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Performance evaluation of principal component analysis in dynamic FDG-PET studies of recurrent colorectal cancer

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Abstract

Performance evaluation of principal component analysis (PCA) of dynamic F-18-FDG-PET studies of patients with recurrent colorectal cancer. Principal component images (PCI) of 17 iteratively reconstructed data sets were visually and quantitatively evaluated. The F-18-FDG compartment model parameters were estimated using polynomial regression. All structures were present in PCI1. PCI2 was correlated with the vascular component and PCI3 with the tumor. The vessel density in the tumor was estimated with a correlation coefficient equal to 0.834. PCA supports the visual interpretation of dynamic F-18-FDG-PET studies, facilitates the application of compartment modeling and is a promising quantification technique.

Keywords: Dynamic positron emission tomography; Principal component analysis; Quantification; Colorectal cancer; Treatment planning; Angiogenesis

1. Introduction

Dynamic 2-deoxy-2-[F-18]fluoro-D-glucose positron emission tomography (F-18-FDG-PET) studies have found use in the diagnosis, staging and therapy effects monitoring of patients with colorectal cancer. They allow visualization of colorectal cancer, detection of tumor recurrences and metastases and evaluation of chemotherapy, radiation therapy as well as gene therapy by quantification of differences in the regional F-18-FDG metabolism [1].

Most of the F-18-FDG-PET studies are visually or semiquantitatively (use of standardized uptake values, SUV [2]) evaluated, while the implementation of Patlak analysis [3,4] and compartment models [5,6] for quantification of PET studies has also been investigated. SUV is relatively robust and reproducible for the same system and comparable acquisition protocols [7]. The metabolic rate of glucose calculated by the Patlak graphical model can differentiate between benign and malignant lesions. However, the determination of this parameter requires the use of an input function, is complex and time-consuming and it is not routinely performed [7]. Compartment models provide precise information about radiopharmaceutical kinetics only when a limited number of compartments and transport rates are required, and could therefore be used in F-18-FDG-PET since a two-tissue compartment model can adequately describe F-18-FDG metabolism. However, the difficulty in obtaining the input function in some cases has resulted in the development of non-compartment approaches such as the Fourier analysis [8] or the fractal dimension [6,9].

The purpose of this study was to evaluate principal component analysis (PCA) as an alternative non-compartment approach for the quantification of dynamic F-18-FDG-PET studies of colorectal tumor recurrences and to assess its accuracy for the anatomical localization of lesions and the detectability of metastases. PCA is concerned with explaining the variance–covariance structure of a set of variables through a few linear combinations of these variables [10]. Its general objectives are data reduction and interpretation [11]. PCA has several applications in nuclear medicine imaging [10,12–18], computed tomography (CT) [19] and magnetic resonance imaging (MRI) [20].

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2. Materials and methods

2.1. Principal component analysis

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. Although p components are required to reproduce the total system variability, often much of this variability can be accounted for by a small number k of the principal components. The k principal components can then replace the initial p variables, and the original data set, consisting of n measurements on p variables, is reduced to a data set consisting of n measurements on k principal components [11].

Let $\mathbf{X}' = (X_1, X_2, \ldots, X_p)$ have covariance matrix Σ, with eigenvalue–eigenvector pairs $(\lambda_1, \mathbf{e}_1), (\lambda_2, \mathbf{e}_2), \ldots, (\lambda_p, \mathbf{e}_p)$ where $\lambda_1 \geq \lambda_2 \geq \ldots \geq \lambda_p \geq 0$. The ith principal component is given by

$$Y_i = \mathbf{e}_i'\mathbf{X} = e_{i1}X_1 + e_{i2}X_2 + \cdots + e_{ip}X_p \ (i = 1, 2, \ldots, p) \quad (1)$$

with $\mathrm{Var}(Y_i) = \mathbf{e}_i'\Sigma\mathbf{e}_i = \lambda_i$ and $\mathrm{Cov}(Y_i, Y_k) = \mathbf{e}_i'\Sigma\mathbf{e}_k = 0$, $i \neq k$.

The total population variance is given by

$$\sum_{i=1}^{p} \mathrm{Var}(X_i) = \sum_{i=1}^{P} \mathrm{Var}(Y_i) = \sum_{i=1}^{p} \lambda_i \quad (2)$$

Consequently, the proportion of total variance due to (explained by) the jth principal component is

$$\frac{\lambda_j}{\sum_{i=1}^{p} \lambda_i} \quad (j = 1, 2, \ldots, p) \quad (3)$$

If most (for instance 80–90%) of the total variance can be attributed to the first few components, then these components can 'replace' the original p variables without much loss of information.

PCA in PET images distinguishes different kinetic components contributing to the same image pixel and summarizes the weights of different components into different principal component images (PCI) (parametric images). Since it is a data driven technique, it cannot separate signals from noise [10] and several data transformation procedures have been proposed in order to improve its performance [21]. The choice of data preprocessing method strongly affects the nature of the information acquired [20] and depends on the amount of available prior knowledge (level of noise in individual images, number of components), on the type of noise distribution and on the purpose of analysis (data compression, filtration, and feature extraction). Samal et al. [21] have compared those methods using simulated data sets. We have also studied the performance of PCA after applying the following data transformation procedures [21]:

(a) Data column-wise centered, CV

$$z_{ij} = y_{ij} - \bar{y}_j \quad (4)$$

where y_{ij} and z_{ij} are the original and the final value of pixel i ($i = 1, \ldots, m$) of frame j ($j = 1, \ldots, n$) and $\bar{y}_j$ is the mean of the jth column of the original data matrix Y,

(b) Data column-wise standardized, CR

$$z_{ij} = (y_{ij} - \bar{y}_j)/s_j \quad (5)$$

where s_j is the standard deviation of the jth column of the data matrix Y,

(c) Data transformed as for correspondence analysis without threshold, CN

$$z_{ij} = y_{ij}\left(\sqrt{\sum_{i=1}^{m} y_{ij}}\sqrt{\sum_{j=1}^{n} y_{ij}}\right)^{-1} \quad (6)$$

(d) Data divided column-wise by the column sum, CS

$$z_{ij} = y_{ij}\left(\sum_{i=1}^{m} y_{ij}\right)^{-1} \quad (7)$$

(e) Data divided column-wise by the column standard deviation, CD

$$z_{ij} = y_{ij}/s_j \quad (8)$$

The row-wise transformation procedures provide excellent results only when the background outside the dynamic structures is carefully masked. Otherwise, the methods fail because of artificial amplification of noise in the background. Since the mask represents unavailable or unacceptable amount of prior knowledge in practice, those procedures were not evaluated [21].

Three criteria were used for the evaluation of the performance of the transformation procedures:

$$\mathrm{index1} = \sum_{j=k+1}^{p} \lambda_j \Big/ \sum_{j=1}^{p} \lambda_j \quad (9)$$

$$\mathrm{index2} = \lambda_{k+1}/\lambda_k \quad (10)$$

$$\mathrm{index3} = \sum_{j=1}^{k} \lambda_j \Big/ (p-k)^{-1} \cdot \sum_{j=k+1}^{p} \lambda_j \quad (11)$$

where λ_j are the eigenvalues of the covariance matrix, p is the total number of principal components and k is the number of eigenvalues explaining most of the data variance. index1 represents the part of total variance of the transformed data remaining after extraction of the first k principal components, equals 0 for noiseless data and increases with increasing noise. index2 demonstrates the quality of separation of the signal from noise and ranges from 0 (for noiseless data) to 1 (for signal indistinguishable from noise) [21]. index3 is an estimate of the signal-to-noise ratio (SNR) improvement of PCI over the original ones [20].

2.2. Patients

The study included 17 patients with colorectal tumor recurrences who were referred on the basis of clinical symptoms and radiologic examinations, either CT or MRI. The final diagnosis was based on the histologic data obtained from surgical specimens. None of the patients had received chemotherapy or radiation therapy at least 3 months prior to the PET study. Informed consent was obtained from each patient. The study was performed in accordance with the institutional review board requirements.

2.3. Data acquisition

Dynamic PET studies were performed after intravenous injection of 300–370 MBq F-18-FDG for 60 min. A 23-frame protocol was used (10 frames of 1 min, 5 frames of 2 min, and 8 frames of 5 min). F-18-FDG was prepared according to the protocol described by Toorongian et al. [22].

A dedicated PET system (ECAT EXACT HR +; Siemens, Erlangen, Germany) was used for the patient studies. The system consists of four rings of 72 bismuth germanate detector blocks. Each block detector is divided into an 8×8 matrix, while the crystal size of an individual detector element is $4.39 \times 4.05 \times 30$ mm. The system allows the simultaneous acquisition of 63 transverse slices with a theoretic slice thickness of 2.4 mm and has a craniocaudal field of view of 15.3 cm. The system was operated in two-dimensional mode (with septa extended). Transmission scans for a total of 10 min were obtained with three rotating germanium pin sources before the first radionuclide application for the attenuation correction of the acquired emission tomographic images.

The PET data were transferred by file transfer protocol to a subnet server system. A web-based interface was used to start and distribute the reconstruction tasks on different computer systems, where the reconstruction programs were running [23]. All PET images were scatter and attenuation corrected [24]. An image matrix of 128×128 pixels was used. The images were reconstructed using an iterative reconstruction algorithm (weighted least-square method, ordered subsets, four subsets, six iterations) running on Pentium platforms (Pentium III 600 MHz, double processor; 512 MB random access memory) and MS Windows 2000 Professional (Microsoft, Redmond, WA).

2.4. Data analysis

The evaluation of the dynamic PET data was performed using the software package Pmod provided in cooperation with the University of Zurich, Switzerland [25,26]. The analysis was based on the semiquantitative approach of calculating the SUV, as introduced by Strauss and Conti [2]:

$$\text{SUV} = \text{tissue concentration (MBq/g)/}\\ \text{(injected dose (MBq)/body weight (g)).}$$

Visual analysis was performed by evaluating the hypermetabolic areas on transaxial, coronal and sagital images. Time–activity curves (TACs) were extracted using volumes of interest (VOIs), that is several regions of interest (ROIs) in different sequential slices over the target area. Irregular ROIs were drawn manually and repositioned visually to compensate for possible patient motion during the acquisition time.

A two-tissue compartmental model was used for the quantification of the dynamic PET studies [5]. The usual method of obtaining the input function is to catheterize an artery and to take blood samples. However, since it is possible to retrieve the input function from the image data accurately [27], we have calculated the mean value of the VOI data obtained from an arterial vessel clearly visualized in the first image of the dynamic series. The recovery coefficient is 0.85 for a diameter of 8 mm and the system described above. Partial volume correction was used only for small vessels with a diameter < 8 mm. A fit of the input curve by a sum of up to three decaying exponentials was implemented to reduce the effect of noise on the parameters estimates. The vascular fraction (VB) was taken into account for the calculation of the transport constant $K1$ and the rate constants $k2$, $k3$ and $k4$. Each model curve was compared with the corresponding TAC. The criterion was to minimize the summed squares (X^2) of the differences between the measured and the model curve [26].

PCA code was developed in C++ (Microsoft Visual Studio 6.0, enterprise edition) according to the formulas presented above. The resulting PCI were initially visually evaluated. Subsequently, VOIs were placed over the tumor recurrences and the muscle in the first two PCI, and the mean counts (pccounts) for each one were calculated. Statistical analysis was performed to explore the possibility of extracting the parameters VB, $K1$ and $k3$ of the two-compartment model from those values, using the Statistica software package (version 6.0; StatSoft, Hamburg, Germany) on a personal computer (Pentium III 600 MHz, double processor; 512 MB RAM) running under Windows 2000 Professional. Polynomial regression up to the second order was used to establish a quantitative relationship between the predictor variables X_i (pccounts) and the response y (VB, $K1$ or $k3$):

$$y = \text{const} + \sum_i a_i X_i + \sum_i b_i X_i^2 \tag{12}$$

The unknown coefficients were computed using a least squares fit, which minimized the sum of the squares of the deviations of the data from the model.

3. Results

We have applied PCA to 17 dynamic F-18-FDG-PET studies. The time required for the analysis of a complete data set (23 frames, 32 slices per frame, 128×128 pixels per slice) was less than 1 min.

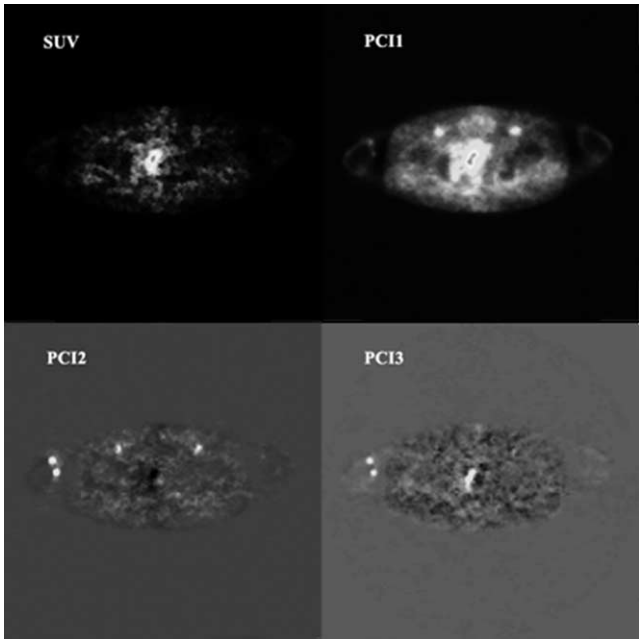

Fig. 1. SUV image (upper left) and the corresponding principal component images PCI1 (upper right), PCI2 (lower left) and PCI3 (lower right). PCI1 looks like a high contrast summed SUV image. PCI2 is dedicated to the vascular component and PCI3 to the tumor component.

In all 17 cases studied, the first principal component image (PCI) looked like a high contrast summed SUV image where all structures were visible, while the second PCI was dedicated to the vascular component (Fig. 1). This observation is in accordance with the fact that the first principal component accounts for the maximum variance in the dynamic data set, whereas subsequent components account for decreasing amounts of variance. In 14 of the cases, the third PCI was clearly correlated with the tumor component and the vessels were slightly seen. In the other studies, the tumor was not discriminated very well due to the physiologic soft-tissue activity. The average amount of variance explained by these components in all studies was 78.3 ± 2.6, 3.7 ± 1.0 and 1.8 ± 0.2 correspondingly. Subsequent PCIs were mainly related to noise. The structures seen in the PCIs are shown in Table 1. Plotting the first three principal components (PC1–PC3) (in Fig. 2 for the same case as in Fig. 1) supported the visual interpretation of the PCIs. The second and the third PCs were similar to TACs of vessels and tumor correspondingly, while all structures TACs contributed to the first PC.

Table 1
Structures present in the SUV and PCI. The numbers represent the fraction of cases

	SUV	PCI1	PCI2	PCI3
Tumor	Yes (17/17) (frame 23)	Yes (17/17)	No (17/17)	Yes (14/17)
Vessel	Yes (17/17) (frame 1)	Yes (17/17)	Yes (17/17)	Slightly (5/17)

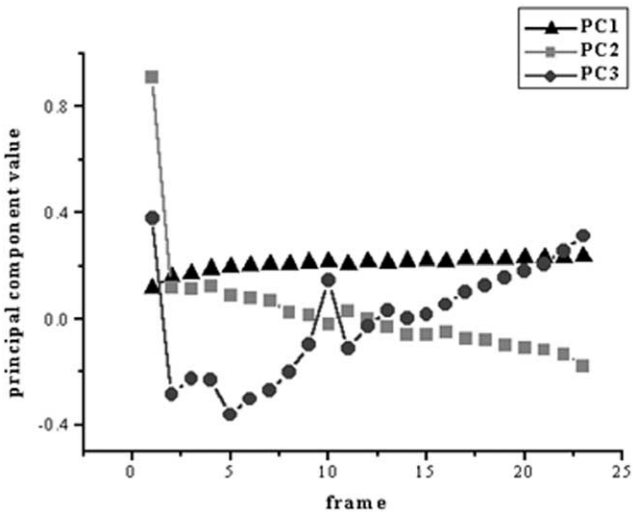

Fig. 2. Principal components PC1 to PC3 plots. PC2 is a typical blood time activity curve (TAC), whereas PC3 is a tumor-wise TAC. All structures TACs contribute to PC1.

Figs. 3 and 4 shows the resulting PCIs after the application of the data transformation procedures described by Eqs. (4)–(8) and the image quality criteria are shown in Table 2. In accordance to the results for simulated data [21], most of the preprocessing methods produced images comparable to or slightly worse than those based on the original data. Both visual (suppressed vessels) and quantitative evaluation (better indices) demonstrated that the best transformation procedure was CS, which unifies the sum over all pixels for each frame.

The results of the polynomial regression indicated that the tumor VB could be modeled as:

$$\mathrm{VB} = \text{constant} + a_1 \times \mathrm{pccounts}_1 + a_2 \times \mathrm{pccounts}_2 + b_1 \times \mathrm{pccounts}_1^2 + b_2 \times \mathrm{pccounts}_2^2.$$

The values of the coefficients are shown in Table 3. The correlation coefficient equaled 0.834 and the plot of the residuals (Fig. 5) confirmed the accuracy of the model.

Parameters $K1$ and $k3$ could not be estimated from PCI. The correlation coefficients of the polynomial regression were 0.666 and 0.734 correspondingly, but the residuals analysis revealed outliers biasing the regression line and leading to higher correlation coefficients than expected.

In order to test the validity of the previously described analysis, we tried to model the muscle VB, but the correlation coefficient was found equal to 0.452. Since the muscle VB has a small approximately constant value that 'falls into the noise region', it cannot be correlated with pccounts.

4. Discussion

This study was focused on the non-compartmental analysis of dynamic F-18-FDG-PET studies of colorectal

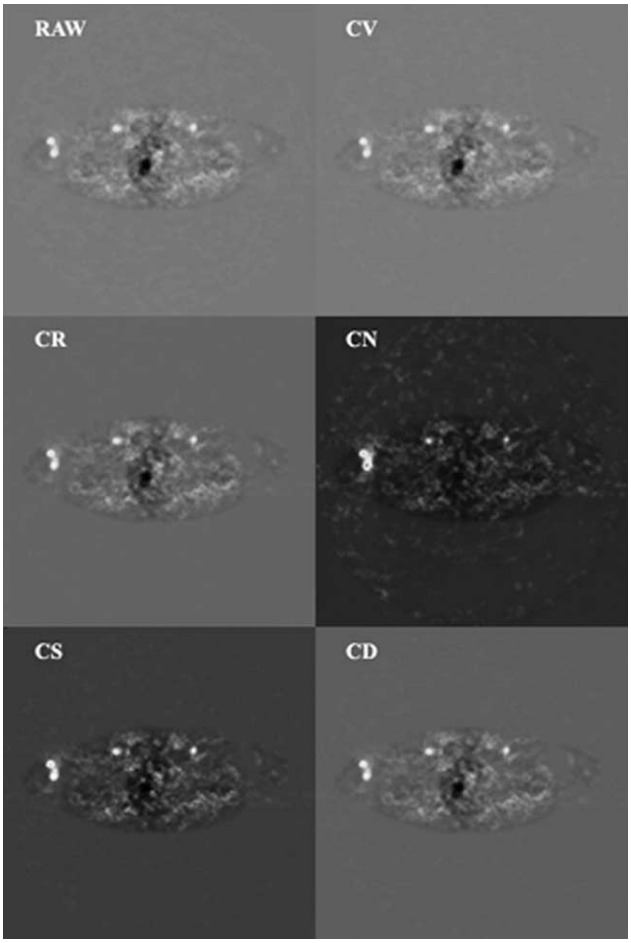

Fig. 3. Principal component image 2 based on the original values (RAW) and after application of data preprocessing: data column-wise centered (CV), data column-wise standardized (CR), data transformed as for correspondence analysis without threshold (CN), data divided column-wise by the column sum (CS) and data divided column-wise by the column standard deviation (CD).

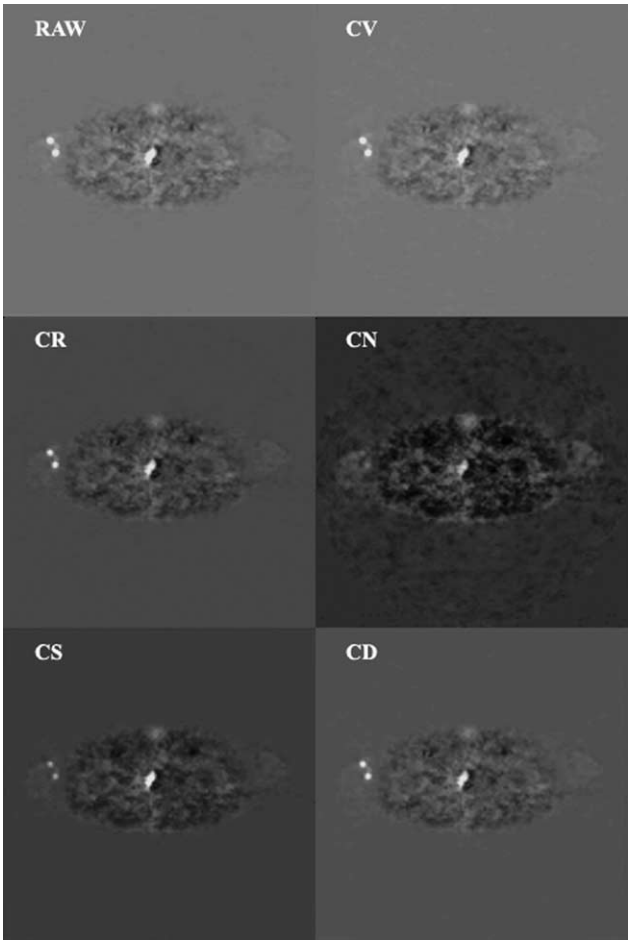

Fig. 4. Principal Component Image 3 based on the original values (RAW) and after application of data preprocessing: data column-wise centered (CV), data column-wise standardized (CR), data transformed as for correspondence analysis without threshold (CN), data divided column-wise by the column sum (CS) and data divided column-wise by the column standard deviation (CD).

tumor recurrences by addressing the problems of quantification and of the enhanced localization of lesions and metastases.

Several methods have been proposed for the quantification of dynamic F-18-FDG-PET studies of colorectal tumors in order to select the most appropriate treatment and to evaluate its results. For their clinical application, these methods should be not only accurate and reproducible, but also easy to implement. SUV, which is a relative measure of activity uptake in a tissue of interest in comparison to the whole-body distribution, is a standard procedure to quantify PET data [7]. However, factors such as the miscellaneous acquisition protocols and different reconstruction methods, lack of scatter correction and variable plasma glucose levels affect the variability of SUV and cause reproducibility problems among different PET institutions [28].

Although the high noise level of a dynamic PET study allows only the application of coarse models, a two-tissue compartment model is considered to be an accurate method for the kinetic analysis of the F-18-FDG metabolism [5]. The retrieval of the input function may be a limitation of the method. Arterial sampling is invasive and therefore not suitable for routine clinical use. The retrieval of the input function from the image data [26] requires the accurate

Table 2
Quality criteria of the principal component images based on the original data set and after applying data preprocessing methods. CS (data divided column-wise by the column sum) is the best approach

	index1	index2	index3
RAW	0.153	0.726	111
CV	0.153	0.726	111
CR	0.154	0.680	110
CN	0.230	0.848	67
CS	0.148	0.672	115
CD	0.154	0.680	110

Table 3
Polynomial regression coefficients for the estimation of tumor fractional blood volume VB. The correlation coefficient is equal to 0.834

Constant	0.7610273
$a1$	−0.0000277
$a2$	0.000000000394
$b1$	−0.0000399
$b2$	0.00000000235

placement of ROIs over the vessels and the resulting TAC of small vessels is subject to errors due to partial volume effects.

The calculation of the metabolic rate of glucose by the Patlak graphical analysis [3,4] requires an input function and a lumped constant that indicates the ratio of F-18-FDG uptake to glucose uptake and is not known for the tumors. As an alternative, the determination of the metabolic rate of F-18-FDG is possible.

A non-compartment approach is the calculation of the fractal dimension [6,9], a parameter based on chaos theory and associated with tumor heterogeneity. It is reproducible and fast and limits the subjectivity and the external factors capable of influencing the diagnostic result. Another non-compartmental approach, the Fourier analysis [8] provides a detailed visualization of the radiopharmaceutical distribution in the target area, avoiding the short-term artifacts that may be present on conventional images, obtained immediately after the tracer injection and revealing tissue inhomogeneity.

PCA 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 ROIs and does not include any model-based

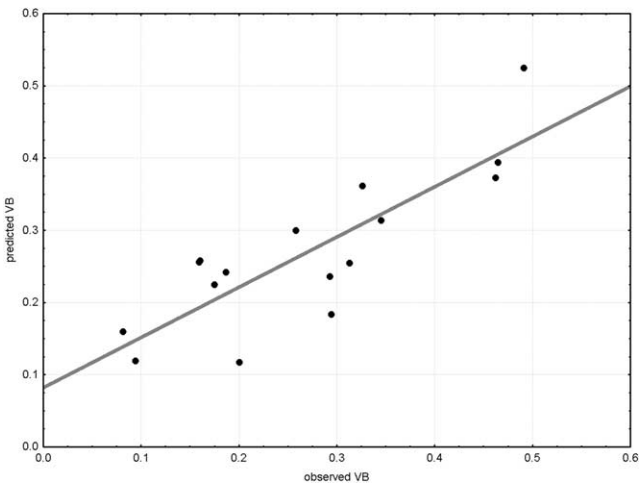

Fig. 5. Polynomial regression line for the tumor fractional blood volume VB estimation based on principal component images 1 and 2. The correlation coefficient equals 0.834.

restrictions, since it is independent of any kinetic model [10,12]. PC images appear with decreasing SNR and therefore only the first few need to be inspected. However, PCA does not give the physiologic importance of each component and side information is essential for interpretation of the results, e.g. TAC or correlative anatomic imaging [12]. PCA is also sensitive to patient motion and image registration may be required in order to improve its accuracy [12].

In medical image processing, PCA has been used for data compression [15] (where it is also known as the Hotelling or the Karhunen–Loève transform), filtration [16], feature extraction [10,13,18], registration [14] and as an initial step in factor analysis [17].

Our study indicated that the first principal component image (PCI) is a high-contrast image that makes feature identification easier. The second PCI is correlated with the vascular component and the third one with the tumor. Subsequent PCIs are related to noise. Therefore, PCA could be used not only for the visual interpretation of the image set by improving the detection of metastases not easily discriminated due to lesions characteristics (size, location etc.), but also as a preprocessing method to facilitate the application of compartment analysis, by increasing the accuracy of manual selection of ROIs [12].

The application of several data transformation procedures to the original data sets did not cause significant improvement in the resulting PCIs in accordance to the results based on simulated data [21]. However, the column-wise division of the data by the column sum provided the best images and justified the time required for the additional preprocessing step (total time for PCA equaled 1 min).

PCA has been so far used only to qualitatively evaluate dynamic data sets. Our study investigated the relationship between PCIs and the kinetic parameters VB, $K1$ and $k3$, which provide information about F-18-FDG pharmacokinetics. Fractional blood volume VB modulates the uptake of the tracer, while the transport constant $K1$ and the rate constant $k3$ are associated with the transport capacity of F-18-FDG and the phosphorylation rate of the radiopharmaceutical correspondingly. Statistical analysis revealed that the tumor VB could be estimated using the first two PCI, while the parameters $K1$ and $k3$ were not related with the PCIs. So PCA consists an alternative method for PET quantification, fast, independent of any kinetic model and useful when the retrieval of the input function is complicated. A comparison of the performance of PCA and other non-compartment methods such as the Fourier analysis or the fractal dimension will help define better its application field and clarify its limitations.

Tumor fractional blood volume has been proposed as an independent prognostic factor [29] and an important parameter potentially capable of modifying treatment planning [30]. Vessel density influences the drug and oxygen access to tumor cells and therefore the response to

chemotherapy or radiotherapy and the efficacy of using hyperbaric oxygen, hypoxic sensitizers or combined chemotherapy. Consequently, the additional information obtained easily by applying PCA to the dynamic F-18-FDG-PET studies could help choosing the appropriate therapy and improve the outcome.

Another potential application of PCA as a quantification technique could be related to angiogenesis. Angiogenesis is the formation of new blood vessels from the existing vascular bed. It is normally suppressed and is observed only transiently during reproduction, development and wound healing. Angiogenesis is also a key pathway required for tumor invasion, growth and metastasis and research has shown that vasculature provides an important target for therapy. Retrospective studies suggest that intratumoral vascularization is an independent prognostic factor and that the presence of vascular endothelial growth factor VEGF in high concentrations in primary cancers is associated with poor prognosis. The development of drugs with suitable pharmacokinetic and toxicity profiles requires new styles of clinical trials, new surrogate biomarkers and dynamic imaging methods (MRI and PET) to assess angiogenesis blocking drugs [31,32]. Since PCA of dynamic F-18-FDG-PET studies allows the estimation of tumor fractional blood volume, it could be used to monitor the effects of both anti-angiogenic treatment and chemotherapy, which work synergistically.

5. Conclusions

PCA supports the visual interpretation of dynamic F-18-FDG-PET studies and facilitates the application of compartment modeling. Preprocessing of the dynamic data set could improve the quality of the resulting images and the accuracy of the method. PCA is also a promising alternative technique for quantification, fast, independent of any kinetic model and useful when the retrieval of the input function is complicated. Treatment planning and assessment of angiogenesis blocking drugs using PCA could be investigated.

6. Summary

Purpose. Dynamic 2-deoxy-2-(F-18)fluoro-D-glucose positron emission tomography (F-18-FDG-PET) studies have found use in the diagnosis, staging and therapy effects monitoring of patients with recurrent colorectal cancer. The performance of PCA of such studies was evaluated.

Procedures. Seventeen iteratively reconstructed dynamic F-18-FDG-PET data sets were included in the study. None of the randomly selected patients had received chemotherapy or radiation therapy at least 3 months prior to the PET study. As reference for the quantification 55–60 min standardized uptake values and a two-compartment tissue model were used. PCI were visually and quantitatively evaluated after the application of several preprocessing methods to the original data sets. Polynomial regression up to the second order was performed to extract the parameters of the F-18-FDG compartment model using the mean counts of tumor VOIs (volume of interest) in the first two PCIs.

Results. The first PCI was a high-contrast image where all structures were present. The second PCI was correlated with the vascular component and the third one with the tumor. Data preprocessing could improve PCI quality. VB, the vessel density in the tumor, could be estimated with a correlation coefficient equal to 0.834. On the contrary, the transport constant $K1$ and the rate constant $k3$ were not related with the PCIs.

Conclusions. PCA supports the visual interpretation of dynamic F-18-FDG-PET studies and facilitates the application of compartment modeling. Preprocessing of the dynamic data set could improve the quality of the resulting images and the accuracy of the method. PCA is also a promising alternative technique for quantification, fast, independent of any kinetic model and useful when the retrieval of the input function is complicated. Treatment planning and assessment of angiogenesis blocking drugs using PCA could be investigated.

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