



Original paper

# Underestimation of $^{68}\text{Ga}$ PET/CT SUV caused by activity overestimation using default calibrator settings

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## ABSTRACT

**Purpose:** A PET/CT scan of a uniformly filled  $^{68}\text{Ga}$  phantom resulted in an unexpectedly low  $\text{SUV}_{\text{mean}}$  of 0.88. A potential contributing cause of underestimation of  $^{68}\text{Ga}$  SUV is overestimation of  $^{68}\text{Ga}$  activity in the Radionuclide Calibrator associated with the PET/CT scanner. To investigate this, a Radionuclide Calibrator cross-calibration exercise was performed.

**Methods:** A source of  $^{68}\text{Ga}$  was measured in 5 Capintec CRC-55tR calibrators using the pre-set  $^{68}\text{Ga}$  calibrator factor of 416, and a Veenstra VDC-505 calibrator using a factor recommended by the manufacturer. The source was then measured in an externally located Fidelis Secondary Standard Radionuclide Calibrator. Manual adjustments were made to the Capintec calibrator factors to match the decay corrected Fidelis measurement, followed by a repeat PET/CT scan of a uniform  $^{68}\text{Ga}$  phantom.

**Results:** The cross-calibration results showed that the 5 Capintec calibrators systematically overestimated  $^{68}\text{Ga}$  activity by 7.8–9.4% (mean 8.5%) compared to the Fidelis. The calibrator factors were adjusted to 456–464 to match the Fidelis measurement, and the repeat phantom scan resulted in a  $\text{SUV}_{\text{mean}}$  of 0.97, within the local tolerance of  $1.00 \pm 5\%$ . The result for the Veenstra calibrator was within the tolerance of  $\pm 5\%$ .

**Conclusions:** Underestimation of  $^{68}\text{Ga}$  SUV was primarily caused by overestimation of  $^{68}\text{Ga}$  activity using the pre-set calibrator factor setting on a Capintec CRC-55tR. Improvement in quantification accuracy was achieved by adjusting the  $^{68}\text{Ga}$  calibrator factor based upon a cross-calibration exercise. We recommend SUV checks using a uniform phantom and regular calibrator cross-calibration exercises for all isotopes used for quantitative PET/CT imaging.

## 1. Introduction

An attractive feature of PET/CT imaging is the ability to accurately quantify concentrations of radioactivity in-vivo [1]. In clinical practice this is typically utilised to calculate a semi-quantitative Standardised Uptake Value (SUV), defined as the radioactive concentration in a volume of interest (VOI) at a single time-point, normalised to the administered activity corrected for radioactive decay and a patient body size metric such as the patient body weight ( $\text{SUV}_{\text{bw}}$ ) (1) [2]. The SUV has routine clinical application in monitoring response to treatment, including stratification into response classes, and scaling image appearance. Several variations on the SUV have been defined, including  $\text{SUV}_{\text{max}}$ ,  $\text{SUV}_{\text{mean}}$  (calculated using the maximum and mean voxel values in the VOI respectively) and  $\text{SUV}_{\text{peak}}$  [3].

$$\text{SUV}_{\text{bw}} = \frac{(\text{Bq/ml})_{\text{VOI}}}{(\text{Bq/g})_{\text{patient}}} \quad (1)$$

Whilst the use of the SUV was initially proposed for 2-deoxy-2- $^{18}\text{F}$  fluoro-D-glucose (FDG) imaging [4], it also has applications in imaging of other positron emitting radiopharmaceuticals used in PET, such as those labelled with Gallium-68 ( $^{68}\text{Ga}$ ). The use of  $^{68}\text{Ga}$  labelled radiopharmaceuticals in PET imaging has increased significantly in recent years, primarily through the use of  $^{68}\text{Ga}$ -DOTA-conjugated peptides (DOTATATE, DOTATOC or DOTANOC) for somatostatin receptor imaging [5], and  $^{68}\text{Ga}$ -PSMA for prostate cancer imaging. The use of the SUV when reporting these images is commonplace, and referenced in Joint EANM and SNMMI guidelines for  $^{68}\text{Ga}$ -PSMA [6].

In order to obtain accurate SUV measurements, a radioactivity concentration calibration (or SUV calibration) is performed, typically recommended quarterly, following servicing of the PET detector system [7]. The calibration process typically involves filling a uniform

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phantom with a known activity concentration of  $^{18}\text{F}$ , determined by activity measurements in the Radionuclide Calibrator (RC) associated with the scanner, and a known phantom volume. An image of the phantom is then acquired on the PET/CT scanner and reconstructed with all appropriate quantitative corrections. This is used to establish a calibration factor ( $\text{CF}_{\text{SUV}}$ ) which converts the scanner output image units (for example count rate per voxel) to the absolute activity concentration in Bq/ml, allowing calculation of SUV using Eq. (1). The accuracy of the SUV calibration can be validated by repeating a uniform phantom scan. When normalising SUV to weight (g), the mean  $\text{SUV}_{\text{bw}}$  within a uniformly distributed phantom should be equal to 1.00 (g/ml). When repeating both the filling and scanning of a uniform phantom, a tolerance of  $1.00 \pm 5\%$  is typically applied [7].

The implementation of the SUV calibration process by major PET/CT scanner manufacturers does not include a separate SUV calibration for alternative PET radionuclides to  $^{18}\text{F}$  such as  $^{68}\text{Ga}$ . Instead, corrections are made to the  $^{18}\text{F}$   $\text{CF}_{\text{SUV}}$  based upon the decay characteristics and emissions of the radionuclide. For example,  $^{68}\text{Ga}$  has a shorter half-life than  $^{18}\text{F}$  ( $^{68}\text{Ga}$ : 67.7 mins,  $^{18}\text{F}$ : 109.8 mins) and a lower positron branching ratio ( $^{68}\text{Ga}$ : 88%,  $^{18}\text{F}$ : 97%). It also has a higher maximum energy positron emission ( $^{68}\text{Ga}$ : 1.9 MeV  $^{18}\text{F}$ : 0.63 MeV) and therefore higher positron range, resulting in a poorer image spatial resolution. In addition, it has a high energy prompt gamma emission at 1.08 MeV with approximately 3% abundance [8]. If these corrections are not correctly applied to the  $^{18}\text{F}$   $\text{CF}_{\text{SUV}}$ , the SUV for other PET radionuclides such as  $^{68}\text{Ga}$  will be inaccurate.

If there is a mis-calibration of the  $^{18}\text{F}$   $\text{CF}_{\text{SUV}}$  due to an inaccurate  $^{18}\text{F}$  activity measurement in the RC, the  $^{18}\text{F}$  SUV in an image will not be affected, as any inaccuracy in activity measurement is present in both the  $\text{CF}_{\text{SUV}}$  and the administered activity, cancelling out the inaccuracy on both sides of the fraction line in Eq. (1). However an inaccurate  $^{18}\text{F}$   $\text{CF}_{\text{SUV}}$  will affect the accuracy of SUV for any other PET radionuclides, including  $^{68}\text{Ga}$ , due to the lack of a separate  $\text{CF}_{\text{SUV}}$  for other radionuclides. Similarly, if the  $^{18}\text{F}$   $\text{CF}_{\text{SUV}}$  is calibrated correctly, but there is an inaccurate activity measurement of  $^{68}\text{Ga}$  in the RC, this will cause a corresponding inaccuracy in  $^{68}\text{Ga}$  SUV. The inaccuracy in  $^{68}\text{Ga}$  activity measurement will not affect the  $^{18}\text{F}$  derived  $\text{CF}_{\text{SUV}}$ , but will result in an inaccurate value for administered activity of  $^{68}\text{Ga}$ , causing an inaccuracy in  $^{68}\text{Ga}$  SUV. For example a 10% overestimation of activity will result in a 10% underestimation of SUV.

The accuracy of activity measurements in a local ‘field instrument’ RC can be verified by a measurement comparison of a radioactive source to a national primary standard, either directly or in a cross-calibration chain via a secondary standard Reference RC. This cross-calibration process can be used to modify default manufacturer-supplied pre-set Calibrator Factors ( $\text{CF}_{\text{RC}}$ ) in order to match the activity measurement in the primary standard. The  $\text{CF}_{\text{RC}}$  converts the charge induced in the RC ionisation chamber by a radioactive source to an activity measurement, and is specific to each individual radionuclide.

In the UK, the primary standard is based at the National Physical Laboratory (NPL) and a Secondary Standard Reference RC is specified as the Fidelis Secondary Standard RC (Southern Scientific, UK). The Fidelis is the latest of a series of secondary standard chambers produced by the NPL, and is based upon an original NPL chamber design and concept [9], with updated electronics. The NPL defines calibration factors (pA/MBq) for the Fidelis for individual radionuclides at specified container types and geometries, and also recommends an acceptable tolerance for a field instrument RC activity measurement of  $\pm 5\%$  compared to a Secondary Standard Reference Calibrator such as the Fidelis [10].

This paper investigates an unexpectedly low  $\text{SUV}_{\text{mean}}$  of 0.88 measured in a uniformly filled  $^{68}\text{Ga}$  phantom imaged on a GE Discovery 710 (General Electric Healthcare, USA) PET/CT scanner.

## 2. Methods

### 2.1. Initial $^{68}\text{Ga}$ uniform phantom

A cylindrical water phantom (5640 ml volume) was filled with a uniform activity concentration of unlabelled  $^{68}\text{Ga}$ . The activity was measured using a Capintec CRC-55tR model RC (Capintec, Inc. USA) on the pre-set  $\text{CF}_{\text{RC}}$  of 416 which is also defined in the Owner’s Manual [11], and corrected for residual activity after insertion into the phantom. An image of the phantom was acquired on a GE Discovery 710 PET/CT scanner using a time per bed position of 5 min, and reconstructed using an OSEM algorithm with 2 iterations, 24 subsets, a Gaussian post-filter of 6.4 mm FWHM, and with quantitative corrections for attenuation, scatter, randoms, dead time, and radioactive decay. The isotope was identified on the scanner as  $^{68}\text{Ga}$ . The  $\text{SUV}_{\text{mean}}$  was measured by taking the average reading of three large circular ROIs placed centrally in adjacent central axial slices through the phantom.

An  $^{18}\text{F}$  SUV calibration had been performed according to manufacturer recommendations within the previous 3 months and had resulted in a measured  $\text{SUV}_{\text{mean}}$  of 1.00 in an  $^{18}\text{F}$  uniform phantom. A cylindrical water phantom was used, with  $^{18}\text{F}$  activity measured on a  $\text{CF}_{\text{RC}}$  of 451, and corrected for residual activity. This is not the default  $^{18}\text{F}$   $\text{CF}_{\text{RC}}$  of 472 which is supplied by Capintec in the Owner’s Manual [11]. This is because we have previously updated our  $^{18}\text{F}$   $\text{CF}_{\text{RC}}$  for all Capintec CRC-55tRs based upon annual cross-calibration exercises against a Fidelis secondary standard RC, using the same methodology as described here for  $^{68}\text{Ga}$ .

### 2.2. $^{68}\text{Ga}$ cross-calibration exercise

An unlabelled source of  $^{68}\text{Ga}$  was eluted from a  $^{68}\text{Ge}/^{68}\text{Ga}$  generator into a 4 ml volume in a P6 vial. The source was then measured in 6 local field instrument RCs, with a maximum activity of 610 MBq. Five of the RCs were the Capintec CRC-55tR model, and the other was a Veenstra VDC-505 model (Veenstra Instruments, now COMECER Netherlands). The measurements on the CRC-55tRs were all performed using the pre-set  $\text{CF}_{\text{RC}}$  of 416. The measurement on the Veenstra VDC-505 was performed using a  $\text{CF}_{\text{RC}}$  recommended by the manufacturer of  $747 \times 1.0$ . The time of each measurement was recorded to the nearest minute with a consistent time-piece. All measurements were made with the same vial, and the effects on activity measurement of using other source container types such as a syringe have not been considered in this study.

The source was then transported to an externally located Fidelis Secondary Standard RC, where it was data-logged to take repeated readings with an interval of 1 s. The Fidelis calibration factor for  $^{68}\text{Ga}$  in a P6 vial provided by the NPL was used, and the average measurement over 10 s was calculated. All field instrument activity measurements were decay corrected to the reference time ( $T_0$ ), defined as the time of the Fidelis measurements to the nearest minute, using a half-life of 67.7 min. The ratios between the Fidelis reference activity measurement ( $A_{\text{ref}}$ ) and the decay corrected field instrument activity measurements ( $A_{\text{measured}}$ ) were then calculated. The difference between  $A_{\text{measured}}$  and  $A_{\text{ref}}$  was also expressed as a percentage of  $A_{\text{ref}}$ .

The Fidelis is routinely directly calibrated against the national primary standard at the NPL with  $^{18}\text{F}$  to a specification of  $\pm 2\%$  and has a complete set of quality assurance procedures performed as recommended by the NPL [10]. A direct calibration against the primary standard with  $^{68}\text{Ga}$  has not been performed due to practical limitations related to the short half-life of  $^{68}\text{Ga}$ . The Fidelis calibration factor (pA/MBq) provided by NPL for  $^{68}\text{Ga}$  is similar to that for  $^{18}\text{F}$ , with the small difference resulting from the higher energy gamma photons also emitted by  $^{68}\text{Ga}$ .

For results outside of the recommended  $\pm 5\%$  tolerance for deviation from the Fidelis reference activity measurement, the field instrument  $^{68}\text{Ga}$   $\text{CF}_{\text{RC}}$ s were adjusted in order to match the Fidelis

measurement. For Capintec RCs, the required  $CF_{RC}$  adjustment can be derived from equations provided in the Owner's Manual [11]. The required  $CF_{RC}$  is linearly related to the chamber response  $R_A$  (2), which is defined as the detector output per unit activity of the radionuclide being measured relative to the detector output per unit activity for a source of  $^{60}\text{Co}$ .

$$CF_{RC} = a(R_A - b) \quad (2)$$

The constants  $a$  and  $b$  represent the slope and intercept with the  $x$  axis of the linear fit. These constants can be derived from the response and required  $CF_{RC}$  for calibrated sources of  $^{60}\text{Co}$  and  $^{57}\text{Co}$ . Using these values as provided in the Owner's Manual, the constants are calculated as;  $a = 1082.6 \pm 5.1$ ,  $b = 0.086 \pm 0.004$ . The uncertainty is related to the variation of individual chamber responses to a source of  $^{57}\text{Co}$ , which is quoted in the Owner's Manual with an uncertainty of  $\pm 2\%$ .

In addition, the ratio between  $A_{ref}$  and  $A_{measured}$  is equal to the ratio between the original chamber response and the required chamber response to result in a measured activity equal to the reference activity. Therefore the following relationship can be derived to calculate the required  $CF_{RC}$  from the original  $CF_{RC}$  and the ratio between  $A_{ref}$  and  $A_{measured}$ .

$$CF_{RC}(required) = a \left( \frac{\frac{CF_{RC}(original)}{a} + b}{\frac{A_{ref}}{A_{measured}}} - b \right) \quad (3)$$

Eq. (3) was applied to calculate the required  $CF_{RC}$  to match the Fidelis reference activity from the original  $CF_{RC}$  (416 for  $^{68}\text{Ga}$  for the CRC-55tR), and the ratio between  $A_{ref}$  and  $A_{measured}$  established from the cross-calibration exercise. This was then rounded to the nearest integer value, as Capintec RCs do not allow non-integer  $CF_{RC}$ s.

### 2.3. Repeat $^{68}\text{Ga}$ uniform phantom

Following adjustment to the  $^{68}\text{Ga}$   $CF_{RC}$ s, a repeat PET/CT scan of a uniformly filled  $^{68}\text{Ga}$  phantom was performed on the same scanner, with activity measurements on a Capintec CRC-55tR RC with updated  $^{68}\text{Ga}$   $CF_{RC}$ . The phantom filling and analysis was identical to that of original  $^{68}\text{Ga}$  uniform phantom prior to the cross-calibration exercise.

## 3. Results

### 3.1. Initial $^{68}\text{Ga}$ uniform phantom

In the initial  $^{68}\text{Ga}$  uniform phantom the measured  $SUV_{mean}$  was 0.88. This is below the local tolerance of  $1.00 \pm 0.05$ .

### 3.2. $^{68}\text{Ga}$ cross-calibration exercise

The results of the RC cross-calibration exercise are summarised in Table 1. The results demonstrate a systematic overestimation of  $^{68}\text{Ga}$  activity of 7.8–9.4% (mean 8.5%) when measuring on the Capintec CRC-55tR model RC using the default  $^{68}\text{Ga}$   $CF_{RC}$  of 416, compared to a Fidelis Secondary Standard RC. This is outside the NPL Guide No. 93 recommended tolerance of  $\pm 5\%$ . The result for the Veenstra calibrator

was within the tolerance of  $\pm 5\%$ . The Capintec  $^{68}\text{Ga}$   $CF_{RC}$ s were adjusted to 456–464 using Eq. (3) to match the Fidelis activity measurement.

The uncertainty in calculated values has been estimated by combining the uncertainties in the following variables; uncertainty in the reference activity (calculated as  $\pm 0.1\%$  using the standard deviation of 10 repeated measurements), uncertainty in  $^{68}\text{Ga}$  activity related to recording measurement times to the nearest minute rather than second ( $\pm 0.5\%$  for each measurement due to decay in  $\pm 30$  s, or  $\pm 0.7\%$  when combining uncertainty in  $A_{ref}$  and  $A_{measured}$ ), and the uncertainty in the constants applied in Eq. (3) due to the variation of individual Capintec RC chamber responses. As repeated measurements of the  $^{68}\text{Ga}$  activity were not taken in the Capintec CRC-55tR RCs, we cannot take the additional uncertainty in  $A_{measured}$  into account; therefore the quoted uncertainties are underestimated. However the repeatability of  $A_{measured}$  was retrospectively estimated by calculating the coefficient of variation of 10 repeated decay corrected measurements of the same  $^{68}\text{Ga}$  source in a Capintec CRC-55tR, which was equal to 0.7%.

### 3.3. Repeat $^{68}\text{Ga}$ uniform phantom

For the repeat  $^{68}\text{Ga}$  uniform phantom scan, with activities measured on Capintec CRC-55tR 1 with an updated  $^{68}\text{Ga}$   $CF_{RC}$  of 457, the measured  $SUV_{mean}$  was 0.97, within the local tolerance of  $1.00 \pm 0.05$ .

## 4. Discussion

At our centre, RC cross-calibrations with a Fidelis Secondary Standard RC are performed annually with  $^{18}\text{F}$ . During these tests a discrepancy in  $^{18}\text{F}$  activity measurement between the Capintec CRC-55tRs and the Fidelis Secondary Standard had been previously identified and corrected for by adjusting the Capintec  $CF_{RC}$  for  $^{18}\text{F}$ , using the methodology described here for  $^{68}\text{Ga}$ . The  $^{18}\text{F}$   $CF_{RC}$  was updated from 472 to 451 for all of our Capintec CRC-55tRs, resulting in an approximately 4% increase in  $^{18}\text{F}$  activity measurement. However we had not previously performed a cross-calibration with  $^{68}\text{Ga}$ .

As previously discussed, a 4% increase in the value for activity measured for  $^{18}\text{F}$  will not affect  $^{18}\text{F}$  SUV, but will affect the SUV of other PET radionuclides such as  $^{68}\text{Ga}$ . However the expected change would be an approximate 4% increase in  $^{68}\text{Ga}$  SUV, which makes the low measured  $^{68}\text{Ga}$   $SUV_{mean}$  of 0.88 even more surprising. Adjusting the  $^{68}\text{Ga}$   $CF_{RC}$  so that the activity measurement was reduced resulted in a measured  $^{68}\text{Ga}$   $SUV_{mean}$  that increased by an approximately equivalent percentage, which is an expected result when applying Eq. (1) to calculate SUV. It is therefore clear that the initial underestimation in  $^{68}\text{Ga}$   $SUV_{mean}$  was primarily caused by the overestimation of  $^{68}\text{Ga}$  activity measurement in the Capintec CRC-55tR RC. Similar results have also been reported in Australia by Bailey et al. [12], indicating that the incorrect pre-set  $^{68}\text{Ga}$   $CF_{RC}$  for Capintec RCs is not an isolated incident.

The explanation for the Capintec CRC-55tR overestimation of  $^{68}\text{Ga}$  activity may be the result of a previous discrepancy between measurements at the primary standards at National Metrology Institutes (NMIs) in the USA and in Europe for both  $^{18}\text{F}$  and  $^{68}\text{Ga}$ . In the USA, the NMI is the National Institute of Standards and Technology (NIST).

Table 1

RC cross-calibration results and derived new calibrator factors for  $^{68}\text{Ga}$ .

RC Model and Name	Default pre-set $^{68}\text{Ga}$ $CF_{RC}$	$^{68}\text{Ga}$ Activity Measurement: Percentage Difference from Fidelis Secondary Standard Reference (Uncertainty in Brackets)	$^{68}\text{Ga}$ $CF_{RC}$ required to match Fidelis Reference Activity (Uncertainty in Brackets)
Capintec CRC-55tR 1	416	+8.1 (6.9–9.3) %	457 (451–464)
Capintec CRC-55tR 2	416	+9.4 (8.2–10.6) %	464 (457–471)
Capintec CRC-55tR 3	416	+7.8 (6.7–9.0) %	456 (449–462)
Capintec CRC-55tR 4	416	+8.2 (7.0–9.4) %	458 (451–464)
Capintec CRC-55tR 5	416	+9.1 (7.9–10.3) %	462 (456–469)
Veenstra VDC-505	$747 \times 1.0$	+3.8 (2.6–4.9) %	–

Capintec, Inc is based in the USA, and the pre-set  $CF_{RC}$ s on Capintec RCs are derived from measurements at NIST. In the UK, the National Metrology Institute is the NPL, which also designs and specifies the Fidelis Secondary Standard RC. A difference between the NIST primary standard and the NPL primary standard will therefore result in an error when comparing an activity measurement on a Capintec RC to a Fidelis Secondary Standard RC. The Veenstra VDC-505 RC was produced in The Netherlands, and its  $CF_{RC}$ s for  $^{18}F$  and  $^{68}Ga$  are derived from the primary standard at the NMI in France (LNE-LNHB).

In 2014, NIST reported a new primary standardisation of  $^{18}F$  in that resulted in a change in  $^{18}F$  activity measurement of approximately +4% [13]. International measurement comparisons between primary standards at NMIs worldwide organised by the Bureau International des Poids et Mesures (BIPM) indicate that this change has resulted in a ‘greatly improved degree of equivalence’ for the NIST  $^{18}F$  primary standardisation in comparison to other primary standards such as those at NPL and LNE-LNHB [14]. Whilst the CRC-55tRs in our department were purchased after 2014, the pre-set  $CF_{RC}$ s may not have taken this change into account, especially as pre-set  $CF_{RC}$ s for individual radionuclides are not always directly calibrated against primary standard measurements, and may instead be estimated based upon nuclear data and standard response curves, which is a potential source of error.

Recently, Capintec have issued updated  $CF_{RC}$ s for both  $^{18}F$  and  $^{68}Ga$  that broadly reflect the results reported in this paper. In May 2018, after the measurements in this study were taken, Capintec published a Technical Bulletin on their website specifying an update in the  $CF_{RC}$  for both  $^{18}F$  and  $^{68}Ga$  (and  $^{133}Ba$  and  $^{137}Cs$ ), ‘based on review of the most recent NIST publications and metrology data’ [15]. The update applied to Capintec models; CRC-PC Smart Chamber HL, CRC-55tR, CRC-55tW, CRC-25R, and CRC-15R, and the recommended  $CF_{RC}$ s are for the NIST SRM geometry of 5 ml in a glass vial of 0.6 mm thickness. The recommended  $CF_{RC}$  for  $^{18}F$  was updated from 472 to 450, with a variance of +4.1%. This is very similar to the  $CF_{RC}$  for  $^{18}F$  of 451 previously established at our centre. The recommended  $CF_{RC}$  for  $^{68}Ga$  was updated from 416 to 442, with a variance of –5.1%. The update does not completely compensate for the 7.8–9.4% overestimation observed in our results (which used a different source container and geometry), but does significantly improve the accuracy of a Capintec RC in measuring  $^{68}Ga$  activity when compared to a reference Fidelis Secondary Standard RC.

The underestimation in  $^{68}Ga$  SUV in the initial  $^{68}Ga$  uniform phantom would have been even greater if the  $CF_{RC}$  for  $^{18}F$  had not been previously updated at our centre, as the overestimation of  $^{68}Ga$  activity would be combined with an underestimation of  $^{18}F$  activity. This would increase the overestimation of  $^{68}Ga$  activity relative to  $^{18}F$  activity, therefore increasing the magnitude of underestimation of  $^{68}Ga$  SUV. This may explain the higher magnitudes of  $^{68}Ga$  SUV underestimation of –13% to –23% reported by the group in Australia [12], compared to the –12% (0.88) measured in this study for the initial  $^{68}Ga$  uniform phantom.

It should be noted that even after adjusting the  $CF_{RC}$  for  $^{68}Ga$  (and previously for  $^{18}F$ ), the  $SUV_{mean}$  in a uniform  $^{68}Ga$  phantom of 0.97 was still < 1.00, albeit within  $\pm 5\%$ . This may be a result of an imperfect application of corrections for  $^{68}Ga$  to the  $^{18}F$  derived  $CF_{SUV}$ . The prompt gamma emission at 1.08 MeV is a potential cause of a mis-correction, although a prompt gamma correction is applied by the scanner. Low recovery coefficients in a PET NEMA Image Quality phantom have also been reported for  $^{68}Ga$  compared to  $^{18}F$  [16]. However this is also contributed to by the poorer spatial resolution of  $^{68}Ga$  PET images due to its increased positron range resulting in more significant partial volume effect losses, which should not affect the SUV in the large volume uniform phantom used in our investigation. Another potential cause of the low SUV is that when filling the uniform phantom the  $^{68}Ga$  activity was measured in a syringe rather than in a vial. Less attenuation is expected in a plastic syringe than a glass vial, and therefore the  $CF_{RC}$  is required to be greater. This is reflected in the recommended  $CF_{RC}$ s in

the May 2018 Technical Bulletin [15] of 447 for 3 ml of  $^{68}Ga$  in a 6 ml syringe, compared to 442 for a vial of  $^{68}Ga$  in the NIST SRM geometry. Separate  $CF_{RC}$ s for syringes were not considered in this study, and therefore the activity in the syringe may have been overestimated when using a  $CF_{RC}$  derived from measurements in a vial, resulting in the underestimation of SUV.

A further consideration is that in November 2018, after the measurements in this study were taken, the NPL published a new set of calibration factors for the Fidelis Secondary Standard RC. These include a new factor for  $^{68}Ga$  (+  $^{68}Ge$ ) in a 10R type1 + Schott vial (the  $^{68}Ge$  in brackets reflects  $^{68}Ge$  contaminants in the  $^{68}Ga$ , which corrections are applied for), following a comparison exercise between NMIs with  $^{68}Ge/^{68}Ga$  [17]. The previous set of calibration factors published by the NPL did not include a factor for  $^{68}Ga$  (+  $^{68}Ge$ ) for this vial type, instead a factor was quoted for a 10 ml P6 vial [18], as used in this study, which makes comparison between the two factors difficult. Following this update, we intend to perform a further cross-calibration exercise with  $^{68}Ga$  in a 10R type1 + Schott vial with the new Fidelis calibration factor to establish whether further updates in our Capintec CRC-55tR  $CF_{RC}$ s are required, and also establish  $CF_{RC}$ s for  $^{68}Ga$  in a syringe.

After identifying an inaccuracy in activity measurement of greater than the tolerance recommended by national guidance it was important to make adjustments that resulted in as accurate a measurement as possible, both to improve the accuracy of PET image quantification, and in order to satisfy legal requirements for accurately reporting the activity administered to the patient [19] and estimating discharge of radioactivity to the environment [20]. However it is also important to ensure that a change such as this is documented appropriately, as adjusting the  $^{68}Ga$   $CF_{RC}$  will linearly effect  $^{68}Ga$  SUVs, with for example a 10% decrease in activity measurement resulting in a 10% increase in all SUVs. There is therefore a risk of a change in SUV due to adjusting the  $^{68}Ga$   $CF_{RC}$  being incorrectly interpreted as a clinical change in the patient, which could erroneously influence patient management decisions with regards to treatment response, for example indicating disease progression rather than stable disease. Therefore it is recommended that the expected percentage change in SUV and date of this change should be recorded in all  $^{68}Ga$  image reports, so that this can be taken into account when comparing  $^{68}Ga$  SUVs to those obtained from images prior to the adjustment of the  $^{68}Ga$   $CF_{RC}$ .

The relatively short half-life of  $^{68}Ga$  can present difficulties in arranging a cross-calibration exercise for centres without local access to both a  $^{68}Ge/^{68}Ga$  generator and either a Secondary Standard Reference RC or the primary standard at a National Metrology Institute. An alternative method is to use a sealed  $^{68}Ge/^{68}Ga$  reference source, which is available for purchase [12], although the accuracy of the source calibration should be checked, as the uncertainties in activity can be large. In future cross-calibration exercises using a  $^{68}Ga$  source we will also endeavour to record measurement times to the nearest second, to allow as accurate a decay correction as possible.

## 5. Conclusions

An underestimation of  $^{68}Ga$  SUV was primarily caused by overestimation of  $^{68}Ga$  activity using the default pre-set calibrator factor setting on a Capintec CRC-55tR Radionuclide Dose Calibrator. An improvement in quantification accuracy was achieved by adjusting the calibrator factor based upon an external cross-calibration exercise.

We recommend SUV checks using a uniform phantom and regular calibrator cross-calibration exercises for all radionuclides used for quantitative PET/CT imaging.

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