric images of the vessel density (VB) and the transport rates k1 to k3. Traditionally, compartment models use an iterative fitting (IF) method to find the least squares between the measured and calculated values over time, which may encounter some problems like

over-fitting of model parameters and lack of reproducibility, especially when handling noisy data or error data. We introduced a machine learning (ML) based kinetic modeling (KM) method, which can fully utilize a historical reference database to build a moderate kinetic model directly dealing with noisy data but not trying to smooth the noises in the image. Also due to the database, our method is capable of automatically adjusting the models using a multi-thread grid parameter searching technique. Furthermore, a candidate competition concept was proposed to combine the advantages of ML and IF modeling methods, which can find a balance between fitting to history data and to unseen target curve. The machine learning based method provides a robust and reproducible solution that is user-independent for VOI-based and pixel-wise quantitative analysis of PET data. Details about this method are described elsewhere [12]. An example of this method is presented in Figure 4.

The calculation of the metabolic rate of glucose by the Patlak graphical analysis is another method, which also requires an input function and a lumped constant that indicates the ratio of ^{18}F-FDG uptake to glucose uptake and is not exactly known for the tumors (Fig. 3, upper middle). Therefore, a value of 1 is used in tumors as an estimate. Parametric Patlak images provide information on the metabolic rate, which has an impact for both diagnosis and treatment management of oncologic patients.

Other non-compartmental approaches have been introduced which have the advantage that no input function is needed. Such an approach is the calculation of the fractal dimension (FD), a parameter based on the chaos theory [10]. We used this approach on ^{18}F-FDG time activity data and calculated parametric fractal images (Figure 3, upper right). The calculation of FD images is reproducible, fast and operator-independent. PCA is another method which can be applied on dPET data. Principal component analysis visualizes regions with different kinetics in a dynamic sequence by explaining the variance-covariance structure of a data set. It does not require any ROI selection and does not include any model-based information. In a previous study in patients with colorectal tumors, we demonstrated that the first component image (PCI) is a high-contrast image that makes feature identification easier. The second PCI is related with the vascular component VB and the third one with the tumor [11].

Another con-compartmental approach consists in the use of SM. Similarity mapping compares the similarity between the time activity curve (TAC) of each pixel and the TAC of a reference ROI is calculated and displayed as an image (similarity map). The similarity map segments the image into regions according to their temporal rather than spatial properties. Similarity mapping images therefore provide spatially differentiated quantitative information describing the physiological behavior of the images structure, which often can not be extracted from the visual inspection of dynamic PET image sequences [11].

We have reported on the use of SM in 20 oncologic patients who underwent ^{18}F-FDG-dPET [11]. The study showed that similarity map rapidly identified structures with similar to the tumor temporal properties and enhanced the detection of metastases that are not easily discriminated in the SUV images due to poor image quality or lesions characteristics (size, location etc). Therefore, similarity mapping based on the squared-sum normalized correlation coefficient measure could successfully be used in the analysis of dynamic ^{18}F-FDG PET data sets in oncology to support the visual interpretation of the studies.

In conclusion, our studies suggest that parametric images will gain importance and find the way into clinical routine due to the improvement of the technical equipment, like computer power, faster data acquisition by new generation PET/CT scanners and more sophisticated software for data evaluation.

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