POINT/COUNTERPOINT

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Total-body PET is ready for prime time

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OVERVIEW

This is an exciting time for PET technology where we anticipate major developments in instrumentation that might lead to breakthoughs in clinical and research applications. Over the years, different design trends have emerged, with PET scanners now available with a broad spectrum of features, from those available commercially for clinical applications to others designed primarily in research laboratories specifically for very high-resolution research applications. The latter category includes organ-specific (brain, breast, prostate) and small-animal imaging systems. There is also a persistent upward adjustment and refinement in both hardware and software components for all of these scanners. Efforts to increase the sensitivity of PET scanners has been at the forefront of endeavors pursued by active researchers in the field. This has been historically achieved by using denser crystals and then moving to fully three-dimensional acquisition mode. Long axial field-of-view (AFOV), while considered in the past, was never a big hit commercially since it was always a means to overcome some other sensitivity compromise. Efforts from a number of research groups led to a new design concept, referred to as total-body (TB)-PET, that has been recently introduced. The technology offers many advantages and allows not significant reductions in the injected tracer dose or acquisition time, but also dynamic whole-body imaging capabilities. The cost of the system remains the major obstacle to wider clinical adoption, hence limiting access to this technology to very few academic centers. In this regard, while some think that TB-PET is a mature technology, ready for prime time, others think that we are still far away from this reality and that its time has not yet come. This is the topic addressed in this month's Point/Counterpoint debate.

Arguing for the proposition is Suleman Surti, PhD. Dr. Surti is a Research Associate Professor at the University of Pennsylvania in the Department of Radiology. Dr. Surti obtained his PhD in Physics at the University of Pennsylvania in 2000 and then continued as

a postdoctoral researcher in the Physics & Instrumentation Group within Radiology until 2003 prior to his faculty appointment. Dr. Surti's PET expertise spans development of detectors and electronics, their incorporation in optimized scanner geometries, evaluation of system performance and data/image correction techniques, and optimization of imaging protocols. He has been actively involved in the development of several systems at Penn ranging from small-animal PET through application specific PET (brain, breast, proton) to whole-body PET (non-time of flight (TOF), TOF, long axial field-of-view).

Arguing against the proposition is Alberto Del Guerra, M.S. Prof. Del Guerra obtained Masters in Physics (Laurea in Fisica) in March 1968 at the University of Pisa (Italy). He is an experimental physicist, who started as a researcher in accelerator physics, high energy physics but transitioned in

the late 1970s to medical physics. He has spent several years of his scientific career abroad (CERN, Daresbury Laboratory (UK), Lawrence Berkeley Laboratory-Berkeley (USA), and University of Washington, Seattle (USA)). He has published more than 400 articles/books/books chapters. He has held scientific and managerial responsibilities in many Italian, European and Worldwide scientific societies: AIFB, AIFM, EFOMP (President), EANM, ECR, IEEE NPSS. He has been General Chair of the 2004 IEEE NSS/MIC Conference in Rome (Italy), was elected as a NPSS ADCOM member representing NMISC (2011–2014), NPSS Distinguished Lecturer (2017-to date), Chair of the JOS NPSS Committee (2018–2019), Chair of the NPSS Fellow Evaluation Committee (2020-to date). He has been/is a regular Reviewer, Associate Editor and Editor-in-Chief for more than 10 scientific journals. He has been an assessor of medical physics/bioengineering projects for many Italian, European and extra European research institutions and for EU (FP6, FP7 and Horizon 2020). He has been one of the promoters of medical physics research in Italy. He has been a full professor of physics at the University of Napoli (1987–1991), Ferrara (1991–1998) and Pisa (1998–2014). He is now a retired Professor of Medical Physics at the University of Pisa.

FOR THE PROPOSITION: SULEMAN SURTI, PH.D

Opening Statement

TB-PET refers to long AFOV systems that can potentially transform PET research and patient care due to significant gains in sensitivity and ability to simultaneously measure dynamic uptake of radiotracers over a large axial coverage of the body.[1,2] Recent development of the two EXPLORER scanners at UC Davis[3] and Penn[4] has demonstrated their technical and practical feasibility. The acquired images provide rich information that is not easily attained with conventional systems, demonstrating the benefits of TB-PET imaging and underscoring the power and versatility of a longer AFOV for clinical and research applications.[5,6]

An evident question related to a wider adoption of TB-PET has to do with the increased cost of a 194 cm long uEXPLORER relative to a 20-25 cm long PET/CT that may not be fully justified financially. However, there may be an optimal length < 2 m for a TB-PET system depending on whether it is used clinically to improve diagnostic quality or increase patient throughput, or to broaden the scope of research applications. Peak sensitivity in a PET system is near maximal for a 70 cm AFOV,[7] while a longer AFOV provides a wider axial range over which this peak sensitivity is achieved. Hence, it is fair to consider two categories of TB-PET scanners: extended AFOV of ≤70 cm (EAFOV) that would have significantly increased sensitivity compared to current clinical scanners and some capability for multi-organ dynamic imaging, and long AFOV of >70 cm (LAFOV) that would be especially useful for studies requiring whole-body dynamic studies.

Clinically, improved sensitivity allows: (a) better detection of smaller or lower uptake lesions, (b) lower injected dose necessary for pediatric imaging, serial imaging, or screening, and (c) short scan times that benefit workflow, and pediatric imaging or enable breath-hold imaging in adults. For research applications, higher sensitivity allows: (a) higher temporal resolution for dynamic imaging, (b) improved quantitation for low-yield isotopes, and (c) delayed imaging at much later time points. Most of these benefits could be attained with EAFOV, while LAFOV provides extended benefits in terms of enabling simultaneous, dynamic imaging of multiple lesions/organs for biodistribution and disease characterization over the entire patient. Early studies from UC Davis and Penn have demonstrated the tremendous promise for achieving many of these goals.[5–8] Hence, there is a clear clinical and research role for EAFOV where at a minimum it will push the AFOV beyond the maximum 30 cm of current, clinical systems. LAFOV expands this role at increased cost but with plateauing benefits beyond 1 m, at which single bed position, eyes-to-thighs imaging at close to maximal sensitivity is feasible.[7] PennPET EXPLORER is located at one site and focused on research applications, but there are several sites in China (beyond UC Davis) that use uEXPLORER for routine studies that will help determine the clinical benefits of these devices. While an optimal AFOV is yet to be determined, these early systems, together with interest expressed by other manufacturers, will keep TB-PET at the forefront of future developments, likely leading to further improvements in performance and more cost-effective solutions.

AGAINST THE PROPOSITION: ALBERTO DEL GUERRA, M.S

Opening Statement

I do appreciate my esteemed opponent's statement and believe it is difficult to counteract his proposition. Yet, I will try to do it using two arguments: one technical and the other one clinical. Since being proposed more than 65 yr ago,[9] PET has struggled with efficient data acquisition. In this respect, a larger solid angle coverage is the most direct way to increase the acquired statistics. The idea of TB-PET was first introduced in the early '80s with the Spherical PET concept.[10] The suggestion was triggered by the possibility of making a full 3D PET reconstruction in the real space. This idea was not pursued because of obvious problems related to inserting a patient in a closed spherical detector. The advantage of increasing solid angle coverage and thereby reducing the dose to the patient was the stimulus for a second idea presented in the late 80s which utilized hybrid gas-detectors in the HIS-PET prototype.[11] The scanner consisted of a hexagonal prism with a module active area of 45 by 45 cm (axial length) to give a coincidence efficiency of 2.2% at the center of the FOV that was much higher than the efficiency of single ring PET scanners of that time. This improved reconstructed spatial resolution to 4 mm (FWHM). Then time of flight (TOF) entered the game, originally with BaF_2 and CSF scintillators

in the late '90s and later on with the advent of the SiPMs and faster scintillators (LSO/LYSO), now achieving a TOF resolution of about 300 ps on commercial PET devices.[12] Hence, the holy grail of whole-body PET is more demanding than just an extended axial PET[13]: it should support higher spatial resolution (better than 4 mm FWHM) and improved TOF capability, better than the actual state-of-the-art of 300 ps. At this time, increased axial length has been realized with promising results. However, improvement of the other two performance parameters is still ongoing. The second argument that I would like to raise is the clinical need of such a device, the advantages for oncological staging and follow-up being crystal clear. On the other hand, more and more clinicians feel the necessity of dedicated organ PET devices for the brain, the breast, and the prostate. Especially the brain has seen the onset of new big initiatives, for example, the Human Brain Project (https://www.humanbrainproject.eu/en/) and the NIH Brain Initiative. Many new dedicated PET scanners are under development for physiology and pathology study of the brain.[14] The issue of the cost should be raised: how many hospitals are prepared to buy a TB-PET instead of a cheaper and dedicated Brain PET[15] for brain oncology, brain degenerative diseases and mental disorders? Hence the second argument is the cost-effectiveness of the scanner; more generally, I am eager to see the results of an extended diagnostic and clinical comparative evaluation of the new device versus a clinical PET/CT, before putting the TB-PET on stage at a "prime time."

REBUTTAL: SULEMAN SURTI, PH.D

I appreciate my colleague's view-point and agree that increasing PET geometric coverage is not a new idea. However, past efforts were hampered for several reasons: nonideal scintillators with limited sensitivity and/or poor energy resolution that prevented fully-3D (septa-less) data acquisition, and large photomultiplier tubes with multiplexed detector designs limiting spatial resolution and increasing deadtime. Lu-based scintillators with SiPMs overcome these disadvantages while providing TOF capability. Hence, these TB-PET systems maximize sensitivity *without* compromising TOF resolution (as good as 240 ps) or spatial resolution (<4 mm).[3,4] The inter-ring gaps in the PennPET Explorer illustrate how system cost can be reduced, and other possible ways are to use sparse detector arrangements[16,17] or even BGO crystals.[18]

Commercial and research brain scanners have previously been developed providing higher spatial resolution (~2 mm) and sensitivity than clinical systems.[19] However, these brain scanners have never been successful commercially since most clinical brain studies are well-handled by clinical machines — studies are easy to schedule and not very demanding in terms of spatial resolution or sensitivity. Efforts have also focused on other organs with high performance systems being developed commercially and in research labs.[19] Adoption of these systems has been limited not due to the capabilities of these devices but more due to an incremental clinical impact.

This is where the transformational nature of TB-PET stands out: delayed imaging all the way out to ten half-lives, dynamic imaging with much higher temporal resolution, improved clinical outcomes through better image quality (reduced motion effects and higher spatial resolution), and the potential for improved understanding of disease by investigations of multi-organ temporal relationships. None of these capabilities are provided by existing clinical systems. Higher spatial resolution and TOF are both important for clinical imaging but it is the increased counts which enable achieving these advantages in the reconstructed image. Latest studies demonstrate the vast potential of TB-PET where the images are superlative relative to existing clinical systems[5,6] and point to the direction of future growth for molecular imaging.

REBUTTAL: ALBERTO DEL GUERRA, M.S

I could not agree more with one of the sentences of my opponent in his opening statement, that is, that the optimal length of the scanner (hence, the cost-effective solution) depends on the application either of clinical or research type. This brings me to a further consideration on the maturity of TB-PET. More than 20 yr ago, hybrid systems entered the field of medical imaging: first PET/CT[20] and later on PET/MR. While PET/CT found its immediate necessity and acceptance from the clinical community due to its cost-effective applications (anatomy and attenuation correction), PET/MR is still struggling to find a "killer application". The reason is due to the different environment they originated from: "*PET/CT design emerged from industry-academic collaboration and was a prototype for human clinical use that stimulated a commercial response*"[21]; PET/MR was invented for small-animal imaging to later become a PET insert for MR brain imaging and then a whole-body PET/MR system. Lower radiation dose and higher soft-tissue contrast are the main advantages of PET/MR with respect to PET/CT. Prostate cancer, head and cardiac imaging are receiving more and more attention by clinicians,[22] especially with the new emerging MR fingerprinting technique, that is, MRF, that will make it possible "*the development of a rapid one-scan, multiple-property approach to quantitative MR imaging*".[23] As a final argument, I would like to remind that moving from a clinically oriented new device to an FDA reimbursement application requires a lot of time, endurance and motivation.[24] I believe to have gently rebutted the enthusiasm of my opponent by showing that there are other available scanners on the floor complementary and/or alternative to TB-PET. All in all, I am convinced that the "prime time" will be reached by TB-PET in the future, but it is not the "right time" yet.

CONFLICTS OF INTEREST

Dr. Surti and Prof. Del Guerra have no relevant conflicts of interest.

REFERENCES

1. 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.
2. Cherry SR, Badawi RD, Karp JS, Moses WW, Price P, Jones T. Total-body imaging: transforming the role of positron emission tomogrsaphy. *Sci Transl Med*. 2017;9:eaaf6169.
3. Spencer BA, Schmall JP, Berg E, et al.Performance evaluation of the EXPLORER total-body PET/CT scanner based on NEMA NU-2 2018 standard with additional tests for extended geometry. IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC); 26 October - 2 November 2019, Manchester, UK.
4. Karp JS, Viswanath V, Geagan MJ, et al. PennPET explorer: design and preliminary performance of a whole-body imager. *J Nucl Med*. 2020;61:136–143.
5. Badawi RD, Shi H, Hu P, et al. First human imaging studies with the Explorer total-body PET scanner. *J Nucl Med*. 2019;60:299–303.
6. Pantel AR, Viswanath V, Daube-Witherspoon ME, et al. PennPET Explorer: human imaging on a whole-body imager. *J Nucl Med*. 2020;61:144–151.
7. Surti S, Pantel AR, Karp JS. Total body PET: why, How, What for? *IEEE Trans Rad Plasma Med Sci*. 2020;4:283–292.
8. 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 USA*. 2020;117:2265–2267.
9. Del Guerra A, Belcari N, Bisogni MG. Positron emission tomography: its 65 years. *La rivista del Nuovo Cimento*. 2016;39:155–223.
10. Cho ZH, Hong KS, Hilal SK. Spherical positron emission tomograph (S-PET) I - performance analysis. *Nucl Instr Meth A*. 1984;225:422–438.
11. Del Guerra A, Bandettini A, Conti M, et al. 3-D PET with MWPCs: preliminary tests with the HISPET prototype. *Nucl Instr Meth A*. 1988;269:425–429.
12. Conti M, Bendriem B. The new opportunities for high time resolution clinical TOF PET. *Clin Trans Imaging*. 2019;7:139–147.
13. Borasi G, Fioroni F, Del Guerra A, Lucignani G. PET systems: the value of added length. *Eur J Nucl Med Mol Imaging*. 2010;37:1629–1632.
14. Majewski S. The path to the ideal brain imager: the race is on, the role for TOF PET. *Nuovo Cimento 43C- Colloquia FATA*. 2019;2020:1–35.
15. Moliner L, Rodriguez-Alvarez MJ, Catret JV, Gonzalez A, Ilisie V, Benlloch JM. NEMA performance evaluation of CareMiBrain dedicated brain PET and comparison with the whole-body and dedicated brain PET systems. *Sci Rep*. 2019;9(1):15484.
16. Yamaya T, Yoshida E, Inadama N, et al. A multiplex “OpenPET” geometry to extend axial FOV without increasing the number of detectors. *IEEE Trans Nucl Sci*. 2009;56:2644–2650.
17. Zein SA, Karakatsanis NA, Issa M, Haj-Ali AA, Nehmeh SA. Physical performance of a long axial field-of-view PET scanner prototype with sparse rings configuration: a Monte Carlo simulation study. *Med Phys*. 2020;47:1949–1957.
18. Zhang Y, Wong W.Design study of a practical-entire-torso PET (PET-PET) with low-cost detector designs. IEEE Nuclear Science Symposium, Medical Imaging Conference and Room-Temperature Semiconductor Detector Workshop (NSS/MIC/RTSD); 29 Oct.-6 Nov. 2016.
19. González AJ, Sánchez F, Benlloch JM. Organ-dedicated molecular imaging systems. *IEEE Trans Rad Plasma Med Sci*. 2018;2:388–403.
20. Beyer T, Townsend D, Brun T, et al. A combined PET/CT scanner for clinical oncology. *J Nucl Med*. 2000;41:1369–1379.
21. Beyer T, Pichler B. A decade of combined imaging: from a PET attached to a CT to a PET inside an MR. *Eur J Nucl Med Mol Imaging*. 2009;36:1–2.
22. Mader CE, Fuchs T, Ferraro DA, Burger IA. Potential clinical applications of PET/MR. *IEEE Trans Rad Plasma Med Sci*. 2020;4:293–299.
23. Panda A, Mehta BB, Coppo S, et al. Magnetic resonance fingerprinting-an overview. *Curr Opin Biomed Eng*. 2017;3:56–66.
24. Barrio JR, Marcus CS, Hung JC, Keppler JS. A rational regulatory approach for positron emission tomography imaging probes: from "first in man" to NDA approval and reimbursement. *Mol Imaging Biol*. 2004;6:361–367.