Editorial

Extremely low dose ^{18}F-FDG PET imaging and its potential use for lung cancer screening

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Comment on: Schaefferkoetter JD, Yan J, Soderlund TA, *et al*. Quantitative Accuracy and Lesion Detectability of Low-Dose FDG-PET for Lung Cancer Screening. J Nucl Med 2016. [Epub ahead of print].

Submitted Dec 04, 2016. Accepted for publication Dec 23, 2016.
doi: 10.21037/tcr.2017.01.22
View this article at: http://dx.doi.org/10.21037/tcr.2017.01.22

Lung cancer is the most common cause of death among both men and women from cancer worldwide. Overall, less than 20% of patients with lung cancer are still alive 5 years after diagnosis (1) although there are significant improvements of treatment. The low survival rate could most likely be due to the low early detection. Most lung cancers are first diagnosed based on symptoms and regular chest X-rays. Symptoms of lung cancer are not very specific and generally reflect damage to the lungs' ability to function normally. In addition, chest X-rays are not reliable enough to find lung tumors in their earliest stages due to their low sensitivity and specificity. Recently, the National Lung Screening Trial (NLST) showed that low-dose computed tomography (LDCT) could reduce modality rate due to lung cancer by 20% compared to chest X-rays screening for the current or former smokers with age of 55 to 74 (2-4). However, due to its limited specificity, LDCT screening also detected more than 18% of all lung cancers which were indolent and led to overdiagnosis in screening for lung cancer (5). Moreover, although LDCT could reduce lung cancer mortality for patients at the high risk in the NLST study, however, 24.2% of the patients were tested positive, but 96.4% of them were false positives (4).

In thoracic oncology, ^{18}F-FDG PET currently plays a major role in clinical diagnosis, staging, prognosis and assessment of response to treatment (6). Combination of glucose metabolic information from PET with CT has been shown to improve accuracy for detecting lung cancer (7). Moreover, PET/CT demonstrated better performance in classifying solitary pulmonary nodules as benign or malignant than either PET or CT alone (8). The synergetic effect of PET and CT could potentially improve the accuracy of screening for lung cancer (9). Recent work has focused on potential lung cancer screening with ^{18}F-FDG PET/CT (9,10), where an overall sensitivity of 88% for diagnosing malignancy and sensitivity of 100% were reported, suggesting PET/CT as an alternative screening method. However, the effective dose corresponding to typical administration of 10 mCi ^{18}F-FDG for a 70 kg adult is about 7 mSv, which is much higher than that at (1.5 mSv) of low dose CT protocol used in the NLST (11). Thus, it is desirable to lower FDG dose for lung cancer screening without sacrificing the diagnostic accuracy. The reconstructed PET image quality is greatly dependent on injected dose or the number of acquired counts. In two previous studies (12,13), methods were developed with a data set of ^{18}F-FDG PET images of tuberculosis (TB) patients acquired on a PET/MR scanner to evaluate low-dose PET images at various true count and noise levels. Count statistics as low as 5×10^6 counts could achieve a fairly high detectability of lung lesions and image quality in terms of liver signal-to-noise ratio, lung lesion contrast-to-noise ratio and ensemble noise. In the article accepted by *The Journal of Nuclear Medicine*, Schaefferkoetter *et al*. (14) utilized the platform established with TB data to quantify the detectability of malignant lung nodules with the

data acquired on ^{18}F-FDG PET/CT. Twenty patients with biopsy-proven primary lung cancer or patients with suspicious radiological abnormalities planned for definitive lung surgery were enrolled. The reduced doses or count were simulated by randomly discarding events in each list mode fractions of original acquired net true counts according to nine predefine true count levels (prompts minus delayed): 0.25×10^6, 0.5×10^6, 1×10^6, 2×10^6, 5×10^6, 7.5×10^6, 10×10^6, 15×10^6 and 20×10^6. PET images were produced with time of flight (TOF) and point spread function (PSF) OSEM algorithm (2 iterations, 21 subsets and 3 mm Gaussian smoothing). Numerical observer models were developed to detect lesions with volume less than 3 cm^3 against 2 board certified radiologists and 1 nuclear medicine physician. Quantitative accuracy in terms of lesion contrast, lesion activity and SNR could be preserved with count statistics less than 5 million, whereas lesion detectability required around 10 million trues. The mean radiation exposure to patients from PET imaging in that work was less than 0.4 mSv, which corresponds to radiation exposure with 0.6 mCi ^{18}F-FDG and is much less than 1.5 mSv of LDCT used in the NLST (11). The potential risks associated with such radiation are negligible for the population at high risk and benefit due to the improved accuracy from PET imaging are greater than the radiation risks.

Further investigations are needed to introduce ^{18}F-FDG PET/CT for lung cancer screening. First, a larger number of lesions with size less than 1 cm are warranted. Only 12 lesions were included in the current work. It may be inadequate to train observer models. Secondly, volume of interest (VOI) was obtained by a simple thresholding method on the full statistics images and the resulting VOIs were copied to the images at the lower count levels. Accurate delineation of lesions is very challenging due to limited spatial resolution and high noise in PET images (15), and this will be more challenging when there is no high-count image in low dose cancer screenings. Thirdly, one challenge of PET quantification for lung cancer imaging is respiratory motion, which leads to blurring of lesions and can cause an underestimation of standardized uptake values (SUV) and overestimation of lesion volume. Respiratory motion could be mitigated by breath-hold methods (16), post-processing methods (17) and PET raw data-driven respiratory motion correction (18). Fourthly, the optimal reconstruction settings including post-reconstruction smoothing filters vary with quantitation tasks (19,20). In the work, OSEM reconstruction with PSF and TOF using default settings for iteration number, subset number and post-reconstruction smoothing filter was employed, which may not be optimal for different count level. Fifthly, attenuation correction (AC) is a prerequisite for PET imaging and quantification. X-ray-based AC is now the most commonly used method and its accuracy depends on voltage and tube current. The effect of LDCT based AC on quantitative PET lung imaging should be evaluated in the future. Sixthly, the different count statistics or injected doses were produced by simulated by randomly discarding events in the PET list mode data stream. However, due to the biology washout effect, this kind of simulation may not be the same as reducing the FDG dose at the beginning. The effect of reducing injected dose on lung lesion quantification and detectability is worthwhile for prospective investigation. Finally, the cost and benefit of low dose ^{18}F-FDG PET/CT for lung cancer screening should be justified. We believe study such as the one reviewed here represent a promising step in the right direction.

Acknowledgments

Funding: This work was supported by the National Natural Science Foundation of China 81671775.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Long Chen (Department of PET-CT center at the Yunnan Tumor Hospital, The Third Affiliated Hospital of Kunming Medical University, Kunming, China; Department of Biochemistry and Molecular Biology of Kunming Medical University, Kunming, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.01.22). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Yan J, Wu Z, Li S. Extremely low dose ^{18}F-FDG PET imaging and its potential use for lung cancer screening. Transl Cancer Res 2017;6(Suppl 1):S99-S101. doi: 10.21037/tcr.2017.01.22