Journal of Nuclear Medicine, published on January 11, 2018 as doi:10.2967/jnumed.117.202861

BRIEF COMMUNICATION

ACCURACY OF DOSE CALIBRATORS FOR GALLIUM-68 PET IMAGING: UNEXPECTED FINDINGS IN A MULTI-CENTRE CLINICAL PRE-TRIAL ASSESSMENT

Dale L Bailey[1,2], Michael S Hofman[3], Nicholas J Forwood[1,2], Graeme J O'Keefe[5], Andrew M Scott[5,6], Winifred M van Wyngaardt[7], Bonnie Howe[7], Olga Kovacev[4] and Roslyn J Francis[4,8] on behalf of ARTnet[4] and the ProPSMA Trial Investigators

[1] Department of Nuclear Medicine, Royal North Shore Hospital, Sydney, Australia

[2] Faculty of Health Sciences, University of Sydney, Sydney, Australia

[3] Molecular Imaging, Department of Cancer Imaging, Peter MacCallum Cancer Institute, Melbourne, Australia

[4] Australasian Radiopharmaceutical Trials Network (ARTnet), Australia

[5] Department of Molecular Imaging and Therapy, Austin Health, and University of Melbourne, Melbourne, Australia

[6] Olivia Newton-John Cancer Research Institute and La Trobe University, Melbourne, Australia

[7] Radionuclide Metrology Group, Nuclear Stewardship, ANSTO, Sydney, Australia

[8] Department of Nuclear Medicine, Sir Charles Gairdner Hospital, Perth, Australia

Address for correspondence:
Prof Dale L Bailey
Department of Nuclear Medicine,
Royal North Shore Hospital,
St Leonards, Sydney, Australia 2065
E: Dale.Bailey@sydney.edu.au
P: +61 (0)2 9926 4440
F: +61 (0)2 9926 4099

RUNNING TITLE: DOSE CALIBRATORS AND GALLIUM-68

Word Count: 2100

Funding Support: This clinical trial is funded by a grant from the The Movember Foundation through the Prostate Cancer Foundation of Australia's Research Program.

ABSTRACT

AIMS: We report the discovery of a systematic miscalibration during the work-up process for site validation of a multi-centre clinical PET imaging trial using ^{68}Ga, which manifested as a consistent and reproducible underestimation in the quantitative accuracy (assessed by SUV) of a range of PET systems from different manufacturers at a number of different facilities around Australia.

METHODS: Sites were asked to follow a strict preparation protocol to create a radioactive phantom with ^{68}Ga to be imaged using a standard clinical protocol prior to commencing imaging in the trial. All sites had routinely used ^{68}Ga for clinical PET imaging for many years. The reconstructed image data were transferred to an imaging core laboratory for analysis, along with information about ancillary equipment such as the radionuclide dose calibrator. Fourteen PET systems were assessed from ten nuclear medicine facilities in Australia with the aim for each PET system being to produce images within ±5% of the true SUV value.

RESULTS: At initial testing, 10 of the 14 PET systems underestimated the SUV by 15% on average (range -13% – -23%). Multiple PET systems at one site, from two different manufacturers, were all similarly affected, suggesting a common cause. We eventually identified an incorrect factory-shipped dose calibrator setting from a single manufacturer as being the cause. The calibrator setting for ^{68}Ga was subsequently adjusted by the users so that the reconstructed images produced accurate values.

CONCLUSION: PET imaging involves a chain of measurements and calibrations to produce accurate quantitative performance. Testing of the entire chain can, however, be simply performed and should form part of any quality assurance (QA) programme or pre-qualifying site assessment prior to commencing a quantitative imaging trial or clinical imaging.

KEYWORDS: PET; standardisation; gallium-68; calibration; trial

INTRODUCTION

There has been a dramatic increase in the last 5-10 years in the number of PET/CT scans performed using gallium-68 (^{68}Ga; $t_{½}$ = 67.6 m) labelled radiopharmaceuticals, such as [^{68}Ga]-DOTATATE (or analogues such as DOTATOC or DOTANOC) for somatostatin receptor imaging and [^{68}Ga]-PSMA for prostate cancer imaging. Gallium-68 is generator-produced from the parent germanium-68 (^{68}Ge; $t_{½}$ = 270.8 d) and is a convenient radio-metal for PET imaging permitting on-site production of the desired radioligand. It is often used in combination with either yttrium-90 (^{90}Y) or lutetium-177 (^{177}Lu) as part of a "theranostic" pairing for radionuclide imaging and therapy. As is the case for fluorine-18 (^{18}F), it is highly desirable to produce quantitatively accurate PET images of the biodistribution of ^{68}Ga radiopharmaceuticals *in vivo*, which has been a traditional strength of PET. To do so requires the PET system to have the ability to reconstruct different radionuclide's concentration accurately. However, most PET system calibration procedures are designed to be calibrated to accurately measure the concentration of ^{18}F, as this is the most commonly used radionuclide in PET imaging, mostly in the form of [^{18}F]-FDG. Accurate quantitative image reconstruction for other radionuclides relies on the reconstruction algorithm incorporating the appropriate physical data for radionuclides other than ^{18}F such as differences in decay mode, branching ratio (β^+ fraction - 88% for ^{68}Ga), half-life, and accurate accounting for prompt γ radiation that can significantly affect some scatter correction algorithms. Gallium-68 also has a higher energy positron (E_{max} = 1.9 MeV) than ^{18}F (E_{max} = 0.63 MeV) which results in slightly poorer spatial resolution in PET, and which is affected by the density of the surrounding media (*e.g.*, lung tissue); the lower the density, the greater path length travelled by the positron before annihilation with an electron, and hence the greater the distance from the point of emission from the radiolabelled molecule to the origin of the annihilation radiation photons detected by the PET system, and so the poorer the spatial resolution. In addition, ^{68}Ga decay by positron emission is

accompanied by a prompt γ emission of ~3.0% abundance at E_γ = 1.08 MeV, further complicating the emission spectrum.

We report on our experience in a national survey of ^{68}Ga PET quantification with an unexpected outcome.

METHODS

A consortium of Australian clinical investigators commissioned ARTnet (the Australasian Radiopharmaceutical Trials Network) to undertake a site validation exercise for a muti-centre clinical trial using [^{68}Ga]-PSMA PET imaging for staging high risk prostate cancer prior to surgery or radiotherapy – the ProPSMA Trial. This study is prospectively registered in the Australian and New Zealand Clinical Trial Registry (ANZCTR Trial No. 12617000005358) and has received institutional ethics approval at each site. The requirements of the site pre-trial assessment included providing quantitatively accurate PET/CT images (within ±5% of true SUV) of the *in vivo* radio-concentration of gallium-68 in solution. The site initiation process used the IEC/NEMA-NU2 body phantom [1] with fillable spherical inserts of varying size to assess the performance of PET systems to be used in the trial. Sites were sent the phantom with instructions as to how to fill the phantom so as to give an 8:1 ratio between the concentration of ^{68}Ga in the spheres compared to the larger background compartment. Sites were instructed to use between 50-200 MBq of ^{68}Ga, wait one hour after calibration and preparation of the phantom before scanning, and to acquire using multiple bed positions in an attempt to replicate similar conditions to those encountered in clinical scanning. The wide range for the amount of radioactivity permitted was to allow for different system configurations and sensitivities, to incorporate a delay (typically 1 hour – ~50% decay for ^{68}Ga) between calibration of the radioactivity and scanning thus reproducing the clinical situation, and so that the scanning could be performed with a high number of total acquired events

in as short a time as practical. Sites used their standard operating procedures for syringes used in the dose calibrator, as for a clinical administration. The operators were instructed to enter the volume of liquid in the background compartment as a weight (9.8 kg) in the "Patient Weight" field of the PET acquisition screen, such that a region interest (ROI) placed over the background area in the resulting images would be expected to give an SUV (Standardised Uptake Value) of 1.0. The reconstructed image data were transferred to an imaging core laboratory (PharmaScint, Sydney, Australia) for analysis, along with information about ancillary equipment such as the radionuclide dose calibrator. Figure 1 shows a schematic and experimental PET/CT fused image of the phantom with the spheres defined to provide image-based ROIs.

(Figure 1 about here)

The phantom and instructions were sent to ten nuclear medicine facilities around Australia where 14 PET/CT systems were assessed.

RESULTS

The initial results and pertinent instrumentation characteristics along with the measured SUV for all sites are shown in Table 1. It shows that a majority of sites and PET systems underestimated the true SUV by around 15% on average (range -13% – -23%). After ruling out repeated (and reproducible) operator error in filling the phantom at multiple sites we undertook a series of investigations in an attempt to identify the cause of the consistent underestimation of the SUV. After exploring a number of potential reasons it was suggested that the error was likely due to an incorrect dose calibrator setting on one manufacturer's calibrators over a number of different models. Curiously at one site (Site D) with two PET/CT systems tested using the same dose calibrator, one showed the same underestimate as many of the other sites while the other was within acceptable limits. This may potentially be due to an incorrect ^{18}F calibration on the underestimated PET system. In the course of these investigations, after eliminating a number of potential causes, an accurate calibration of one site's dose calibrator (Site A) with a traceable

source was undertaken by the local national nuclear science organisation in Australia (ANSTO[1]) and, subsequently, a reference source of ^{68}Ge/^{68}Ga ("Bench/Mark", RadQual, Idaho, USA, Model: BM06V-20-681XS) was obtained for verifying dose calibrator accuracy on a routine basis. The incorrect dose calibrator setting as the cause of the problem was subsequently confirmed both experimentally and in discussions with representatives of the SNMMI Clinical Trials Network (CTN).

(Table 1 about here)

After identifying the cause, all sites undertook a remedial programme to adjust the dose calibrator setting for ^{68}Ga. This involved either obtaining a traceable ^{68}Ge/^{68}Ga reference standard suitable for use in the dose calibrator, or using a source of ^{68}Ga to iteratively adjust the dose calibrator setting by a scaling factor determined from the PET images that would result in the correct SUV. To do this, the sites determined the percentage error in the initial SUV value from the reconstructed images and, with a ^{68}Ga source in the dose calibrator, modified the channel setting until the dose calibrator reading was changed by the same amount as the percentage error. Subsequently, a new scan was acquired on the altered dose calibrator setting to verify the accuracy after the change. The change that was required varied slightly between sites but the factory preset value of 416 was changed to between 436 – 505 to achieve the correct value. After these actions all sites obtained an acceptable SUV of ~1.0 for ^{68}Ga (table 1). A manufacturer-supplied application note does suggest that sites should change the dose calibrator setting for ^{68}Ge (not ^{68}Ga) from 416 to 472 and then adjust the channel setting until the correct value is obtained [2]. As all sites with dose calibrators from this supplier were set to 416 we assume that

[1] Australian Nuclear Science & Technology Organisation, Sydney

this is the setting that the device leaves the factory with. The latest version of the Owner's Manual does not contain a suggested channel setting for either ^{68}Ga or ^{68}Ge [3].

DISCUSSION

The Australasian Radiopharmaceutical Trials network (ARTnet) is a nuclear medicine imaging and therapy clinical trials group established as a joint venture between the two peak bodies that represent the field of nuclear medicine in Australia and New Zealand - the Australasian Association of Nuclear Medicine Specialists (AANMS) and the Australian and New Zealand Society of Nuclear Medicine (ANZSNM). ARTnet provides members of the sponsoring organisations, individual investigators, other clinical trials groups and external organisations such as pharmaceutical and equipment companies with access to nuclear medicine facilities capable of undertaking clinical trials. Part of this access is also to provide support in standardising radiopharmaceutical production, imaging protocols and data analysis.

In this short communication we have reported on a systematic deviation in calibration of dose calibrators from one vendor that was seen in multiple centres throughout Australia. In effect, what we were doing was using the PET system as a dose calibrator - assuming that the system had been correctly set up for ^{18}F - to check the measurement for ^{68}Ga. Gallium-68 presents unique challenges for dose calibration as, firstly, the 68 min physical half-life makes it difficult to produce a source at a site where it can be compared to a traceable reference standard and then shipped to a remote PET facility, and secondly, the co-emission of high-energy γ photons along with the positron requires the manufacturer to take this into account. To address the first issue sites can purchase a ^{68}Ge/^{68}Ga reference source suitable for use in the dose calibrator.

Accurate quantification of ^{68}Ga has significant clinical implications. SUV parameters are increasingly used for consistency in scaling the black and white or colour scales so that the

intensity of uptake is comparable across multiple time points. They are also used to measure response assessment in order to define response or progression following therapy. In centres already performing clinical ^{68}Ga imaging, caution is warranted following correction of the dose calibrator settings, as SUV values will not be directly comparable to old studies; a comment at the bottom of reports detailing the date of ^{68}Ga calibration change and expected percentage variation may be warranted to alert reporters and clinicians. Finally, accurate determination of radiation exposure to the patient (which is a secondary endpoint of the ProPSMA study), necessitates accurate knowledge of ^{68}Ga administered activity.

Simple checking of the reconstructed SUV in a uniform phantom containing water and the positron-emitting radionuclide in question is easy to perform and, in our view, should be a component of any PET QA programme. The surprising results that we found provide compelling evidence of the value of an appropriate site validation and QA programme prior to commencing not only a clinical imaging trial, but also for routine clinical imaging.

ACKNOWLEDGMENTS

Many individuals from the Australian nuclear medicine community contributed useful input to solving this issue including Daniel Badger, David Binns, Amanda Brason, Paul Brayshaw, Jason Callahan, Dominic Mensforth, Stewart Midgely, Jackson Price, Paul Roach as well as John Sunderland from the US-based SNMMI Clinical Trials Network (CTN). Their contributions are gratefully acknowledged.

Michael Hofman is supported by a Clinical Fellowship Award from the Peter MacCallum Foundation. Andrew Scott is supported by an NHMRC Senior Practitioner Fellowship.

COMPLIANCE WITH ETHICAL STANDARDS

Funding: This clinical trial is funded by a grant from the The Movember Foundation through the Prostate Cancer Foundation of Australia's Research Program, and administered through the University of Melbourne.

Conflict of Interest: All authors declare that they do not have any conflicts of interest to report related to this communication.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

REFERENCES

1. NEMA, *NU 2-2012 Performance Measurements of Positron Emission Tomographs*. (2012), National Electrical Manufacturers' Association: USA.
2. Capintec, *CRC-25 Family Application Note* 5102-5066 Rev. A.
3. Capintec, *CRC-25PET Owner's Manual*. (2017) 9250-0124 Rev. L.

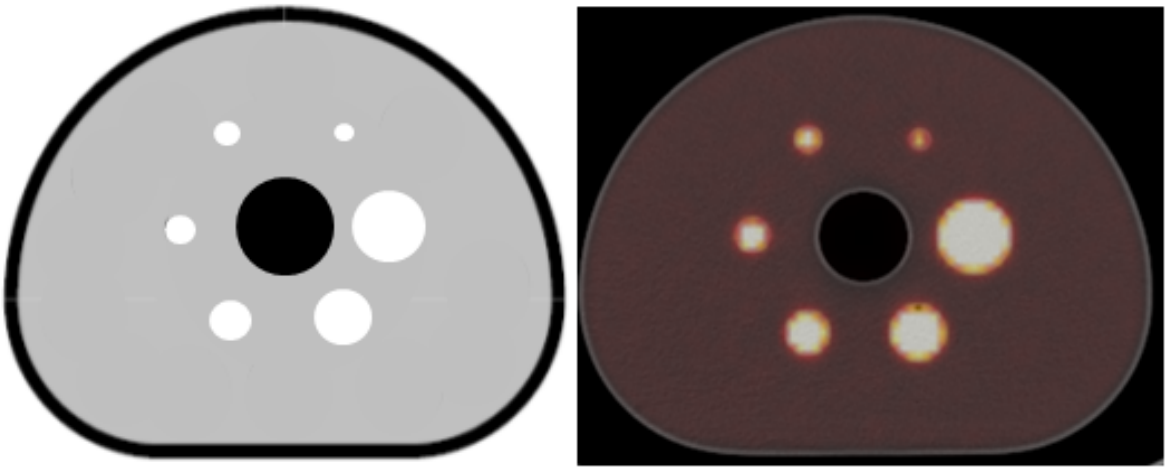

FIGURE 1. IEC/NEMA-NU2 Body Phantom schematic (left) and fused PET/CT image from the trial with a transverse section through the level of the spheres (right).

Table 1. Initial measurements for ^{68}Ga quantification accuracy (SUV) on the 14 PET/CT systems. The shaded rows indicate measurements which significantly underestimated the true SUV.

Site	PET Model	Dose Calibrator Model	Initial Dose Calibrator channel setting for ^{68}Ga	Initial SUV	Final Dose Calibrator channel setting for ^{68}Ga	Final SUV
A	Siemens Biograph mCT	CRC-25PET	416	0.86	460	1.02
B	Siemens Biograph	CRC-15R	416	0.77	505	0.95
B	GE Discovery 690	CRC-15R	416	0.85	505	1.00
B	GE Discovery 710	CRC-15R	416	0.85	505	1.01
B	GE Discovery 710	CRC-15R	416	0.87	505	1.03
C	Siemens Biograph mCT	CRC-25PET	416	0.84	503	1.00
D	Philips Gemini TF/64	CRC-25PET	448	0.86	Not changed	Pending
D	Philips Gemini TF/128	CRC-25PET	448	0.95	Not changed	-
E	Siemens Bioraph TruePoint	ATOMLAB 500	10.1	0.87	9.4	1.02
F	GE Discovery 690	ATOMLAB 200	12.4	0.98	Not changed	-
G	Siemens Biograph mCT Flow	CRC-55tR	416	0.78	436	0.95
H	Siemens Biograph mCT Flow	CRC-25PET	423	0.99	Not changed	-
I	Siemens Biograph mCT Flow	ATOMLAB 300	N/A	0.98	Not changed	-
J	GE Discovery 710	CRC-55PET	416	0.87	Pending	Pending