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Improved discrimination between benign and malignant LDCT screening-detected lung nodules with dynamic over static ^{18}F -FDG PET as a function of injected dose

Qing Ye^{1,2,3}, Jing Wu¹, Yihuan Lu¹, Mika Naganawa¹, Jean-Dominique Gallezot¹, Tianyu Ma^{2,3,*}, Yaqiang Liu^{2,3}, Lynn Tanoue⁴, Frank Detterbeck⁵, Justin Blasberg⁵, Ming-Kai Chen¹, Michael Casey⁶, Richard E. Carson¹, and Chi Liu¹

¹Department of Radiology and Biomedical Imaging, Yale University, USA

²Department of Engineering Physics, Tsinghua University, China

³Key Laboratory of Particle & Radiation Imaging, Ministry of Education (Tsinghua University), China

⁴Yale Lung Screening and Nodule Program, Department of Internal Medicine, Yale University, USA

⁵Thoracic Oncology Program, Yale Cancer Center, Yale University, USA

⁶Molecular Imaging, Siemens Medical Solutions USA, Inc., USA

Abstract

Lung cancer mortality rate can be significantly reduced by up to 20% through routine low-dose computed tomography (LDCT) screening, which, however, has high sensitivity but low specificity, resulting in a high rate of false-positive nodules. Combining PET with CT may provide more accurate diagnosis for indeterminate screening-detected nodules. In this work, we investigated lowdose dynamic ^{18}F -FDG PET in discrimination between benign and malignant nodules using a virtual clinical trial based on patient study with ground truth. Six patients with initial LDCT screening-detected lung nodules received 90-min single-bed PET scans following a 10 mCi FDG injection. Low-dose static and dynamic images were generated from under-sampled list-mode data at various count levels (100%, 50%, 10%, 5%, and 1%). A virtual clinical trial was performed by adding nodule population variability, measurement noise, and static PET acquisition start time variability to the time activity curves (TACs) of the patient data. We used receiver operating characteristic (ROC) analysis to estimate the classification capability of standardized uptake value (SUV) and net uptake constant K_i from their simulated benign and malignant distributions. Various scan durations and start times (t^*) were investigated in dynamic Patlak analysis to optimize simplified acquisition protocols with a population-based input function (PBIF). The area under curve (AUC) of ROC analysis was higher with increased scan duration and earlier t^* . Highly similar results were obtained using PBIF to those using image-derived input function (IDIF). The AUC value for K_i using optimized t^* and scan duration with 10% dose was higher than that for SUV with 100% dose. Our results suggest that dynamic PET with as little as 1 mCi FDG could

*Corresponding author. maty@mail.tsinghua.edu.cn.

provide discrimination between benign and malignant lung nodules with higher than 90% sensitivity and specificity for patients similar to the pilot and simulated population in this study, with LDCT screening-detected indeterminate lung nodules.

Keywords

FDG PET; lung cancer screening; kinetic modeling; low dose

1. Introduction

Lung cancer is one of the most common cancers worldwide with high mortality and morbidity. Early diagnosis plays an important role in improving survival. The lung cancer mortality rate can be significantly reduced by up to 20% through routine low-dose computed tomography (LDCT), rather than high-dose diagnostic CT, screening as demonstrated by the National Lung Cancer Screening Trial (NLST) research team (National Lung Screening Trial Research *et al.*, 2011). A large number of institutes and associations, such as American College of Chest Physicians (ACCP), have recommended screening with LDCT for high-risk population (Detterbeck *et al.*, 2013). However, LDCT lung cancer screening has been reported to have high false-positive rates of about 86–96% (Shlomi *et al.*, 2014). The sensitivity and specificity of baseline LDCT are about 93.8% and 73.4%, respectively (Shlomi *et al.*, 2014). A recent report stressed that 1.57 million pulmonary nodules will be identified in the US annually, but only 63,000 will become malignant within 2 years (Gould *et al.*, 2015). For indeterminate small nodules, follow-up LDCT scans are performed within 3–6 months or after 1 year depending on the size and imaging characteristics of the nodules. Changes in nodule size are often estimated through calculations of volume doubling time based on CT measurements. Invasive diagnosis procedures, such as biopsy, surgery and bronchoscopy are also used to determine nodule malignancy. The low specificity of LDCT leads to a large number of unnecessary invasive procedures, over-diagnosis, and subsequent overtreatment that can result in additional complications (Humphrey *et al.*, 2013; Patz *et al.*, 2014). For example, among 649 cases with a positive screening result in the NLST trial, 73 developed major complications after an invasive procedure, and 16 died within 60 days of an invasive procedure (National Lung Screening Trial Research *et al.*, 2011). Therefore, accurate non-invasive means of nodule evaluation with high specificity are greatly and urgently needed.

Positron emission tomography (PET) with fluorodeoxyglucose (FDG) has a great advantage by providing metabolic information. PET has the potential to precisely diagnose an indeterminate nodule as benign or malignant immediately, rather than waiting for follow-up LDCT scans or invasive procedures (Schrevers *et al.*, 2004; Bastarrika *et al.*, 2005). From the first 6 years of the Continuous Observation of SMOKing Subjects (COSMOS) study in Europe, the sensitivity and specificity of PET/CT were, respectively, 82% and 92% for baseline-detected nodules (Veronesi *et al.*, 2015). It has also been demonstrated that PET predicts lung cancer malignancy independently from volume doubling time derived from multiple LDCT scans (Ashraf *et al.*, 2011). When PET and CT results are in accordance, there is only about 5% probability of false diagnosis based on the study of 40 patients

(Ashraf *et al.*, 2011). Therefore, following up indeterminate lung nodules with combined PET/CT has a great potential to improve results compared with follow-up LDCT scans alone. By using low-dose techniques to acquire CT data for PET/CT scans, both LDCT and PET information can be acquired at the same session to improve diagnostic accuracy.

The average effective dose for a standard dose chest CT was estimated to be around 7 mSv (Caroline, 2014). Although radiation exposure to lung cancer screening patients has been reduced to below 1 mSv for a single LDCT, annual screening procedures may still be associated with increased risk of radiation-related malignancy (Mascalchi and Sali, 2017). The number of CT scans required to cause 1 radiation-induced cancer was estimated to be 720 and 1566 for 40-year-old women and men, respectively (Sharma *et al.*, 2015). In order to establish the utility of PET/CT for the lung cancer screening patient population with a low malignancy rate, the radiation dose of PET/CT should be reduced to control the overall exposure. The dose of PET should ideally be comparable to that of LDCT or even lower. An effective radiation dose of about 0.6 mSv can be achieved with about 1 mCi FDG injection, representing only 10% of the standard 10-mCi dose (Huang *et al.*, 2009).

The semi-quantitative parameter standardized uptake value (SUV) has been the predominant quantification method used in static PET. The molecular imaging field, however, has long recognized the potential of dynamic PET with kinetic analysis to provide more accurate and sensitive information. For dynamic PET, data acquisition may start immediately with tracer injection and continue for up to 90 min for FDG. Proper use of such dynamic data requires kinetic modeling approaches including compartmental modeling or graphical analysis to obtain the tracer net uptake constant K_i , which can be more sensitive and specific than conventional SUV, albeit at the expense of longer scan duration and additional analysis complexity (Gupta *et al.*, 1998; Dimitrakopoulou-Strauss *et al.*, 2002). However, dynamic PET scans could become more clinically feasible using graphical analysis and simplified protocols. Simplified protocols, which do not start immediately after tracer injection, can shorten the scan duration by incorporating population-based input functions (PBIF). With shorter scan durations, the possibility of body motion could also be reduced.

Recent work has explored low-dose static PET imaging of indeterminate nodules for lung cancer screening. A lower limit of ~ 10 million true counts, corresponding to ~ 0.5 mCi injection, has been shown to be feasible for the detection of lung cancer nodules (Schaefferkoetter *et al.*, 2015; Schaefferkoetter *et al.*, 2017; Yan *et al.*, 2016). However, no dynamic PET studies have been reported to investigate various count levels in the application of lung cancer screening. Our work here hypothesizes that low-dose dynamic FDG PET/CT could provide improved diagnostic accuracy when replacing follow-up LDCT scans. It aimed to investigate the diagnosis performance of dynamic PET imaging as a function of injected dose for screening patients. Here, we estimated the capability to discriminate between benign and malignant nodules for both static and dynamic PET. A virtual clinical trial was performed based on real patient scans. The feasibility of simplified protocols for dynamic PET was also investigated.

2. Materials and methods

2.1 Patient population

Six patients (5 male, 1 female; age 61–85 y; weight 65–110 kg) from the Yale Lung Nodule Program with baseline LDCT screening detected indeterminate lung nodules were enrolled in the dynamic PET/CT lung cancer study in the Yale PET Center. In total, there were ten solid nodules with sizes of 6–30 mm initially observed by baseline LDCT. The gold standard for all the nodules was determined (8 benign, 2 malignant) as part of the standard of care based on either resection and histology analysis, or size change between baseline and follow-up LDCT scans (typically 3–6 months apart). The research dynamic PET/CT scans were performed after the baseline LDCT, but prior to resection or follow-up LDCT scans.

2.2 Data acquisition and processing

2.2.1 PET/CT scan.—For each patient, a single-bed PET/CT scan was performed on the Siemens Biograph mCT. Dynamic PET data were acquired for up to 90 minutes starting with injection of 10 mCi FDG. The dynamic data were binned into 27 frames of 10×30 s and 17×300 s. We used Siemens e7 tool to reconstruct dynamic images with ordered subsets expectation maximization (OSEM) algorithm (21 subsets, 3 iterations), incorporating point spread function (PSF) and time-of-flight (TOF) information, followed by 3-mm Gaussian smoothing. Attenuation, normalization, random, decay, and scatter corrections were incorporated. Post-reconstruction image registration among dynamic frames was performed for patients with obvious body motions. Static images were also reconstructed using 60–80 min post-injection data. The reconstructed image size was $400 \times 400 \times 109$, with voxel size of $2.04 \times 2.04 \times 2.03$ mm³.

2.2.2 Low-dose data generation.—Low-dose PET data were generated by independent random down-sampling of patient list-mode data (Gatidis *et al.*, 2016). Events were randomly discarded according to different count (dose) levels of 100%, 50%, 10%, 5%, and 1%. The number of independent data replicates at each dose level were 1 for 100% counts, 2 for 50% counts, and 10 for all other count levels. The same reconstruction method described in Section 2.2.1 was applied to the low-count static and dynamic PET data, with no additional smoothing applied.

2.2.3 Image analysis.—The reconstructed static and dynamic images of all count levels were analyzed. We manually drew regions of interest (ROIs) on the static images with 100% counts, containing left ventricle (LV) blood pool, aorta, and nodules. Regions were drawn carefully to minimize spill-over effects with other adjacent organs. Nodule mean SUV values were determined from the static images. As shown in *figure 1*, ROI-based kinetic modeling was applied to the dynamic frames. A two-tissue irreversible (2Ti) compartmental model (Bentourkia and Zaidi, 2007) and Patlak graphical analysis (Patlak *et al.*, 1983) were used to calculate microparameters (K_1 , k_2 , k_3 , V_B) and net uptake parameter K_i , respectively. Parametric images were also generated from voxel-based Patlak analysis.

For the dynamic analysis, we chose image-derived input function (IDIF) for kinetic modeling. The LV blood pool has been used for IDIFs, however, for patients with nodules

located in the upper lung, the PET data might not fully include LV in the field of view (FOV). The use of the aorta can solve this problem and reduce errors by increasing input function ROI size (van der Weerd *et al.*, 2001; Dimitrakopoulou-Strauss *et al.*, 2006). In this study, we also manually drew ROIs in the central area of both ascending and descending aortas. The average concentration from the blood LV and aorta ROIs was used for most patients, or from aorta only for patients without LV in the FOV.

2.2.4 Virtual clinical trial.—In order to characterize the capability of PET to discriminate between benign and malignant nodules, a simulated virtual clinical trial was performed based on nodule kinetic parameters obtained from the patient data. Figure 2 shows the simulation process, consisting of three steps: 1) introduction of biological variation, 2) generation of time activity curves (TACs) and input function, and 3) quantitative analysis.

The kinetic parameters of K_1 , k_2 , k_3 of each nodule and the input function from each patient study were used to guide the simulation of virtual patient TACs. Biological variability was added to K_1 of each nodule with 9% coefficient of variation (CV) based on previously published patient data (Wangerin *et al.*, 2015; Wangerin *et al.*, 2017) to extend nodule population. All other kinetic parameters remained unchanged. For each real nodule, we simulated 100 virtual nodules based on its kinetic parameters with various K_1 values.

To further extend the virtual patient population, a noise model based on the kinetic parameters and patient input function was applied to each virtual nodule to simulate a large number of TACs and input functions (Jovkar *et al.*, 1989; Logan *et al.*, 2001; Tomasi *et al.*, 2009). The additive noise follows Gaussian distribution with zero mean. The variances of tissue (nodule) and plasma tracer concentrations (C_T, C_P) are described in equation (1)

$$\text{var}(C_T(t_i)) = \alpha_T^2 \frac{e^{\lambda t_i} C_T^{\text{model}}(t_i)}{\Delta t_i} \quad \text{var}(C_P(t_i)) = \alpha_P^2 \frac{e^{\lambda t_i} C_P^{\text{model}}(t_i)}{\Delta t_i} \quad (1)$$

where t_i is the middle time of the i^{th} frame, Δt_i is the frame duration, and λ is the decay constant. C_P^{model} and C_T^{model} are noise-free concentrations of plasma and tissue (nodule) in the noise model. Tri-exponential fitted IDIFs from patient data were used as C_P^{model} . C_T^{model} was calculated using the 2Ti compartmental model with C_P^{model} and each set of virtual kinetic parameters. The tissue concentration noise scale factor α_T was estimated from real data by dividing the weighted residual sum of squares (WRSS) by the degree of freedom in the nonlinear regression process according to equation (2). In this equation, N_{frame} and $N_{\text{parameters}}$ are the number of frames (27) and kinetic parameters (4).

$$\text{WRSS} = \sum_{i=1}^{N_{\text{frame}}} \frac{[C_T^{\text{model}}(t_i) - C_T(t_i)]^2}{e^{\lambda t_i} C_T^{\text{model}}(t_i) \Delta t_i} \quad \alpha_T^2 = \frac{\text{WRSS}}{N_{\text{frame}} - N_{\text{parameters}}} \quad (2)$$

α_T was determined by fitting data from each count level and the averaged α_T over all replicates was used for each count level.

As the noise level is inversely related to the size of ROI, the plasma concentration noise scale factor α_S can be calculated from α_T determined in equation (2) according to equation (3), where $N_{voxel,T}$ and $N_{voxel,P}$ are the number of voxels in the nodule ROI and input function ROI, respectively.

$$\alpha_P^2 = \alpha_T^2 \frac{N_{voxel,T}}{N_{voxel,P}} \quad (3)$$

For each set of virtual nodule kinetic parameters, 100 replicates of noisy TACs were generated. In total, 80,000 benign and 20,000 malignant virtual TACs were simulated. This ratio between benign and malignant nodules reflects the prevalence rate in the screening population. The virtual clinical trial was repeated for the different count levels, as described in Section 2.2.2.

Static and dynamic analysis were performed on each simulated TAC to generate SUV and K_i values. For static PET acquisition, even though the typical target starting time is 60 min post injection, there are large variabilities in routine clinical practice (Kurland *et al.*, 2016). In this study, we estimated such variability from 64 consecutive FDG PET patient scans acquired at Yale-New Haven Hospital, ranging from 49 min to 86 min post injection. The mean acquisition starting time was 66 min and the standard deviation was 8 min.

2.2.5 Investigation of simplified dynamic PET protocols.—For dynamic PET, we generated K_i values from simulated TACs using Patlak analysis. Scan data acquired after the start time (t^*), which was set to 20 min post injection in our study, were used to estimate the slope, K_i . To reduce the total scan duration, simplified acquisition protocols that only require tissue TAC data after t^* were investigated. Without PET data acquired prior to t^* , the full input function cannot be obtained from images, thus PBIF was used in Patlak analysis for simplified protocols. To derive PBIF templates, IDIFs of the 6 screening patients and 10 subjects from another FDG study using the same injection protocol and scanner were used. Following the method proposed in Zanotti-Fregonara *et al.*, 2013, input functions were fitted with a tri-exponential function and normalized according to the integral over 90 minutes. We used the “leave-one-out” approach in evaluation, i.e. the PBIF for each subject was calculated by averaging normalized input functions of all the other subjects. The subject-specific PBIF was scaled according to the image-derived blood pool activity in the delayed scan data. Rather than using blood samples to scale, as in (Zanotti-Fregonara *et al.*, 2013), the integral of the IDIF during the scan time starting at t^* for each simplified protocol was used to calculate the scaling factor.

In order to identify optimal simplified acquisition protocols, we chose various scan durations and t^* values. The scan duration varied from 30 to 60 min, and t^* varied from 5 to 60 min. The integrals of PBIFs of various acquisition protocols were calculated to compare the

accuracy of PBIFs vs. IDIFs. The K_i values derived using the PBIF were also compared with those using the IDIF.

2.2.6 Classification capability.—The simulated distributions of SUV and K_i values were used to estimate the classification capability through receiver operating characteristic (ROC) analysis (Metz, 1978; Barrett *et al.*, 1993). As shown in *figure 3*, ROC curves were generated from true positive fraction (TPF) and false positive fraction (FPF) for a range of cut-off values to distinguish benign and malignant nodules. The area under curve (AUC) values were calculated for each ROC curve as the figure of merit. Higher AUC values indicate superior discrimination between benign and malignant nodules. The sensitivity (true-positive fraction) and specificity (true-negative fraction) were estimated directly from the curves with corresponding cut-off values.

3. Results

3.1 Image analysis results

Reconstructed CT, SUV and parametric K_i images of two sample patients with 6-mm nodules are shown in *figure 4*. The nodules were clearly visible in both SUV and K_i images, and higher nodule-to-background contrast was observed in the K_i images for both patients.

Figure 5 shows SUV and K_i images at various count levels for another patient with an 8-mm nodule. In general, the SUV images have lower noise while the K_i images have higher contrast. Although reconstructed images were noisier with lower counts, as expected, this 8-mm nodule can be clearly visualized in the SUV images with counts as low as 5–10%. For the K_i images, the nodule can still be observed in the 10%-count image, but not in the 5%-count image, suggesting that the low dose limit for K_i to detect small lung nodules is ~ 10% dose for this patient population.

We performed ROI-based analysis of the static and dynamic PET images. Figure 6 shows ratios of SUV, K_i and α_T across all the down-sampled replicates at various count levels as compared to those of the 100%-count images. The mean SUVs remained accurate with 10% and 5% counts, while the standard deviations increased with lower count levels. When the count level reached 1%, the mean SUV showed underestimation, perhaps due to inaccurate scatter estimation and correction when counts are very low (Schaefferkoetter *et al.*, 2017). The K_i measures were more sensitive to low-count data than SUV. K_i values derived from Patlak analysis (20–90 min) were less sensitive to noise than the K_i values derived from 2Ti fitting. The 10%-count dynamic PET using Patlak analysis could still provide accurate average K_i values across the nodule population. Figure 6(d) shows noise scale factors of nodules according to equation (2) from all the low-dose replicates, which provided guidance to virtual clinical trial. The averaged ratios of α_T at 50%, 10%, 5%, and 1%-count levels to that at 100%-count level were about 1.2, 2.4, 3.1, and 6.3, respectively.

Table 1 summarizes the mean, standard deviation and range of parameters obtained from TACs of 100%-count human dynamic PET scans, which were used as noise-free parameters in the virtual clinical trial. The parameters of benign nodules showed two groups, labeled

here as Group 1 and Group 2, with Group 2 having higher SUV and K_i values than Group 1. The parameters of 2 malignant nodules are shown instead of range.

3.2 Evaluation of PBIF

We investigated the accuracy of PBIF by comparing the 90-min integral values of PBIFs and IDIFs for the 6 patients. As shown in *table 2*, the average relative difference was less than 4% using the PBIF, indicating the accuracy and feasibility of PBIF for dynamic FDG PET. The mean and standard deviations of the integral values of PBIF were estimated across various combinations of t^* and scan durations. Details of the differences between integral values of PBIF and IDIF are presented in the supplemental material.

3.3 Simulated distributions

Figure 7 shows estimated SUV and K_i distributions for all the simulated replicates at various count levels. The distributions for benign nodules showed two peaks groups, corresponding to the parameters in Table 1, with Group 2 having higher SUV and K_i values than Group 1. The SUV distributions of benign Group 2 nearly overlapped with the SUV distributions of malignant nodules, while the K_i distributions of Group 2 were separated from those of malignant nodules. With decreased count levels, both SUV and K_i distributions became wider due to increased noise-induced variance. This induces greater overlap between benign and malignant distributions at lower count levels, indicating increased difficulty to distinguish nodules. At < 10% count levels, SUV benign distributions still suggested bimodality while K_i benign distributions did not. The K_i distributions derived from 20–90 min Patlak analysis using IDIF were almost identical to those using PBIF, which are presented in supplemental material.

Figure 8 shows reconstructed images of four sample nodules selected from three different distribution groups. For the benign nodules of Group 2, the SUV activities were close to that of the malignant nodule, while the K_i values were close to that of the benign nodule in Group 1. The sample benign nodules in Group 2 were confirmed to be inflammation due to post-radiation therapy of nearby lymph nodes, indicating that K_i might be more specific than SUV for such cases.

3.4 Classification capability

The AUC results of ROC analysis for different imaging protocols are shown in *figure 9*. In general, longer acquisition duration and earlier t^* led to higher AUC values. For 100%-count data, the AUC values of K_i were higher than that of SUV (~ 60–80 min post injection). It strongly indicated that K_i from dynamic PET can provide superior discrimination between benign and malignant nodules than SUV. When the counts were decreased, the AUC values decreased for both SUV and K_i . K_i was more sensitive to low-count induced noise than SUV, but 10%-dose dynamic PET can still provide superior classification performance when proper scan duration and t^* were chosen, for example, 40-min scans. Highly similar results in discrimination between benign and malignant nodules were observed when using IDIF as compared to PBIF, as shown in supplemental material. The simplified protocols have great potential to facilitate practical clinical adoption of this methodology.

As shown in *figure 10*, we chose sample imaging protocols to compare the ROC AUC at different count levels: (1) SUV, (2) Patlak K_i derived from 20–90 min data with IDIF, (3) Patlak K_i derived from 20–60 min data with IDIF, and (4) Patlak K_i derived from 20–60 min data with PBIF. With 100%-dose, the AUC values of K_i were substantially higher than that of SUV. For 20–90 min data, the AUC results of IDIF and PBIF were nearly identical and could not be distinguishable. With decreased counts, all AUC values declined, and the AUC of K_i decreased faster than that of SUV. However, K_i with 10% dose still showed higher AUC values than that of SUV with 10% dose and even with 100% dose. Similar ROC AUC values were observed for the dynamic analysis using IDIF and PBIF.

The specificity values of the above four imaging protocols are listed in *table 3* when choosing a cut-off value giving 94% sensitivity, which matches that of baseline LDCT in the NLST trial report. The specificity of static PET was ~ 68% for both 100% and 10% counts. This suggests that increasing the injection dose might not improve the sensitivity and specificity of SUV. Moreover, as presented in supplemental material, increasing the static scan duration (to make it closer to that of the dynamic acquisitions) might also not improve the sensitivity and specificity.

For dynamic PET, the specificities were > 90% for 100%-count data and were between 77–90% for 10%-count data, as K_i is more sensitive to low-count induced noise than SUV. Our results demonstrated that as little as 10% dose with dynamic PET imaging can achieve superior sensitivity and specificity to conventional 100%-dose static PET for our simulated population. The optimal injected dose for other populations needs further investigation.

4. Discussion

In this study, by comparing the AUC values of ROC analysis, we found that dynamic FDG PET was superior to static PET in the discrimination between benign and malignant lung nodules. Simplified protocols with PBIF was demonstrated to be feasible in dynamic PET scans, which may facilitate clinical adoption. In the proposed virtual clinical trial, dynamic PET showed higher classification capability than static PET, even at 10% count level.

It is also promising that dynamic FDG PET may be helpful in differentiating malignant from inflammatory nodules. While numerous studies have reported that inflammatory and infectious nodules may show high SUV uptake similar as malignant nodules in static PET analysis (Chen *et al.*, 2017; Kubota *et al.*, 2006; Kato *et al.*, 1995), it is not reliable enough to characterize the nodules as benign or malignant by SUV values alone. Dual time point ^{18}F -FDG PET, which estimates the percentage changes between early and delayed SUV, has been proposed to increase diagnostic accuracy (Zhuang *et al.*, 2001; Suga *et al.*, 2009; Shimizu *et al.*, 2015), by investigating different FDG uptake patterns of inflammatory and malignant nodules over time. However, dual time point FDG PET showed limited diagnostic value, due to the large variability in the SUV estimation at two time points (Chen *et al.*, 2016). Dynamic PET analysis, which estimates the net uptake rate K_i , provides more accurate description of FDG uptake pattern through kinetic modeling. With the consideration of input function incorporated in the kinetic modeling, K_i provides normalized estimation for different subjects by the area under input function curve. This normalization

reduces the inter-subject variability and is more objective than the normalization by injected dose and body weight in the calculation of SUV. K_i also corrects for non-metabolized FDG uptake, which can account for a significant fraction of total uptake for low-metabolizing tumors. Therefore, dynamic PET analysis is more promising to improve the diagnosis accuracy between inflammatory and malignant nodules.

We have investigated simplified protocols with PBIF and shortened scan durations in dynamic PET. The quantification results using PBIF were comparable to those using IDIF. The combination of PBIF and Patlak analysis makes the shortened scan duration feasible. With the simplified protocols, the dynamic PET scan for the diagnosis of screening-detected nodules could be more clinically flexible if proper t^* and scan duration are chosen. As in the example shown in *table 3*, a dynamic PET with an acceptable 40-min scan duration (20–60 min) showed higher specificity than a 20-min static PET with comparable sensitivity. Without the need for blood samples, the 40-min dynamic PET scan may improve diagnostic accuracy with a little longer scan duration than static PET. The scan durations were not matched when comparing static and dynamic PET. However, extending the SUV scan duration did not substantially improve the discrimination between benign and malignant nodules. Static scan period at later time points, when tracer uptake approaches to equilibrium status, may provide superior SUV results. While this study focuses on FDG PET, the feasibility of simplified dynamic protocols should be examined for other lung cancer tracers, such as FMISO and FLT.

The detection capability, quantitative parameters and classification capability results in our study indicated that 10% dose might be the low dose limit for dynamic PET with Patlak graphical analysis. The specificity of K_i with proper t^* and scan duration at 10% dose level is higher than that of SUV at full dose level. In general, 10% of the standard dose, which is about 1 mCi FDG injection, might be a suitable choice for low-dose dynamic PET scan of similar nodule populations to our simulation, assuming longer scan durations are feasible. With 10% injection dose, we could reduce radiation dose of PET to about 0.6 mSv, leading to a combined radiation dose of low-dose PET and low-dose CT (around 0.5 mSv) to ~ 1 mSv, with sensitivity and specificity both higher than 90%. Concrete analysis of an optimal injected dose, which depends on the makeup of clinical populations and involves tradeoffs between radiation-induced cancer risks and the needs for high accuracy detection of malignant nodules, is suggested under specific circumstances. It's not within the purview of this paper to make any quantitative risk/reward assessment of the tradeoffs.

For low-dose dynamic PET imaging with simplified protocols, additional improvement of imaging methods requires further investigation, such as noise reduction, motion correction and direct parametric reconstruction. Smoothing can be used for low-dose data, which may decrease the noise level and help to obtain results closer to 100% counts (Yu *et al.*, 2016a). The amount of body motion, which induces image blurring and underestimation of tracer uptake, in a short scan duration can be less as compared to a longer scan. Regardless of the scan durations, body motion correction method might be needed to improve the quality of parametric imaging (Lu *et al.*, 2017). In addition, improved scanner technology, such as higher TOF resolution, would further improve the signal-to-noise ratio in the reconstructed

images (Vandenberghe *et al.*, 2016), allowing even shorter dynamic scan duration or lower injection dose.

In this study, we performed a virtual clinical trial based on patient data to evaluate the classification capability with ROC analysis. The potential difference in the definition of ROIs on the low-dose PET images is expected to be minimal. For LDCT screening-detected nodules with known location and size, similar ROIs can be drawn on the various low-dose PET images with the guidance of CT images in the fused PET/CT images. A noise model generated from weighted leastsquares regression was applied to simulate TACs. The noise model included variability in PET data acquisition and image reconstruction. Comparing to generating TACs from reconstructed images with simulated sinograms (Wangerin *et al.*, 2017), our noise model directly estimated variability of TACs. Mean noise levels among all the down-sampled replicates were calculated at various count levels. To extend the population of nodules, we added variability to the parameter K_1 that is related somewhat to blood flow. Since the estimates of k_2 and k_3 are correlated, their biological variability were not introduced in the population. As previous studies showed that the variability of K_1 for one nodule in repeated scans is about 9% (Weber *et al.*, 1999; Wangerin *et al.*, 2017), we do not expect the virtual nodules to change category from benign to malignant or vice versa after introducing the 9% CV to K_1 . Therefore, our method of generating virtual nodules to simulate a large patient population is reasonable.

However, due to the limited number of patients, the extended nodule population was not sufficient and showed bimodal distributions in *figure 7*. The variability in populations, which may be due to presence of infection and inflammation, affects the diagnostic performance of FDG PET imaging. Limited number of nodules, especially two for malignant nodules, may lead to narrow SUV and K_i distributions. The CV of malignant K_i distributions, which was ~ 0.2 with 100% dose in the simulated clinical trial, was smaller than those (~ 0.7) in other larger populations (Gupta *et al.*, 1998; Laffon *et al.*, 2018). The CV difference between this study and other studies can also be caused by the fact that the screening-detected malignant nodules in our study are small-size subcm tumors in its early stage, which is different from the populations with larger size lesions in Gupta *et al.*, 1998 and Laffon *et al.*, 2018. With a larger scale clinical trial in the future, the parameter distributions and ROC analysis can be more realistic. Additional patient recruitment is ongoing through a recently funded multi-year project to further investigate the role of low-dose and dynamic PET in lung cancer management.

Our work has some limitations. First, respiratory motion correction was not performed in this work, which would affect the original SUV and K_i values derived from patient studies. While most existing motion correction methods are only applicable to static PET, recent developments of motion correction methods applicable to dynamic PET might be needed in further studies (Yu *et al.*, 2016b). Another issue is that the generation of 10% data through discarding list-mode data might not be identical to the real 10% data. Our under-sampling methods assumed that the ratio between the true and random events is independent of count level; this is a worst-case situation since the generated low count data have higher random rates (Schaefferkoetter *et al.*, 2017). Thus, we expect the performance of our low-dose imaging methods optimized with down-sampled 10%-dose data to be slightly better for the

actual low-dose studies. Moreover, a larger scale clinical trial is needed to simulate more realistic distributions, address confounding factors due to infection and inflammation, and further investigate the classification capability in the future.

5. Conclusion

We performed a virtual clinical trial and ROC analysis based on patient data to investigate the diagnosis performance of dynamic FDG PET as a function of injected dose in the application of discriminating indeterminate screening-detected lung nodules. The feasibility of simplified protocols with shortened scan duration and PBIF was demonstrated for dynamic FDG PET analysis. We found that 10%-dose dynamic PET analysis could provide superior discrimination between benign and malignant nodules than conventional 100%-dose static PET analysis for many dynamic scan periods. Concrete analysis of an optimal injected dose, which may be around 10% dose, was suggested for the population with screening-detected small nodules presented in this study. Replacing follow-up LDCT with clinically feasible low-dose dynamic PET/CT may reduce unnecessary invasive procedures and provide more accurate diagnosis for the screening-detected lung nodules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Illustration of dynamic image analysis for each low-dose replicate. TACs and IDIFs were generated from dynamic reconstructed images. ROI-based analysis includes nonlinear regression of 2Ti model and Patlak analysis. Voxel-based analysis was accomplished by Patlak analysis.

Figure 2.

Process of generating virtual patient data based on real patient scans. Biological variability was added to K_1 to extend the population. Based on the simulated K_1 and noise level estimated from patient data, TACs and input functions were simulated for various count levels. SUV was computed from static analysis with acquisition start time variability consistent with clinical practice. K_i was generated from dynamic Patlak analysis with simplified protocols.

Figure 3. Illustration of classification capability estimation for SUV and K_i distributions among all the simulated datasets of a given count level using ROC analysis.

Figure 4.

CT, SUV and K_i images for two sample patients. The first row shows a benign nodule while the second row shows a malignant nodule.

Figure 5. SUV and K_i images at various count levels for a sample patient with an 8-mm lung nodule. Left: SUV using 60–80 min post-injection data. Right: K_i images generated from voxel-based Patlak analysis using IDIF with t^* of 20 min.

Figure 6.

Ratios of parameters at various count levels compared to those with 100% counts: (a) nodule SUV; (b) nodule K_i derived from nonlinear regression with the 2Ti compartmental model; (c) nodule K_i derived from Patlak analysis (20–90 min); (d) tissue noise scale factors in equation (2). Mean and standard deviation from the low-count replicates are shown.

Figure 7.

Distributions generated from the virtual clinical trial at various count levels. SUV derived from ~ 60–80 min (with acquisition variability) data (left), K_i derived from 20–90 min Patlak analysis using PBIF (right) are compared.

Figure 8.

SUV (first row) and K_i (second row) images of sample nodules. A benign nodule selected from Group 1 (first column), benign nodules selected from Group 2 (second column), and a malignant nodule (third column) are compared.

Figure 9.

ROC AUC values of K_i with different scan durations as a function of fit start time, t^* , compared with the AUC values of SUV (~ 60–80 min post injection, red lines) at various count levels. K_i values were also generated by Patlak analysis using data from t^* up to 90 min postinjection (black lines).

Figure 10.

AUC values of SUV and K_i with several sample protocols at various count levels.

Table 1.

Parameters of benign and malignant nodules generated from 100%-dose PET analysis (mean $\pm$ standard deviation, range)

Parameters	Benign nodules Group 1 (n=5)	Benign nodules Group 2 (n=3)	Malignant nodules(n=2)
SUV (g/mL)	1.08 $\pm$ 0.28 (0.68–1.45)	2.37 $\pm$ 0.10 (2.29–2.48)	2.56 $\pm$ 0.13 (2.47, 2.65)
K_1 (mL/min/cm ³)	0.038 $\pm$ 0.017 (0.021–0.063)	0.059 $\pm$ 0.023 (0.040–0.084)	0.051 $\pm$ 0.052 (0.014, 0.088)
k_2 (/min)	0.572 $\pm$ 0.327 (0.202–1.059)	0.315 $\pm$ 0.146 (0.158–0.445)	0.470 $\pm$ 0.130 (0.378, 0.562)
k_3 (/min)	0.045 $\pm$ 0.036 (0.014–0.086)	0.029 $\pm$ 0.018 (0.018–0.050)	0.409 $\pm$ 0.509 (0.769, 0.049)
V_B (mL/cm ³)	0.063 $\pm$ 0.035 (0.009–0.090)	0.195 $\pm$ 0.062 (0.155–0.267)	0.192 $\pm$ 0.009 (0.186–0.198)
K_1 of 2Ti model (μ L/min/cm ³)	2.3 $\pm$ 0.7 (1.6–3.3)	4.8 $\pm$ 0.7 (4.1–5.4)	8.3 $\pm$ 1.8 (9.6, 7.0)
K_1 of Patlak analysis (μ L/min/cm ³ , $t^* = 20$ min)	2.5 $\pm$ 0.9 (1.7–3.8)	4.9 $\pm$ 0.9 (4.1–5.9)	8.9 $\pm$ 2.6 (10.7, 7.0)

Table 2.

The integral values of IDIF and PBIF for different patients (mean $\pm$ standard deviation)

Patient index	IDIF integral (kBq·min/mL)	PBIF integral (kBq·min/mL)	Relative differences
1	1556.9	1561.8 $\pm$ 3.9	0.3% $\pm$ 0.3%
2	890.1	887.2 $\pm$ 15.0	-0.3% $\pm$ 1.7%
3	980.7	1014.8 $\pm$ 27.0	3.5% $\pm$ 2.8%
4	1636.7	1694.4 $\pm$ 32.8	3.5% $\pm$ 2.0%
5	1206.9	1219.6 $\pm$ 28.1	1.1% $\pm$ 2.3%
6	1084.4	1125.9 $\pm$ 24.9	3.8% $\pm$ 2.3%

Table 3.

Sensitivities and specificities of SUV (g/mL) and K_i ($\mu\text{L}/\text{min}/\text{cm}^3$) with 100% and 10% counts. The cutoff threshold was chosen to give about 94% sensitivity.

Protocols	100% count			10% count		
	Cut-off	Sensitivity	Specificity	Cut-off	Sensitivity	Specificity
SUV (~ 60–80 min)	2.14	94%	68%	2.06	94%	69%
K_i (20–90min IDIF)	6.2	94%	98%	5.7	94%	90%
K_i (20–60min IDIF)	5.6	94%	92%	4.4	94%	77%
K_i (20–60min PBI)	6.0	94%	93%	4.9	94%	79%