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March 4, 2020

Michael Layton, Director
Division of Materials, Safety, Security, State and Tribal Programs
Office of Nuclear Material Safety and Safeguards
Nuclear Regulatory Commission

Dear Michael,

I wanted to update you on two topics that are relevant to the NRC independent evaluation of the 1980 NRC internal policy that exempts all infiltrations that exceed Subpart M reporting thresholds from reporting.

Recently, an article - "Topical Sensor for the Assessment of Injection Quality for 18F-FDG, 68Ga-PSMA and 68Ga-DOTATATE Positron Emission Tomography" - was published in the Journal of Medical Imaging and Radiation Sciences. Here is a link: https://www.jmirs.org/article/S1939-8654(20)30003-5/pdf A hard copy of the full-text is attached for your review.

Like the previous article I sent you, this is another article that is important to your independent evaluation; it also demonstrates that the assumption underlying the NRC 1980 exemption policy is incorrect - extravasations are NOT “virtually impossible to avoid”, but in fact, can be almost completely avoided. In this paper, an Australian center reported a 1.1% partial extravasation rate in 296 consecutive patients. This paper demonstrates that the injection approach taken in most Australian nuclear medicine centers results in high quality injections.

Additionally, I am attaching a hard copy of a letter, dated 2/26/2020, from the Organization of Agreement States (OAS) to the NRC Commissioners. The letter clarifies the OAS position on the January 28, 2020 NRC public presentation. Please note that the OAS Board, which represents the position of all 39 member states, is pleased your team is conducting an independent evaluation. Additionally, the OAS Board notes that they also support the ACMUI **dissenting opinion** on reporting of extravasations – the OAS agrees that extravasations that exceed the medical event reporting limits should be reported. In addition to the attachment, here is the link to the letter: https://adamswebsearch2.nrc.gov/webSearch2/main.jsp?AccessionNumber=ML20058C783

In addition to the Australian and OAS evidence, please be aware that the novel dosimetry method has been submitted for publication. Additionally, Lucerno is waiting on 19 more deidentified images of moderate to significant infiltrations from our customers to be sent to

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us to perform dosimetry. As we evaluate these images and perform dosimetry, we will supply you with the results.

Thank you for the consideration of this additional evidence that supports the need for extravasation reporting.

Sincerely,

DocuSigned by:
Ron Lattanze
0C2FCDBE78A7435...

Ron Lattanze
Chief Executive Officer

Enclosures
1. Paper published in JMIRS
2. OAS Board letter to NRC

cc:
Chris Einberg
Lisa Dimmick
Said Daibes
Kellee Jamerson
Donna-Beth Howe

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Research Article

Topical Sensor for the Assessment of Injection Quality for 18F-FDG, 68Ga-PSMA and 68Ga-DOTATATE Positron Emission Tomography

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ABSTRACT

Introduction: Calculation of the standard uptake value (SUV) and image quality in positron emission tomography (PET) hinges on accurate dose delivery. Extravasation or partial extravasation of the radiopharmaceutical dose can undermine SUV and image quality, and contribute to unnecessary imaging (time and CT dose). Topical sensor characterisation of injections has been reported, with extravasation rates ranging from 9% to 23% for 18F-FDG after manual injection.

Method: A single site, single PET/CT scanner was used to characterise injections using an autoinjector with standardised apparatus, flush volume and infusion rate using 18F-FDG, 68Ga-PSMA and 68Ga-DOTATATE; more reflective of Australian PET facilities. 296 patients with topical application of LARA sensors were retrospectively analysed.

Results: Only 1.1% of studies showed evidence of partial dose extravasation. In total, 9.1% were identified to have an injection anomaly (including venous retention). No statistically significant differences were noted across the radiopharmaceuticals for demographic data. Although not demonstrating a statistically significant correlation, there was more extravasated doses associated with female patients ($P = .334$), right side ($P = .372$), and hand injections ($P = .539$). Extravasation was independent of dose administered ($P = .495$), the radiopharmaceutical ($P = .887$), who injected the dose ($P = .343$), height ($P = .438$), weight ($P = .607$) or age ($P = .716$). Extravasation was associated with higher glucose levels ($P < .001$), higher t-half ($P = .019$) and higher aUCR10, tc50, aUCR1 and c1 (all $P < .001$).

Conclusion: Topical monitoring and characterisation of PET dose administration is possible and practical with the LARA device. Extravasation and partial extravasation of PET doses are not only readily detected but they are also preventable. The LARA device can provide the insights into variables that could eliminate extravasation as a cause of image quality or SUV accuracy issues.

RÉSUMÉ

Introduction : Le calcul de la valeur de fixation normalisée (SUV) et la qualité de l'image en tomographie par émission de positrons (TEP) reposent sur l'administration d'une dose précise. L'extravasation ou l'extravasation partielle de la dose de produit radiopharmaceutique peut nuire à la SUV et à la qualité de l'image, et contribuer à de l'imagerie inutile (temps et dose de TDM). Une caractérisation topique de la sonde a été signalée pour les injections, avec des taux d'extravasation allant de 9 à 23 % pour le 18F-FDG après injection manuelle.

Méthodologie : Un seul appareil de TEP/TDM sur site unique a été utilisé pour caractériser les injections faites au moyen d'un autoinjecteur avec appareillage, volume de rinçage et taux d'infusion normalisés avec utilisation de 18F-FDG, 68Ga-PSMA et 68Ga-DOTATATE; plus représentatif des installations de TEP en Australie. L'analyse rétrospective a porté sur 296 patients avec application topique de sondes LARA.

Résultats : À peine 1,1 % des études ont montré des signes d'extravasation partielle de la dose. Au total, 9,1 % ont présenté une anomalie d'injection (incluant la rétention veineuse). Aucune différence statistiquement significative n'a été constatée entre les produits radiopharmaceutiques pour les données démographiques. Bien qu'il n'y ait pas de corrélation statistiquement significative, l'extravasation de dose a été plus fréquente chez les femmes ($P = ,334$) et pour l'injection du côté droit ($P = ,372$) et dans la main ($P = ,539$). L'extravasation était indépendante de la dose administrée ($P = ,495$), du produit radiopharmaceutique utilisé ($P = ,887$), de la personne ayant fait l'injection ($P = ,343$), de la taille ($P = ,438$), du poids ($P = ,607$) ou de l'âge ($P = ,716$) des patients. L'extravasation était associée à des taux de glucose plus élevés ($P < ,001$), à une demi-vie plus longue ($P = ,019$) et à un niveau plus élevé de aUCR10, tc50, aUCR1 et c1 ($P < ,001$ pour tous).

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Conclusion : La surveillance et la caractérisation topiques de l'administration de la dose en TEP sont possibles et pratiques avec l'appareil LARA. L'extravasation et l'extravasation partielle de la dose de TEP sont non seulement facilement détectables, mais peuvent aussi être prévenues. L'appareil LARA peut donner un aperçu des variables susceptibles d'éliminer l'extravasation comme cause des problèmes de qualité d'image ou de précision de la SUV.

Keywords: PET; 18F-FDG; 68Ga-PSMA; extravasation; LARA

Introduction

Positron emission tomography (PET) and quantitative values such as the standard uptake value (SUV) have been well documented to change management of 38% of oncology patients [1]. Clinically, PET and SUV, traditionally for 18F-FDG and now also for 68Ga-PSMA and 68Ga-DOTATATE, require pharmacokinetic assumptions including predictable dose delivery. Extravasation or infiltration occurs when the dose, or part thereof, is administered outside the venous system [2–4]. Partial extravasation of the intravenous (IV) dose administration undermines predictability of dose delivery and potentially the accuracy of SUV calculations [2]. The dose administration should be a bolus over approximately 1 minute [3]. The subsequent uptake period varies from 45 to 60 minutes but for accurate SUV consistency of timing is required. Partial extravasation, even with complete resolution during the uptake period, changes the kinetics into the tumour; rendering the SUV less accurate. The decreased activity imaged and the trickle effect into the vascular space associated with extravasated injections can degrade overall image quality [3]. The impact of partial extravasation on image quality and quantitation depends on pharmacokinetics of the infiltration: the proportion extravasated, the proportion and rate of any dose that re-enters circulation relative to the imaging time, and the proportion that does not migrate from the extravasated site within the effective imaging window [4]. Nonetheless, the precise impact on image quality and quantitation cannot be determined at this time [4]. Traditionally, the administration of PET doses have not been monitored as might be expected of CT and MRI contrast and this, in part, reflects the very small relative volume of the PET dose and reliance on direct (manual) injection.

There have been a number of studies of extravasation rates with significant variation in the reported rate. A study of 400 patients [5] indicated that the extravasation rate was 10.5% but 31% of those would have been undetected with standard imaging protocols (arms outside the field of view). A small subcohort of patients were reimaged and it was determined that the SUV was lowered by approximately 10% in studies with extravasation [5]. In another study, an analysis of 1367 patient studies, 18% demonstrated extravasation which was quantitated to represent between 1% and 22% of the injected dose [6]. A smaller single-centre analysis reported 38% of patients with extravasated doses [7]. Although an indication of dose extravasation may include pain or swelling at the site of injection, visual evaluation of images post-PET procedure is perhaps the most common approach. Because the injection site may be outside the field of view with whole-body PET performed typically with the arms hyperextended above the head, this method is not always accurate [3]. Consequently, the studies outlined previously are likely to underestimate extravasation rates. A broader literature review suggests the detectable extravasation rate (likely to be an underestimate) ranges from 3% to 23% [4].

A simple method for detecting extravasation is the use of the LARA (Lucerno Dynamics, LLC, Cary, NC) device that uses topically applied scintillation sensors to monitor activity migration in from the injection site during the uptake phase. Williams et al [2], used a topical device (LARA) in FDG PET patients and demonstrated that it helped to detect partial dose extravasation independent of the imaging protocol and provided dynamic data that assisted in characterising the extravasation. Visual detection of extravasated doses identified 38% incidence but the addition of the LARA device demonstrated the true extravasation rate was in fact 55% [7]. Wong et al used the topical device to determine PET extravasation rates across 7 institutions identifying extravasation rates. Although technologists were aware injections were being monitored and had been counselled on the importance of injection quality (perhaps lowering natural extravasation rates), they were not privy to the data acquired for each injection. The extravasation rate was reported to range from 1.9% to 15.7%. Four sites underwent an improvement cycle and re-evaluated PET injections which resulted in a 48% reduction in extravasation rates. The key observations from this study included that it was only 18F-FDG injections, hand, wrist, or forearm injections have higher extravasation rates than the antecubital fossa injections, higher doses increase extravasation rate, decreasing weight is associated with increased extravasation, and decreasing flush volume is associated with increased extravasation [4]. It is perhaps pertinent to differentiate dose extravasation from venous retention with rapid and complete resolution.

The aim of this investigation was to provide an Australian context to extravasation rates in PET using the quality assurance device (LARA). Specifically, to evaluate the role of topical sensors for characterisation of extravasation rates for PET using 18F-FDG, 68Ga-PSMA and 68Ga-DOTATATE, and utilising a single injection method using an autoinjector; radiopharmaceutical profile and autoinjector use is typical in Australia. Automatic injectors reduce contamination risk and staff radiation doses; however, the point of injection is not supervised to detect extravasation. An occlusion sensor is generally fitted that raises an alert if the pressure reaches 3 bar.

Method

This was a single-centre, single PET/CT scanner department as a quality improvement initiative forming standard care. The project was approved by institutional ethics committee for retrospective analysis of the data. LARA systems were set up in 3 injection/uptake rooms. In each uptake room, LARA sensors (Lucerno Dynamics) were applied to the subject using adhesive pads 7 cm proximal to the injection site and the same site on the contralateral arm (reference arm) (as previously described; [7]). These sensors were connected to a small recording device which sits in a holder nearby. The subject was reclined in a chair in a comfortable position. The KARL100 autoinjector was then connected through the wall to the cannula to begin the injection, and the uptake phase as standard protocol. The auto injection machine administers the correct dose into the syringe and the dose is administered to the patient via the Rad-inject pump over 1 minute. The Rad-inject pump then performs a double syringe flush at the same rate as the primary infusion.

Patients referred for 18F-FDG, 68Ga-DOTATATE and 68Ga-PSMA PET/CT studies underwent LARA monitoring as part of their standard care. The patient was cannulated in any vein, generally the antecubital fossa. A 20-gauge needle was used unless circumstances demanded a different gauge. After dose administration, sensors collected data at 1 second intervals throughout the uptake phase (generally 50 minutes when 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 were extracted and presented as a time-activity curve (TAC). The injection side is displayed as a black curve and the reference side as red (Figure 1). For 18F-FDG manual injections, and autoinjections using the Bayer Intego system with higher doses (in the order of 10–20 mCi), analysis tools have been previously validated to produce an injection score. Good injections are generally associated with a negative score whereas scores over 200 typically indicate part of the dose remains at the injection site. While these software tools were analysed, a number of limitations associated with validity for this patient cohort demanded manual interpretation. These included the lower doses used for patient administration (less than half), the shape of the curve generated by the KARL100 autoinjector administration consistently over 1 min with a double syringe flush with 1 min infusions followed by the balance of 80 mL flush infusion during uptake rather than shorter bolus typical of manual injection, the use of 68 Ga radiopharmaceuticals that are yet to be validated by the software.

The manual interpretation of TACs considered several factors but is fundamentally based on understanding ideal injection TACs. Ideal injection TACs are consistently similar in features with the reference counts remaining low while the injection counts rapidly peak after injection 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 was considered. The TAC counts for the injection sensor relative to the reference sensor were evaluated at various points during the uptake period. The time for the injection sensor to reduce to double the reference sensor counts was examined. The area under the curve (AUC) ratios between injection and reference sensor on the TACs were also examined. Specifically, the following metrics were collected and analysed:

- aUCR10 is the area under the curve (AUC) ratio between the AUC for the injection and reference curves limited to the period 1–10 minutes after injection.
- aUCR1 is the AUC ratio between the AUC for the injection and reference curves limited to the period 60 to 90 seconds after injection.
- c1 is the average counts per second recorded by the injection sensor during the interval between 60 and 90 seconds after injection.
- CEndINJ is the average counts per second recorded by the injection sensor at the end of a scan.
- CEndREF is the average counts per second recorded by the reference sensor at the end of a scan.
- t-Half 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.
- ndAvg1 is the difference in counts at injection and reference sensors, normalised by dose, during the interval between 60 and 90 seconds after injection.
- ndAvg is the difference in counts at injection and reference sensors, normalised by dose, after 4 minutes after injection.
- The TAC "score" is a linear, weighted combination of these metrics, where the weights are determined from a logistic regression.

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

The statistical significance was calculated using the chi-square analysis for nominal data and Student's *t*-test for continuous data. The Pearson chi-square (χ^2) test was used for categorical data with normal distribution and the likelihood ratio chi-square (G^2) test for categorical data without normal distribution. The *F* test analysis of variances was used to determine statistically significant differences within grouped data. A *P* value less than .05 was considered significant. Normality of distribution was determined using the Shapiro-Wilk W test with a *P* value less than .05 indicating that the data vary significantly from normality. The differences between independent means and proportions were calculated with a 95% confidence interval (CI). CIs without an overlap and/or those which did not include zero were considered to support a statistically significant difference

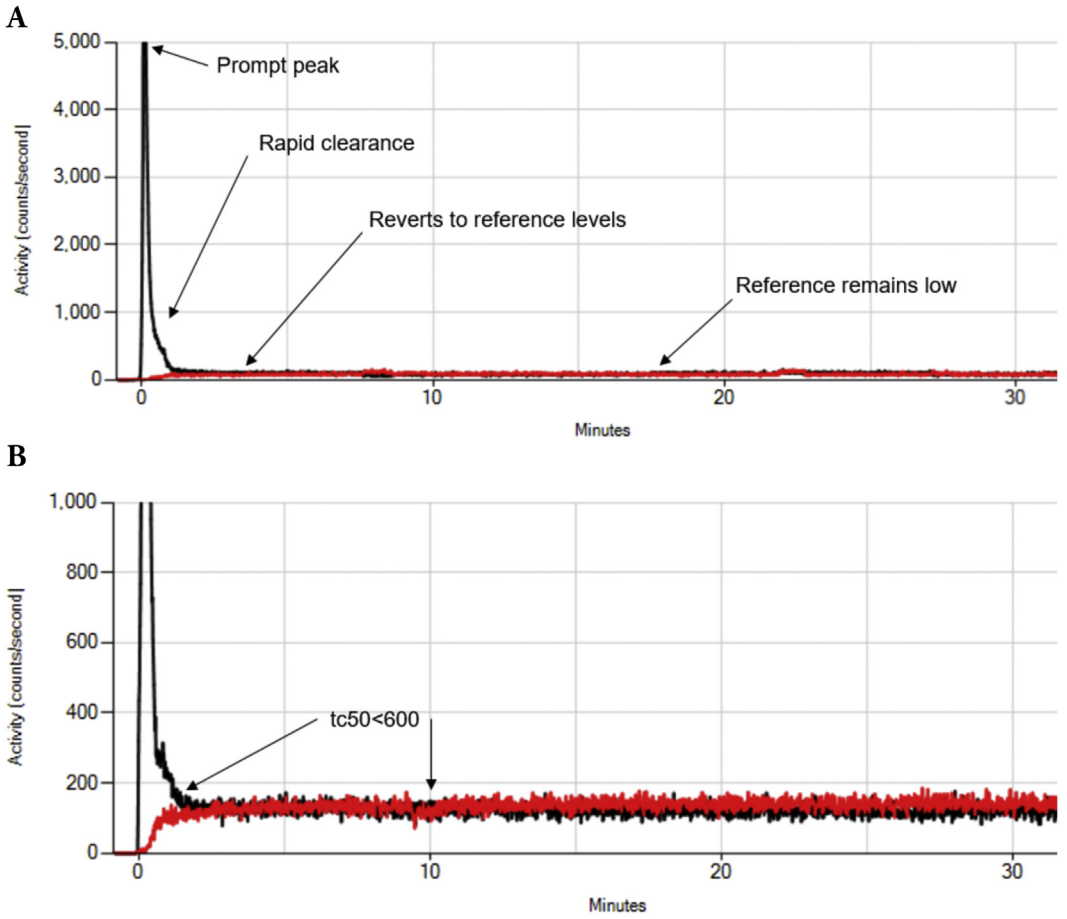

Figure 1. Annotated normal TAC (A. or top) and standard normal TAC with tc50 (B. or bottom) with the injection curve in black and the reference curve in red. High count data are truncated in the software to ensure the relationship between injection and reference curves are graphically discernible. Key features of a normal TAC include prompt peak after injection, rapid clearance with reversion to reference levels, and a low reference level. The tc50 or point where the injection curve is less than twice that of the reference curve should also be less than 600 (10 min). TAC, time-activity curve.

whereas confidence intervals with an overlap and/or those that included zero represented differences for which chance could not be excluded as the cause.

Results

Pooling all patients, 301 patient studies were acquired with 5 being omitted due to absent data, leaving 296 valid cases. Only 4 (1.3%) studies demonstrated evidence of extravasation (Figure 2), whereas 9.1% (27) demonstrated some abnormality associated with dose administration (largely slow venous clearance in the TAC). Other key demographic data and differences among the different radiopharmaceuticals is summarised in Table 1.

With only 4 cases of extravasated doses among 296 studies, there was inadequate statistical power to draw any conclusions (Figure 2). Although not demonstrating a statistically significant correlation, there was more extravasated doses associated with female patients ($P = .334$), right side ($P = .372$), hand injections ($P = .539$); there is a 2.1 higher chance of extravasation for hand, wrist or forearm injections over antecubital fossa. The TAC score ($P = .119$) was confounded by changes to scores associated with nonextravasated but abnormal TACs due to venous retention. Extravasation was independent of dose administered ($P = .495$), the radiopharmaceutical ($P = .887$), who injected the dose ($P = .343$), height ($P = .438$), weight ($P = .607$) or age ($P = .716$). Breaking the staff performing injection into experienced (10+ years) versus less experienced (<5 years) grouping, the junior staff had a 1.44 higher likelihood of experiencing extravasation on the TAC. Extravasation was associated with higher glucose levels ($P < .001$), higher t-half ($P = .019$) and higher aUCR10, tc50, aUCR1 and c1 (all $P < .001$).

When considering abnormal TACs (extravasation plus venous retention that resolves rapidly as shown in Figure 3), abnormal TACs were independent of the radiopharmaceutical ($P = .160$), who injected the dose ($P = .140$), glucose level ($P = .714$), weight ($P = .259$) or age ($P = .233$). Breaking the staff performing injection into experienced vs. less experienced grouping, the junior staff had a 2.01 higher likelihood of experiencing an abnormal TAC (although juniors also 1.33 times more likely to inject in the right arm). While not demonstrating a statistically significant correlation, there was more abnormal TACs associated with male patients

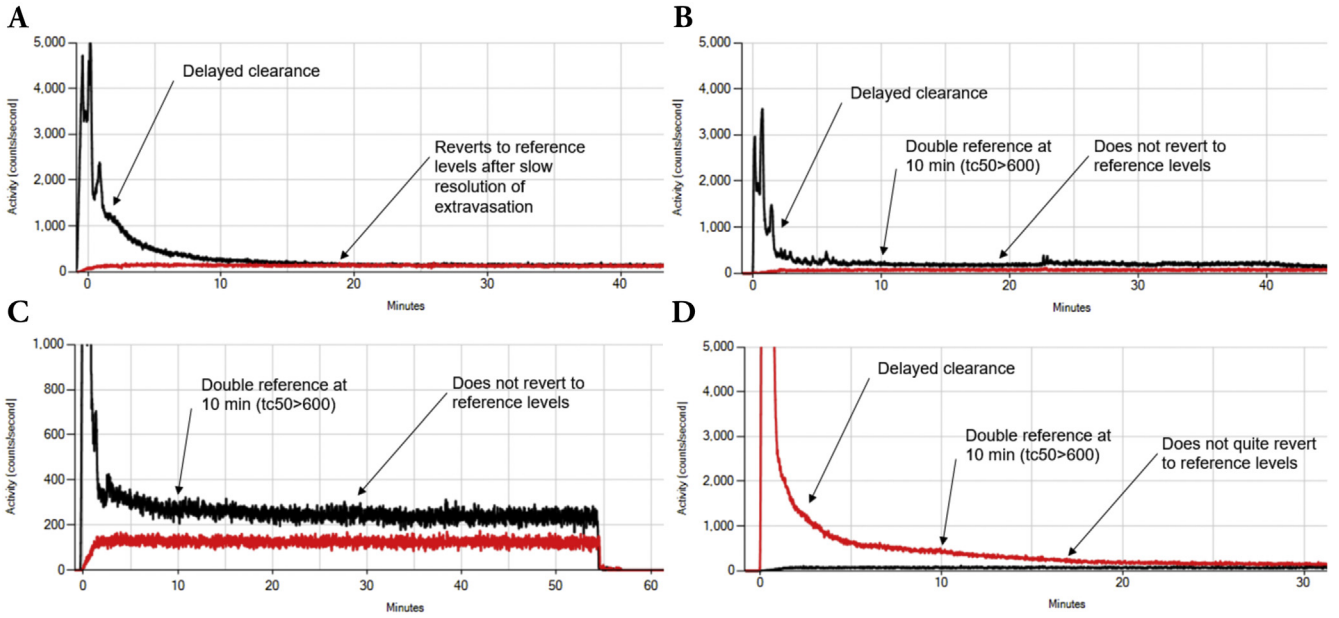

Figure 2. Annotated abnormal TAC indicating dose extravasation. Only A recorded a TAC score (744.8) indicative of extravasation while C had a marginal score of 114.8 (less than 200). The TAC score of B was −664.4 indicative of a good injection. There was no score for D as it was a 68 Ga dose but it should be noted that the injection and reference sensors have been reversed. The tc50 is 10 minutes or greater, consistent with prediction of extravasation even if it resolves before scanning. TAC, time-activity curve.

($P = .439$) and hand injections ($P = .539$); there is a 1.32 higher chance of abnormal TAC for hand, wrist, or forearm injections over antecubital fossa. Abnormal TACs for the injection were associated with right-sided injections ($P = .028$), height ($P = .006$), higher t-half ($P = .006$) and higher aUCR10, tc50, aUCR1 and c1 (all $P < .001$). The TAC score demonstrated a difference in the mean from −267.3 to 237.2 for abnormal TACs ($P < .001$). The TAC score is higher for abnormal injections but also with patient height ($P = .018$) and in males ($P = .028$), and correlates closely with t-half ($R^2 = 0.221$), aUCR10 ($R^2 = 0.436$) and tc50 ($R^2 = 0.265$).

Discussion

The detected extravasation rates were lower than reported in the literature with only 1.3% compared with the expected 9%–23%. This is likely to reflect a number of important factors. The use of an autoinjector in all patients not only reduces staff doses but provides a more consistent and slower delivery of the bolus, standardised large (80 mL) flush volume (reducing venous retention), large gauge cannula (over butterfly), and an alarm that detects resistance changes during injection. While a large study of extravasation rates comparing manual injection to autoinjectors is yet to be published, a small study using the Bayer Intego autoinjector (98 patients) revealed a 3% extravasation rate for the autoinjector compared with a 9% extravasation rate for manual injection [8].

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; 68 Ga based radiopharmaceuticals, autoinjector slow bolus with double flush characteristics (Figure 4), and significantly lower patient doses (approximately 5 mCi compared with the 10 mCi or more the system has been validated against). This suggests that utility may be improved with validation against local cases for each user and these data have driven modifications to the algorithm at Lucerno to 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 previously 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. That is, less than 600 indicates (seconds) no impact on SUV, greater than 1200 indicates negative impact on SUV calculation, whereas 600–1200 suggests margin risk and interpretative caution is advised. The tc50 value could be correlated with the degree of extravasation and used for SUV correction; although further investigation is recommended.

The TAC is also susceptible to patient movement that may change the proximity of a sensor to a source (including patient organs) or shielding levels between the sensor and sources. This may create spikes in the TAC (Figure 5A). Nonetheless,

Table 1
Summary of Demographic Data

	All	18F-FDG	68Ga-PSMA	68Ga-DOTATATE	*P*
Proportion of studies (%)	100	65.5	31.1	3.4	
Extravasation rate (%)	1.3	1.5	1.1	0	.887
Abnormal TAC (%)	9.1	11.3	5.4	0	.160
Mean dose (MBq)	187.1 (95% CI 181.8 to 192.4)	204.1 (95% CI 197.4 to 210.8)	152.9 (95% CI 150.4 to 155.5)	171.2 (95% CI 136.5 to 205.9)	<.001
Mean height (cm)	170.4 (95% CI 169.2 to 171.6)	169.3 (95% CI 168.0 to 170.6)	172.9 (95% CI 170.3 to 175.6)	168.4 (95% CI 159.9 to 176.8)	.008 (PSMA vs FDG only)
Mean weight (kg)	83.9 (95% CI 81.5 to 86.3)	80.9 (95% CI 78.0 to 83.4)	90.0 (95% CI 85.7 to 94.3)	86.3 (95% CI 69.1 to 103.5)	<.001 (PSMA vs FDG only)
Male (%)	71.0	59.3	100	50.0	.008
Over 70 years (%)	55.7	50.5	66.3	60.0	.032
Mean blood sugar	-	5.6 (95% CI 5.4 to 5.8)	-	-	-
80 mL Flush (%)	96.3	96.9	94.6	100	.148
20 Gauge cannula (%)	85.8	81.9	93.5	90.0	.105
Antecubital injection (%)	86.1	84.0	91.3	80.0	.333
Left side injection (%)	70.3	68.0	72.8	90.0	.271
Experienced injector (%)	66.9	64.4	73.9	50.0	.405
Mean injection score	-	−209.5 (95% CI to 253.3 to −165.7)	-	-	-
Mean t-half	25.3 (95% CI 20.3 to 30.3)	22.9 (95% CI 19.0 to 28.6)	31.5 (95% CI 17.6 to 45.4)	13.4 (95% CI 10.8 to 16.1)	.206
Mean aUCR10	1.4 (95% CI 1.3 to 1.6)	1.6 (95% CI 1.4 to 1.7)	1.2 (95% CI 0.9 to 1.4)	1.0 (95% CI 0.7 to 1.2)	.007 (PSMA vs FDG only)
Mean tc50	172.3 (95% CI 124.3 to 220.3)	195.2 (95% CI 128.5 to 261.9)	135.6 (95% CI 71.1 to 200.0)	66.2 (95% CI 37.1 to 95.4)	.384
Mean aUCR1	4.9 (95% CI 4.1 to 5.6)	6.1 (95% CI 5.1 to 7.1)	2.6 (95% CI 1.6 to 3.6)	2.0 (95% CI 1.3 to 2.6)	<.001
Mean c1	419.1 (95% CI 382.6 to 455.7)	538.7 (95% CI 496.7 to 580.7)	193.0 (95% CI 143.9 to 242.1)	179.8 (95% CI 128.9 to 230.8)	<.001

TAC, time-activity curve.

the rapid generation of the TAC allows on-the-fly assessment of injection quality and identification of potential sources of error in SUV or negative impact on image quality. Anomalies in the TAC can be rapidly evaluated to optimise outputs (Figure 5B). One disadvantage of autoinjectors is that the injection itself is unsupervised and an apparatus failure may see all or part of the dose leak from the system, readily identifiable on the TAC (Figure 5B) [9].

Extravasation appears to be more likely in female patients, administrations on the patient's right side, and hand administrations. The same observations are made for all abnormal administrations (eg, venous retention) except male instead of female predilection. Although the TAC score was useful in identifying any abnormal injection, it was less effective for extravasation itself as discussed previously. A number of other automated measures, which contribute to determination of the TAC score, may be better as independent identifiers of extravasation including t-half, aUCR10, aUCR1 and tc50; each with strong correlation. Although these generally perform at or about that of the TAC score, tc50 appears to have a stronger predictive capability. Using a tc50 cutoff of 600, 100% sensitivity and 95.9% specificity for identifying extravasation was noted. Using the same cutoff, for identifying all abnormal TAC, a sensitivity of 68.8% and specificity of 94.3% was determined. That is, if at 10 min (600 seconds), the reference curve is less than 50% of the value of the injection curve, careful consideration should be given to an anomalous injection.

Although the use of topical sensors and automated scoring would not add incremental clinical value without validation against low-dose injections via autoinjectors for a range of radiopharmaceuticals, the TACs are sensitive to identification of abnormal injection characteristics and aid in characterising the anomaly. Furthermore, the system obviates the need for imaging of the injection site to evaluate potential extravasation. Given the importance of SUV to patient management, the topical evaluation of injection characteristics, whether extravasation or venous retention with clearance, provides valuable insight into SUV integrity. In some cases, it may prevent wasted time and increased radiation dose associated with scanning patients with significant infiltration (or leaked) dose.

The limitations of this study included the absence of a gold standard. As a retrospective evaluation, patients were not subjected to additional imaging of injection sites or dynamic imaging to ascertain grounded truth. At this time, the amount of activity extravasated and its subsequent pharmacokinetic behaviour cannot be sufficiently determined to accurately correct SUV. The sensors themselves are not positioned directly over the injection site and thus make calculations based on proximity to infiltration sites which may miss small amounts of extravasation or venous retention and underestimate the extravasation rate. There may also be susceptibility to interference from adjacent activity concentrations not uniform between injection and reference sensors. The reported incidence of venous retention may reflect the postinjection

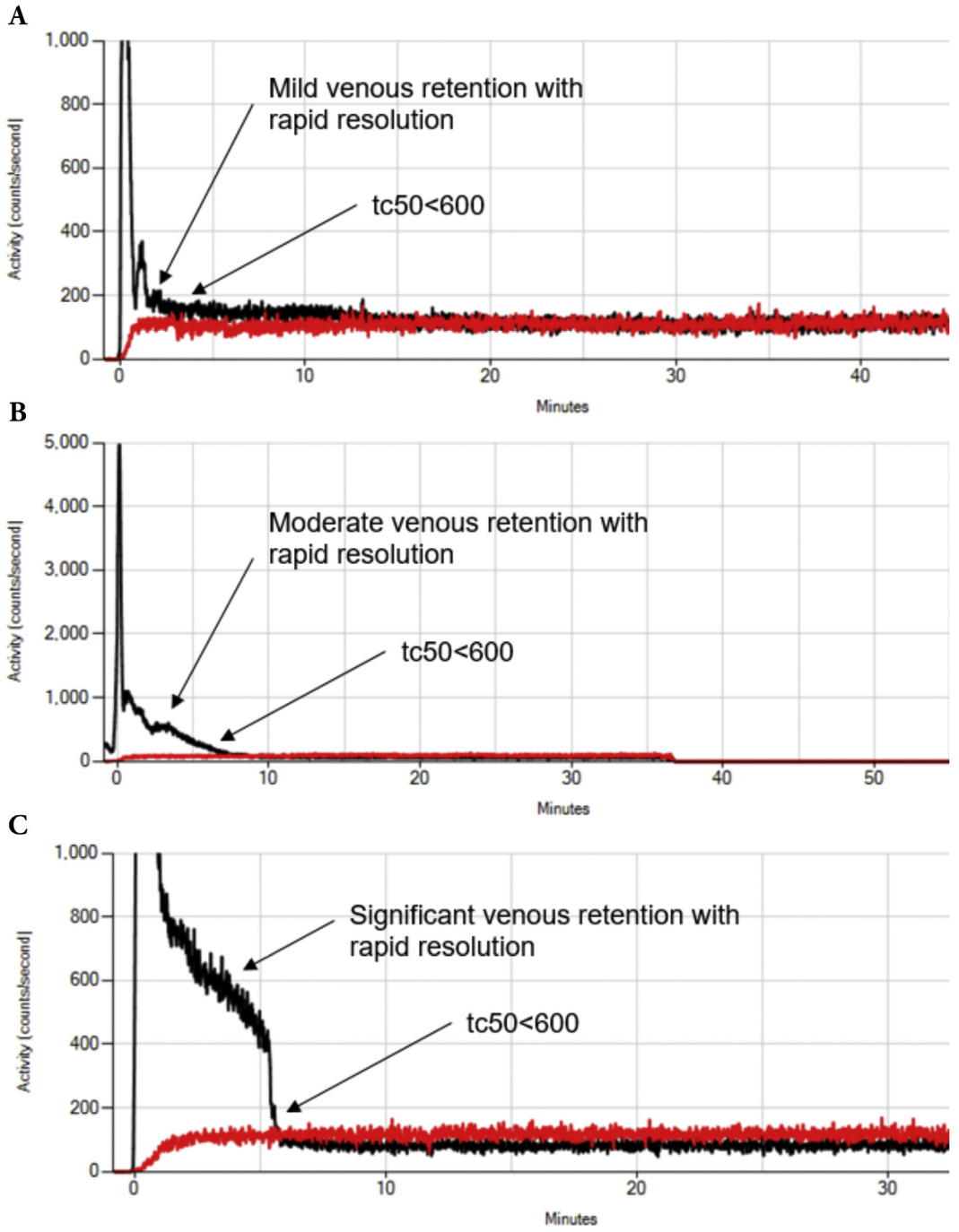

Figure 3. Examples of TACs with venous retention that quickly resolves (less than 10 min) into the vascular pool leaving no evidence of dose extravasation but potentially altering the pharmacokinetic behaviour of lesions and the SUV calculation including mild (A), moderate (B) and significant (C). The tc50 is less than 10 minutes in each case, consistent with resolution of venous retention. TAC, time-activity curve.

need for patients to remain still so that sensors do not pick up noise or come free (lose contact). Under normal circumstances the small movements a patient may make in a limb could significantly reduce the venous retention observations. Less than 100% compliance reflected busy periods (4th unmonitored uptake room) rather than ambivalence, but there is potential for the results to include a bias that underrepresents extravasation rates.

Conclusion

Topical monitoring and characterisation of PET dose administration is possible and practical with the LARA device. Automated scoring for a variety of doses, radiopharmaceuticals and injection methods is an important next step. Extravasation and partial extravasation of PET doses are not only readily detected but they are also preventable. The LARA device can

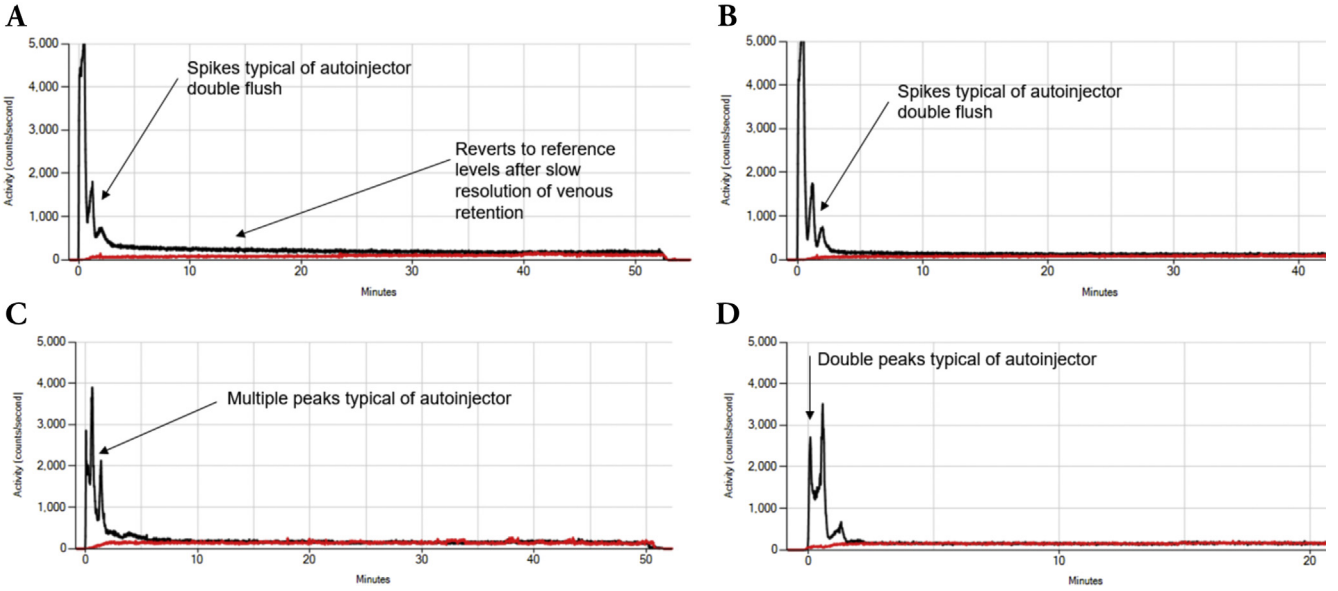

Figure 4. Automated scoring confronts a number of difficulties including a broader peak associated with 1 minute constant infusion and secondary syringe flush peaks associated with the autoinjector slow flushing the syringe twice. Figures A through D provide various manifestations of the changes to the shape of the peak of the TAC due to the slow auto-innjetcor bolus and multiple flushes.

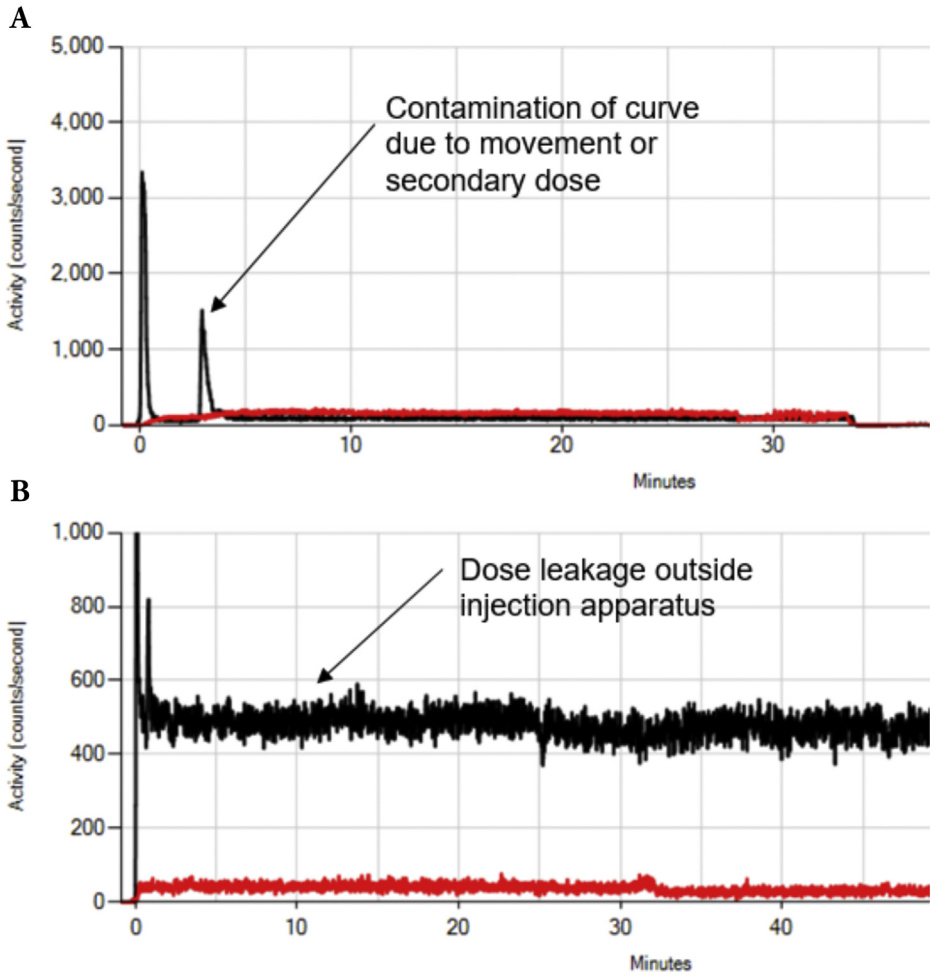

Figure 5. A number of other artefacts may be evident on TACs including patient movement or transient proximity to other sources (A), and dose leakage from the apparatus (B). TAC, time-activity curve.

provide the insights into variables that allow education, training and change to procedure, that could eliminate extravasation as a cause of image quality or SUV accuracy issues.

Acknowledgements

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Organization of Agreement States

February 26, 2020

US NRC Chairman and Commissioners
U.S. Nuclear Regulatory Commission
Mail Stop O-16 B33
Washington, DC 20555-0001

Dear Chairman Svinicki, Commissioners Baran, Caputo and Wright:

Thank you for the opportunity to present the Organization of Agreement State (OAS) positions at the January 28, 2020 Commission meeting: Discussion on Medical Uses of Radioactive Materials. The OAS Board (Board) hopes this letter will clarify our position and better address some of the questions and topics covered during that meeting. We have separated these into four categories that include: I. Training and Experience (T&E), II. Medical Events (ME) and Abnormal Occurrences (AO), III. Patient Release Criteria, and IV. Organizational Positions.

I. TRAINING AND EXPERIENCE

1. The Board believes there is no data that suggests a shortage of authorized users (AU). This belief is built on the feedback of our members, interactions with licensees, and work by NRC staff and the Advisory Committee on the Medical Uses of Isotopes (ACMUI). Additionally, the National Materials Program (NMP) would provide for one less barrier to new AUs by moving away from evaluation of T&E.

2. The Board fully supports the NRC staff's position as presented in SECY-20-0005, "Rulemaking Plan for Training and Experience Requirements for Unsealed Byproduct Material", specifically that NMP-approved specialty boards are best suited to determine qualifications and competencies of medical personnel. Specialty board requirements and examinations should reinforce knowledge and practices that provide for safety of the patient, workers and the public. Part of the approval for these boards could be verifying a competency-based focus on radiation safety aspects (i.e. dose planning and verification, written directive requirements, medical event criteria, emergency procedures and decontamination, supervised users and roles, reporting, patient release criteria, etc.).

3. When formulating our position, we asked ourselves is there an analogous regulatory body that has such oversight to approve or deny whether a physician can perform a medical function? We are unaware of any and assert the NMP's regulations for authorized users appear unique. This seems to fall under the practice of medicine and is a primary reason for the Board to support changing the T&E regulations.

4. The basis for current T&E hours is absent and the required hours are arbitrary. An unintended consequence of these arbitrary requirements was that some specialty boards adopted that criteria into their certification steps. Whether the NMP establishes these criteria or not, those specialty boards must evaluate their own board requirements necessary to train competent medical professionals. If the NRC staff recommendations are followed, then any recognized specialty boards will include strong radiation safety elements.

5. The NMP should be risk informed and consider value added by regulations. Less than 5% of medical events in 2017 and 2018 mention training as a potential related cause. Countless hours are spent by license reviewers to add AUs that are often not physically present during radiopharmaceutical administration. A better approach would be for the NMP to focus on overseeing those individuals actually handling materials, medical devices and the procedures governing administrations.

6. The Board does not advocate for verifying AU credentials during inspections in lieu of adding them through licensing. This would transfer the problem from licensing staff to inspectors and could extend the time needed for medical inspections by several factors. Licensing staff will attest that it is rare when a licensee provides all required credentialing documentation correctly the first time. Reviewing this information during an inspection is not only impractical but may leave facilities with AUs who lack appropriate T&E. The Board believes this would be a step backwards and we maintain that NMP recognized specialty boards are the best option for determining AU qualifications and competency.

7. Evaluating T&E as proposed is truly a rare opportunity, a chance for transformation and evaluation of decades' old practices. We need to consider the idea of making a shift to better align our regulation with the medical policy statement, increase safety focus elsewhere, save limited NMP staff time, and remove a regulatory barrier for new users and materials.

II. MEDICAL EVENTS AND ABNORMAL OCCURRENCES

1. The Board supports maintaining the current ME thresholds. It is understood that many of these do not cause serious health consequences; however, MEs are almost always the result of some error. These errors may be of a human nature, engineering design, or procedural failing. The reporting criteria assists the NMP in evaluating common causes and possible corrective actions. NMP staff can share these lessons with industry and fellow regulators to reduce unintended future events.

2. When actual detriment is caused and the errors require medical attention, those MEs should remain categorized as an AO. The Board recognizes the necessity for distinction between MEs and AOs. MEs are there so that we can fulfill our roles as regulators, but AO criteria exists to highlight hazards to the Commission and Congress over what is causing actual and immediate harm to the public.

3. The Board is happy to hear the Commission has directed an independent review of extravasations. We support the ACMUI's dissenting opinion in their final report, dated October

23, 2019, that MEs are possible by the injection of a radiopharmaceutical into an unintended tissue and should be reported upon occurrence. Whether there is immediate harm or not has no bearing on the reporting criteria; it is only a matter of dose with the current ME rule.

III. PATIENT RELEASE CRITERIA

1. The NMP places a large amount of responsibility on patients to avoid dosing members of the public, but it is up to the AU to determine if those patients will be able to follow those protective instructions. The Board generally agrees with NRC staff, our current regulations adequately protect the population while affording flexibility and discretion to physicians.

2. Where the Board disagrees with NRC staff is in context to the draft Regulatory Guide 8.39 (DG-8057), we believe the 5 mSv limit should be considered for all doses received from a patient over the course of a year, not on a per treatment basis. This would require facilities to evaluate past and future treatments in their release criteria.

3. Prescriptive limits for certain treatments should only be established when there are known thresholds for safety concerns; the questions about insurance and reimbursement are beyond the scope of the NMP.

IV. ORGANIZATIONAL POSITIONS

1. OAS and Conference of Radiation Control Program Directors (CRCPD) sometime differ in their perspective and opinions. This is most likely due to their differing memberships and focus. OAS is comprised of state staff that work on inspecting and licensing radioactive materials; our members make up a large portion of the NMP. The CRCPD is comprised of state staff beyond those who regulate radioactive materials, such as machine sources of radiation, non-ionizing radiation, and nuclear emergency responders. CRCPD also allows affiliate members to join who may be individuals from industry or other non-regulatory organizations.

2. The Board is elected by the Agreement States to represent the majority view of the states. Comments are solicited from all members when crafting a comment letter. If there are disagreements or differing views received, the Board tries to reconcile the differences or encompass those views in comment letters whenever practical.

Please let us know if you have any further questions and we will be happy to provide explanation.

Sincerely,

Terry W. Derstine

Terry Derstine, Chair
OAS Board