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Assessing the absolute quantitative accuracy of Positron Emission Tomography for Cu-64 using traceable calibrated phantoms

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HIGHLIGHTS

- A PET-CT scanner was calibrated using phantoms with traceable ^{18}F activity.
- Subsequent scans of calibrated ^{18}F, ^{64}Cu phantoms demonstrated incomplete recovery.
- Scans of calibrated ^{68}Ge phantoms showed incomplete but consistent recovery.
- A method is proposed that corrects imaging data for systematic recovery errors.

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ABSTRACT

Using uniform cylindrical phantoms containing calibrated solutions of ^{18}F and ^{64}Cu, we evaluated for the first time the accuracy with which the activity concentration of ^{64}Cu can be quantified on an absolute basis using Positron Emission Tomography (with X-ray Computed Tomography, PET-CT). The scanner was first calibrated for ^{18}F using the manufacturer's calibration protocol and a phantom with an activity concentration value traceable to the U.S. National standard. By using a similarly calibrated ^{18}F solution phantom, we were able to determine a correction factor that can be applied to the ^{64}Cu imaging data that gave a result that is consistent with 100% recovery with a combined standard uncertainty of 2%. We also demonstrate how a calibrated, solid phantom containing ^{68}Ge as a long-lived ^{18}F surrogate can be used to monitor and transfer the correction factor to other studies.

1. Introduction

The use of Positron Emission Tomography with X-ray Computed Tomography (PET-CT) as a quantitative tool in the diagnosis and treatment of disease is increasing in part because of the rapid advances in instrumentation and software. However, the true quantitative utility of this modality can only be realized when the entire system, which includes both the scanner and activity calibrator, are calibrated on an absolute basis against National standards.

The process for calibrating the activity calibrator in a traceable way is well-established (IAEA, 2006), but is not always implemented in the clinic. To do so requires a solution with an activity concentration value that is traceable to a National standard and the ability to quantitatively transfer (preferably by mass) the solution into the exact geometry in which the clinical measurements will be made while properly evaluating the associated uncertainties. Commercial companies can also provide traceable, geometry-specific calibration sources for this purpose, but this approach has yet to be widely adopted.

The routine calibration of a PET-CT scanner is generally carried out clinically by scanning either a solid epoxy test object ("phantom") with a known quantity of ^{68}Ge or a cylindrical phantom that contains an aliquot of a ^{18}F solution whose activity is typically determined with an activity calibrator. Unless the activity calibrator was calibrated against a traceable standard of the same radionuclide and in the same geometry, and the transfer of solution was done quantitatively, the activity concentration in the phantom cannot be considered traceable. At the current time, only one manufacturer of solid epoxy phantoms containing ^{68}Ge has established direct traceability to NIST for the activity concentration, thus the scanners that have a traceable calibration using these types of phantoms are a minority.

For clinical applications that use only relative measurements (i.e., measurement of ratios in different regions at a single time point), the lack of absolute calibration has a minor influence on the clinical decisions being made. However, for applications in which the activity value

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is important, such as in internal dosimetry for treatment planning, or when the comparability of data across multiple clinical sites at multiple time points is critical, as in a clinical trial for new drugs, absolute calibration is required. Traceable calibration of the scanner is particularly useful for monitoring the long-term performance of the scanner, since every measurement can be linked to a fixed standard. This minimizes the variability in the data that is due to fluctuations in the activity calibration so that instrumental effects become more apparent.

One radionuclide for which imaging data would benefit from absolute calibration is ^{64}Cu. Its decay properties make it ideal for use in "theranostic" radiopharmaceuticals, which can act as both diagnostic and therapeutic agents. Current research is focused on potential uses for neuroendocrine (Ferrari et al., 2015) and prostate (Singh et al., 2016) cancers and melanoma (Qin et al., 2014) as just a few examples. Image-based dosimetry is needed for optimized trial data and treatment planning for the many ^{64}Cu-based drugs being developed, just as with any other radiopharmaceutical.

A number of National Metrology Institutes (NMIs), including the National Institute of Standards and Technology (NIST) have standardized ^{64}Cu solutions, thereby enabling traceable sources of this radionuclide to be produced around the world (Bergeron et al., 2017; Bé et al., 2012; Luca et al., 2012; Wanke et al., 2010). The short half-life of 12.7003 ± 0.0020 h (Bé, 2011) and relatively small (at the moment) research community make routine preparation and distribution of standards impractical. Instead researchers continue to rely on calibration settings provided by activity calibrator manufacturers for their measurements. This also means that the PET-CT scanners will continue to be calibrated for ^{18}F or ^{68}Ge and will rarely be calibrated for ^{64}Cu directly.

The effect that the decay properties of a particular radionuclide have on the quantitative accuracy of PET-CT, particularly for nuclides with complex decay schemes such as ^{64}Cu, has not been systematically studied. Moreover, the uncertainties associated with extracting activity values from PET-CT imaging data for one radionuclide when the system is calibrated for another have not been previously considered in a way consistent with international guidelines for assessing uncertainties (JCGM, 2008).

In the first study of its kind, we have used liquid phantoms with activity concentrations traceable to our primary standards to calibrate the PET-CT scanner installed at NIST for ^{18}F and evaluated the quantitative accuracy for $^{64}CuCl_2$ solutions in a uniform phantom under different counting conditions. The purpose of the study was to quantify for the first time the best-case accuracy that could be expected from imaging a uniform phantom for a radionuclide with a complex decay scheme when the instrumentation is calibrated against another radionuclide. Considerable emphasis was placed on determining realistic uncertainties, based on the Guide to Uncertainty in Measurement (GUM, JCGM, 2008).

The use of calibrated solutions and a phantom preparation method that preserves traceability to the NIST primary standards for ^{18}F and ^{64}Cu give a unique aspect to this work in that for the first time, there is a "true" activity value that can be assigned to the phantoms. This provides a way to quantify not only the recovery, but also the uncertainties, on an absolute basis. The results of this study are expected to provide a "best-case" analysis, since the geometry used is one of the simplest available and does not consider effects such as partial volume or patient movement, which are two of the most important sources of systematic error. In addition, the evaluation of specific reconstruction parameters on the uncertainty is outside of the scope of this investigation; we have used the default settings for the most common acquisition and reconstruction protocols for our particular scanner.

2. Materials and methods

The timeline for the measurements made in this study is depicted in Fig. 1.

Prior to conducting the experiments described in this paper, the PET-CT scanner that was used experienced a downtime of more than 6 months due to failure of components not directly related to the imaging systems. The scanner was maintained in a powered-up state during that time. The system had been calibrated about one month prior to the failure and measurements had been taken to validate the calibration in terms of both Standardized Uptake Value (SUV, usually defined as the activity in a region of interest divided by the product of the total injected activity and the mass of the patient) and activity concentration.

Once the system came back up, we implemented a program of regular measurements of a set of calibrated ^{68}Ge solid epoxy phantoms to monitor the system performance.

The scanner was calibrated again about a month prior to the ^{64}Cu phantom measurements specifically to prepare for those studies. The calibration was validated for SUV and activity concentration three days before the ^{64}Cu phantom scans.

The details of the phantom preparations, scanning protocols, and data analysis methods are given below.

2.1. ^{18}F phantom preparation and scanner calibration

The data for this study were acquired on a Philips Gemini-TF 16 CT slice PET-CT scanner (Philips Medical Systems, Cleveland, OH)[1] that was installed at NIST in September 2010. The system is normally calibrated at least semi-annually using the manufacturer's SUV calibration protocol, with additional calibrations performed prior to major imaging studies or after major repairs.

Briefly, the SUV calibration protocol consists of preparing a 20 cm diameter × 30 cm length cylindrical (poly)methylmethracrylate (PMMA) phantom using a calibrated solution of ^{18}F (typically as [^{18}F] fluordeoxyglucose, FDG). In the clinical application of the procedure, the phantom is partially filled with distilled water, followed by the addition of nominally 900 MBq of ^{18}F by syringe. The activity of the added ^{18}F is determined by a difference measurement of the syringe before and after addition. After agitating to ensure complete mixing, the phantom is then completely filled with additional distilled water.

We modified this procedure by performing each transfer by mass, recording both dispensed and contained masses from/to each container at each step. The contents of the ^{18}F syringe received by a commercial radiopharmacy (Cardinal Health, Beltsville, MD USA) are first dispensed into a small polyethylene beaker, then taken up into a polyethylene aspiration pycnometer and weighed. A small amount (nominally 40 mg) of the ^{18}F solution is gravimetrically transferred into a 5 mL glass NIST-style ampoule that contains a pre-weighed amount (nominally 5 mL) of distilled water. The remainder of the ^{18}F solution is then gravimetrically transferred to the cylindrical phantom that had been weighed empty and then filled to about 90% of its volume with distilled water and weighed prior to the introduction of the activity. The phantom is sealed and agitated to ensure complete mixing and then filled with distilled water such that no air bubbles are present and reweighed. The ampoule is then flame sealed and both it and the phantom are checked for external contamination.

While the phantom is positioned for scanning and the scan parameters entered into the scanner acquisition computer, the ampoule is measured in a Vinten 671 ionization chamber (Woods et al., 1983) with a Keithley 6517A electrometer (collectively referred to as the "VIC") using the standard ampoule holder in order to determine the total activity. The measurements in this work consisted of 200 determinations of the ionization chamber current taken at 2 s intervals. After background subtraction, the measured ionization current is converted to

[1] Certain commercial equipment, instruments, or materials are identified in this paper to foster understanding. Such identification does not imply recommendation by the National Institute of Standards and Technology, nor does it imply that the materials or equipment identified are necessarily the best available for the purpose.