BRIEF COMMUNICATION

Accuracy of Dose Calibrators for ^{68}Ga PET Imaging: Unexpected Findings in a Multicenter Clinical Pretrial Assessment

Dale L. Bailey[1,2], Michael S. Hofman[3], Nicholas J. Forwood[1,2], Graeme J. O'Keefe[4], Andrew M. Scott[4,5], Winifred M. van Wyngaardt[6], Bonnie Howe[6], Olga Kovacev[7], and Roslyn J. Francis[7,8]; on behalf of ARTnet[7] 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]Department of Molecular Imaging and Therapy, Austin Health, and University of Melbourne, Melbourne, Australia; [5]Olivia Newton-John Cancer Research Institute and La Trobe University, Melbourne, Australia; [6]Radionuclide Metrology Group, Nuclear Stewardship, ANSTO, Sydney, Australia; [7]Australasian Radiopharmaceutical Trials Network (ARTnet), Australia; and [8]Department of Nuclear Medicine, Sir Charles Gairdner Hospital, Perth, Australia

We report the discovery of a systematic miscalibration during the work-up process for site validation of a multicenter 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 several 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 before 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 10 nuclear medicine facilities in Australia, with the aim for each PET system being to produce images within 5% of the true SUV. **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 is simple, however, and should form part of any quality assurance program or prequalifying site assessment before commencing a quantitative imaging trial or clinical imaging.

Key Words: PET; standardization; ^{68}Ga; calibration; trial

Over the last 5–10 y, there has been a dramatic increase in the number of PET/CT scans performed using radiopharmaceuticals labeled with ^{68}Ga (half-life, 67.6 m), such as ^{68}Ga-DOTATATE (or analogs such as DOTATOC or DOTANOC) for somatostatin receptor imaging and ^{68}Ga-PSMA for prostate cancer imaging. ^{68}Ga is generator-produced from the parent ^{68}Ge (half-life, 270.8 d) and is a convenient PET radiometal permitting on-site production of the desired radioligand. It is often used in combination with either ^{90}Y or ^{177}Lu as part of a theranostic pairing for radionuclide imaging and therapy. As is the case for ^{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 be able to accurately reconstruct the concentration of different radionuclides. However, most PET systems are 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 requires that the reconstruction algorithm incorporate the physical data for radionuclides other than ^{18}F, such as differences in decay mode, branching ratio (β^+ fraction, 88% for ^{68}Ga), and half-life, and accurate accounting for prompt γ-radiation, which can significantly affect some scatter correction algorithms. ^{68}Ga also has a higher-energy positron (maximum energy, 1.9 MeV) than ^{18}F (maximum energy, 0.63 MeV), which results in slightly poorer spatial resolution in PET and is affected by the density of the surrounding medium (e.g., lung tissue). The lower the density, the greater the pathlength traveled by the positron before annihilation with an electron and, hence, the greater the distance from the point of emission from the radiolabeled molecule to the origin of the annihilation radiation photons detected by the PET system and, thus, the poorer the spatial resolution. In addition, ^{68}Ga decay by positron emission is accompanied by a prompt γ-emission of approximately 3.0% abundance at a γ-energy of 1.08 MeV, further complicating the emission spectrum.

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

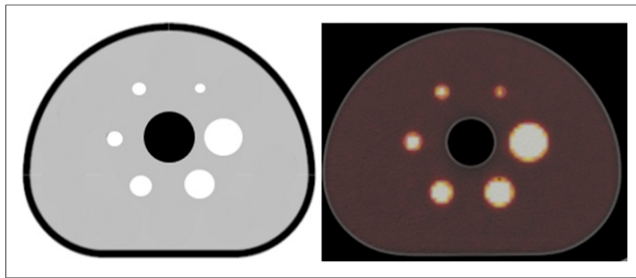**FIGURE 1.** Schematic of IEC/NEMA-NU2 body phantom (left), and transverse PET/CT section through level of spheres (right).

MATERIALS AND METHODS

A consortium of Australian clinical investigators commissioned the Australasian Radiopharmaceutical Trials Network (ARTnet) to validate the sites for a multicenter clinical trial using ^{68}Ga-PSMA PET imaging for staging high-risk prostate cancer before surgery or radiotherapy—the ProPSMA Trial. This study is prospectively registered in the Australian and New Zealand Clinical Trial Registry (trial 12617000005358) and has received institutional ethics approval at each site. The requirements of the pretrial site assessment included providing quantitatively accurate PET/CT images (within 5% of the true SUV) of the in vivo radioactive concentration of ^{68}Ga in solution. The pretrial assessment 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. The phantom was sent to the sites (10 Australian nuclear medicine facilities, where 14 PET/CT systems were assessed) along with instructions on how to fill it so as to obtain an 8:1 ratio between the ^{68}Ga concentration in the spheres and the ^{68}Ga concentration in the larger background compartment. The sites were instructed to use between 50 and 200 MBq of ^{68}Ga, to wait 1 h after calibration and preparation of the phantom before scanning, and to acquire the scan using multiple bed positions to

replicate conditions similar to those encountered in clinical scanning. The wide range of radioactivity was permitted to allow for different system configurations and sensitivities and to incorporate a delay (typically 1 h for ~50% decay of ^{68}Ga) between calibration of the radioactivity and scanning, thus reproducing the clinical situation and allowing the scanning to be performed with a high number of total acquired events as quickly as practical. The sites applied their standard operating procedures for syringes used in the dose calibrator, as they would in clinical administration. The operators were instructed to enter into the "Patient Weight" field of the PET acquisition screen a weight of 9.8 kg for the volume of liquid in the background compartment, such that a region of interest placed over the background area in the resulting images would be expected to give an SUV 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 image of the phantom, with the spheres defined to provide image-based regions of interest.

RESULTS

The initial results and pertinent instrumentation characteristics, along with the measured SUV for all sites, are shown in Table 1. Most sites and PET systems underestimated the true SUV by around 15% on average (range, 13%–23%). After ruling out the possibility that operators at multiple sites had repeatedly (and reproducibly) filled the phantom incorrectly, we explored several other potential causes for the consistent underestimation. One suggested possibility was that the error was due to an incorrect dose calibrator setting on one manufacturer's calibrators over several different models. Interestingly, at site D, with two PET/CT systems tested using the same dose calibrator, one system produced the same underestimate as many of the other sites whereas the other system was within acceptable limits; such a difference

TABLE 1
Measurements for ^{68}Ga Quantification Accuracy (SUV) on 14 PET/CT Systems

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 Healthcare Discovery 690	CRC-15R	416	0.85	505	1.00
B	GE Healthcare Discovery 710	CRC-15R	416	0.85	505	1.01
B	GE Healthcare 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 Biograph TruePoint	ATOMLAB 500	10.1	0.87	9.4	1.02
F	GE Healthcare 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	Not applicable	0.98	Not changed	—
J	GE Healthcare Discovery 710	CRC-55PET	416	0.87	Pending	Pending

Shaded rows indicate measurements that significantly underestimated true SUV.

might be due to an incorrect ^{18}F calibration on the underestimating PET system. The Australian Nuclear Science and Technology Organization performed an accurate calibration of site A's dose calibrator with a traceable source, and subsequently, a reference source of ^{68}Ge/^{68}Ga (Bench/Mark model BM06V-20-681XS; RadQual) was obtained for routine verification of the accuracy of the dose calibrator. An 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.

All sites then adjusted the dose calibrator setting for ^{68}Ga, either by obtaining a traceable ^{68}Ge/^{68}Ga reference standard suitable for the calibrator or by using a source of ^{68}Ga to iteratively adjust the calibrator setting by a scaling factor—determined from the PET images—that would result in the correct SUV. For the latter method, the sites determined the percentage error in the initial SUV from the reconstructed images and, with a ^{68}Ga source in the calibrator, modified the channel setting until the calibrator reading was changed by the same amount as the percentage error. Subsequently, a new scan was acquired using the altered dose calibrator setting to verify the accuracy after the change. The required change to obtain an acceptable SUV of about 1.0 for ^{68}Ga varied slightly among sites, ranging from 436 to 505 (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 dose calibrators from this supplier were set to 416, we assume that this is the factory setting. The latest version of the owner's manual does not contain a suggested channel setting for either ^{68}Ga or ^{68}Ge (3).

DISCUSSION

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 and the Australian and New Zealand Society of Nuclear Medicine. ARTnet provides members of the sponsoring organizations, individual investigators, and other clinical trial groups and external organizations, such as pharmaceutical and equipment companies, with access to nuclear medicine facilities able to perform clinical trials. Part of this access is also to provide support in standardizing radiopharmaceutical production, imaging protocols, and data analysis.

In this brief communication, we have described a systematic deviation in calibration for one vendor's dose calibrators—a deviation that was seen in multiple centers throughout Australia. In effect, what we did was use 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. ^{68}Ga presents unique challenges for dose calibration. First, the 68-min physical half-life makes it difficult for a source to be produced at a site where it can be compared with a traceable reference standard and then to be shipped to a remote PET facility. Second, the PET manufacturer has to take into account the coemission of high-energy γ-photons along with the positron. To address the first issue, sites can purchase a ^{68}Ge/^{68}Ga reference source 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 color scales so that the intensity of uptake is comparable across multiple time points. They are also used to assess response or progression after therapy. In centers already performing clinical ^{68}Ga imaging, caution is warranted after correction of the dose calibrator settings, as SUVs will not be directly comparable to previous studies; a comment at the bottom of reports detailing the date of the ^{68}Ga calibration change and the 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) requires accurate knowledge of the administered ^{68}Ga activity.

CONCLUSION

In our view, any PET quality assurance program should include a simple check of reconstructed SUV using a uniform phantom containing water and the positron-emitting radionuclide in question. The surprising results that we found provide compelling evidence of the value of an appropriate program for site validation and quality assurance, not only before commencing a clinical imaging trial but also for routine clinical imaging.

DISCLOSURE

ACKNOWLEDGMENTS

REFERENCES

1. *NEMA NU 2-2012: Performance Measurements of Positron Emission Tomographs.* Arlington, VA: National Electrical Manufacturers Association; 2013.
2. *CRC-25 Family Application Note 5102-5066, Revision A.* Florham Park, NJ: Capintec, Inc.
3. *CRC-25PET: Owner's Manual.* Florham Park, NJ: Capintec, Inc.; 2017. Manual 9250-0124, revision L.