Topical Sensor for the Assessment of Positron Emission Tomography Dose Administration; Metric Performance with an Autoinjector

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Footline: PET dose injection quality
Abstract

Introduction:
Extravasation or partial extravasation of the radiopharmaceutical dose quality in positron emission tomography (PET) can undermine standard uptake value (SUV) and image quality. A topical sensor (Lara) has been validated using a number of metrics to characterise injection quality following manual injection. An assessment of the performance of these metrics for autoinjector administration has been undertaken.

Method:
A single site, single PET/CT scanner was used to characterise injections using a KARL100 autoinjector with standardised apparatus, flush volume and infusion rate using Rad-inject pump (1 min infusion followed by 2 syringe flushes) for 18F-FDG, 68Ga-PSMA and 68Ga-DOTATATE. 296 patients with topical application of Lara sensors were retrospectively analysed using conventional statistical analysis and an artificial neural network.

Results:
Partial extravasation was noted in 1.1% of studies with 9.1% (inclusive of partial extravasation) identified to have an injection anomaly (eg. venous retention). Extravasation was independently predicted by the time elapsed as the counts recorded by the injection sensor fall from the maximum value to within 200% of the reference sensor counts (tc50) greater than 1200 seconds, the difference in counts for injection and reference sensors, normalized by dose, from 4 minutes post injection (ndAvgN) greater than 25, and the ratio of the average counts per second recorded by the injection sensor at the end of a monitoring period to those of the reference sensor (CEnd ratio) greater than 2.

Conclusion:
Extravasation and partial extravasation of PET doses are readily detected and differentiated using TAC metrics. The metrics can provide the insights that could inform image quality or SUV accuracy issues. Further validation of key metrics are recommended in a larger and more diverse cohort.
**Introduction**

Positron emission tomography (PET) and the standard uptake value (SUV) have been well documented to change management of 38% of oncology patients (1). PET and SUV rely on pharmacokinetic assumptions that assume an extravasation free injection. Extravasation occurs when part or all of the administered dose is injected outside the venous system or leaks into surrounding tissue (2,3,4). This may occur due to errors in placement of the needle or dislodgement. Dislodgement might occur in response to injection volume, injection pressure, movement or a number of patient factors. Partial extravasation of the intravenous (IV) dose administration undermines predictability of dose delivery, image quality and the accuracy of the SUV (2).

An examination of partial extravasation rates in 400 patients (5) reported a rate of 10.5% with 31% of those being undetected using standard imaging protocols (arms outside the field of view). A second study provided an analysis of 1367 patient studies and reported an 18% extravasation rate involving between 1% and 22% of the injected dose (6). A smaller single centre analysis reported 38% of patients with extravasated doses (7). Identifying and characterising PET dose partial extravasation confronts a number of challenges in the clinical setting. Firstly, the injection site is generally outside the field of view (arms up) and undetected. Second, dose administration techniques (infusion, autoinjectors) may prevent visual identification of signs of extravasation (pain and swelling) at the time of injection. Third, when partial extravasation is noted, quantifying the extent of extravasation and correcting SUV is not readily achievable. Consequently, the studies outlined above are likely to underestimate extravasation rates and impact. A broader literature review suggests the detectable extravasation rate (likely to be an underestimate) ranges from 9-23% for manual administrations (4).

A simple method for detecting and potentially characterising PET dose extravasation is the use of topically applied scintillation sensors to monitor activity migration from the injection site during the uptake phase. The only commercially available device designed for this purpose is the LARA (Lucerno Dynamics, LLC, Cary, NC, USA) device. The performance of the LARA device, to detect partial dose extravasation and provided dynamic data that assisted in characterising the extravasation, has been widely reported for manual administration of 18F-FDG (2,4,7). For 18F-FDG injections, hand, wrist or
forearm injections have higher extravasation rates than the antecubital fossa injections, higher PET doses increase extravasation rates, decreasing weight is associated with increased extravasation, and decreasing flush volume is associated with increased extravasation (4).

Generally, the administration of PET doses has not been monitored in the clinical scenario and this may reflect, compared to CT and MRI contrast administration, the very small relative volume of the PET dose, benign local consequences of extravasation and reliance on direct (manual) injection. It is important in principle and using detection systems, to differentiate dose extravasation, extravasation with complete resolution during the uptake period, and venous retention with rapid and complete resolution. The LARA device is coupled to Lucerno Dynamics proprietary software whose algorithm generates a number of metrics that guide decision making regarding dose injection quality and differentiation of extravasation and venous retention or other anomalies.

The aim of this investigation was to provide an evaluation of the quality assurance tool (LARA) and associated metrics. Specifically, to evaluate the role of metrics for characterisation of extravasation utilising the autoinjector injection method. Autoinjectors reduce contamination risk and staff occupational radiation exposure, however, the point of injection is not supervised to detect extravasation and the bolus profile may vary associated with the infusion process.

**Method**

The project was approved by institutional ethics committee for retrospective analysis of the data from a quality improvement initiative forming standard care in a single centre, single PET/CT scanner department. Patient’s referred for 18F-FDG, 68Ga-DOTATATE and 68Ga-PSMA PET/CT studies underwent LARA monitoring as part of their standard care. Patients were cannulated in any vein, generally the antecubital fossa. A 20-gauge needle was used unless circumstances demanded a different gauge. In each of 3 injection uptake rooms, LARA sensors (Lucerno Dynamics, LLC, Cary, NC, USA) were set up and applied to the subject using adhesive pads 7cm proximal to the injection site and the same site on the contralateral arm (reference arm) using the previously described method (7). The KARL100 autoinjector was connected through the wall to the cannula with the injection delivered to the patient.
via the Rad-inject pump over 1 minute. The Rad-inject pump then performed a double syringe flush at the same rate as the primary infusion. The total planned volume of the flush was standardized to 80 mL. After dose administration, sensors collected data at 1 second intervals throughout the uptake phase (generally 50 minutes before the patient was escorted to the scanning room). Once removed from the patient, the recording device was connected to a computer and data uploaded to the Lucerno platform, where it was interpreted by the software.

Analysis
The LARA data was extracted and presented as a time-activity curve (TAC) with the typical display showing the injection side in black and the reference side in red (figure 1). While the LARA metrics have been previously validated for manual injections of 18F-FDG using doses in the order of 10-20 mCi, a number of limitations associated with validity for this patient cohort demanded manual interpretation. These included the lower doses used for patient administration (5-10 mCi), the shape and width of the curve generated by the KARL100 autoinjector administration, and the use of 68Ga radiopharmaceuticals.

The manual interpretation of TACs was based on understanding ideal injection TACs; reference counts remaining low while the injection counts rapidly peak (c1) before rapidly declining to meet the reference levels (figure 1). Examination of the slope of the bolus injection on the TAC as it approaches the reference sensor TAC needs consideration (tHalf). The TAC counts for the injection sensor relative to the reference sensor was also evaluated at various points during the uptake period (CEndINJ, CEndREF, ndAvg1 and ndAvg). The time for the injection sensor to reduce to double the reference sensor counts was calculated (tc50) and the area under the curve (AUC) ratios between injection and reference sensor on the TACs was determined at multiple time points (aUCR10 and aUCR1). Specifically, the following metrics were calculated and analysed (figure 2):

- The aUCR10 is the AUC ratio between the injection and reference curves during the period 1-10 minutes post injection.
- aUCR1 is the AUC ratio between the injection and reference curves from 60 to 90 seconds post injection.
- c1 is the average counts per second recorded by the injection sensor during the interval between 60 and 90 seconds post injection.
- CEndINJ is the average counts per second recorded by the injection sensor at the end of a monitoring period.
- CEndREF is the average counts per second recorded by the reference sensor at the end of a monitoring period.
- tHalf is the average time in seconds for counts recorded by the injection sensor to fall to half of a previous value.
- tc50 is the time elapsed (in seconds) as the counts recorded by the injection sensor fall from the maximum value to within 200% of the reference sensor counts (ie. reference is 50% of the value of the injection curve).
- ndAvg1 is the difference in counts for injection and reference sensors, normalized by dose, during the interval between 60 and 90 seconds post injection.
- ndAvgN is the difference in counts for injection and reference sensors, normalized by dose, from 4 minutes post injection.
- The TAC “score” is a linear, weighted combination of these metrics, where the weights are determined from a logistic regression. Good injections are generally associated with a negative score while scores over 200 typically indicate part of the dose remains at the injection site.

These metrics are calculated automatically by the Lucerno algorithm without operator input.

The statistical significance was calculated using Chi-Square analysis for nominal data and Student’s t test for continuous data. The F test analysis of variances was used to determine statistically significant differences within grouped data. A P value less than 0.05 was considered significant.

**Results**

There were 296 valid cases with 1.3% (4) demonstrating evidence of extravasation on the TACs (figure 3) while 9.1% (27) inclusive of extravasation cases demonstrated some abnormality associated with dose administration (largely slow venous clearance in the TAC). Other key demographic data and differences amongst the different radiopharmaceuticals is summarised in table 1.
No statistically significant differences were noted between normal, abnormal (venous retention) and extravasated sub-groups with respect to dose (P=0.060) despite normal having a mean lower dose, radiopharmaceutical (P=0.315) despite a higher proportion of abnormal and extravasated studies being 18F-FDG, the person performing the injection (P=0.414), patient weight (P=0.529), age (P=0.365), gender (0.245) despite men showing a higher proportion of vascular retention and women a higher proportion of extravasation, location of injection (P=0.561) although there was a 2.1 times higher chance of extravasation for hand, wrist or forearm injections over antecubital fossa, or orientation (P=0.09) although there was higher proportion of abnormal and extravasated doses on the right side. A number of statistically significant differences were noted amongst the calculated metrics for the different injection outcomes (table 2). It should be noted that one study where the dose leaked from the injection apparatus was classified for these purposes as extravasation as the resulting TAC paralleled an extravasation curve. A number of TACs, particularly for 68Ga-PSMA, were truncated early with production of an end of curve count anomaly which could create an aberrant CEnd ratio (figure 4) requiring correction of the CEndINJ and CEndREF.

While the mean values showed discriminatory power between normal, abnormal and extravasated doses, at an individual dose level (indicated by the range and interquartile range), few metrics provided a defined cut-off between classifications. Specifically, there was overlap of not just the range for the injection score across the injection outcomes (table 2) but also the interquartile range. Conversely, tc50, ndAvgN and the newly created CEnd ratio demonstrated distinct cut-offs between extravasated injections and other injections (bold in table 2). The tc50 and CEnd ratio might also be used as a cut-off to indicate whether injection characteristics should be considered to influence SUV calculation. Furthermore, at the interquartile range level, ndAvgN also provided a cut-off to differentiate a normal injection from an abnormal (non-extravasated) injection with venous retention.

**Artificial Neural Network Analysis**

The previous statistical evaluation reported limitations associated LARA metrics for autoinjector TACs, including the TAC score. Extravasation was independently predicted by a tc50 greater than 1200, ndAvgN greater than 25 and CEnd ratio greater than 2. In this evaluation, the original data was re-evaluated using
an artificial neural network (Neural Analyser version 2.9.5). The purpose was to demonstrate the usefulness of machine learning as a parallel analysis approach with conventional statistical analysis (8-10), and to confirm or refute observations using conventional statistical analysis.

There were 36 input variables in 296 patients including extracted metrics, demographic data, injection parameters, and outcomes. A single binary output was an extravasated injection evidenced by the manual examination and characterisation of the TAC as previously described, or no extravasation (normal and other anomalies like venous retention). A correlation matrix (heat map) was calculated to identify redundancy amongst variables and exclusion where appropriate. Logistic correlations revealed dependency of the outcome (extravasation) on a number of variables with those of significance including tc50 (1.0), CEnd ratio (0.974) and ndAvgN (0.786) which supported the previous statistical analysis. The initial network architecture after omission of redundancy included 12 scaling layer inputs, 1 hidden layer of 3 nodes using a logistic activation function (defines the output of each node based on its input) and a single probabilistic layer (binary). The weighted squared error method was used to determine the loss index because there was an imbalance between positive and negative outputs (grounded truth). The neural parameters norm weight was employed as the regularisation method to control neural network complexity. A Quasi-Newtonian training method was employed using gradient information to estimate the inverse Hessian for each iteration of the algorithm (no second derivatives). The loss function associated with the training phase estimated the error associated with the data the neural network observed which reduced from 1.405 to 0.010 after 21 iterations. The selection loss is a measure of the neural networks’ agility (generalisability to new data) and in this case the error decreased from 1.452 to 0.0002 after 21 iterations. This indicates the need to optimise the final architecture.

A growing inputs method was used to calculate the correlation for every input against each output in the data set. Beginning with the most highly correlated inputs, progressively decreasing correlated inputs were added to the network until the selection loss increased and this allowed identification of the optimal number of inputs. Similarly, an incremental order method was used for input order selection, starting with the minimum order and adding perceptrons (and complexity) until the loss increased. The final architecture of the neural network reflects the optimised subset of inputs and order with the lowest
selection loss. In this case, the selection loss rose significantly for the second input with the training loss near optimal for 1 input. Thus, the optimal number of inputs was determined to be 1 with a training loss less than 0.001 and selection loss of 0.011. The optimal order was also 1 (single perceptron) with a training loss of 0.013 and selection loss less than 0.001. The final architecture had 1 scaling input layer (tc50), 1 hidden layer of a single node (perceptron) and a binary probabilistic output.

The final architecture was evaluated using a number of tests indicating robust validation using a subset of the original patient data. Using receiver operator characteristics (ROC) analysis demonstrated an AUC of 1.0. This correlates with a sensitivity of 100% and specificity of 100% and this is reflected in the confusion matrix (100% true positives, 100% true negatives, 0% false negative and 0% false positive). The cumulative gain analysis demonstrates excellent positive performance against random classification with a maximum gain score of 0.983.

Discussion

Partial extravasation of the patient dose, even with complete resolution during the uptake period, significantly changes the radiopharmaceutical kinetics and impacts the accuracy of the SUV. This arises due to the decreased activity imaged and the trickle-effect into the vascular space associated with extravasated injections (3). The precise impact of partial extravasation on SUV will depend on the pharmacokinetics of the infiltration; the proportion of the dose extravasated and the proportion and rate of any dose that re-enters circulation (4). While the precise impact on image quality and quantitation is difficult to determine (4), a tc50 calculation above 1200 seconds will almost certainly have a deleterious impact on SUV calculation and, subject to the proportion of the dose extravasated being greater than 5%, a tc50 between 600 and 1200 seconds may also result in SUV calculation errors but should prompt interpretative caution. A tc50 below 600 seconds indicates normality or venous retention with rapid clearance and negligible impact on SUV. Further investigation and validation of this metric is warranted for this purpose.

For 18F-FDG studies, the TAC score above 200 was only achieved in 33.3% of cases and this is likely to reflect the lack of validation against parameters used at this site; autoinjector slow bolus with double
flush triple peaks and significantly lower patient doses (approximately 5mCi compared to the 10mCi used for validation of the score metric). For classification of an extravasated dose, a score cut-off of 200 produced a 33% sensitivity and 96.8% specificity for the 18F-FDG subgroup. No alternative cut-off improved this performance. Clearly the utility may be improved with metrics that accommodate the broader bolus, slower clearance times and variations to patient dose. Indeed, the sensitivity and specificity in this study is well short of that previously reported (82% and 100%) in studies using 18F-FDG and manual injection only (4).

The automatically calculated metrics outlined above are particularly vulnerable to a broader bolus from slower administration and this is reflected in the less than optimal predictive performance of metrics dependent on curve behaviour in the first 5 minutes, including the TAC score. Metrics independent of behaviour of the TAC over the first 5 minutes (eg. tc50) were demonstrated to be more robust predictors of extravasation and, indeed, differentiation of extravasation versus venous retention and might be readily considered a marker for determining deleterious impact of injection kinetics on SUV calculation (eg. the tc50). A more detailed analysis of each metric calculated automatically in the Lucerno platform includes (figure 3):

- The aUCR10 assumes a tight bolus peaking at 1 minute post injection with rapid clearance which would produce a near 1:1 ratio for a normal injection. Abnormal injections depend on retention of injection sensor activity beyond 1 minute to produce a ratio beyond 2:1. Unfortunately, this metric is skewed by any delay in clearance (eg. venous retention), broader bolus and primary/secondary peaks associated with the autoinjector. While it may be less effective for differentiating normal from abnormal vascular retention, it should be sufficiently sensitive to predict extravasation. This metric is dose dependent so variability will occur with different dose activities administered.

- aUCR1 is limited to the period 60 to 90 seconds post injection and as such is more susceptible to variations in the TAC associated with the autoinjector and, thus, lower discriminatory power including for extravasation. This metric is dose dependent so variability will occur with different dose activities administered.
• c1 is the average counts per second recorded by the injection sensor during the interval between 60 and 90 seconds post injection. This will fluctuate with the dose administered and the radiopharmaceutical. The value of c1 is reliant on a tight bolus and thus the broader bolus of the autoinjector infusion combined with the multiple slow flushes (secondary and tertiary peaks) will undermine the rigor of this metric in predicting variation from normal as well as the efficacy of differentiating extravasation from venous retention. This metric is dose dependent so variability will occur with different dose activities administered.

• CEndINJ and CEndREF are likely be susceptible to variations in monitoring time. Indeed, there was a wide variety of monitoring periods ranging from 20 minutes through to 60 minutes. Nonetheless, identifying an end point beyond 20 minutes should exhibit, in the absence of extravasation, convergence of CEndINJ and CEndREF. Individually the metrics are not particularly useful as discriminators despite CEndINJ being higher for extravasation. These metrics are dose dependent so variability will occur with different dose activities administered.

• tHalf is a mean half clearance rate which should be higher for extravasated injections. Clearance is also delayed for venous retention and the clearance rate is confounded by the secondary and tertiary peaks associated with the autoinjector. It would be possible to employ mathematical curve stripping to extract a single curve representative of clearance but given the sensors are not positioned over the injection site itself, it may be more useful to express tHalf as the half clearance time for a specific period after the normal bolus period. For example, a tHalf from 5-10 minutes and a second from 10-20 minutes would provide more useful metrics to differentiate normal, venous retention and extravasated injections.

• tc50 appears to be the most useful metric for differentiating extravasation from other injection outcomes and perhaps makes the previously suggested 5-10min and 10-20min half clearance calculations redundant. A normal TAC including in patients with venous retention should see the injection counts approach the reference counts (to the point of injection being double or less the reference counts) by 10 minutes. A tc50 greater than 600 (seconds) suggests abnormality but a tc50 greater than 1200 (20 minutes) may offer a useful marker for certainty of extravasation.
- ndAvg1 is confounded by the broader peak and secondary/tertiary peaks associated with the autoinjector, and in patients exhibiting venous retention. This decreases the discriminatory value of this metric.
- ndAvgN should have good discriminatory power between normal injections (including with autoinjectors) and abnormal injections. Amongst abnormal injections, there may be difficulty differentiating venous retention from extravasation at 4 minutes post injection.
- The TAC score is a linear, weighted combination of these metrics. While the weights are determined from a logistic regression, in the case of the unique characteristics of TACs for the KARL100 autoinjector and Rad-inject pump, this may be simply multiplying redundancy. That is, multiplying metrics that offer the same insight and using multipliers that lack correlation.

CEnd ratio is a new metric introduced in this project that expresses the relationship of CEndINJ and CEndREF as a ratio. A ratio approximating 1:1 indicates normality at that time (normal injection or rapid resolution of venous retention) and is thought to offer a useful tool for differentiation of extravasation from other anomalies and normal injections.

A number of other automated measures, which contribute to determination of the TAC score, may be better as independent identifiers of extravasation including tc50 and ndAvgN. Using a tc50 cut-off of 600 seconds, 100% sensitivity and 100% specificity for identifying extravasation was noted using both conventional statistical analysis and artificial neural network analysis. That is, if at 20 min (1200 seconds), the reference curve is less than 50% of the value of the injection curve, careful consideration should be given to an extravasated injection. As previously discussed, a cut-off of 600 seconds provides 100% sensitivity but only 95% specificity with venous retention among the false positive cases. A cut-off of 25 for ndAvgN demonstrated 100% sensitivity and 99.7% specificity for classifying extravasation, although 100% sensitivity and specificity was noted for 18F-FDG studies only. The cut-off of zero (0) was used to classify abnormal TACs (venous retention but excluding extravasation) from normal TACs with a 95.5% sensitivity and 41.4% specificity. This project proposed the new metric CEnd ratio which, using a cut-off of 2, provides 100% sensitivity and specificity in classifying extravasation.
The use of topical sensors and automated scoring would add incremental clinical value with further validation of all metrics against low dose injections via autoinjectors for a range of radiopharmaceuticals. The predictive power of existing Lucerno metrics and those introduced in this project with respective cut-offs also need to be further validated but could provide deeper insight into injection behaviour. The TACs and metrics are sensitive to identification of extravasated injections which helps to characterise dose behaviour and obviate the need for imaging of the injection site. Specifically, the following are recommended markers but warrant further validation:

- tc50 greater than 1200 indicates extravasation and a negative impact on SUV,
- tc50 less than 600 indicates a normal injection or venous retention that resolves and no impact on SUV should be expected,
- tc50 between 600 and 1200 is not extravasated but needs careful assessment of poor bolus kinetics and the impact on SUV,
- ndAvgN less than 0 indicates a normal injection,
- ndAvgN greater than 25 indicates extravasation,
- ndAvgN between 0 and 25 suggests vascular retention but may be a normal injection,
- CEnd ratio greater than 2 indicates extravasation.

Artificial neural network analysis suggested scores generated by multiple metrics compounds error and includes redundancy; unnecessarily complex and increasing potential error. While CEnd ratio and ndAvgN were identified with tc50 as the key variables with very high correlation, use of these metrics in combination provide no greater predictive capability than tc50 alone; a case of Ockham’s razor.

Identification of the presence of extravasation does not provide an indication of actual impact on image quality or SUV accuracy. Further research is required to differentiate clinically important extravasation from evidence of clinically insignificant extravasation. The US NRC, with respect to radiopharmaceutical administration, have determined that extravasation frequently occurs, it is virtually impossible to avoid, and does not consider extravasation to be misadministration. As a result, extravasation avoids reporting and accountability requirements of misadministration. This study contradicts this position, with use of an autoinjector technique not only reducing staff doses but demonstrating that very low levels of extravasation are possible. Potentially eliminating extravasation for PET studies is possible and every
effort to achieve this reduction is essential to enhance image quality, improve SUV accuracy/reliability, and minimize unintentional radiation exposure to patient tissue. The recognition of extravasated doses as misadministration with associated investigation and reporting requirements of regulators in Australia may also be a factor in reducing rates.

Conclusion
Topical monitoring and characterisation of PET dose administration is possible and practical with the Lara device with careful consideration and validation of individual metrics. Extravasation and partial extravasation of PET doses are readily detected and differentiated using TAC metrics. The metrics can provide the insights that could inform image quality or SUV accuracy issues. Importantly, extravasation or partial extravasation of PET doses can be minimized with the use of an autoinjector. Further validation of key metrics are recommended in a larger and more diverse (radiopharmaceuticals, injection methods) cohort with discrimination between clinical significant and clinical insignificant extravasation cases.

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### Table 1: Summary of demographic data for the pooled data and for each radiopharmaceutical.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>18F-FDG</th>
<th>68Ga-PSMA</th>
<th>68Ga-DOTATATE</th>
<th>P</th>
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<tbody>
<tr>
<td>Proportion of studies</td>
<td>1.0</td>
<td>0.66</td>
<td>0.31</td>
<td>0.03</td>
<td></td>
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<tr>
<td>Extravasation rate (%)</td>
<td>1.3</td>
<td>1.5</td>
<td>1.1</td>
<td>0</td>
<td>0.887</td>
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<td>Abnormal TAC (%)</td>
<td>9.1</td>
<td>11.3</td>
<td>5.4</td>
<td>0</td>
<td>0.160</td>
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<tr>
<td>Mean dose (MBq)</td>
<td>187.1 (95% CI 181.8-192.4)</td>
<td>204.1 (95% CI 197.4-210.8)</td>
<td>152.9 (95% CI 150.4-155.5)</td>
<td>171.2 (95% CI 136.5-205.9)</td>
<td>&lt;0.001</td>
</tr>
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<td>Male (%)</td>
<td>71.0</td>
<td>59.3</td>
<td>100</td>
<td>50.0</td>
<td>0.008</td>
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<td>Antecubital injection (%)</td>
<td>86.1</td>
<td>84.0</td>
<td>91.3</td>
<td>80.0</td>
<td>0.333</td>
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<td>Left side injection (%)</td>
<td>70.3</td>
<td>68.0</td>
<td>72.8</td>
<td>90.0</td>
<td>0.271</td>
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<td>Experienced injector* (%)</td>
<td>66.9</td>
<td>64.4</td>
<td>73.9</td>
<td>50.0</td>
<td>0.405</td>
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<tr>
<td>Mean injection score</td>
<td>-209.5 (95% CI -253.3 to -165.7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Mean tHalf</td>
<td>25.3  (95% CI 20.3-30.3)</td>
<td>22.9 (95% CI 19.0-28.6)</td>
<td>31.5 (95% CI 17.6-45.4)</td>
<td>13.4 (95% CI 10.8-16.1)</td>
<td>0.206</td>
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<td>Mean aUCR10</td>
<td>1.4 (95% CI 1.3-1.6)</td>
<td>1.6 (95% CI 1.4-1.7)</td>
<td>1.2 (95% CI 0.9-1.4)</td>
<td>1.0 (95% CI 0.7-1.2)</td>
<td>0.007 (PSMA vs FDG only)</td>
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<tr>
<td>Mean tc50</td>
<td>172.3 (95% CI 124.3-220.3)</td>
<td>195.2 (95% CI 128.5-261.9)</td>
<td>135.6 (95% CI 71.1-200.0)</td>
<td>66.2 (95% CI 37.1-95.4)</td>
<td>0.384</td>
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<td>Mean aUCR1</td>
<td>4.9 (95% CI 4.1-5.6)</td>
<td>6.1 (95% CI 5.1-7.1)</td>
<td>2.6 (95% CI 1.6-3.6)</td>
<td>2.0 (95% CI 1.3-2.6)</td>
<td>&lt;0.001</td>
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<td>Mean c1</td>
<td>419.1 (95% CI 382.6-455.7)</td>
<td>538.7 (95% CI 496.7-580.7)</td>
<td>193.0 (95% CI 143.9-242.1)</td>
<td>179.8 (95% CI 128.9-230.8)</td>
<td>&lt;0.001</td>
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<td>Mean cEndINJ</td>
<td>118.1 (95% CI 113.4-122.9)</td>
<td>129.1 (95% CI 123.6-134.7)</td>
<td>98.0 (95% CI 90.0-106.0)</td>
<td>90.1 (95% CI 65.8-114.4)</td>
<td>&lt;0.001 (FDG vs both 68Ga)</td>
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<td>Mean CEndREF</td>
<td>123.8 (95% CI 119.8-127.9)</td>
<td>134.3 (95% CI 129.8-138.8)</td>
<td>101.9 (95% CI 95.3-108.4)</td>
<td>122.8 (95% CI 103.0-142.6)</td>
<td>&lt;0.001 (PSMA vs FDG &amp; DOTATATE)</td>
</tr>
<tr>
<td>Mean CEnd ratio</td>
<td>1.02 (95%CI 0.96-1.08)</td>
<td>1.00 (95%CI 0.93-1.08)</td>
<td>1.08 (95%CI 0.96-1.18)</td>
<td>0.79 (95%CI 0.46-1.12)</td>
<td>0.214</td>
</tr>
<tr>
<td>Mean ndAvg1</td>
<td>19.0 (95% CI 15.1-22.9)</td>
<td>25.1 (95% CI 20.5-29.8)</td>
<td>8.3 (95% CI 6.1-15.1)</td>
<td>-1.1 (95% CI -21.6 to 19.3)</td>
<td>&lt;0.001 (FDG vs both 68Ga)</td>
</tr>
<tr>
<td>Mean ndAvgN</td>
<td>-0.22 (95% CI -1.4 to 1.0)</td>
<td>0.49 (95% CI -1.02 to 2.00)</td>
<td>-1.1 (95% CI -3.3 to 1.1)</td>
<td>-6.0 (95% CI -12.7 to 0.6)</td>
<td>0.110</td>
</tr>
</tbody>
</table>

*Greater than 10 years clinical experience.
### Table 2: Summary of metrics against outcome of injection.

<table>
<thead>
<tr>
<th>Description</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Extravasated</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose (MBq)</td>
<td>Consistent with figure 3A</td>
<td>Consistent with figure 3B (vascular retention)</td>
<td>Consistent with figure 3C (infiltrated)</td>
<td>0.060</td>
</tr>
<tr>
<td>Male (%)</td>
<td>185.1</td>
<td>208.6</td>
<td>199.7</td>
<td>0.060</td>
</tr>
<tr>
<td>Antecubital injection (%)</td>
<td>70.6</td>
<td>86.4</td>
<td>60.0</td>
<td>0.245</td>
</tr>
<tr>
<td>Left side injection (%)</td>
<td>72.1</td>
<td>54.6</td>
<td>40.0</td>
<td>0.090</td>
</tr>
<tr>
<td>Experienced injector (%)</td>
<td>68.4</td>
<td>54.5</td>
<td>40.0</td>
<td>0.414</td>
</tr>
<tr>
<td>Score (FDG only) mean (95% CI) range (IQ range)</td>
<td>-267 (-306 to -229)</td>
<td>182 (64-299)</td>
<td>589 (294-885)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>thalf mean (95% CI) range (IQ range)</td>
<td>23.1 (17.9-28.3)</td>
<td>48.4 (30.2-66.6)</td>
<td>6.5-191.0 (22.2-65.8)</td>
<td>0.023</td>
</tr>
<tr>
<td>t50 mean (95% CI) range (IQ range)</td>
<td>1.2 (1.1-1.3)</td>
<td>2.7 (2.4-3.1)</td>
<td>6.7 (6.0-7.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>aUCR10 mean (95% CI) range (IQ range)</td>
<td>4.0 (3.3-4.7)</td>
<td>12.0 (9.5-14.4)</td>
<td>2.5-70.1 (4.5-12.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>c1 mean (95% CI) range (IQ range)</td>
<td>378 (342.9-412.7)</td>
<td>833 (711-955)</td>
<td>897 (642-1153)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CEndINJ mean (95% CI) range (IQ range)</td>
<td>114.7 (110.1-119.3)</td>
<td>130.5 (114.6-146.4)</td>
<td>251.0 (217.7-284.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CEndREF mean (95% CI) range (IQ range)</td>
<td>125.3 (121.2-129.4)</td>
<td>121.2 (107.0-135.5)</td>
<td>83.2 (53.2-113.2)</td>
<td>0.023</td>
</tr>
<tr>
<td>ndAvg1 mean (95% CI) range (IQ range)</td>
<td>0.93 (0.89-0.97)</td>
<td>1.09 (0.95-1.24)</td>
<td>3.14 (2.82-3.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ndAvgN mean (95% CI) range (IQ range)</td>
<td>13.5 (10.1-17.0)</td>
<td>66.8 (54.8-78.9)</td>
<td>107.3 (81.9-132.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
List of Figures

Figure 1: Annotated normal TAC (with the injection curve in black and the reference curve in grey). High count data is truncated in the software to ensure the relationship between injection and reference curves are graphically discernible. Key features of a normal TAC include prompt peak post injection (c1), rapid clearance (tHalf) with reversion to reference levels (ndAvgN) and a low reference level (CEndINJ compared to CEndREF). The tc50, or point where the injection curve is less than twice that of the reference curve, is also less than 600 seconds (10 min) and the difference between injection and reference curves at 4 min (ndAvg1) is low with the rapid clearance.
Figure 2: Annotated abnormal TAC indicating dose extravasation. A. highlights the AUC for the injection sensor (grey region) for aUCR10 on a patient with venous retention while B. highlights the AUC (grey region) for the reference sensor. The aUCR10 is calculated as a ratio of the AUC from A to the AUC from B. C. highlights the AUC for the injection sensor (grey region) for aUCR1 in a patient with extravasation of the dose while D. highlights the AUC (grey region) for the reference sensor. The aUCR1 is calculated as a ratio of the AUC from C to the AUC from D.
Figure 3: Annotated TACs for normal (A), normal with autoinjector multiple peaks and wider bolus (B), venous retention with resolution (C), extravasation without resolution (D). Each TAC is annotated with the Lucerno metrics automatically generated for monitored injections.
Figure 4: Sample 68Ga-PSMA TACs terminated early with generation of count anomalies erroneously used for CEndINJ and CEndREF calculations. Visual inspection of each TAC should allow identification and mitigation of risk, including identifying the correct CEnd point.