

RESEARCH ARTICLE

How Long of a Dynamic 3'-Deoxy-3'-[¹⁸F]fluorothymidine ([¹⁸F]FLT) PET Acquisition Is Needed for Robust Kinetic Analysis in Breast Cancer?

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Abstract

Purpose: To quantitatively evaluate the minimally required scanning time of 3'-deoxy-3'-[¹⁸F]fluorothymidine ([¹⁸F]FLT) positron emission tomography (PET) dynamic acquisition for accurate kinetic assessment of the proliferation in breast cancer tumors.

Procedures: Within a therapeutic intervention trial, 26 breast tumors of 8 breast cancer patients were analyzed from 30-min dynamic [¹⁸F]FLT-PET acquisitions. PET/CT was acquired on a Gemini TF 64 system (Philips Healthcare) and reconstructed into 26 frames (8 × 15 s, 6 × 30 s, 5 × 1 min, 5 × 2 min, and 2 × 5 min). Maximum activity concentrations (Bq/ml) of volume of interests over tumors and plasma in descending aorta were obtained over time frames. Kinetic parameters were estimated using in-house developed software with the two-tissue three-compartment irreversible model (2TCM) (K_1 , k_2 , k_3 , and K_i ; $k_4 = 0$) and Patlak model (K_i) based on different acquisition durations (T_d) (10, 12, 14, 16, 20, 25, and 30 min, separately). Different linear regression onset time (T_0) points (1, 2, 3, 4, and 5 min) were applied in Patlak analysis. K_i of the 30-min data set was taken as the gold standard for comparison. Pearson product-moment correlation coefficient (R) of 0.9 was chosen as a limit for the correlation.

Results: The correlation of kinetic parameters between the gold standard and the abbreviated dynamic data series increased with longer T_d from 10 to 30 min. k_2 and k_3 using 2TCM and K_i using Patlak model revealed poor correlations for dynamic PET with $T_d \leq 14$ min (k_2 : $R = 0.84, 0.85, 0.86$; k_3 : $R = 0.67, 0.67, 0.67$; K_i : $R = 0.72, 0.78, 0.87$ at $T_d = 10, 12, \text{ and } 14$ min, respectively). Excellent correlations were shown for all kinetic parameters when $T_d \geq 16$ min regardless of the kinetic model and T_0 value ($R > 0.9$).

Conclusions: This study indicates that a 16-min dynamic PET acquisition appears to be sufficient to provide accurate [¹⁸F]FLT kinetics to quantitatively assess the proliferation in breast cancer lesions.

Key words: 3'-Deoxy-3'-[¹⁸F]fluorothymidine ([¹⁸F]FLT), Kinetic modeling, Dynamic PET, Breast Cancer, Acquisition duration

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Introduction

Breast cancer is one of the most common cancers in the USA and the second leading cause of cancer death among women. In 2017, an estimated 252,710 new invasive breast cancer cases and approximately 40,610 women and 460 men breast cancer deaths occurred [1]. Positron emission tomography (PET) as a non-invasive molecular imaging technique has been widely explored with respect to applications in breast cancer diagnosis [2–5]. While 2'-deoxy-2'-[^{18}F]-fluoro-D-glucose ([^{18}F]FDG) has been used as the main PET tracer in breast cancer to reflect glucose metabolism of breast tumors [2, 6–8], other PET tracers such as [^{11}C]methionine as well as [^{11}C]thymidine and [^{18}F]fluorothymidine ([^{18}F]FLT) have also shown clinical potential and values in breast cancer disease detection and therapy response monitoring [6].

[^{18}F]FLT-PET gained much attention in the recent years due to its ability to non-invasively quantify cell proliferations in breast cancer and has shown its promising role in breast cancer diagnosis [9–11], breast tumor grading [9], breast tumor heterogeneity visualization [9], early change detection during chemotherapy [12, 13], and long-term therapy response prediction [7, 10, 13]. Comparing to [^{18}F]FDG-PET, [^{18}F]FLT-PET has better specificity during and after treatment and does not seem to be accumulating in inflammatory processes [14]. It is capable of better differentiating inflammatory tissues from tumors in breast cancer treatment [9] and more predictive of longer-term treatment outcome with early changes [10].

It has been demonstrated that dynamic [^{18}F]FLT-PET with kinetic analysis such as tracer influx constant K_i and transport constant K_1 is sensitive and robust in assessing and monitoring breast cancer therapy response [7, 10, 12, 13]. Currently reported dynamic [^{18}F]FLT-PET acquisitions in breast cancer take about 45 to 95 min, which is time-consuming and uncomfortable which also makes it difficult for clinical routine applications [10, 15]. The long scan time brings challenges in patient comfort and causes related motion artifacts on PET images. The generated bulky data require sophisticated data processing and kinetic analysis.

In this study, a shortened dynamic [^{18}F]FLT-PET acquisition protocol was proposed and evaluated through Patlak plot and the two-tissue compartment model kinetic analysis. It aimed to optimize the dynamic [^{18}F]FLT-PET in breast cancer with minimum required acquisition time to reduce patient burden and improve system efficiency without compromising imaging quality and quantitative assessment. The established shortened acquisition protocol is to be used as a reference in guiding clinical [^{18}F]FLT dynamic PET imaging in breast cancer.

Materials and Methods

Patients

Twenty-six breast tumor data sets from eight breast cancer patients (age 51.75 ± 11 years, weight 74.33 ± 11.11 kg) were included in this study.

Dynamic PET Procedure

All PET/CT scans were performed using a Gemini TF 64 system (Philips Healthcare). After patient positioning, 30-min dynamic PET scans were initiated immediately after bolus injection of [^{18}F]FLT (10.3 ± 0.4 mCi). PET list mode data were reconstructed using 3D row action maximum likelihood algorithm (3D RAMLA) in 26 frames (8×15 s, 6×30 s, 5×1 min, 5×2 min, and 2×5 min, Fig. 1). Six additional subset dynamic PET data sets were reconstructed and generated using shortened acquisition durations ($T_d = 10, 12, 14, 16, 20,$ and 25 min, separately) (Fig. 1).

Image and Data Processing

All reconstructed images were transferred to the Extended Brilliance Workspace (EBW, Philips Healthcare) for data analysis and evaluation. Spherical volume of interest (VOI) was placed over plasma in the descending aorta well away from the edge (Fig. 2a), and adaptive VOIs by region-grow algorithms were generated to outline breast tumors to obtain

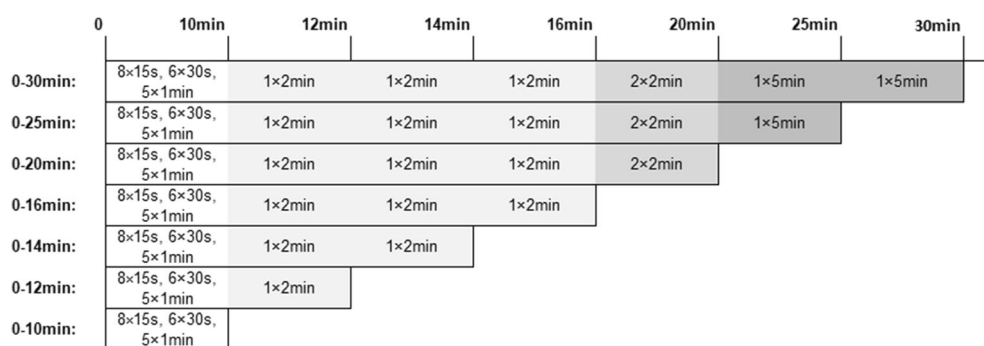


Fig. 1. Shortened [^{18}F]FLT dynamic PET acquisition durations and time frames used in PET reconstruction as well as kinetic analysis. Thirty-minute acquisition is reduced to shorter acquisitions with the duration of 10, 12, 14, 16, 20, and 25 min.

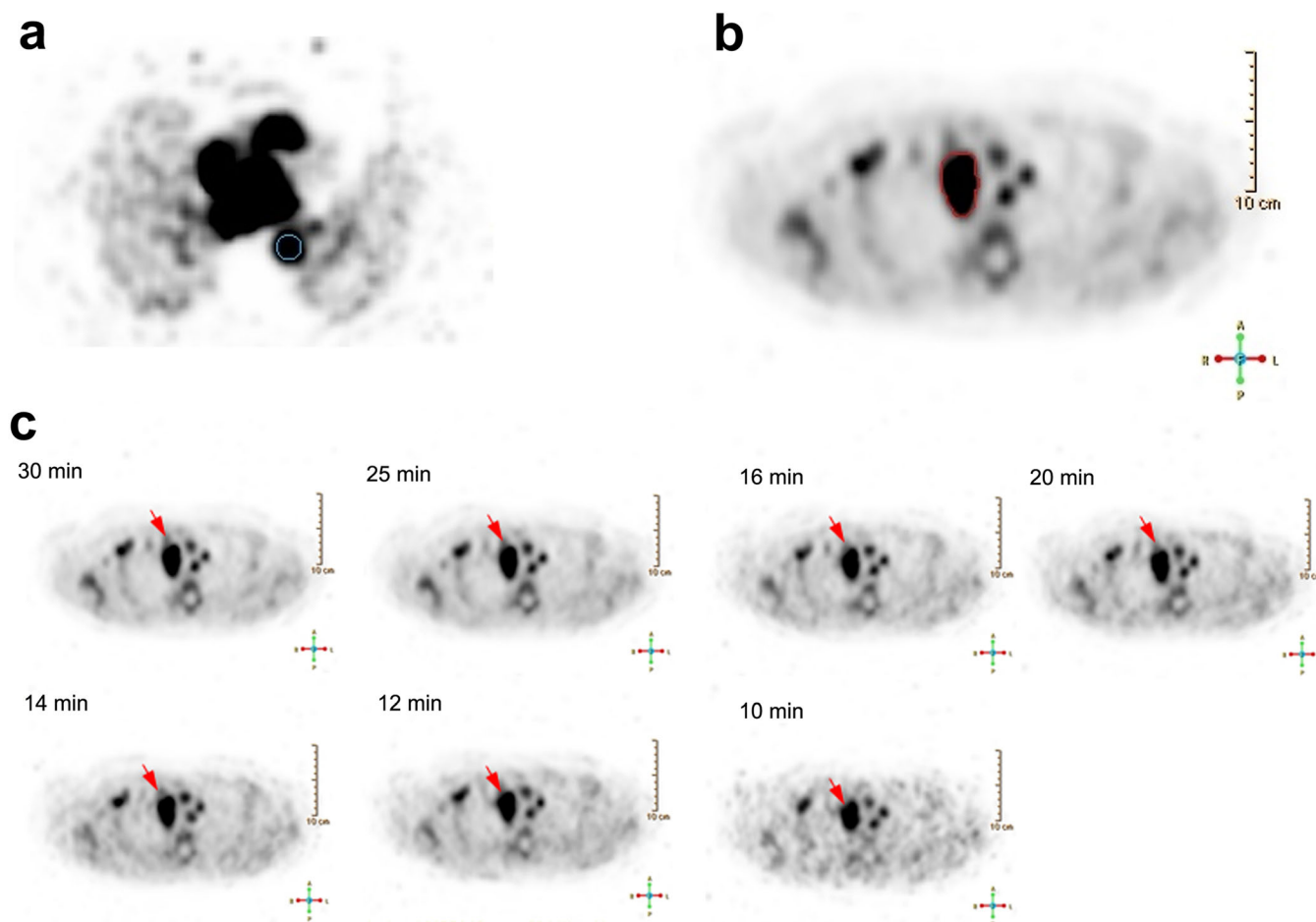


Fig. 2. Examples of **a** 3D spherical VOI placement for a plasma uptake at descending aorta, **b** adaptive VOI contours for tumor uptake, and **c** tracer uptake of tumors and image quality of dynamic [^{18}F]FLT-PET with various acquisition durations (red arrow indicates the location of the target tumor).

the maximum activity concentration (Bq/ml) across all frames (Fig. 2b). Fig. 2c shows an example of PET images under various acquisition durations.

With in-house developed software, kinetic parameters were calculated by both the two-tissue three-compartment irreversible model (2TCM) using the classic iterative Levenberg-Marquardt algorithm and the Patlak model. 2TCM usually consists of plasma, free ligand/non-specific binding in tissue and specific binding, with four rate constants K_1 – k_4 estimated to describe the exchange of the radiotracer between blood and tissue [16]. In the case of [^{18}F]FLT, K_1 reflects forward transport, k_2 the reverse transport, k_3 the phosphorylation rate, and k_4 the dephosphorylation rate [17]. k_4 was set to be zero in this study. The kinetic parameter K_i representing the net influx of radiotracer into the irreversible compartment was obtained using $K_i = K_1 \times k_3 / (k_2 + k_3)$ with the plasma input [18]. On the other hand, Patlak model as a graphical analysis model using linear regression to identify the tracer kinetics [19] estimates its key parameter K_i by calculating the slope value of the linear regression. Several onset time points for the Patlak linear regression (T_0) were specified in this study to

determine the time after which the linear approximation is valid (1, 2, 3, 4, and 5 min, separately). Kinetic parameters estimated from 30-min data sets using 2TCM were taken as the gold standard for comparison.

The mean and maximum SUV values (SUV_{mean} and SUV_{max}) with various T_d were collected to assess the quality of the dynamic PET images together with signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) which are defined as follows [20]:

$$\text{SNR} = \frac{\text{SUV}_{\text{mean}_{\text{liver}}}}{\text{SD}_{\text{liver}}}$$

$$\text{CNR} = \frac{\text{SUV}_{\text{mean}_{\text{tumor}}} - \text{SUV}_{\text{mean}_{\text{background}}}}{\text{SD}_{\text{tumor}}}$$

A circular 2D ROI with the diameter of 50 mm was placed over a normal liver area on the axial image to obtain the SUV_{mean} and SD values. Adaptive 3D VOIs by region-grow were placed for tumors, and spherical 3D VOIs with a diameter of 20 mm were placed on normal breast tissues in a

consistent manner across all dynamic frames. SUV_{max} values were compared between dynamic PET with shortened T_d and the original 30-min acquisition.

Statistical Analysis

Two-tailed T test (Microsoft Excel 2016) was applied for the comparisons of SNR, CNR, and SUVs between the values obtained by the shortened data series and those by the 30-min data series. Statistical significance was set at $p < 0.05$ for all tests. Pearson product-moment correlation coefficient (R) of 0.9 was chosen as a limit.

Results

Dynamic [¹⁸F]FLT-PET images with various acquisition durations were visually evaluated. Twenty-three out of 26 lesions could be clearly defined at $T_d = 10$ min. Only 3 lesions required longer acquisition durations for tumor delineation ($T_d > 16$ min). The average size of the 23 lesions is 21 ± 11 mm and 9 ± 3 mm for the remaining 3 lesions. Tumor contouring could be easily defined in all

images, while the visual quality was apparently improved as the acquisition duration increased (Fig. 2c).

Two quantitative analyses were performed to further evaluate the image quality of the shortened dynamic [¹⁸F]FLT-PET compared to the 30-min data sets. The first one was conducted by determining SNR (Fig. 3a) and CNR (Fig. 3b). Statistically significant difference was revealed between the 10-min data and the 30-min data with $p = 0.016$ for SNR and $p = 0.008$ for CNR, while no significant difference obtained for the shortened acquisition durations (from 12 to 25 min) compared to the 30-min data (SNR: $p = 0.357, 0.519, 0.710, 0.493,$ and 0.686 ; CNR: $p = 0.098, 0.073, 0.054, 0.148,$ and 0.257 at $T_d = 12, 14, 16, 20,$ and 25 min, respectively). The second quantitative analysis was performed for SUV_{max} (Fig. 3c) and SUV_{mean} (Fig. 3d). No statistical significance was reached for the comparison based on either SUV_{max} or SUV_{mean} (SUV_{max} : $p = 0.373, 0.337, 0.327, 0.407, 0.577,$ and 0.679 ; SUV_{mean} : $p = 0.278, 0.327, 0.265, 0.358, 0.552,$ and 0.641 at $T_d = 10, 12, 14, 16, 20,$ and 25 min, respectively). SUV measurements appeared robust across shortened dynamic [¹⁸F]FLT-PET acquisitions. Based on these results, shortened acquisition with $T_d \geq 12$ min can

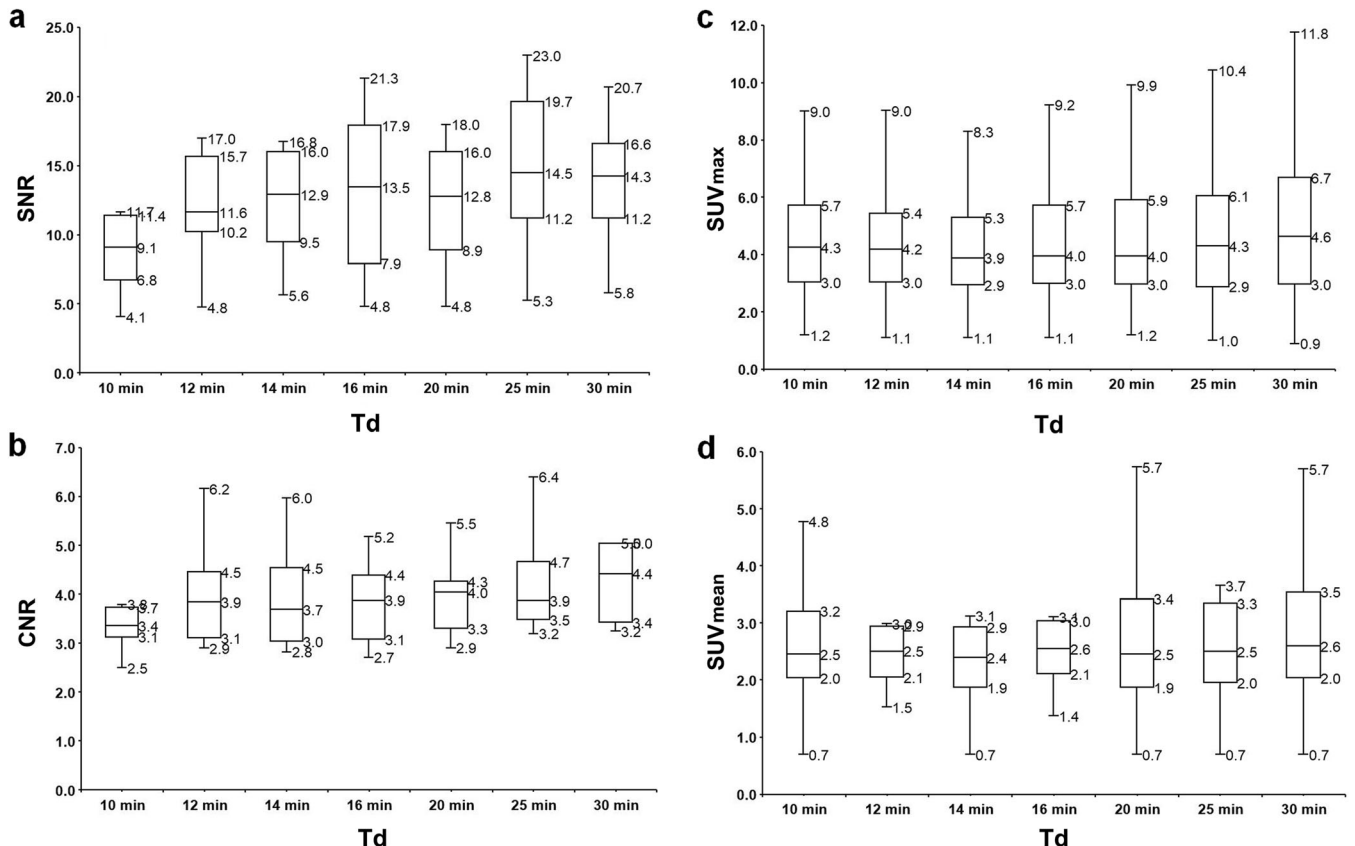


Fig. 3. Boxplot of **a** SNR, **b** CNR, **c** SUV_{max} , and **d** SUV_{mean} distribution as a function of acquisition duration (T_d). Five values (minimum, first quartile, median, third quartile, and maximum in bottom-up order) are summarized. Statistically no significant differences found between the shortened acquisition durations ($T_d = 12$ to 25 min) and the 30-min data for SNR, CNR, and SUV, except $T_d = 10$ min.

provide good quality dynamic images with stable CNR, SNR, and SUV measurements.

Kinetics analysis was performed to verify the quantification accuracy of the kinetic parameters with the shortened acquisitions, as shown in Fig. 4. Using Patlak model, K_i values from all data sets at different onset time ($T_0 = 1\text{--}5$ min) are given in Fig. 4a, and the correlations of K_i between shortened and 30-min data sets can be found in Fig. 4b. While the correlation consistently increases with longer acquisition duration, K_i values at $T_d \geq 16$ min presented with high correlations ($R = 0.90$ at $T_d = 16$ min, 0.97 at $T_d = 20$ min, and 1.00 at $T_d = 25$ min), and K_i values at $T_d \leq 14$ min revealed relatively poor correlations ($R < 0.9$). Onset time T_0 did not seem to have significant impact on differentiating the excellent and poor correlations of K_i when using the Patlak model. Kinetic parameters (K_i , K_1 , k_2 , and k_3) estimated by 2TCM are shown in Fig. 4c, with corresponding correlations between shortened and 30-min data sets given in Fig. 4d. It demonstrates more consistent measurements of K_1 , k_2 , and k_3 (in terms of median, first quartile, and third quartile distributions) for $T_d \geq 16$ min than $T_d \leq 14$ min (Fig. 4c). Correlation coefficients of K_i and K_1 appeared to be robust and excellent with all shortened acquisitions ($R > 0.9$ for T_d

from 10 to 25 min) and increased as increasing the acquisition duration for k_2 and k_3 (Fig. 4d). k_2 and k_3 showed excellent correlation when $T_d \geq 16$ min (k_2 : $R = 0.94$ at $T_d = 16$ min, 0.93 at $T_d = 20$ min, and 1.00 at $T_d = 25$ min; k_3 : $R = 0.94$ at $T_d = 16$ min, 0.95 at $T_d = 20$ min, and 0.99 at $T_d = 25$ min) and relatively poor correlations when $T_d \leq 14$ min (k_2 : $R = 0.84$ at $T_d = 10$ min, 0.85 at $T_d = 12$ min, and 0.86 at $T_d = 14$ min; k_3 : $R = 0.67$ at $T_d = 10$, 12 , and 14 min). Based on these results, shortened acquisitions with $T_d \geq 16$ min provide robust measurements of kinetic parameters.

K_i values calculated from Patlak model and 2TCM are compared and shown in Fig. 5. As increasing T_d from 10 to 30 min, the correlation coefficient gradually increased. Excellent correlations were found when $T_d \geq 14$ min ($R = 0.93$ at $T_d = 14$ min, 0.96 at $T_d = 16$ min, 0.98 at $T_d = 20$ min, 0.98 at $T_d = 25$ min, and 0.99 at $T_d = 30$ min), compared to $T_d \leq 12$ min ($R = 0.83$ at $T_d = 10$ min and 0.88 at $T_d = 12$ min). T_d at 14 min could well differentiate the good and poor correlation.

Correlation between SUV_{max} and kinetic parameters (K_i , K_1 , k_2 , and k_3) using 2TCM under $T_d = 10, 12, 14, 16, 20, 25$, and 30 min was additionally evaluated, and the results are shown in Fig. 6. It appeared to be very good correlation

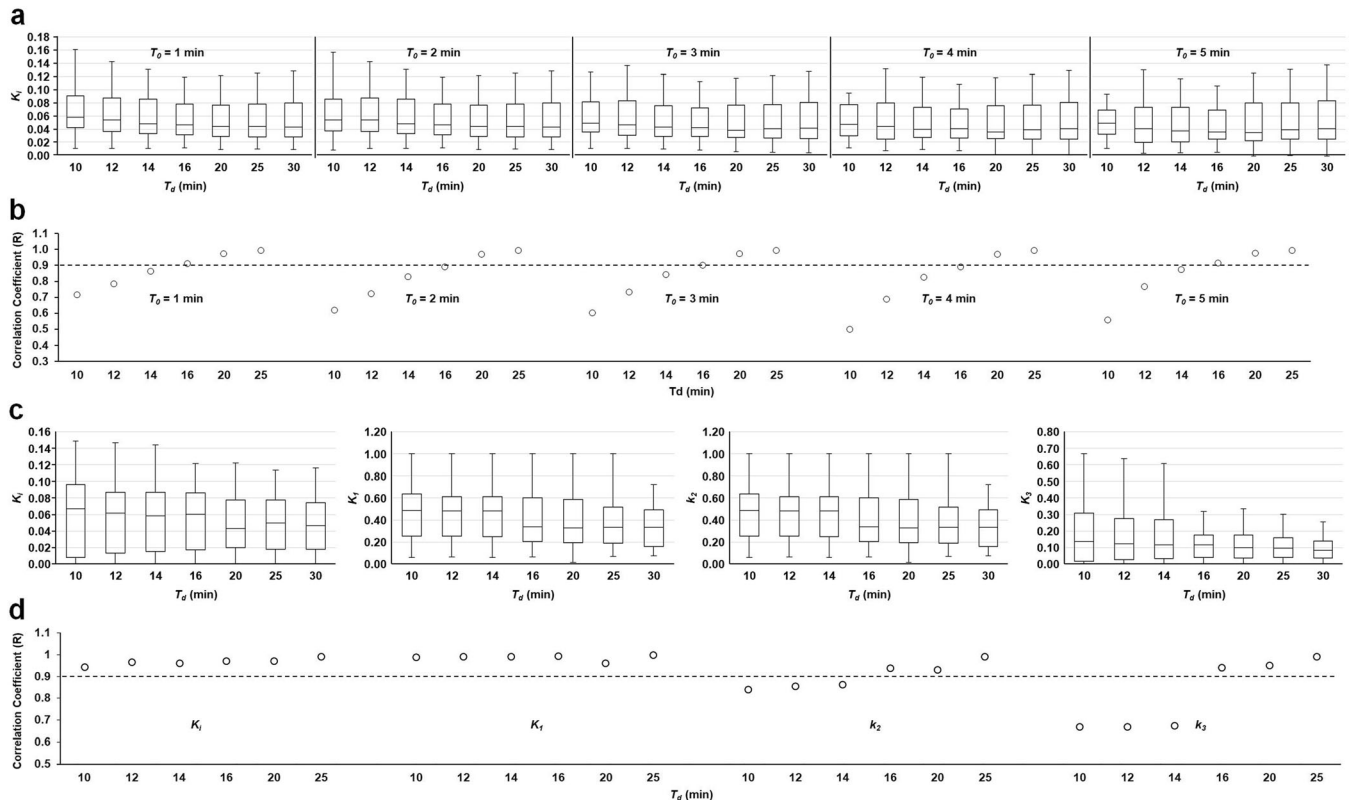


Fig. 4. Results of kinetic parameters of [^{18}F]FLT dynamic PET with shortened acquisitions compared to 30-min acquisition. **a** Boxplot of Patlak K_i as a function of T_d at onset time points (T_0) of 1, 2, 3, 4, and 5 min; **b** correlations of Patlak K_i between shortened and 30-min acquisitions; **c** boxplot of 2TCM kinetic parameters (K_i , K_1 , k_2 , and k_3) as a function of T_d ; and **d** correlations of 2TCM kinetic parameters between shortened and 30-min dynamic acquisitions. Overall shortened acquisitions with $T_d \geq 16$ min could enable robust estimate of kinetic parameters.

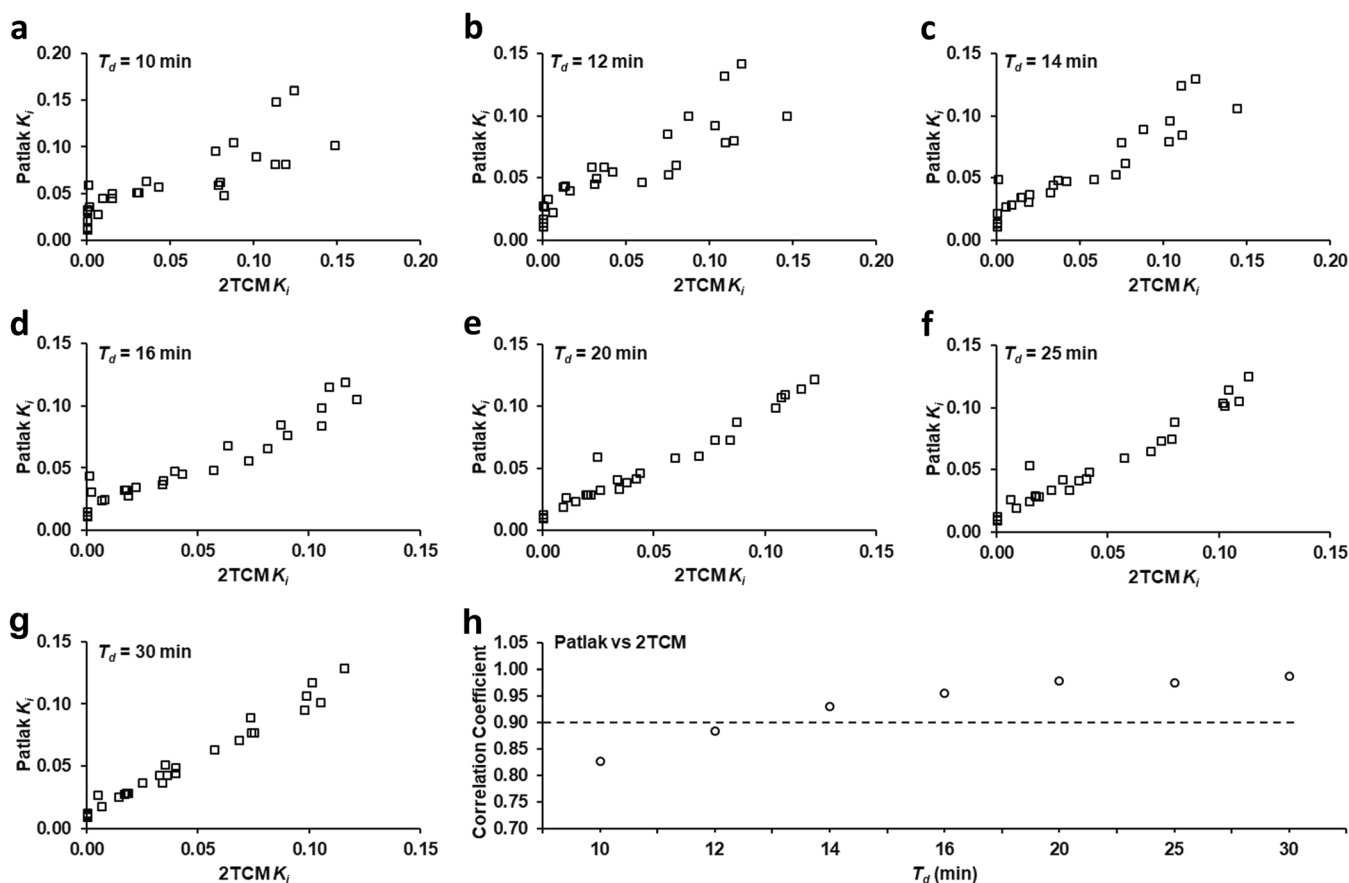


Fig. 5. Comparison of calculated K_i values between Patlak and 2TCM methods. **a–g** scatterplot of Patlak K_i as a function of $2TCM K_i$ for each of the 26 breast tumors under [¹⁸F]FLT dynamic acquisition durations from 10 to 30 min. **h** Correlation coefficients of K_i estimate from both models as a function of acquisition duration. Excellent correlation ($R \geq 0.90$) was found for shortened acquisition durations at $T_d \geq 14$ min.

between $2TCM K_i$ and SUV_{max} ($R = 0.87, 0.89, 0.90, 0.91, 0.93, 0.93$, and 0.95), while no strong correlation was found between SUV_{max} and other parameters (K_1 : $R = 0.63, 0.61, 0.60, 0.60, 0.56, 0.53$, and 0.45 ; k_2 : $R = 0.72, 0.69, 0.68, 0.53, 0.49, 0.39$, and 0.27 ; k_3 : $R = 0.76, 0.78, 0.78, 0.75, 0.75, 0.73$, and 0.73).

Discussion

While dynamic [¹⁸F]FLT-PET performed on breast cancer patients undergoing chemotherapy has been demonstrated to be helpful in assessing cancer treatment response and predicting the long-term outcome [7, 10, 12, 13], it is challenging to have it implemented in clinical routine applications because of the prolonged scan time. To the best of our knowledge, few studies in breast cancer patients have been published with respect to the use of shortened dynamic PET acquisition. Practically, shortened procedures are requested by patients and patient advocates. Our results showed that compared to 30-min dynamic [¹⁸F]FLT-PET imaging, ≥ 12 -min dynamic acquisition could provide good quality images for tumor delineation with stable CNR, SNR, and SUV measurements, ≥ 16 -min dynamic acquisition

could enable robust and accurate [¹⁸F]FLT kinetic analysis, and ≥ 14 -min dynamic acquisition may lead to well-correlated K_i estimate using different methods (Patlak vs 2TCM). Overall, we propose that a 16-min shortened dynamic [¹⁸F]FLT-PET acquisition appears to be long enough to facilitate all and will be clinically practicable and feasible from a patient perspective.

Although dynamic [¹⁸F]FLT-PET can provide multiple parameters for more detailed tumor response assessment, it is restricted by the limited z-axial field of view of current PET scanners. Specific anatomic regions including the target lesions need to be determined in advance and kept for all follow-up dynamic PET scans. During follow-up examinations and therapy response evaluations, breast cancer metastases as well as recurrent diseases usually occur and need to be detected [21, 22]. Therefore, a modified protocol can be designed with a shortened dynamic [¹⁸F]FLT-PET acquisition over the target area and followed by a multiple-bed position static acquisition. The modified protocol may add additional advantages for not only evaluating response of target lesions but also detecting other possible lesions.

Various kinetic models were proposed for quantifying dynamic PET data. The two-tissue compartment model is the

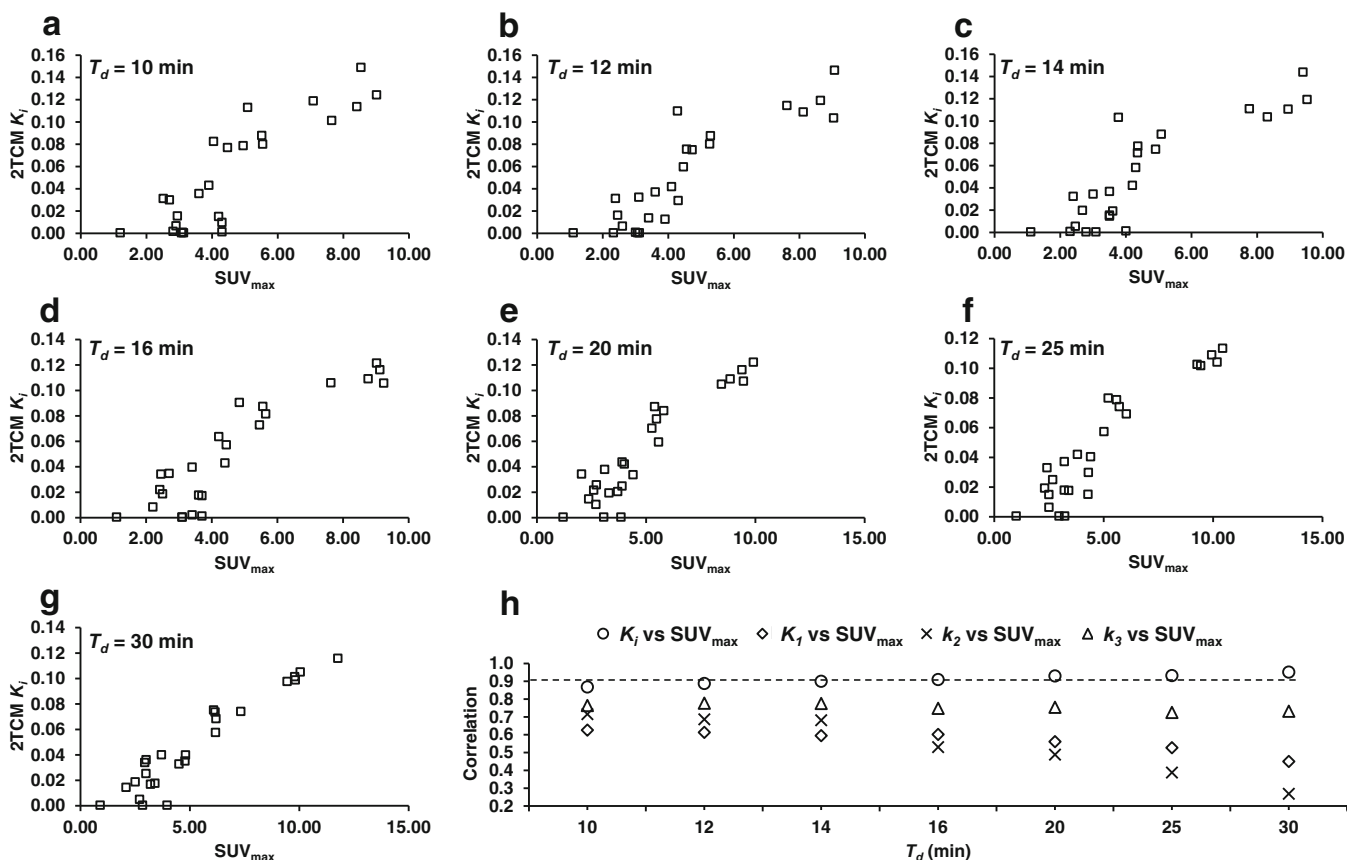


Fig. 6. Correlation between SUV_{\max} and kinetic parameters (K_i , K_1 , k_2 , and k_3) using 2TCM. **a–g** Scatterplot of 2TCM K_i as a function of SUV_{\max} at each of the [^{18}F]FLT dynamic acquisition durations. **h** Correlation between 2TCM kinetic parameters and SUV_{\max} as a function of acquisition duration. Excellent correlation ($R \geq 0.90$) was found between K_i and SUV_{\max} for shortened acquisition durations at $T_d \geq 12$ or 14 min.

most widely applied model in dynamic PET kinetic analysis, while Patlak as a simplified graphical model is gaining its importance in dynamic PET kinetics assessment in recent years [23, 24]. Previous studies have demonstrated that these models could provide valuable kinetic information to evaluate breast cancer treatment response with traditional dynamic PET acquisitions [14, 25–27]. In our study to evaluate the feasibility of reducing the time required for dynamic [^{18}F]FLT-PET scans, it is worth pointing out that we set $k_4 = 0$ for ≤ 30 -min dynamic PET kinetic analysis using 2TCM, while for longer [^{18}F]FLT PET imaging (e.g., 120 min), k_4 might be notable [17]. According to our findings, both models gave well-correlated common kinetic parameter K_i particularly for dynamic [^{18}F]FLT-PET acquisition of ≥ 14 min, and as increasing the acquisition duration, changes of K_i distribution appeared to be more obvious using Patlak model than 2TCM.

Patlak linear regression onset time T_0 is another essential factor for generating accurate kinetic parameter and therefore was evaluated. T_0 determines the slope of the linear regression line and affects K_i estimate. Since dramatic tracer transportation occurs immediately after tracer injection, no

steady state can be reached between plasma and the reversible compartments at the very beginning [19]. In order to minimize the impact of prompt tracer transportation, T_0 with various onset time points for Patlak linear regression [19, 28–31] were suggested. In our study, onset time points from 1 to 5 min were tested to confirm the impact of different T_0 on K_i estimation for the shortened dynamic acquisition. We found that the tested T_0 did not affect K_i estimation apparently, and no dramatic tracer transportation was identified 1 to 5 min post [^{18}F]FLT injection. In addition, our data indicated that even a 5–16-min dynamic acquisition ($T_0 = 5$ min) provided accurate K_i estimate. Using the same shortened [^{18}F]FLT dynamic PET data and reconstruction method, 1 min is suggested to be the onset time point for Patlak linear regression in our study. To assure the accuracy, a study with larger data size is required to confirm the findings.

In addition to the dynamic [^{18}F]FLT PET that we explored in this study, [^{18}F]FDG as the most widely used radiotracer is worth testing for clinical applications of implementing shortened dynamic PET acquisition. [^{18}F]FDG displays different uptake patterns in breast tumors

from [¹⁸F]FLT according to several clinical studies as well as small animal studies [10, 32]. Within the same breast cancer patient pool or mouse model, [¹⁸F]FLT uptake could reach maximal peak or a plateau after approximately 5 to 10 min, compared to that [¹⁸F]FDG uptake which gradually increases without reaching a plateau within 60 min post injection. The robustness of the 16-min shortened dynamic [¹⁸F]FLT-PET acquisition may be partially contributed by the specific uptake pattern of [¹⁸F]FLT. It is possible that the [¹⁸F]FLT-based findings in this study may not reflect the truth for [¹⁸F]FDG, and a 16-min dynamic acquisition may not be robust for [¹⁸F]FDG applications in breast cancer, which needs [¹⁸F]FDG-specific evaluation to confirm. In our view, comparison of the performance of multiple radiotracers will also help to establish more robust shortened dynamic PET acquisition protocols.

It is necessary to point out that the metabolite correction for [¹⁸F]FLT-PET using two-tissue compartment model was not specifically performed in the evaluation of this pilot study. Researchers found that at 60 min, about 74 % of the blood activity of [¹⁸F]FLT was unmetabolized, and a single sample yielded data with mean errors of 2.2 % for metabolite analysis [33]. Ideally, measurement of metabolites in blood is recommended to properly understand more the kinetics of [¹⁸F]FLT when evaluating tumor proliferation. This could be added into future studies. This study is limited by the relatively small patient pool, and a larger study with more evaluable tumors and metastases will be necessary to confirm the predictive values.

Lastly, while this study was aiming to investigate whether or not clinical dynamic [¹⁸F]FLT PET acquisition could be shortened from the current widely used 45–95-min window [11, 15, 34], we additionally evaluated the correlation between SUV_{max} and kinetic parameters (K_i , K_1 , k_2 , and k_3). In general, SUV as a semi-automatic biomarker can be simply calculated compared to the kinetic parameter determination of dynamic imaging. It would be time-efficient to do a routine static PET only without dynamic PET, if there is a strong correlation between SUV measurements and kinetic parameters. Our data showed that there is a good correlation between SUV_{max} and the K_i parameter under various acquisition durations ($T_d = 10–30$ min); however, no strong correlation was found between SUV and other kinetic parameters such as K_1 , k_2 , and k_3 . Further, as increasing T_d , the correlation between SUV_{max} and K_1 as well as between SUV_{max} and k_2 becomes less, while the correlation between SUV_{max} and k_3 stayed unchanged.

Our study was not powered to answer the question whether an SUV_{max}-only assessment is sufficient to provide equivalent conclusions compared kinetic model-based assessment, but instead focus on the impact of acquisition duration. A shorter duration will be more acceptable to patients and thus enable further clinical investigations regarding the most appropriate acquisition approach for this proliferation agent.

Conclusions

This study indicates that a 16-min dynamic PET acquisition appears to be sufficient to provide accurate [¹⁸F]FLT kinetics to quantitatively assess the proliferation in breast cancer lesions. It demonstrates the ability of the shortened [¹⁸F]FLT dynamic PET imaging without influencing the kinetic quantification for therapy response assessment, making the use of dynamic acquisitions more clinically feasible.

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Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

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