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Reporting Nuclear Medicine Injection Extravasations as Medical Events

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Reporting Nuclear Medicine Injection Extravasations as Medical Events

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General Comment

Please see the attached PDF document that represents the views of John Sunderland, PhD and Stephen Graves, PhD from the University of Iowa regarding the NRC's request for comments on "Reporting Nuclear Medicine Injection Extravasations as Medical Events"

Attachments

NRC Public Comment Infiltration_Final

By way of introduction, we are two PhD medical physicists from the University of Iowa with formal training in nuclear medicine imaging and therapy, radiation biology, and dosimetry measurement. Dr. Graves additionally is a board-certified radiation oncology and nuclear medicine physicist. Dr. Sunderland has been managing PET clinical and research facilities for nearly 25 years.

We have been following the NRC Rulemaking on Reporting Nuclear Medicine Injection Extravasations as Medical Events with quite some interest. In reading through the peer-reviewed medical literature on the subject, the NRC's own summary rulemaking documents, and associated public comments, it is clear this is an emotional topic. Patients are understandably concerned about safety, and physicians and technologists are understandably concerned about significant disruption to standard procedures that would in their experience add little to no value to patient safety. As is always the case in situations like this, a rationale balance between actual (not imagined) risk and necessary resources should be sought. At the heart of the problem is what appears to be a lack of good data, and associated good science, and an understanding of the global clinical situation to support a national policy - should one be needed.

To cut to the chase, we are supportive of NRC's Option 3, "Extravasation events that require medical attention for suspected radiation injury" as a non-dose-based option for reporting extravasations. This seems most appropriate, because

- It keeps the focus on actual patient safety issues.
- It avoids the vagaries associated with relying on absorbed dose estimates where the kinetics and associated radioactivity measurement are largely unknown.
- It provides a means of centralized record-keeping for actual deterministic radiation skin injury. This would in the long term provide valuable guidance to the field, if it is necessary.

From a scientific standpoint, language that has been proposed for a dose-based reporting criteria suggests the use of an arbitrary and inaccurate approach to the dosimetry problem ("a 5 cubic centimeter sphere of tissue, [or] a contiguous 10 square centimeters of skin"), and the dosimetric endpoint (equivalent dose of 0.5 Sv) is not evidence-based in terms of what would be clinically concerning. In the realm of stochastic effects, it seemingly doesn't matter whether the activity stayed in the subcutaneous space, or whether it went where it was intended to go in the body – the whole body stochastic risk is likely unchanged (or even reduced in the case of extravasation). Therefore, a higher limit, consistent with deterministic effects from fluoroscopy or EBRT data would be more relevant. With that said, we do not feel that the aforementioned assumptions regarding distribution volume, and time-residence, allow for sufficient dosimetric accuracy to support a dose-based criteria.

We would like to go on the record to try to add some structured perspective to the situation, referring to actual data that we believe adds some much-needed rigor to the discussion. What we feel is compelling about the following analysis is that it seems consistent with most peer-

reviewed literature which previously seemed discordant, but aligns when viewed from the appropriate perspective.

There are two primary issues, wherein radiobiology coupled with the science of radiation measurement can add substantively to the discussion. The first primary issue is the frequency of infiltrations/extravasation in the nuclear medicine field. The second is a more careful look at radiation doses to the skin and what radiation dose to the skin from infiltration events is of true medical concern.

To look at the first issue
– the frequency of infiltration events – NRC themselves use a figure of 15%, a figure which appears to be provided by the petitioner. NRC extrapolates that 15% figure to the potential of 28,000 reportable infiltration related "medical events" per year. It is unclear where that 15% comes from, although it is somewhat consistent with a 2011 manuscript by Osman et al[1] that claimed a 10% infiltration rate as defined by being able to visualize the injection site on the Maximum Intensity Projection image. Although there may be others.

We would like to counter that 15% estimate with what we would consider a more rigorous scientifically sound approach that we recently published to add some rigor and objectivity to the discussion.[2] In 2022 we initiated a multi-center study that collected 1000 PET/CT patient studies from ten imaging sites. PET was chosen primarily due to its ability to easily and accurately quantitatively measure localized radioactivity in the scanner's field of view. To avoid bias, a variety of institutions were chosen including, an academic medical center, private radiology groups, private oncology groups, a community hospital, multispecialty groups, and a research facility. Consecutive patients that had the injection site in the field of view were studied. Detailed methodology is in the manuscript. Interestingly all 10 sites used the recommended venous cannulation for injections. 6% used port access, when available. Three patients had PICC lines. Highlight results are enumerated below.

1) In this study there were zero patients for whom more than 1% of the injected activity was found at the injection site.
2) 985 of the 100 patients had less than 2 μCi at the injection site. 2 μCi, on average, is about 0.02% of the injected activity. So, in 98.5% of the cases, less than 0.02% of the activity was at the injection site. That is less than 2 ten-thousandths of the injected activity, which I think we could all agree, is not an infiltration event.
3) Importantly, in 460 out of the 1000 patients, activity was "clearly visualized" at the injection site. Note that the 2011 manuscript used visualization at the injection site as criteria for a dose infiltration reported a 10% infiltration rate. We think this result somewhat consistent with the 46% "visualization" rate we saw in our study using PET scanner technology that was likely, on average, a decade newer than that of the 2011 study. The primary difference between the published 2011 study and ours is that we performed the actual activity measurements associated with these visualizations. Our results strongly suggest that visualization, alone, is not a meaningful criterium for infiltration, and that the remarkably high sensitivity of PET imaging coupled with low background in peripheral tissues can lead to visually

deceiving conclusions. Because of this remarkable sensitivity, coupled with the ability to trivially measure the activity at the injection site, visualization should clearly not be used as a criteria to identify infiltration events.

4) Six patients had greater than 10 μCi at the injection site. None of the six were greater that 50 μCi. Note that the lower 10 μCi threshold is, on average, about 0.1% of the injected activity. The 50 μCi upper limit is still only 0.5% of the average injected activity. Interestingly, of the six patients with more than 10 μCi at the injection site, only three were actual infiltrations; the others were either external contamination or activity trapped in external tubing or fittings.
5) Without finding any clinically significant infiltrations in our sampling of 1000 patients from 10 institutions, a statistical assessment of frequency of clinically significant infiltrations was challenging. However, using a binomial distribution statistical calculation, we concluded with 95% confidence that the per-administration probability of a PET infiltration event comprised of >1% of injected activity is between 0.00% and 0.37%. This is substantially below NRC's 15% that they used in their estimate. Interestingly halfway between 0.0% and 0.37% is 0.18%, which is the NRC's stated frequency of chemotherapy extravasations. Since professionals with roughly the same qualifications perform these injection and infusions, having these rates align would make sense.

This is not to suggest that major infiltration events do not happen. There are clear reports that they do. It is simply the frequency that we are trying to nail down.

It is also important to note that the number of deterministic medical events from radiation damage to the skin due to infiltration in the literature numbers probably less than 30 out of tens of millions of injections over the past several decades. This includes a rigorous meta-analysis of the literature in 2017 by van der Pol,[3] and a rigorous search by Osborne through the FDA's FAERS adverse event reporting database and its European counterpart EV database[4]. The critical point here is that adverse events do rarely occur, to be certain. The actual rate appears to lie somewhere between 1 per million injections and one per 10 million injections.

It is also important to note that this quite low rate of infiltrations may be one reason why the Nuclear Medicine community is somewhat surprised and defensive with regard to this "controversy". It simply stems from their experience that this is not a common or frequent problem. We don't think this diminishes the fact that we need to pay attention to the potential for serious infiltration events, but the question of whether there is a pressing need for regulatory measures would be better informed with a reasonable estimate of frequency and severity of actual events, rather than anecdotal and inflammatory rhetoric (on either side of the argument).

The second issue
is how best to measure radiation dose to the skin. The skin is a relatively complex organ, with many functions and a complex anatomy that deserves a more careful treatment than the current literature offers. Skin, and more particularly, the highly prolific cells in the epidermis

(which is about 50 microns in thickness) are quite radiation sensitive, and probably among the most sensitive cells in the body to radiation. We know a lot about the radiation sensitivity of the epidermis from external beam radiation therapy, where skin injury is quite common. We also see similar skin injury in lengthy fluoroscopic procedures. We have good data here, too. Typically, we see minor, but true deterministic radiation effects at a range between 2-10 Gray to the epidermis. Deterministic skin injury events at 2 Gray are uncommon, but possible for people with particularly sensitive skin. Skin injury from absorbed doses in this range manifests itself as skin erythema (reddening of the skin, like a sunburn). This can happen right away, or there can be delays of days or weeks before manifestation. These are generally short-term effects, and they typically resolve without intervention. They are correctly classified as skin injury but are generally neither serious nor permanent. Above 10 Gray to the epidermis you can see blistering, moist desquamation, and the potential for permanent skin damage, however it is important to note that this is dose to the epidermis, and not the entire skin anatomy, that consists of several layers. It is our contention that the layered anatomy of the skin, and the dynamics of injected dose infiltration in the skin sub-anatomy matters considerably and should be used to calculate radiation dose to the various substructures of the skin, including most importantly, the epidermis.

Understanding the anatomy of the skin, and just as importantly the distribution of an infiltrated injected activity relative to the skin anatomy is critical to assessing risk to skin injury, which is what we understand is NRC's objective. Skin, working from the outside in, consists of the highly proliferative and radiation sensitive epidermis that is about 50 microns thick. Just underneath the epidermis is the dermis. The dermal layer in the arm and wrist is about 1 mm thick. It is a little thicker, on average, in males than females. It decreases in thickness by a little with age. The dermis is tough, fibrous, and largely consists of collagen. It is largely acellular, although there are certainly some cellular structures and functions inherent to the dermal tissue. But the cellular component is not particularly proliferative therefore not particularly radiation sensitive. Beneath the dermis is the subcutaneous tissue, also known as the hypodermis. The hypodermis is largely the fat layer beneath the skin, so most of this tissue simply consists of fat cells. The thickness of the hypodermis is highly variable depending upon body habitus. It can be anywhere from several mm to a centimeter or more. Underneath the hypodermis is muscle encased in a relatively thick and tough connective tissue. Importantly, in all cases, the veins that are large enough to access with needles and canula lie at the very bottom of the fatty hypodermis just above the interface with muscle.

Importantly, when injected activity is infiltrated in a patient, it fills space between fractures in the hypodermis fat cells, and the hypodermis expands substantially to accommodate the excess fluid associated with the infiltrate. This behavior is also well documented in the literature in various subspecialty journals including dermatology, anesthesiology, and fluid dynamics. We did some very preliminary experiments, and it does not appear that the infiltrate penetrates significantly into the dermis. It largely stays in the fat and diffuses laterally where it is taken up primarily by the lymphatics. Work by Osborne suggests a biological half-life of approximately 30 minutes.[5] We performed Monte Carlo calculations using MCNP v6.2 where we simulated a activity infiltration with dimensions 3.1cm x 4.6 cm x 0.68 cm. These dimensions were taken

from an actual infiltration from reference 1 that were taken from the CT scan. We assumed that only 10% of hypodermic activity concentration somehow diffused into the dermis (10:1 concentration ratio), and the rest remained in the hypodermis. Based upon our animal experiments, we think this concentration ratio is a very conservative assumption. We propagated betas, gammas, and secondary electrons and tabulated doses in each of the skin sub-tissues.

The bottom line is that even if a full 10 mCi F-18, or 5 mCi Ga-68 injected activity was infiltrated into a patient (with the above geometry), the dose to the radiation sensitive epidermis would be substantially below 2 Gray, the threshold for even the most sensitive skin to experience a deterministic skin reaction. With our assumptions and calculations, it would be virtually impossible to cause true skin injury with diagnostic F-18 or Ga-68 clinical injections, even under worst case full-injected-activity infiltration circumstances. The tissue-specific dose distribution shows that (1) the vast majority of local dose absorption is from the beta particle (positron) energy deposition and (2) the fibrous dermis acts as an effective "beta shield" that serendipitously protects the sensitive epidermis from the positrons that don't have enough energy to penetrate through the dermis. It is important to note that if we modeled radionuclides with higher beta energies, that the protective function of the dermis would be substantially diminished, however for clinically used F-18 and Ga-68 we simply see little to no chance for skin damage even under worst case conditions.

Importantly, this result seems consistent with the experience in the nuclear medicine field. That is, there are approximately 2 million PET scans performed per year (2017 number), and to date there have been zero reports, to our knowledge, of diagnostic administrations having caused discernible deterministic skin injury. Other radiation absorbed dose calculations reported in the literature that do not consider skin anatomy have generated true potential for skin damage (>2 Gray). But since no such reports of actual skin injury from PET radiopharmaceuticals have appeared in the literature, and significant PET dose infiltrations have certainly occurred over the past several decades, this suggests there is more going on than the simplistic previously published dosimetric approaches address.

Targeted Radionuclide Therapy

Frankly, the more interesting and important question in our mind is what are the risks associated with therapeutic radionuclide infusions? This is a growing field for which we have less historical data, and for which much higher radioactivities are injected than in the diagnostic case. We would argue that more attention be paid in this space, as intuitively, there should be a higher chance of skin injuries with larger doses being injected.

We have expanded our Monte Carlo simulations into the realm of targeted radiopharmaceutical therapy. Specifically, we have performed simulations with Lu-177 and Y-90. These Monte Carlo characterizations are not yet complete, as we have not yet simulated the impact of different geometries, however the early results are quite interesting. The beta energy of Lu-177 is even lower than F-18, and so its tissue penetration is less. In our simulations, dose to the epidermis

was only 0.0256 Gy/mCi infiltrated, suggesting that 70-80 of mCi of Lu-177 would need to be infiltrated to achieve the threshold of 2 Gray for deterministic skin injury (>2 Gy). It is important to remember that 2 Gy is only the very lowest threshold, and doses as high as 7-8 gray often have no discernable effect (data from the external beam radiation therapy space). On the other hand, Y-90 has a substantially higher beta energy than Lu-177, F-18, or even Ga-68. On average Y-90 betas travel 2.5 mm is tissue, and can travel as far as 10-11 mm. Under these conditions, the dermis is only a weak beta shield. Dose to the epidermis from infiltrated Y-90 are estimated to be about 0.57 Gy/mCi, suggesting that only 3-4 mCi infiltrated may be sufficient to potentially cause skin damage. What is particularly interesting about these preliminary results is that they, too, seem consistent with trends in the literature. That is, in van der Pol's review article on extravasations in 2017, 8 case of therapeutic extravasations causing tissue injury were identified.[3] Five of the 8 reported cases were from Y-90 labeled radiopharmaceuticals. Zero were from Lu-177. There was a single I-131, one Sr-89, and one P-32 (notably Sr-89 and P-32 have similar beta range characteristics to Y-90). We have only found two case reports of Lu-177 infiltrations in the literature (Arveschoug 2020)[6] and Schlenkhoff (2017)[7], both of which had infiltrations estimated at approximately 100 mCi, neither of which reported any skin injury, even with patient follow-up.

Our conclusions suggest that risk of deterministic skin injury in PET imaging is near zero based upon both the infrequent occurrence, but more importantly the Monte Carlo dosimetry estimates performed with positron emitters that suggest that it would be nearly impossible to achieve an absorbed dose to the epidermis that would case skin injury. This is consistent with the fact that over the last 30 years of PET imaging and tens of millions of injected doses, there have been no reported skin injuries, to our knowledge.

We would also like to comment upon the danger of relying upon calculated absorbed radiation dose as grounds for medical event reporting. In a recent NRC comment document from Lucerno Dynamics dated 2/16/23, 5 infiltration events were illustrated and reported with radiation dose estimates ranging between 10 Gy-24.4Gy to 5 grams of tissue using "Radiopharmaceutical Infiltration Dose Estimation" software. We know from decades of experience from external beam radiation therapy and fluoroscopy that if these radiation absorbed doses were accurate, several of these patients would have experienced grizzly and permanent skin injury. Yet no report of even minor skin injury was reported, despite looking for it. Reports like this are inconsistent with scientific reported literature and would appear to either demonstrate a severe misunderstanding of existing science or are meant to be purposefully inflammatory and misleading. Neither of which contribute meaningfully to policy decisions. If we are not mistaken, this is the same organization that is spreading the 15% injected dose infiltration rate for nuclear medicine studies, which appears to be approximately 100 times higher than the actual true observed rate.

We would also like to comment about several other questions posed by NRC in their 4/19/2023 Federal Register notice.

Regarding “Definitions” Question 1: There remains inconsistency regarding the nomenclature surrounding what to call injected activity that inadvertently enters the tissue space. Historically, the terms infiltration and extravasation have been used interchangeably in the nuclear medicine literature. However, in the general medical literature “extravasation” has a specific definition and refers to injectates that are vesicants – chemicals that are irritants capable of causing tissue damage. In context, this has typically meant they may be capable of causing blistering, tissue sloughing or necrosis. Although radiation can do this in high enough doses, in the diagnostic space, at least in PET, this does not seem likely, and so we would suggest the term infiltration be used when there is no reasonable expectation of tissue damage. Extravasation would be a better term to describe events where deterministic tissue damage actually occurs. With this differentiation, a clearer distinction between the seriousness associated with an injected radiopharmaceutical inadvertently entering the tissue space would be immediately clear.

Regarding “Procedures” Question 9: We would recommend that a medical event notification be initiated when a physician identified an injury as being due to radiation. The threshold of “medical attention” would not seem to meet the true safety endpoint that NRC is intending to identify.

Regarding “Healthcare Inequities”, we did parse our data on 1000 patients into racial categories including patients of color and found not meaningful evidence that infiltration rates or quantities were higher in darker skinned individuals. Our nurses at the University of Iowa who perform the majority of our canulations claim no more difficulty in accessing veins in persons with darker skin. These observations, however, can be considered anecdotal and certainly non-conclusive.

I hope that NRC and the other interested parties will excuse the length of this commentary, however we believe its content will add some needed perspective and some rigor to the ongoing discussion. We, at least, believe that the NRC is attempting to fill its perceived statutory role in this process. Some, apparently, believe this is mission creep into the practice of medicine. We make no judgement here, but from what we see, NRC is showing some patience in “trying to get it right”. At the same time, we know very clearly that the nuclear medicine community takes patient safety remarkably seriously. We see this every day with our technologist, nurse, and physician colleagues, for whom patient safety is of absolute primary importance. Always. Our front-line technologists and nurses, in particular, are fierce advocates for our patients. Always. Any group insinuating that there is some conspiracy amongst the tens of thousands of caregivers in the Nuclear Medicine community aiming to sweep an important safety issue under the rug is not acting in good faith or has not meaningfully engaged the community.

With the advent of radiotherapeutics growing rapidly, it is perhaps a good time to start looking a bit more closely at this situation. So perhaps NRCs attention to this issue is actually timely, and Option 3, if administered conservatively, may provide an excellent means to track data moving forward.

All this being said, our advice is to slow down, and get it right. If we need more information, then lets move forward and try to collect the data before any potentially draconian measures are put in place. We owe it to the patients, and we owe it to the practitioners to get it right the first time.

Respectfully submitted,

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