HHS Public Access

Author manuscript

Eur J Nucl Med Mol Imaging. Author manuscript; available in PMC 2022 December 01.

Published in final edited form as:

Eur J Nucl Med Mol Imaging. 2021 December ; 48(13): 4138–4141. doi:10.1007/s00259-021-05214-5.

Dynamic PET imaging with ultra-low-activity of ^{18}F-FDG: unleashing the potential of total-body PET

Xiaoli Lan[1,2], **Kevin Fan**[3], **Ke Li**[3], **Weibo Cai**[3]

[1]Department of Nuclear Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[2]Hubei Key Laboratory of Molecular Imaging, Wuhan, China

[3]Departments of Radiology and Medical Physics, University of Wisconsin–Madison, 1111 Highland Avenue, Madison, WI, USA

Total-body positron emission tomography (PET) has been a true revolution of modern biomedical instrumentation following its initiation about 5 years ago, when Simon Cherry and Ramsey Badawi from the University of California, Davis received a $15.5 million, 5-year NIH Grant to lead the consortium in September 2015 [1, 2]. By May 2018, the fabrication of the first total-body PET scanner was completed by the consortium with aid from several industrial collaborators. The scanner has a 194 cm axial field-of-view for PET imaging provided by > 500,000 detector elements, as well as an 80-row, 160-slice CT scanner for anatomical imaging and PET attenuation correction [3, 4], and was later called the uEXPLORER PET/CT scanner (United Imaging Healthcare Co., Ltd.). This scanner has a coincidence time window of 4.5–6.9 ns (ring difference dependent), an energy resolution of 11.7% @ 511 keV, and a time resolution of 430 ps. In terms of sensitivity based on the NEMA NU-2 phantom, it was ~ 190 kcps/MBq (70 cm length) and ~ 150 kcps/MBq (200 cm length) respectively [5].

In November 2018, the first human images from the uEXPLORER scanner were presented at a Total-body PET workshop, which were acquired at the Department of Nuclear Medicine, Zhongshan Hospital, Fudan University (Shanghai, China). A 61-year-old male healthy volunteer was injected with 7.8 mCi of ^{18}F-FDG, with just 1 min of data acquisition providing good quality PET images [4]. At the beginning of the EXPLORER consortium, it was claimed that with the total-body PET scanner, one could: image better (e.g., reconstruct at higher resolution and detect smaller lesions), image faster (e.g., perform total-body PET in 15–30 s and reduce respiratory motion), image longer (e.g., image for 5 more half-lives due to the 40-fold increase in dynamic range), and image gently (e.g., use 40-fold reduction of radioactivity dose which will enable PET scans in the young population, as well as more repeated scans in the adult population) [1].

Xiaoli Lan, xiaoli_lan@hust.edu.cn; LXL730724@hotmail.com; Weibo Cai, wcai@uwhealth.org.

Conflict of interest All authors declare that they have no conflicts of interest.

Studies with human participants or animals This article does not contain any studies with human participants or animals performed by any of the authors.

These claims were successfully demonstrated through a series of well-designed studies and publications over the last 2 years [4, 6-11]. Indeed, this state-of-the-art scanner possesses many advantages over previously developed PET/CT scanners. In this issue of *European Journal of Nuclear Medicine and Molecular Imaging*, Dr. Shi, Dr. Gu, and colleagues reported that total-body dynamic PET imaging with ultra-low-activity (0.37 MBq/kg) conferred equal performance to full-activity (3.7 MBq/kg) PET imaging when investigating the kinetic metrics of ^{18}F-FDG in 20 human subjects [12].

When analyzing the feasibility of ultra-low-activity total-body PET dynamic imaging for mathematical quantification of the kinetic parameters of ^{18}F-FDG, 5 s per frame were used for the initial 3 min after ^{18}F-FDG injection, and 3 min per frame were used for the remainder of the scan. In this well-designed and well-executed study, findings revealed that (1) No significant difference in rate constants (k_1, k_2, k_3) in any organ was found between the full-activity and ultra-low-activity groups. (2) All of the fitted models showed excellent goodness-of-fit in full-activity and ultra-low-activity groups, with the full-activity group models exhibiting smaller Akaike Information Criterion (AIC) and Schwarz Criterion (SC), which was expected. The only statistically significant differences were found in the brain. (3) Clear PET images of comparable quality were acquired for the ultra-low-activity group from 12 min onward after ^{18}F-FDG injection. (4) PET data from the full-activity group generated significantly larger prompt counts than the ultra-low-activity group, including true, scatter, random, effective (true + scatter), and noise equal count (NEC), which were all expected. However, the percentage of effective counts in the full-activity group was significantly smaller than the ultra-low-activity group (~ 36% vs. ~ 60%, $P < 0.001$), which was attributed to higher percentage of random fraction in the full-activity group.

With comparable performance in image quality and kinetic analysis, several major advantages of total-body uEXPLORER scanner with ultra-low-activity of ^{18}F-FDG are provided. One benefit relates to smaller median effective radiation dose in the ultra-low-activity group compared to the full-activity group (2.817 vs. 7.296 mSv, $P < 0.001$), which was largely due to the reduction of ^{18}F-FDG-imparted dose from 4.886 mSv (range of 3.445–5.153) in the full-activity group to 0.419 mSv (range of 0.333–0.582) in the ultra-low-activity group ($P < 0.001$). Importantly, the effective radiation dose of the ultra-low-activity group was mainly comprised of a CT dose of ~ 2.4 mSv, which is more than 5 times the effective radiation dose of ^{18}F-FDG. In addition, the file size of the raw PET data is ~ 10 times smaller for the ultra-low-activity group (~70 GB for the 75-min dynamic PET scan) when compared to the full-activity group (~720 GB). The smaller size of raw PET data not only required much less storage space, but also enabled faster data processing/reconstruction/transport. Even though data storage space is usually not an issue in the modern era, leaner raw data are still highly desirable in the routine clinical workflow to ensure faster image reconstruction and analysis. Total-body PET imaging with ultra-low-activity of ^{18}F-FDG is clearly highly advantageous in this regard, especially in major hospitals with a large number of patients scheduled every day.

In the work by Liu et al., a low-dose whole-body CT scan was performed before ^{18}F-FDG PET scan for each subject [12]. This CT scan was used for attenuation coefficient (AC) instead of disease diagnosis, with its effective radiation dose (~ 2.4 mSv) being

significantly lower than a typical diagnostic body CT exam and the CT component of a typical modern PET/CT exam (~ 5–10 mSv) [13-15]. With the constant advancements of CT tube and detector technologies [16], patient-specific scan technologies, and artificial intelligence (AI)-based CT dose reduction technologies (e.g., TrueFidelity Deep Learning Image Reconstruction from GE Healthcare [17, 18], Advanced Intelligent Clear-IQ Engine from Canon Medical Systems USA Inc. [19-21], among others), there is considerable promise for the CT component of whole-body PET/CT exam to routinely achieve sub-mSv effective doses in the future, which means the entire whole-body PET/CT exam with ultra-low-activity of ^{18}F-FDG can be accomplished under 2 mSv. This will provide unprecedented possibilities for a variety of clinical scenarios such as longitudinal scans of (cancer) patients when monitoring the therapeutic response [22, 23], as well as routine (repeated) scans in pediatric patients [24].

A few aspects of the uEXPLORER PET/CT scanner may deserve to be further investigated in the future. First, dynamic PET scans typically require larger injection doses of radioactivity to ensure sufficient signal-to-noise ratio for accurate data analysis. For most clinical management of oncologic patients, static PET scans are performed which can tolerate even lower radioactivity than dynamic PET scans. In future studies, even lower ^{18}F-FDG dose could be injected for static PET scans, fulfilling the original claim of 40 times lower dose/higher sensitivity. Second, such ultra-low-activity injection could provide unprecedented insight for first-in-human studies of novel tracers by enabling non-invasive whole-body pharmacokinetic analysis in all tissue. This is especially important for ^{11}C- or ^{18}F-based tracers that require elaborate and lengthy synthesis. The low radiochemical yield will not be a limiting factor with the uEXPLORER PET/CT scanner, and we look forward to future studies of novel tracers in metastatic cancer setting. Third, aside from the pharmacokinetic studies shown here, the differences in ^{18}F-FDG avidity within the tumor may also be analyzed to investigate tumor heterogeneity. In a recent proof-of-principle case study, 60-min dynamic total-body PET/CT scans of cancer patients were carried out [7]. It was found that the time-activity curves (TACs) extracted from regions-of-interest in different areas of the tumor mass indicated high heterogeneity: although tracer (i.e., ^{18}F-FDG) delivery was likely the same across the tumor mass, the ^{18}F-FDG uptake rate in different areas of the tumor was quite different. Fourth, with the exceptional sensitivity and temporal resolution, dynamic whole-body PET scans can also enable radiotracer angiography, which may become a one-stop shop for a wealth of information and eliminate unnecessary CT or MR angiography procedures in various clinical settings [7]. Fifth, such ultra-low-activity dynamic and static PET/CT scans will require validation in large cancer patient cohorts, similar to a recent study reported by the same group which used half-dose (1.85 MBq/kg) of ^{18}F-FDG, and was able to get better quality PET/CT images than that of conventional PET/CT with full-activity ^{18}F-FDG in lung cancer patients [8]. Lastly, PET scans at later time points may offer important information, such as differentiating cancer from inflammation based on dual-time-point ^{18}F-FDG PET scans. In addition, faster PET/CT scans can significantly shorten the acquisition time without compromising lesion detectability and image quality. For example, it was found that acceptable subjective PET image quality could be achieved with 60- and 30-s scans after full-activity (4.4 MBq/kg) ^{18}F-FDG injection [11]. For future systematic and routine studies in these areas, the scanner

performance will not be the limiting factor, logistics will be the major challenge especially in medical centers with a high daily clinical workload.

Both the clinical and preclinical total-body PET scanners hold tremendous potential for various biomedical applications, and the scientific community is looking forward to what can be done in the immediate future to unleash their full potential. Along the way of building the clinical total-body PET/CT scanner, the EXPLORER consortium also built a prototype PET scanner for high sensitivity and total-body imaging of non-human primates, called the mini-EXPLORER [25]. Recently, Berg et al. reported PET imaging of rhesus monkeys with the primate mini-EXPLORER scanner [26]. The authors compared four different tracers, all ^{89}Zr-labeled antibodies, and were able to acquire high quality PET images for up to 30 days after tracer injection (~ 10 decay half-lives of ^{89}Zr). Such long-term serial PET imaging could help answer many biological questions about the in vivo behavior of (radiolabeled) antibodies, with the appropriate biological experiments to supplement the PET scans to validate the biological meaning/relevance of the long-term PET imaging data [27], since the radioactivity at 30 days post-injection might be largely dissociated from the antibody, especially with a residualizing metal such as ^{89}Zr.

Currently, total-body PET/CT scanners are very expensive and only available at a few major medical centers. Total-body PET is still in its early days, which is similar to the 1970s when PET scanners were initially developed [28, 29]. With continued development and optimization of the scanner, as well as cost reduction, we believe total-body PET/CT scanners will become widely available in the future, just like PET/CT scanners have replaced PET scanners [30, 31]. Now that the proof-of-principle studies have been carried out, more systematic and sophisticated studies will be needed in the future to fully unleash the potential of total-body PET/CT scanner. Without any doubt, total-body PET/CT scanner will be an indispensable tool for humankind’s ultimate victory over cancer, as well as catalyzing more preclinical/clinical applications and disciplines (e.g., pediatric disorders, peripheral vascular diseases, tracking of transplanted cells) [32-35].

Acknowledgments

Funding The authors are grateful for financial support from the National Natural Science Foundation of China (Nos. 81630049 and 82030052), the University of Wisconsin–Madison, and the National Institutes of Health (P30CA014520).

References

1. Cherry SR, Badawi RD, Karp JS, Moses WW, Price P, Jones T. Total-body imaging: transforming the role of positron emission tomography. Sci Transl Med. 2017;9. 10.1126/scitranslmed.aaf6169.
2. Cherry SR, Jones T, Karp JS, Qi J, Moses WW, Badawi RD. Total-Body PET: Maximizing sensitivity to create new opportunities for clinical research and patient care. J Nucl Med. 2018;59:3–12. 10.2967/jnumed.116.184028. [PubMed: 28935835]
3. Zhang X, Zhou J, Cherry SR, Badawi RD, Qi J. Quantitative image reconstruction for total-body PET imaging using the 2-meter long EXPLORER scanner. Phys Med Biol. 2017;62:2465–85. 10.1088/1361-6560/aa5e46. [PubMed: 28240215]
4. Badawi RD, Shi H, Hu P, Chen S, Xu T, Price PM, et al. First human imaging studies with the EXPLORER Total-body PET scanner. J Nucl Med. 2019;60:299–303. 10.2967/jnumed.119.226498. [PubMed: 30733314]

5. Spencer BA, Berg E, Schmall JP, Omidvari N, Leung EK, Abdelhafez YG, et al. Performance evaluation of the uEXPLORER Total-body PET/CT scanner based on NEMA NU 2–2018 with additional tests to characterize long axial field-of-view PET scanners. J Nucl Med. 2020. 10.2967/jnumed.120.250597.
6. Feng T, Zhao Y, Shi H, Zhang X, Wang G, Badawi RD, et al. Total-Body Quantitative Parametric Imaging of Early Kinetics of FDG. J Nucl Med. 2020. 10.2967/jnumed.119.238113.
7. Sui X, Liu G, Hu P, Chen S, Yu H, Wang Y, et al. Total-body PET/computed tomography highlights in clinical practice: experiences from Zhongshan Hospital, Fudan University. PET Clin. 2021;16:9–14. 10.1016/j.cpet.2020.09.007. [PubMed: 33218606]
8. Tan H, Sui X, Yin H, Yu H, Gu Y, Chen S, et al. Total-body PET/CT using half-dose FDG and compared with conventional PET/CT using full-dose FDG in lung cancer. Eur J Nucl Med Mol Imaging. 2020. 10.1007/s00259-020-05091-4.
9. Zhang X, Cherry SR, Xie Z, Shi H, Badawi RD, Qi J. Subsecond total-body imaging using ultrasensitive positron emission tomography. Proc Natl Acad Sci U S A. 2020;117:2265–7. 10.1073/pnas.1917379117. [PubMed: 31964808]
10. Zhang X, Xie Z, Berg E, Judenhofer MS, Liu W, Xu T, et al. Total-body dynamic reconstruction and parametric imaging on the uEXPLORER. J Nucl Med. 2020;61:285–91. 10.2967/jnumed.119.230565. [PubMed: 31302637]
11. Zhang YQ, Hu PC, Wu RZ, Gu YS, Chen SG, Yu HJ, et al. The image quality, lesion detectability, and acquisition time of (18)F-FDG total-body PET/CT in oncological patients. Eur J Nucl Med Mol Imaging. 2020;47:2507–15. 10.1007/s00259-020-04823-w. [PubMed: 32424483]
12. Liu G, Hu P, Yu H, Tan H, Zhang X, Yin H, et al. Ultra-low-activity total body dynamic PET imaging allows equal performance to full-activity PET imaging for investigating kinetic metrics of ^{18}F-FDG in healthy volunteers. Eur J Nucl Med Mol Imaging. 2021. 10.1007/s00259-020-05091-4.
13. Martí-Climent JM, Prieto E, Morán V, Sancho L, Rodríguez-Fraile M, Arbizu J, et al. Effective dose estimation for oncological and neurological PET/CT procedures. EJNMMI Res. 2017;7:37. 10.1186/s13550-017-0272-5. [PubMed: 28439843]
14. Hemke R, Yang K, Husseini J, Bredella MA, Simeone FJ. Organ dose and total effective dose of whole-body CT in multiple myeloma patients. Skelet Radiol. 2020;49:549–54. 10.1007/s00256-019-03292-z.
15. McCollough CH, Bushberg JT, Fletcher JG, Eckel LJ. Answers to common questions about the use and safety of CT scans. Mayo Clin Proc. 2015;90:1380–92. 10.1016/j.mayocp.2015.07.011. [PubMed: 26434964]
16. McCollough CH, Chen GH, Kalender W, Leng S, Samei E, Taguchi K, et al. Achieving routine submillisievert CT scanning: report from the summit on management of radiation dose in CT. Radiology. 2012;264:567–80. 10.1148/radiol.12112265. [PubMed: 22692035]
17. Greffier J, Hamard A, Pereira F, Barrau C, Pasquier H, Beregi JP, et al. Image quality and dose reduction opportunity of deep learning image reconstruction algorithm for CT: a phantom study. Eur Radiol. 2020;30:3951–9. 10.1007/s00330-020-06724-w. [PubMed: 32100091]
18. Park C, Choo KS, Jung Y, Jeong HS, Hwang JY, Yun MS. CT iterative vs deep learning reconstruction: comparison of noise and sharpness. Eur Radiol. 2020. 10.1007/s00330-020-07358-8.
19. Naganawa S, Nakamichi R, Ichikawa K, Kawamura M, Kawai H, Yoshida T, et al. MR imaging of endolymphatic hydrops: utility of iHYDROPS-Mi2 combined with deep learning reconstruction Denoising. Magn Reson Med Sci. 2020. 10.2463/mrms.mp.2020-0082.
20. Singh R, Digumarthy SR, Muse VV, Kambadakone AR, Blake MA, Tabari A, et al. Image quality and lesion detection on deep learning reconstruction and iterative reconstruction of Submillisievert chest and abdominal CT. AJR Am J Roentgenol. 2020;214:566–73. 10.2214/ajr.19.21809. [PubMed: 31967501]
21. Ueda T, Ohno Y, Yamamoto K, Iwase A, Fukuba T, Hanamatsu S, et al. Compressed sensing and deep learning reconstruction for women's pelvic MRI denoising: utility for improving image quality and examination time in routine clinical practice. Eur J Radiol. 2020;134:109430. 10.1016/j.ejrad.2020.109430. [PubMed: 33276249]

22. Paul DM, Ghiuzeli CM, Rini J, Palestro CJ, Fung EK, Ghali M, et al. A pilot study treatment of malignant tumors using low-dose (18)F-fluorodeoxyglucose ((18)F-FDG). Am J Nucl Med Mol Imaging. 2020;10:334–41. [PubMed: 33329935]

23. Borra A, Morbelli S, Zwarthoed C, Bianchi A, Bergesio F, Chauvie S, et al. Dual-point FDG-PET/CT for treatment response assessment in Hodgkin lymphoma, when an FDG-avid lesion persists after treatment. Am J Nucl Med Mol Imaging. 2019;9:176–84. [PubMed: 31328023]

24. Masselli G, De Angelis C, Sollaku S, Casciani E, Gualdi G. PET/CT in pediatric oncology. Am J Nucl Med Mol Imaging. 2020;10: 83–94. [PubMed: 32419977]

25. Berg E, Zhang X, Bec J, Judenhofer MS, Patel B, Peng Q, et al. Development and evaluation of mini-EXPLORER: a long axial field-of-view PET scanner for nonhuman primate imaging. J Nucl Med. 2018;59:993–8. 10.2967/jnumed.117.200519. [PubMed: 29419483]

26. Berg E, Gill H, Marik J, Ogasawara A, Williams S, van Dongen G, et al. Total-body PET and highly stable chelators together enable meaningful ^{89}Zr-antibody-PET studies up to 30 days post-injection. J Nucl Med. 2020;61(3):453–60. 10.2967/jnumed.119.230961. [PubMed: 31562219]

27. Rosenkrans ZT, Cai W. Total-body PET imaging for up to 30 days after injection of (89)Zr-labeled antibodies. J Nucl Med. 2020;61: 451–2. 10.2967/jnumed.119.236166. [PubMed: 31806778]

28. Phelps ME, Hoffman EJ, Mullani NA, Ter-Pogossian MM. Application of annihilation coincidence detection to transaxial reconstruction tomography. J Nucl Med. 1975;16:210–24. [PubMed: 1113170]

29. Ter-Pogossian MM, Phelps ME, Hoffman EJ, Mullani NA. A positron-emission transaxial tomograph for nuclear imaging (PETT). Radiology. 1975;114:89–98. 10.1148/114.1.89. [PubMed: 1208874]

30. Beyer T, Townsend DW, Czernin J, Freudenberg LS. The future of hybrid imaging-part 2: PET/CT. Insights Imaging. 2011;2:225–34. 10.1007/s13244-011-0069-4. [PubMed: 23099865]

31. Townsend D, Beyer T, Czernin J. 20 years of PET/CT: a conversation with David Townsend and Thomas Beyer. J Nucl Med. 2020;61:1541–3. 10.2967/jnumed.120.257725. [PubMed: 33139396]

32. Kung BT, Seraj SM, Zadeh MZ, Rojulpote C, Kothekar E, Ayubcha C, et al. An update on the role of (18)F-FDG-PET/CT in major infectious and inflammatory diseases. Am J Nucl Med Mol Imaging. 2019;9:255–73. [PubMed: 31976156]

33. Brandão SCS, Ramos JOX, de Arruda GFA, Godoi E, Carreira L, Lopes RW, et al. Mapping COVID-19 functional sequelae: the perspective of nuclear medicine. Am J Nucl Med Mol Imaging. 2020;10:319–33. [PubMed: 33329934]

34. Wei W, Ehlerding EB, Lan X, Luo QY, Cai W. Molecular imaging of β-cells: diabetes and beyond. Adv Drug Deliv Rev. 2019;139: 16–31. 10.1016/j.addr.2018.06.022. [PubMed: 31378283]

35. Wei W, Rosenkrans ZT, Liu J, Huang G, Luo QY, Cai W. ImmunoPET: concept, design, and applications. Chem Rev. 2020;120:3787–851. 10.1021/acs.chemrev.9b00738. [PubMed: 32202104]