limited quantitative accuracy of dosimetry based on planar scans. A SPECT/CT-based dosimetry study is already in preparation. Consequently, we saw no need to report preliminary results, which soon will become obsolete anyway. The other reason is the challenging interpretation of dosimetry data in predicting clinical consequences of systemic radioligand therapy. The latter issue is now addressed by Pretze et al., who mention various physical and radiation biologic aspects of this theme. We appreciate receiving such an instructive letter, stimulating a fruitful academic discussion.

First, Pretze et al. mention further radionuclides that could serve as alternatives to [177]Lu. Indeed, the amount of [176]Yb that is needed for the production of high-specific-activity ^{177}Lu without [177m]Lu impurities (half-life, 161 d) is limited. Consequently, the costs for producing no-carrier-added ^{177}Lu are relatively high. Routine availability of [161]Tb and [67]Cu is currently even worse than for [177]Lu. In contrast, [188]Re is readily available from a well-established generator system and, if generators are eluted regularly, converts it into reduced radionuclide costs by approximately a power of 10. The current shortage of ^{177}Lu-PSMA-617 in the United States (Pluvicto from Novartis has been on the Food and Drug Administration's shortage list since March 7, 2023) illustrates the logistic challenges of airfreight delivery even between well-developed countries. In regions with a lower airport density, just-in-time delivery of [177]Lu (half-life, 6.7 d) radiopharmaceuticals is likely an illusion, and the same applies to [161]Tb (half-life, 6.9 d) and [67]Cu (half-life, 2.6 d). Hence, the 70-d half-life of the [188]W/[188]Re generator is the most reasonable option to have local access to PSMA radioligand therapy at all.

Next, the letter addresses the challenge of projecting absorbed doses based on small-animal studies to human beings. Hence, studies in pigs would be required. However, beyond radiation geometry, the specific expression of PSMA in the proximal kidney tubules has to be considered. A study comparing human PSMA with its rat and pig orthologs exhibits different glutamate carboxypeptidase II expression levels among the species studied (2). Therefore, we considered the theranostic approach a more responsible way to continue clinical development; that is, innocuous ^{99m}Tc-PSMA-GCK01 imaging will be used to extrapolate the dosimetry of [188]Re-PSMA-GCK01 therapy in men.

Pretze et al. estimated that the same activities of [188]Re-PSMA may convert into a 1.7 times higher kidney dose but only a 51% absorbed dose to tumors with a mass of 10 g when compared with ^{177}Lu-PSMA-617. This is not too much away from our own preliminary approximation. However, because of its higher β-energy, [188]Re theoretically performs better against larger tumor lesions (23–32 mm) than does [177]Lu (3). In a tumor model that is very similar to the typical clustered PSMA expression pattern in prostate cancer, the increased cross-fire effect of [188]Re improved its intercluster microdosimetry (4). Pretze et al. emphasized that the antitumor activity of [188]Re-PSMA could be about 25% higher than identical absorbed doses delivered by ^{177}Lu when dose-rate effects are considered. However, it is worth mentioning that the biologically effective dose concept, which is based on the linear-quadratic model, was developed for external-beam radiotherapy, but its appropriateness for radioligand therapy still needs confirmation.

In summary, considering the dosimetric consequences of replacing ^{177}Lu with [188]Re may not be enough because there are no validated tools to simulate the radiation biologic consequences. Even if physical absorbed doses—1 surrogate for the therapeutic index of a radiopharmaceutical—may be lower than for ^{177}Lu-PSMA-617, we consider it warranted to assess the antitumor activity of [188]Re-PSMA-GCK01 using a patient-related endpoint, for example, prostate-specific antigen response in a clinical trial.

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Response to "Critique and Discussion of 'Multicenter Evaluation of Frequency and Impact of Activity Infiltration in PET Imaging, Including Microscale Modeling of Skin-Absorbed Dose'"

TO THE EDITOR: We read with interest a recent commentary printed in *Frontiers in Nuclear Medicine* entitled "Critique and Discussion of 'Multicenter Evaluation of Frequency and Impact of Activity Infiltration in PET Imaging, Including Microscale Modeling of Skin-Absorbed Dose'" (1) that took issue with the science presented in our recent publication in *The Journal of Nuclear Medicine* (2). We felt that a reply was in order, as although several relevant points were made, other criticisms appear to be unfounded or based on false assumptions.

The first clarification is the insinuation that the Society of Nuclear Medicine and Molecular Imaging "fostered" the work presented in the article. This is categorically not the case. The experimental idea, design, and execution was neither funded, suggested, coerced, nor otherwise influenced by the society or society leadership beyond expressing an interest that the research be published. Project design and leadership were primarily from the lead author. Coauthors on the paper were just that—significant active scientific and experimental contributors to the work.

The second clarification relates to the unjustified statement that the paper's conclusions started with an assumption that diagnostic radiopharmaceutical infiltrations are not a concern. To the contrary,

safety concerns were the primary justification for initiation of our study. After hearing about alleged 15%–20% infiltration rates, we initiated a safety review at our facility with about 50 patients to determine whether we were experiencing this reported frequency of problematic injections. We expanded our safety assessment to additional patients for confirmation. A subsequent literature review revealed 2 important scientific incongruities. The first was that several single-institution studies reported high rates (>15%) of activity infiltrations, which were inconsistent with our measurements. This finding was also inconsistent with reported rates of injection infiltrations in chemotherapy and CT contrast injections, which stand at around 0.2% (3,4). The second puzzling issue related to published reports of infiltrated injection with absorbed dose estimates above 10 Gy, a level at which one would expect to see literature reports of deterministic skin injury from external-beam radiation therapy. However, no such injuries have been reported from diagnostic administrations. The scientific method dictates that when current models do not correctly predict experimental results, new hypotheses and models be developed and tested that better fit and explain observed phenomena. Both the frequency of reported infiltrations and the safety aspects associated with dose infiltrations appeared to conflict with known science and data. No presumption of safety was made in any aspect of the study design or results.

The several typographic errors identified in the article are correctly identified, and we entirely accept responsibility for these. However, we do not believe they meaningfully detract from the substance of the research work presented.

Several methodologic concerns were expressed about both the frequency-of-infiltration study and the Monte Carlo dosimetry model.

MONTE CARLO DOSIMETRY MODEL

Regarding the Monte Carlo dosimetry model, significant concern was expressed that our geometry excluded muscle from the distribution volume of an infiltrated radiopharmaceutical injection. We stand behind our distribution model that limits activity to the subcutaneous tissue and, to a lesser extent, the dermis. Muscle is encapsulated in the epimysium, which is a thick connective tissue layer that is composed of coarse collagen fibers in a proteoglycan matrix. The epimysium surrounds the entire muscle and largely isolates it from macroscopic rapid exchange of fluids from surrounding tissue, even under pressure. Unless the radiopharmaceutical is accidentally directly injected into the muscle, there is no direct pathway into muscle tissue. Further, our review of PET/CT infiltrations invariably shows the infiltrate limited to the skin layer, with no detectable component in the muscle above expected background. Figure 6A of the article demonstrates that, in an animal model, fluid introduced under pressure in the subcutaneous tissue is contained within the fat space and does not enter muscle. We strongly disagree with the criticism that "the muscle tissue adjacent to the injection site is valid as both a source and target volume" and is "inappropriately ignored … in the dosimetry model." We stand by its inclusion as a target organ only. We agree that in the unlikely event of an intramuscular injection, muscle would need to be a source and target organ, but we would then exclude all skin structures as source volumes, as tissue exchange is improbable.

Even in the unlikely event of a direct intramuscular injection, the distribution volume in the muscle is large, which would dilute the infiltrate over a larger volume, thus reducing absorbed dose. Further,

muscles are among the least proliferative and most radiation-resistant cells in the body. Only at doses in excess of 40 Gy (functional changes) (5) or 60–80 Gy (significant tissue injury) (6) do we see tissue effects in muscle tissue, and these absorbed doses are in excess of those achievable with diagnostic quantities of PET radiopharmaceuticals. The significant concern voiced for damage to muscle tissue as an unstudied risk is entirely unfounded and ignores decades of radiation biology experience from external-beam radiation therapy.

There was concern expressed that we did not compare our Monte Carlo results against existing published models. In fact, we did perform several dose estimates of the skin using several existing published models (not reported). The results of these dose calculations were entirely consistent with the literature, and only when simulating approximately 100% infiltration of administered activity did absorbed doses exceed values for which we would expect to see deterministic and observable skin reactions (2–10 Gy, mild temporary effects; >15 Gy, high probability of serious or permanent injury) (7). Yet we found no such reports in the literature for diagnostic PET radiopharmaceuticals. It was precisely the failure of conventional dosimetry methods to explain observed phenomena (or lack thereof) that prompted the development of the proposed model that accounts for skin tissue subanatomy. Modeling accounted for an approximately 40-min biologic half-life combined with the physical half-life of the radionuclide under study. The biologic half-life was derived from a typical 30-min combined biologic and physical half-life reported by Osborne (8).

We freely admit that this is only an early-phase model, but we think it holds promise to assess safety risk more accurately in the event of a significant infiltration event than do the current more simplistic methods, which appear to correctly calculate absorbed dose when using a somewhat arbitrarily assumed tissue mass but incorrectly predict risk. We are in the process of expanding the scope of simulation to include a wider range of radionuclides and geometries and expect these results to be published within a year.

The opinion piece further objects to our using a subcutaneous injection model to describe fluid dynamics when a radiopharmaceutical is infiltrated. They state, "Subcutaneous administrations are very different than intravenous and are not an appropriate basis for model definition." We agree fully that subcutaneous administrations are very different from intravenous injections. However, we do firmly believe that subcutaneous administrations are precisely analogous to infiltrated intravenous administrations. Veins accessed for intravenous administrations reside exclusively in the subcutaneous tissue, and when injectate leaks into surrounding tissue under pressure through a blown vein or from around the puncture site of the vein itself, the leakage will invariably enter the subcutaneous fat layer given the anatomic confines. The fat layer is a remarkably accommodating and elastic structure to contain the excess fluid introduced under pressure. References supporting this were provided in the original article. We maintain confidence in our geometric model defining the behavior of infiltrated injectate and its time course and disagree strongly that our model is inappropriate; we consider our approach to be a substantially more appropriate physical model than currently used approaches.

FREQUENCY-OF-INFILTRATION STUDY

Regarding the frequency-of-infiltration study, it was initiated because of the discordant results between our institution and the

reports in the literature describing much higher rates. It became apparent on reading the literature that the primary difference from our internal institutional analysis was that we measured activity at the injection site, where reports of significantly higher infiltration rates were based solely on "visualization" of activity.

We absolutely stand by our belief that visualization is an inappropriate criterion to characterize a meaningful infiltration event. The clinical utility of PET in oncologic applications is entirely dependent on the modality's exquisite sensitivity. Virtually all PET scanners will clearly visualize a 2-cm-diameter tumor with ^{18}F-FDG at an SUV of 4. With a typical injection activity and body weight, this tumor will have, very approximately, 37 kBq (1 μCi) of activity, or about 0.01% of the injected activity. This implies, particularly in the low-background injection site, that PET is capable of visualizing this amount of activity. Categorizing 0.01% of the injected activity as a reportable or significant infiltration event, by virtue of visibility, is categorically wrong and misleading, particularly since the activity could instead be trivially quantitated in less than a minute from the image data. It is based on these observations that we now believe we clearly understand the discrepancies between our institutional results and these other visualization-based literature reports, which we consider misleading for the above reasons.

Missing from the literature was a body of quantitative measurements of activity at the injection site. This was considered a significant information gap that this study intended to fill. The true incidence rate for significant infiltration events remains unanswered and will depend entirely on a formal definition, which is beyond the scope of the article and our expertise and responsibility. But it will hopefully be better informed because of the data reported.

Criticisms were made implying inherent bias in the data reported. We believe the study took reasonable efforts to avoid bias in data collection. Intentionally, a variety of institutions (10 total) were chosen, including an academic medical center, private radiology groups, private oncology groups, a community hospital, multispecialty groups, and a research facility. Consecutive patients who had the injection site in the field of view were studied. To avoid statistical overweighting, no single site was allowed to contribute more than 200 studies. Consistent analysis methods were used to quantitate activity at the injection site. Criticism was leveled that "training and experience levels of participating technologists" was not reported, and "an unknown number of images with injection sites outside of the field of view were excluded from the study." Regarding the latter concern, we believe strongly this did not in any way statistically bias results. With regard to technologist training (many sites were small enough to not have on-site reading physicians), we are confident that this diverse array of 10 different institutions represented an array of different technologist skill levels and is almost certainly a more accurate sampling of the technologist population than the largely single-center studies on which the author and his company base their estimates.

The critique further states that "The results from this paper only reflect what happened in these few centers during undefined observation periods and cannot be applied to the practice of nuclear medicine generally." As we believe ours is a largely unbiased sample, we believe strongly that it is entirely generalizable to the broader PET imaging community. Injection practices in the larger nuclear medicine community may or may not be similar, as we made no attempt to sample this broader space. However, regarding the Monte Carlo dose estimation methods, we do believe the approach is broadly applicable to the entire practice of nuclear medicine. This criticism about generalization from a well-sampled population is a particularly odd comment and concerning for several reasons. First, it flies in the face of the entire field of statistics, which is based on unbiased sampling of a much larger population where the sample is considered mathematically representative of that larger population—to within calculable confidence intervals. Second, this is a self-defeating argument coming from an individual and company who have continuously based comments to the Nuclear Regulatory Commission and other organizations on arithmetic extrapolation from much smaller, less controlled, and more statistically biased reports.

Finally, in our article we somewhat arbitrarily categorized infiltration of less than 1% of total activity at the injection site as being "not a clinically meaningful infiltration event" for the sake of simple statistical analysis. This in no way implies, nor means to imply, that an infiltration of more than 1% is a clinically meaningful infiltration event. The absorbed dose estimates from the Monte Carlo analysis suggest that even at a 100% injection infiltration, we would not expect a patient to experience deterministic skin injury, which is entirely consistent with the lack of reported events in the literature over the last several decades. The question of a threshold for compromised image quality or quantitation was not addressed by the article. As such, the frequencies of "clinically meaningful extravasations" calculated in the critique based on a 1% threshold are dramatically overstated.

DISCUSSION

We find that most of the criticisms leveled are unfounded and based on what we see as fundamental misconceptions regarding injection anatomy and physiology, radiation biology, and even statistics. We remain confident in the experimental methods used in the collection of injection infiltration frequency data in the PET imaging space, and we believe these methods are superior in quality to those of previously reported studies because of the number of patients studied, the variety of imaging sites sampled, and the actual measurement of activity at the injection site rather than simple reporting of visualized activity. We also believe the physical model used in our Monte Carlo model, accounting for major skin subanatomies, is a necessary addition to the infiltration skin dosimetry paradigm given the failure of current models to predict the lack of reported deterministic skin injury events in this space. We further stand by our Monte Carlo starting boundary conditions whereby we confine activity to the subcutaneous fat and dermis, and we disagree strongly that the exchange with muscle tissue is appropriate (although this would serve to reduce skin/epidermal dose, which is the primary tissue of concern).

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