Is Dynamic Total-body PET Imaging Feasible in the Clinical Daily Practice?

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Research Article

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Abstract

Purpose

Dynamic PET (dPET) imaging of multi-temporal frames can quantitate tracer kinetics and has been mostly used in the research rather than clinical daily practice due to the long acquisition time. The total-body PET/CT scanner can generate fine time-activity curves (TACs) in dPET imaging and provide temporally synchronized pharmacokinetics in the entire human body. To investigate the feasibility in daily practice, the study aimed to explore the shortest acquisition time of dPET imaging.

Methods

Ten patients who underwent an 18F-FDG total-body dPET examination were retrospectively enrolled. Both the Patlak graphic analysis (Ki) and irreversible two tissues compartment model (i2TCM) analysis (K1, k2, k3) were used to calculate the kinetic parameters with different shortened acquisition durations. These kinetic parameters at various organs/tissues and lesions were compared with those obtained from the reference 60min acquisition. In addition, a hybrid approach combining the initial 20-min dPET data and the static PET scan at 55-60 min post-injection was proposed, and the kinetic parameters were calculated and compared with the references.

Results

Patlak Ki derived from the first 50-min dPET acquisition showed no significant difference in healthy organs/tissues compared with the reference (all p > 0.05), while the lesions can be visually distinguished even in the initial 20-min Ki images. In the i2TCM analysis, the kinetic parameters — K1, k2, k3 of 30-min dPET acquisition showed no significant difference for healthy organs/tissues and lesions compared to 60-min dPET acquisition (all p > 0.05). The kinetic parameters obtained from the proposed hybrid approach can provide reliable kinetic parameters as well as those obtained in the static PET imaging.

Conclusions

The dPET total-body imaging can be shortened to 30 min to generate reliable kinetic parameters with i2TCM. Additionally, the hybrid approach provides both robust tracer metabolic information and the conventional standard uptake values (SUVs), demonstrating its feasibility in clinical practice.

Introduction

Dynamic position emission tomography (dPET) with 18F-fluorodeoxyglucose (18F-FDG) is a powerful imaging tool to noninvasively collect glucose metabolic information and pharmaceutical kinetic parameters in-vivo [1]. Different from the static PET which provides a semi-quantitative index (SUV) at a certain time point post injection [2, 3], dPET quantitates the kinetic parameters of glucose metabolism in combination with pharmacokinetic models [4, 5]. Previous studies have demonstrated the superiority of dPET imaging in differential diagnosis, tumour staging and the evaluation of treatment response in
oncology [6-11]. Unfortunately, the use of dPET imaging is usually confined within the research areas due to its long acquisition time.

To date, efforts has been made to reduce the acquisition time of dPET imaging in several specific cases such as primary lung cancer, brain glioma, and nasopharyngeal carcinoma [12-15]. Because of the limited axial field of view (AFOV) of the conventional PET scanners, these studies only covers a part of human body in the dPET imaging. Despite that whole-body dPET collected with either continuous bed motion or step-and-shoot multi-bed position provides a key measure to perform the precise diagnosis at locoregional area [16-19], the synchronized acquisition of temporal and spatial information is under expectation. With the advent of the total-body PET/CT scanner with a 194-cm long AFOV (uEXPLORER, United Imaging Healthcare, China), it is possible to collect both pathological and physiological information for the entire human body in one bed position [4, 20-22]. Additionally, the high PET sensitivity of the total-body scanner allows to generate time-activity curves (TACs) with fine structure.

Thus, we hypothesized that it can affect dPET acquisition and kinetic parameters characterizing. This study aims to explore the influence brought by the sensitivity improvement of the state-of-the-art total-body scanner on the acquisition settings and the kinetic parameters, and investigate its feasibility in clinical practice.

**Methods**

**Patients**

This retrospective study consecutively enrolled 10 patients (5 females and 5 males, age: 53.7±13.9 year, weight: 63.3±8.6 kg) who underwent a total-body 18F-FDG dPET imaging at Shanghai Jiao Tong University Renji Hospital between 28th Dec 2020 and 27th Nov 2021. In this study, the clinical purpose of dPET imaging included cancer staging/restaging (hepatic carcinoma, pancreatic cancer, breast cancer, lung cancer, gallbladder cancer, and cervical cancer) and tumour screening. Blood glucose level of all patients was not higher than 7 mmol/L prior to the scan. This study was approved by the Institutional Review Board of Shanghai Jiao Tong University Renji Hospital, and written informed consents were obtained from all patients in this study.

**Dynamic acquisition protocol**

All patients fasted for at least 6 h before 18F-FDG administration. Total-body dynamic 18F-FDG PET/CT scan was performed with a weight-based injection of 4.4 MBq/kg (247-319 MBq). The patients were instructed to be immobilized and fastened with a belt during the acquisition and positioned in supine position with feet pointing towards the scanner (feet first supine) with arms down. A CT scan was performed before PET acquisition for attenuation correction and anatomical localization using a fixed tube voltage of 120 kV with an auto-mAs technique for dose modulation. All patients underwent a 60-min
dPET scan, and one of them had an additional delayed PET scan at 180-min post-injection for qualified display of the pelvic lesion. The workflow is schematically depicted in Fig. 1.

**Image reconstruction**

PET raw data were reconstructed into 92 frames (24×5s, 20×30s and 48×60s). The standard order subset expectation maximization (OSEM) algorithm was used as well as time-of-flight (TOF) and point-spread function (PSF) modelling with the following parameters: 3 iterations, 20 subsets, 256×256 matrix, 600-mm FOV, 2.89-mm slice thickness, and a Gaussian post filter with a full width at half maximum (FWHM) of 3 mm. In addition, all PET reconstructions included standard corrections like decay, scatter, random, dead time, attenuation, and normalization.

The Patlak graphic analysis (linear fitting) and the irreversible two tissues compartment model (i2TCM) analysis (non-linear fitting) were both used in this study. For Patlak graphic analysis, the selected frames include the first 10 to 60 min, 10 to 50 min, 10 to 40 min, 10 to 30 min and 10 to 20 min (referred to as G60, G50, G40, G30 and G20, respectively). The G60 was considered as a reference in this study. For the i2TCM analysis, the TACs from dPET were truncated into different groups: G60 (0 to 60 min), G50 (0 to 50 min), G40 (0 to 40 min), G30 (0 to 30 min) and G20 (0 to 20 min).

Moreover, a hybrid approach was proposed which combines the initial 20-min dPET data and the static PET scan at 55-60 min post-injection, allowing for providing both the kinetic and the static parameters, referred to as GHybrid20. The i2TCM analysis was used to obtain the kinetic parameters in this proposed approach.

**Image analysis**

To determine the shortest dPET acquisition time, we compared the quantitative parameters derived from the two different analysis methods – Patlak graphic analysis and i2TCM. For both methods, the input function was derived from the descending aorta. For the analysis of healthy organs/tissues, the regions-of-interest (ROIs) were manually delineated on the homogenous area as large as possible at gray matter, lung, muscle, spleen, pancreas and liver. ROIs were drawn on lesions at the transverse slice with the largest cross-section area.

**Patlak graphic analysis**

The glucose metabolism rate (Ki) of ROIs can be quantitatively measured by linear fitting method. The pixel-wise parametric Ki images were calculated with a commercialized software (uKinetics, United Imaging Healthcare, China) on the dedicated workstation (uWS-MI, United Imaging Healthcare, China).

**Irreversible two tissues compartment model (i2TCM) analysis**
Utilizing a research tool (PMOD Technologies Ltd., Zuerich, Switzerland), the kinetic parameters (K1, k2 and k3) were calculated based on the i2TCM model of FDG. K1, k2, k3 represent the influx of the tissues, the venous clearance out of the tissues, and the phosphorylation rate inside the tissues, respectively [23]. Notably, while Ki is referred to as the net flux of FDG transported from plasma to the tissue and metabolized, k3 represents the phosphorylation rate which is much higher in cancer cells for its aggressive proliferation [24-26].

Statistical analysis

The statistical analyses were performed using R project (version 4.0.4). Wilcoxon signed rank test was applied to evaluate the consistency in the organs/tissues in the following groups: G20 and G60, G30 and G60, G40 and G60, as well as GHybrid20 and G60. To test the correlations of kinetic parameters, linear regression (least-square approach) was performed on the K1, k2, and k3 between GHybrid20 and G60, where the confidence interval (CI) was set as 95%. Pearson’s coefficient (r2) was calculated. Statistical significance was considered for a p-value less than 0.05.

Results

Patlak graphic analysis

Figure 2 illustrates parametric Ki images for different groups, where each voxel value is corresponding to the glucose metabolism rate (Ki) that were originated from Patlak graphic analysis. The image became noisier along with the reduction of the acquisition time, and the image quality of images degraded Ki. However, the lesions with abnormal glucose metabolism rate can be identified in the Ki images even in G20. A metastatic lesion at the liver could be visually identified with an FDG dPET of G20 (Fig. 2). For lesion detection, the acquisition time can be reduced to 20 min.

To further investigate the feasibility, we calculated the Ki from different dPET acquisition at healthy organs/tissues and compared them with the reference (Table 1). Unfortunately, Ki value of G20 showed significant differences at almost all the organs/tissues (all p < 0.05) except for the gray matter (p = 0.14). Even in G40, there was still a significant difference at the liver (p = 0.028), and only in G50 no significant difference was found.

Irreversible two-tissue compartment model analysis

Different from Ki, the i2TCM analysis by non-linear fitting method characterizes the metabolic parameters of FDG in the pharmacokinetic process: K1 (influx of the tissue), k2 (venous clearance out of the tissue), and k3 (the phosphorylation rate inside the tissue). Table 1 lists the p-value for K1, k2, k3 at the selected organs/tissues, where no significant difference for both K1 and k2 (all p > 0.58) was observed between all groups. However, the value of k3 was significantly different at the lung and pancreas only in G20 (lung, p
These findings revealed that the minimum dPET acquisition can be reduced to 30 min. Furthermore, we evaluated the glucose metabolism of lesions. Different from those in the healthy tissues (detailed in supplementary Figures), the values of K1, k2 and k3 were robust even when the dPET acquisition was reduced to 20 min. Compared with the reference, all the kinetic parameters (K1, k2 and k3) of the lesions showed no significant differences (as shown in Fig. 3). This finding indicates that the 20-min dPET acquisition is reasonable for lesion detection with i2TCM method.

Regarding the lesion detection, GHybrid20 can be with the same performance as G20 since the GHybrid20 contains data in G20. The kinetic parameters (K1, k2 and k3) of GHyribd20 at the healthy organs/tissues were further investigated. Compared with the reference, there were no significant differences regarding K1, k2 and k3 in GHybrid20 (all p > 0.33). Moreover, in the linear regression analysis between GHybrid20 and G60 at the healthy organs/tissues (shown in supplementary figures), the kinetic parameters were strongly correlated with those from the reference at almost all the healthy organ/tissues ($r^2 > 0.66, p > 0.33$) while only k3 at the lung indicated a weak correlation ($r^2 = 0.199, p = 0.0005$). The worse correlation at the lung might be due to the TACs influenced by the respiratory motion. Thus, the GHybrid20 seems to be an alternative approach to the dPET parametric imaging for almost the entire human body examination.

A case of a 71-year-old patient with cervical cancer who underwent dPET acquisition was shown in Fig. 4. Several inflammatory lymph nodes at the chest, which were invisible in the standard static PET images at 60 min post injection, were successfully identified in the delayed static PET image acquired at 180 min post injection. Intriguingly, the parametric image of K1 depicted the inflammatory lymph nodes at the chest at early time. Despite the parametric images from G40, G50, and G60 have visually higher image contrast and less noise than these of G20 and G30, the inflammations of the lymph nodes at chest were still visually identifiable at the initial 20-min acquisition. Therefore, the proposed hybrid approach, GHybrid20, is promising in clinical practice, such as inflammation diagnosis.

**Discussion**

This study investigated the reduction of 18F-FDG dPET acquisition by the uEXPLORER have been studied by two different approaches: Patlak graphic analysis (linear fitting) and i2TCM (nonlinear fitting). It indicated that the determination of kinetic parameters required different acquisition durations for lesions and healthy organs/tissues as well as fitting methods. Neither in Patlak graphic analysis nor i2TCM analysis, the characterization of kinetic parameters can be performed less than a 20-min acquisition for lesions with abnormal glucose metabolism. For Patlak graphic analysis, the acquisition time can be merely reduced to 50 min, in sharp contrast with 20-min dPET acquisition for the lesions. For the i2TCM analysis, the dPET acquisition can be shortened to 30 min while achieving the reliable kinetic parameters (K1, k2, k3) at the selected healthy organs/tissues.

As known, cancer cells generally harbour a glucose-avid uptake due to the proliferation of tumour cell and the overexpression of GLUT-1 glucose transports, and it is of great importance to quantitate the glucose
metabolism rate for the characterization of the tumour. Although Patlak graphic analysis provides an approximate overall measurement of metabolized FDG (Ki), i2TCM analysis precisely describes kinetic process via GLUT-1-dominated glucose transports (K1 and k2) and hexokinase-controlled glycolysis rate (k3). The accurate measures seem to be more robust than Patlak Ki along with the reduction of the acquisition time in dPET imaging. These kinetic parameters have been proven as valuable prognostic markers in oncology. For example, it was reported that higher k3 was related to a shorter progression-free survival (PFS) in patients with myeloma [27]. Combining with the standard SUV, k3 has been proved as a useful parameter in tumour grading and therapy monitoring [27-29]. Thus, the kinetic parameters (especially k3), calculated from the non-linear fitting method is potentially of great clinical significance.

Furthermore, our study revealed that the reduction of the acquisition time with these two fitting methods was organ-dependent. In the brain, the optimal acquisition duration was 20 min for Patlak Ki and 20 min for non-linear fitting parameters (K1, k2, k3). The acquisition time is relatively shorter than 30 min in the previous study using a PET scanner with short AFOV [30]. This may be due to the high sensitivity of the total-body PET/CT scanner which provides a TAC with fine structure and excellent signal-to-noise ratio. In addition, the input function was extracted from descending aorta instead of carotid artery. For the imaging of the chest, our study demonstrated that the acquisition time can be shortened to 30 min with both Patlak graphic analysis and i2TCM analysis. This was consistent with the results of Torizuka et al. that less than 30-min acquisition at lung yields the same results as the routine 60-min protocol [12] with the non-linear fitting method. Regarding the examination of the abdomen (liver, pancreas and spleen), a 30-min dPET acquisition was sufficient to obtain the comparable parameters with the reference with the non-linear fitting method. As for the linear fitting method used in the abdomen (liver), the shortest duration was still restricted to 50 min, which was consistent with the results reported by Ma et al. [31].

Although the dPET acquisition time might be reduced by a factor of 2, in the routine clinical diagnosis SUV derived from static PET imaging is still of importance. Samimi et al. [32] suggested a short dPET coupled with static PET acquisition as an alternative approach. However, its feasibility in total-body dPET imaging was unknown. Therefore, a hybrid protocol of dPET imaging, combining a 20-min dPET and a static PET at 55-60 min post injection, was proposed and validated with the i2TCM analysis. This hybrid protocol has several advantages: firstly, the healthy organs/tissues measurement could be confidently performed for the relatively high correlation coefficients with the reference G60; secondly, the hybrid protocol only requires an acquisition of 20 min which is equivalent to that in the step-and-shoot scan using the conventional PET scanners; thirdly, the static PET images provides clinically confident evidence in disease staging, lesion localization and the response of treatment, etc. However, the accuracy of this hybrid approach may be affected by the change of patient position in the two separated acquisition (0-20 min and 55-60 min post-injection). It can be solved by manually drawing the identical ROIs in the dPET images as well as in the static images with reference to the body structures. The data from ROIs in the static images should be appended to the TACs from the dPET images to calculate the kinetic parameters. Briefly, the proposed hybrid protocol in total-body dPET imaging enables an accurate evaluation of the disease in oncology.
However, there are several limitations in this study. Firstly, the limited number of the enrolled patients in this study may result in a statistical bias. Secondly, the variability of the diseases from this retrospective study was limited. Assuming that the type of the disease may affect the generality of the results, it should be validated in future studies. Furthermore, the acquisition protocol of different radiotracers for PET imaging, such as 11C-methionine, can be investigated for total-body dPET imaging.

Conclusion

The dynamic PET acquisition could be shortened to 30 min on the total-body PET/CT scanner to generate reliable kinetic parameters with the i2TCM analysis. Additionally, the hybrid approach can provide both robust tracer metabolic information and the conventional SUV measurement in a tolerated acquisition duration, demonstrating its feasibility in clinical practices.

Declarations

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Conflicts of interest/Competing interests

All authors declare that they have no conflict of interest.

Availability of data and material

Data are available on request to the corresponding author.

Code availability

Not applicable.

Authors' contributions

Study conception and design: Yumei Chen, Gang Huang and Jianjun Liu

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Supervise the study, revise and finalize the manuscript: Yumei Chen, Gang Huang and Jianjun Liu

All authors commented on previous versions of the manuscript and read and approved the final manuscript.

**Ethics approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Consent to participate**

Written informed consents were obtained from all patients in this study.

**Consent for publication**

Patients signed informed consent regarding publishing their data and photographs for scientific use.

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Tables
Table 1 P values of the comparison of kinetic parameters ($K_i, K_1, k_2, k_3$) in the selected organs/tissues of different acquisition time to the reference G60.

| Organs   | Lung |          |          |          | Liver |          |          |          |
|----------|------|----------|----------|----------|-------|----------|----------|----------|
|          | Ki   | K1       | k2       | k3       | Ki    | K1       | k2       | k3       |
| G50      | 0.63 | 0.68     | 0.76     | 0.8      | 0.75  | 1        | 1        | 0.95     |
| G40      | 0.31 | 0.53     | 0.97     | 0.63     | 0.028 | 0.9      | 0.65     | 0.56     |
| G30      | 0.063| 0.63     | 0.79     | 0.63     | < 0.01 | 0.95     | 0.9      | 0.75     |
| G20      | 0.011| 0.58     | 0.88     | 0.029    | < 0.01 | 1        | 0.9      | 0.61     |
| Ghybird20| N.A. | 0.97     | 0.85     | 0.35     | N.A.  | 0.85     | 0.63     | 0.31     |

(Table continues)

| Organs   | Gray Matter |          |          |          | Muscle |          |          |          |
|----------|-------------|----------|----------|----------|--------|----------|----------|----------|
|          | Ki          | K1       | k2       | k3       | Ki     | K1       | k2       | k3       |
| G50      | 0.91        | 0.8      | 0.97     | 0.44     | 0.53   | 0.91     | 0.74     | 0.58     |
| G40      | 0.5         | 0.9      | 0.74     | 0.66     | 0.12   | 0.97     | 0.97     | 0.97     |
| G30      | 0.68        | 0.97     | 0.74     | 0.85     | 0.043  | 1        | 0.91     | 0.85     |
| G20      | 0.14        | 0.58     | 0.8      | 0.44     | < 0.01 | 0.91     | 0.8      | 0.8      |
| Ghybird20| N.A.        | 0.85     | 0.85     | 0.85     | N.A.   | 0.97     | 0.74     | 0.53     |

(Table continues)

| Organs   | Pancreas |          |          |          | Spleen |          |          |          |
|----------|----------|----------|----------|----------|--------|----------|----------|----------|
|          | Ki       | K1       | k2       | k3       | Ki     | K1       | k2       | k3       |
| G50      | 0.28     | 0.97     | 0.97     | 0.74     | 0.74   | 0.97     | 0.97     | 0.91     |
| G40      | 0.14     | 0.91     | 0.74     | 0.63     | 0.22   | 1        | 1        | 0.91     |
| G30      | 0.015    | 0.85     | 0.74     | 0.39     | < 0.01 | 0.97     | 0.91     | 0.44     |
| G20      | < 0.01   | 0.68     | 0.8      | 0.043    | < 0.01 | 0.8      | 0.63     | 0.14     |
| Ghybird20| N.A.     | 0.97     | 0.97     | 0.58     | N.A.   | 0.91     | 0.85     | 0.28     |

N.A, not applicable.
Table 2 The Pearson's coefficient of kinetic parameters from i2TCM (K1, k2, k3) analysis between GHybrid20 and G60

| Organs          | Lung   | Liver   | Gray Matter | Muscle   | Pancreas | Spleen |
|-----------------|--------|---------|-------------|----------|----------|--------|
| K1              | 0.665  | 1       | 0.991       | 1        | 0.999    | 0.998  |
| k2              | 0.0417 | 0.997   | 0.944       | 999      | 0.907    | 0.997  |
| k3              | 0.199  | 0.845   | 0.664       | 0.932    | 0.715    | 0.931  |

Figures

Figure 1

Schematic diagram of the dynamic and 5-min static PET at 60-min post-injection. The full dynamic acquisition time was 60 min. Static PET images were acquired at 55-60 min post injection. The Patlak graphic analysis (dark-blue lines) was performed on the groups with acquisition time of 10-20 min, 10-30 min, 10-40 min and 10-50 min. For two-tissue compartment model analysis (sky-blue lines), the subgroups were 0-20 min, 0-30 min, 0-40 min and 0-50 min.
Figure 2

The parametric images (Ki) of a 56-year-old female with gallbladder cancer after a resection. The metastatic lesion was identified in the liver (red arrow) in the maximum intensity projection (MIP) and transverse images even in G20.
Figure 3

The comparison of kinetic parameters (K1, k2, k3) of the lesions from different acquisition time with the reference G60. Compared with the reference, all the kinetic parameters showed no significant difference even in G20 (all $p \geq 0.86$).
Figure 4

The MIP and transverse images of a 71-year-old female with cervical cancer. The parametric images of Ki (a) from 20 to 60 min showed clear visualization of the inflammatory lymph nodes (red arrows). The same lymph nodes were also detected in the delayed images (180 min post-injection, b right) and cannot be identified in the standard static images (55-min post-injection, b left).

Supplementary Files

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