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Growing Need for a Standardized Response to Radiopharmaceutical Extravasations

Michael Richard Drelich
University of Alabama at Birmingham

GROWING NEED FOR A STANDARDIZED REPONSE TO RADIOPHARMACEUTICAL EXTRAVASATIONS

by

MICHAEL R. DRELICH

EMILY CAFFREY, COMMITTEE CO-CHAIR
CHARLES WILSON, COMMITTEE CO-CHAIR
REMO GEORGE

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MICHAEL R. DRELICH

HEALTH PHYSICS

ABSTRACT

Extravasations are medical occurrences where an injected or infused pharmaceutical is unintentionally deposited into the soft tissue near the injection site, rather than into the bloodstream. With radiopharmaceuticals, extravasations can result in potentially large radiation doses to skin and tissue. The current rate of extravasations in clinical settings is estimated to be between 3-23%. In the interest of patient safety, a clearer understanding of the dosimetry and differences in extravasation scenarios to simplify dose estimation is needed. Similarly, the NRC is considering modifying regulations to include extravasations as reportable medical events rather than to continue considering them as patient interventions. Numerous papers have applied the Fano Theorem for dose estimations, yet these estimations reveal inconsistencies in the assumptions regarding tissue density, volume, mass, and clearance rates. Dose estimates often indicate that deterministic effects are probable, but these rarely are observed. There is no standard solution for dose calculations for extravasations. To be fully prepared to meet the 24-hour reporting requirements for medical events, a standard must be developed. This research aims to review and compare existing literature to determine the best practices for radiation safety programs' response to extravasation events. Methods of dose calculations include the use of publicly available software such as IDAC, modified versions of VARSKIN+, Monte-Carlo methods, and use of the Fano Theorem. More work is still needed for accurate

determination of the effective half-life of extravasated radiopharmaceuticals and reliably determining the fraction of extravasated material. Extravasation scenarios vary widely and there are questions regarding the regulatory need to determine skin dose versus tissue dose and whether this regulation is truly needed for patient safety if deterministic effects are generally not observed and stochastic effects are not sufficiently studied.

Keywords: Radiopharmaceuticals, Extravasation, Dosimetry, Nuclear Medicine, Regulation, Patient Safety.

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INTRODUCTION

Extravasations occur when pharmaceuticals are inadvertently deposited into soft tissue, rather than the intended bloodstream. These events, also known as infiltrations, are a significant concern in medical settings. The potential for substantial radiation doses from radiopharmaceuticals to skin and tissue raises critical questions about patient safety, dosimetry, and the need for regulatory adjustments. Currently estimated to occur at rates ranging from 3% to 23% (Wong et al. 2019, Kim et al. 2020, Tarpey et al. 2023), extravasations demand a comprehensive understanding to facilitate accurate dose estimation and response protocols.

The Nuclear Regulatory Commission (NRC) is contemplating a shift in regulations, considering categorizing extravasations as reportable medical events rather than patient interventions (USNRC 2020, USNRC 2022). This transition reflects a growing recognition of the unique risks associated with these incidents. While previous research has employed several methods for dose estimations, inconsistencies persist due to various issues with assumptions as will soon be discussed (Castronovo et al. 1988, Bonta et al. 2011, Osborne et al. 2021, Berry and Kendrick 2022, Wilson et al. 2022, Tsorxe and Hayes 2023). The prevailing dose estimates suggest deterministic effects are likely, yet these effects are rarely observed (van der Pol et al. 2017).

The absence of a standardized approach for dose calculations further complicates the response to extravasations. To address the potential 24-hour reporting requirements for medical events, there is a pressing need for the development of a comprehensive standard. This research endeavors to review and compare existing literature, focusing on radiation safety programs' responses to extravasation events. Various methods of dose calculations, including the use of software like IDAC, VARSKIN+, Monte-Carlo simulations, and manual calculations, mostly through the application of the Fano Theorem, will be explored.

In this context, the research aims to assess the effectiveness of these methods, identify gaps in current understanding, and propose avenues for further investigation. The determination of the effective half-life of extravasation radiopharmaceuticals and reliable assessment of the fraction of extravasated material are vital components of this inquiry. Given the wide-ranging nature of extravasation scenarios, questions persist about the regulatory necessity to differentiate between skin and tissue dose, particularly when deterministic effects are infrequently observed, and stochastic effects remain insufficiently studied.

BACKGROUND

What Are Extravasations?

Extravasation refers to the unintentional leakage of intravenously (IV) administered medications, including radiopharmaceuticals, into the surrounding tissues rather than the intended intravascular route. This occurrence can lead to various adverse effects, depending on the type of medication and the amount that has extravasated (Kim et al. 2020, Tarpey et al. 2023). For radiopharmaceuticals, the primary concern is the potential for localized radiation exposure, which can result in tissue damage or necrosis in the worst cases.

The term “infiltration” is often used interchangeably with extravasation, but there is a nuanced difference between the two. Infiltration describes the leakage of non-vesicant substances—those that do not cause blistering or severe tissue injury—into the surrounding issue. In contrast, extravasation specifically refers to the leakage of vesicant substances, which are capable of causing severe tissue damage (Tarpey et al. 2023). While the distinction between these terms is clinically relevant, particularly in terms of the potential for tissue damage and the required response, in the context of radiopharmaceuticals, the focus is often on extravasation due to the higher risk associated with radioactive materials. However, understanding both processes is vital for healthcare professionals to implement appropriate preventative and response measures.

Extravasations and infiltrations can occur due to various factors, including but not limited to improper IV catheter placement, catheter dislodgement, vein fragility, high injection pressure, and the chemical nature of the injected substance (Kim et al. 2020). In the case of radiopharmaceuticals, the specific characteristics of the drug, including its activity, volume, and administration technique, play critical roles in the risk and potential severity of an extravasation.

Background on Extravasations in Other Fields

Extravasations are not unique to nuclear medicine. Oncology and radiology are other fields that have tackled the dangers of extravasations. Extravasation during chemotherapy administration is a critical and potentially severe complication. It has been recognized since the early days of chemotherapy use, with increasing attention over the years as the arsenal of chemotherapeutic agents and the population of cancer patients continue to grow (Boschi and Rostagno 2012, Nicola et al. 2016, Hwang et al. 2018, Kim et al. 2020, Roditi et al. 2022, Tarpey et al. 2023).

The dangers of extravasations are multifaceted and can range from minor local irritation to severe complications requiring surgical intervention. The severity of the injury depends on the agent involved, the volume and concentration of the agent extravasated, and the promptness and effectiveness of the intervention. The more severe injuries that can be posed by these agents include severe blistering, ulceration, and tissue necrosis (Boschi and Rostagno 2012, Nicola et al. 2016, Hwang et al. 2018, Kim et al. 2020, Roditi et al. 2022, Tarpey et al. 2023).

The current rate of extravasation incidents in oncology has significantly decreased compared to the past, thanks to advances in technology, improved clinical protocols, and heightened awareness among healthcare professionals. Historically, extravasation rates were higher due to less sophisticated IV administration techniques, limited understanding of the risks associated with certain chemotherapeutic agents, and a lack of comprehensive training for oncology nurses and staff. Additionally, the establishment of standardized protocols for the immediate management of suspected extravasations, including the use of antidotes and specific post-extravasation care, has minimized the severity of injuries when they do occur. These advancements, combined with ongoing education and training programs focused on extravasation prevention and response, reflect substantial progress in safeguarding patients against this complication (Doellman et al. 2009, Boschi and Rostagno 2012, Nicola et al. 2016, Jackson-Rose 2017, Hwang et al. 2018, Kim et al. 2020, Roditi et al. 2022, Tarpey et al. 2023).

Original NRC Ruling as Patient Intervention

In 1980, the Nuclear Regulatory Commission (NRC) determined that extravasations should not be classified as a misadministration requiring report. This decision was predicated on the frequency of extravasation occurrences and the inherent challenges in completely avoiding them during medical procedures, calling them “virtually impossible to avoid” (USNRC 1980, McElroy 1986, ACMUI 2020).

Subsequent developments in the regulatory landscape saw a refinement of the terms and criteria associated with the reporting of medical incidents. Notably, in 2002, the regulatory framework evolved from focusing on misadministrations to encompassing a broader

category of “Medical Events”, which aimed to capture a wider range of deviations from prescribed medical treatments (USNRC 2002). Despite these changes, extravasation continued to be regarded as an event that did not necessitate reporting under the revised Medical Event criteria, reflecting a sustained perspective that such occurrences are more aptly considered within the scope of medical practice rather than regulatory oversight (USNRC 2018, ACMUI 2020).

A critical aspect of the discourse on extravasation and its regulatory treatment involves the distinction between intentional and unintentional patient actions that influence treatment outcomes. The concept of “patient intervention” emerged as a significant consideration, originally intended to describe direct physical actions by patients that result in a deviation from the intended treatment. Over time, this concept was broadened to include passive or unintentional outcomes arising from anatomical or physiological conditions, effectively categorizing them as involuntary forms from patient intervention. This expanded interpretation acknowledges the complexity of medical treatment outcomes, recognizing that deviations are not always within the control of medical practitioners and, therefore, should not invariably necessitate reporting as Medical Events, particularly in instances where no unintended permanent functional damage occurs (ACMUI 2020).

The recommendations articulated within this framework advocate for a nuanced approach to the reporting obligations, proposing that the definition of patient intervention should encompass both voluntary and involuntary actions by patients. However, it is posited that only interventions resulting in significant harm warrant classification as Medical Events.

This approach seeks to strike a balance between the need for regulatory oversight and the recognition of the inherent complexities of medical practice. It underscores the importance of concentrating regulatory resources on incidents with significant safety implications, while avoiding undue encroachment on medical judgement and the dynamics of patient care (USNRC 2022, USNRC 2023).

Current Rulemaking

Increased Usage of Radiopharmaceuticals

The increasing usage of radiopharmaceuticals in medicine represents a significant shift in the therapeutic landscape, especially concerning the treatment of cancer and other ailments. Historically, the application of radiopharmaceuticals was primarily for diagnostic purposes, utilizing SPECT and PET to visualize and diagnose diseases. However, recent years have witnessed a remarkable boom in radiopharmaceutical research focused on therapeutic uses, indicating a paradigm shift towards their use in treating diseases directly (Pini et al. 2022).

This burgeoning interest in therapeutic radiopharmaceuticals is driven by the ever-expanding understanding of cancer biology and the identification of new molecular targets (Pini et al. 2022). This has dramatically broadened the spectrum of therapeutic applications, suggesting that nearly any radionuclide could potentially serve as a cure for cancer or other diseases. The types of emitters being explored include alpha and beta particles, each offering their own unique advantages. Alpha emitters, for instance, are known for their high linear energy transfer (LET), which allows them to deliver potent doses of radiation over a

short range, thereby minimizing damage to surrounding healthy tissues. Beta emitters have longer ranges and are suitable for targeting larger tumor masses or disseminated diseases. One challenge with these emitters is managing extravasation, given their high doses of localized radiation and relatively short ranges.

The shift towards therapeutic uses of radiopharmaceuticals is not merely an expansion of their application but signifies a broader transition in medical practice. Where once the focus was on diagnosing and imaging diseases, the future appears to be equally, if not more, invested in treating diseases using the same principles. This evolution is underscored by the concept of theranostics, which combines diagnostic imaging and therapy using radiolabeled agents targeting specific molecular patterns or metabolic pathways. This approach not only allows for the targeted treatment of diseases such as cancer but also enables real-time monitoring of treatment efficacy and disease progression, tailoring therapy to individual clinical needs. Fortunately, the same principle enabling highly localized radiation doses also facilitates precise tracking and dosimetry, enhancing safety in case of complications (Pini et al. 2022).

The explosion of interest and research in therapeutic radiopharmaceuticals is setting the stage for a future where their use is common, if not more so, than traditional pharmaceuticals for certain conditions. This trend is particularly evident in the treatment of cancers, where radiopharmaceuticals offer a promising avenue for precision medicine, targeting the disease at the molecular level and minimizing harm to healthy tissues. As research continues to advance, the potential for radiopharmaceuticals to treat a wide range

of diseases seems increasingly likely, heralding in a new era of nuclear medicine (Pini et al. 2022). With the increasing utilization of radiopharmaceuticals, a proportional rise in the incidence of extravasations can be anticipated.

Lucerno Dynamics Petition

In recent developments within the nuclear medicine field, Lucerno Dynamics has taken a proactive stance in addressing the regulatory approach towards radiopharmaceutical extravasations. The company, known for the development of the Lara® System, which is designed to detect and characterize extravasations, has advocated for the NRC to reevaluate and amend its policies regarding the reporting of such events. Lucerno Dynamics argues, based on evidence that they have gathered, that extravasations are preventable and potentially harmful to patients (Lattanze 2020, Lucerno Dynamics 2024).

Lucerno Dynamics' engagement with the NRC began in earnest in 2018, when the company presented evidence challenging the longstanding regulatory perspective that considered extravasations as unavoidable and thus exempt from medical event reporting. Despite this initiative, the Advisory Committee on the Medical Uses of Isotopes (ACMUI) initially recommended retaining the existing exemption, leading to Lucerno Dynamics to petition the NRC with further research and evidence. The NRC's decided to conduct an independent evaluation of the issue in January 2020. The ACMUI, upon review, reiterated its previous recommendation (ACMUI 2020, Lucerno Dynamics 2024).

In response, Lucerno Dynamics submitted a formal petition for rulemaking to the NRC in May 2020. The petition proposed specific changes to 10 C.F.R. § 35.2 (“Definitions”) and 10 C.F.R. § 35.3045 (“Report and Notification of a Medical Event”), advocating for the inclusion of certain extravasations that result in significant radiation doses (exceeding 0.5 Sv or 50 rem to tissue) within the medical event reporting requirements (Lattanze 2020, USNRC 2020).

The dialogue between Lucerno Dynamics and the NRC revealed the intricacies of adapting established regulatory frameworks to accommodate new technologies. This interaction spotlights the ongoing negotiation between technological innovation within the industry and the evolution of regulatory standards, propelling a broader discussion on refining safety and reporting protocols in light of such advancements. While the initiative by Lucerno Dynamics to advocate for revised extravasation reporting rules might initially appear as a strategy to enhance the marketability of their Lara® System, it has also underscored emerging concerns within the nuclear medicine community.

The increasing utilization of theranostics and therapeutics has introduced new dimensions. This shift accentuates the need for a reevaluation of safety protocols to address the unique risks posed by these more complex and higher-risk procedures. Lucerno Dynamics’ push for regulatory change, therefore, has spurred a dialogue around the issue of patient safety in the context of theranostics’ growing role in nuclear medicine.

This expanded dialogue highlights the necessity for the industry to be agile in adjusting to the evolving landscape of radiopharmaceuticals. While regulatory frameworks are typically not known for their agility, there is an opportunity over time to petition these regulations to be flexible enough, allowing the industry space to grow and innovate without compromising patient or public safety. As the field progresses, it becomes critical for industry stakeholders to proactively adapt to immediate and future challenges, ensuring that advancements in practices are effectively integrated within the existing regulatory landscape.

Current Proposed Language and Timeline

In the ongoing rulemaking process concerning the reporting of extravasations in nuclear medicine as medical events, the NRC has proposed amendments to 10 C.F.R. § 35. These amendments are designed to refine the framework for evaluating, reporting, and managing incidents of extravasations, with an emphasis on enhancing patient safety and care within the field of nuclear medicine. The NRC's proposed rule language specifically addresses the need for licensees to develop, implement, and maintain written procedures that ensure the high-confidence detection and timely reporting of extravasations requiring medical attention for suspected radiation injury (USNRC 2022, USNRC 2023).

As part of this rulemaking effort, the NRC has sought feedback from stakeholders through a series of questions aimed at improving the proposed language and ensuring the practicality of the new requirements. These questions span various aspects of the rulemaking, including the determination of appropriate terminology, the identification of

effective procedures for minimizing extravasations, and the development of criteria for suspected radiation injury and medical attention. The feedback received in response to these questions will play a crucial role in refining the rule's provisions and addressing any concerns raised by the medical community and other stakeholders (USNRC 2022).

The NRC has outlined an estimated timeline for the completion of this rulemaking process. The publication of a proposed rule and draft implementation guidance is expected in Fall 2024, marking a significant step forward in formalizing the new requirements. Following a period for public comment and further refinement, the final rule and implementation guidance are anticipated to be issued in Spring 2026. This timeline reflects the NRC's commitment to a thorough and deliberative process, ensuring that the final regulations are well-considered, effective, and capable of enhancing safety practices in the administration of radiopharmaceuticals (USNRC 2022, USNRC 2023).

By establishing clear reporting requirements and enhancing the framework for managing these incidents, the NRC aims to improve patient outcomes and reinforce the safety protocols surrounding the use of radiopharmaceuticals. The engagement of stakeholders throughout this process ensures that the final rule will be informed by a wide range of perspectives, ultimately leading to more effective and practicable regulations for the nuclear medicine industry.

Established Deterministic Dose Thresholds

Deterministic effects, which are dose-dependent and increase in severity with higher radiation doses, are a critical consideration when thinking about patient safety. For skin, the thresholds for deterministic effects have been well documented and studied (Johnson and Birky 2012, Bushberg et al. 2020).

SINGLE-SITE ACUTE SKIN-DOSE RANGE (GY)[c–e]	NCI (2006) SKIN REACTION GRADE	APPROXIMATE TIME OF ONSET OF EFFECTS[e,f]			
		Prompt <2 wk	*Early 2–8 wk*	*Mid Term 6–52 wk*	*Long >40 wk*
0–2	Not applicable	No observable effects expected at any time			
2–5	1	Transient erythema	Epilation	Recovery from hair loss	None expected
5–10	1–2	Transient erythema	Erythema, epilation	• Recovery • At higher doses: prolonged erythema, permanent partial epilation	• Recovery • At higher doses: dermal atrophy induration
10–15	2–3	Transient erythema	• Erythema, epilation • Possible dry or moist desquamation • Recovery from desquamation	• Prolonged erythema • Permanent epilation	• Telangiectasia[g] • atrophy induration • Skin likely to be weak; atrophic
>15	3–4	• Transient erythema • After very high doses: edema and acute ulceration, long-term surgical intervention likely to be required	• Erythema, epilation • Moist desquamation	• Dermal atrophy • Secondary ulceration due to failure of moist desquamation to heal, surgical intervention likely to be required • At higher doses: dermal necrosis, surgical intervention likely to be required	• Telangiectasia[g] • Dermal atrophy induration • Possible late skin breakdown • Wound might be persistent and progress into a deeper lesion • Surgical intervention likely to be required

Figure 1. Tissue Reactions from a Single-Delivery Dose to the Skin of the Neck, Torso, Pelvis, Buttocks, or Arms (Bushberg et al. 2020)
Reprinted with permission from Jerrold T. Bushberg PhD, J. Anthony Seibert PhD, Edwin M. Leidholdt, Jr. PhD, John M. Boone PhD, The Essential Physics of Medical Imaging, 4th Edition, Wolters Kluwer Health, Inc., 2020

At the lower end of the spectrum, skin exposure to 2-5 Gy can result in transient erythema and epilation. These effects are typically temporary, with the skin showing mild reactions that usually resolve without long-term consequences. This initial reaction serves as an important indicator for the need for vigilance and possible clinical intervention to manage and monitor the skin's response to radiation exposure.

With an increase in dose to 5-10 Gy, the skin's response intensifies, leading to more pronounced transient erythema and the potential for permanent epilation. This dose range indicates a more serious level of skin injury, where the effects may not fully revert, highlighting the importance of accurate dose assessment and management in treatment planning to prevent such outcomes.

As the dose escalates to 10-15 Gy, patients may experience dry desquamation, characterized by the peeling or flaking of the skin. This condition signifies a notable reaction to radiation, necessitating clinical management to mitigate discomfort and prevent further skin damage.

Exposures greater than 15 Gy are associated with severe skin reactions, including moist desquamation and the possibility of necrosis. These high doses inflict significant damage to the skin tissues, potentially leading to permanent injury and the loss of skin integrity. Clinical management at this stage is complex, focusing on treating the symptoms, preventing infections, and supporting wound healing to restore skin health.

In contrast to skin, muscle tissue is understood to be less radiosensitive, with no widely recognized deterministic dose thresholds established. The resilience of muscle tissue to radiation exposure means that it is generally considered to have a higher tolerance for radiation without manifesting severe deterministic effects observed in more radiosensitive tissues like the skin. This understanding underscores the important of tissue-specific knowledge in management and prevention of radiation-induced injuries, ensuring that

treatment protocols and response procedures are tailored to the varying sensitivities of different tissues to radiation.

DOSE ASSESSMENT METHODS

Manual Calculation

Spheres Model

A major aspect when dealing with localized deposits of radiopharmaceuticals is the process of calculating a dose assessment for extravasations. The manual approach is grounded in the application of the Fano Theorem, which has been a frequent mention in literature for this purpose (Attix 2008, Bonta et al. 2011, Berry and Kendrick 2022). The Fano Theorem posits that "In a medium of a given composition exposed to a uniform flux of primary radiation, the flux of secondary radiation is also uniform and independent of the medium's density or any variations in density from point to point." This theorem is particularly pertinent to the scenario of extravasated radiopharmaceuticals, where we can assume a homogenous pocket of radiopharmaceutical.

To facilitate the calculations, an assumption is adopted that the extravasated radiopharmaceutical forms a spherical volume. This assumption provides a model of the distribution of radiation. The selection of the volume for the calculations is informed by the total volume of the extravasated liquid, which includes not only the radiopharmaceutical but also any saline or other co-administered agents that may have also been extravasated.

In selecting a density value for the calculations, taking a conservative approach, the International Commission on Radiological Protection (ICRP)'s density value for soft tissue is utilized, which is 1.00 grams per cubic centimeter. This choice is made in contrast to the slightly higher ICRP density values for skin and muscle, which are 1.10 and 1.04 grams per cubic centimeter, respectively (ICRP 2003). The rationale behind this selection lies in the aim to ensure a conservative estimate that adequately represents a generalized scenario without overestimating the density, which could lead to unconservative estimates in the dose assessment.

The analysis of the localized nature of extravasations assumes that photon interactions are relatively negligible, based on the premise that within the dense, homogenous sphere of extravasated material, beta and alpha radiation significantly contribute to the dose due to their shorter range and higher interaction likelihood within the affected area. Given their lower probability of interaction, photons are deemed less critical to the overall dose assessment in this context. This approach prioritizes the immediate and localized effects of alpha and beta radiation, simplifying the calculation by focusing on the interactions that most significantly impact the radiation dose from extravasated radiopharmaceuticals.

This section aims to outline the theoretical foundation and methodological approach for accurately assessing the radiation dose from extravasated radiopharmaceuticals, leveraging the principles of the Fano Theorem to navigate the complexities inherent in such calculations.

For simplicity and greater understanding, all expected units are provided in brackets within the equations.

Begin by taking the definition of a Gray by meaning one Joule per kilogram to calculate dose for a given activity A(t):

$$1\text{Gy} = 1\frac{\text{J}}{\text{kg}} \Rightarrow \dot{D} = \frac{A(t)[\text{Bq}] * I * E_{avg}[\text{MeV}] * 1.602x10^{-13}[\frac{\text{J}}{\text{MeV}}]}{M[\text{kg}]}$$

Then, take the equation for activity at a given time:

$$A(t) = A_0 e^{-\lambda t}$$

Substituting the activity at a given time into the equation and integrating to infinity allows for the calculation of the total dose over the entire decay and clearance of the extravasated radiopharmaceutical. To better align with available data in the event of an extravasation, the equation can be adjusted by replacing the mass (M) with the density (ρ) of the tissue multiplied by the volume (V) of tissue affected.

$$\int_0^t \dot{D}dt = \int_0^\infty \dot{D}dt = D[\text{Gy}] = \frac{1.602x10^{-4}\left[\frac{\text{J}\cdot\text{g}}{\text{MeV}\cdot\text{kg}}\right] A_0[\text{MBq}]\, I\, E_{avg}[\text{MeV}]}{\lambda[\text{s}^{-1}]\, \rho\left[\frac{\text{g}}{\text{cm}^3}\right] V[\text{mL}]}$$

It's important to acknowledge the balance between accuracy and realism in the process of using this method to calculate a dose assessment. This method is simplified by the assumptions regarding uniformity and negligible photon interactions but demonstrates a practical approach to a complex issue. Though the ability is there to precisely calculate the

dose by including every intensity and energy for any given radionuclide, restraint should be taken to include only those with impactful contributions to the total dose.

An advantage of this methodology is its accessibility; it can be included in any written protocol or procedure and executed by anyone possessing the requisite math skills, making it a valuable tool in a wide range of settings. Furthermore, results derived from this approach have shown close alignment with those obtained through more sophisticated methods, such as Monte-Carlo simulations and IDAC, as evidenced in literature.

However, it's important to recognize the limitations of this method. Its manual nature makes it more susceptible to human error, which can introduce inaccuracies and poor decisions in corresponding patient care. Additionally, in scenarios that may require a rapid response, this method may not meet those needs due to the time required to perform calculations manually. Despite these drawbacks, the method's shown effectiveness in aligning closely with accepted practices and its capability to be employed by individuals with basic mathematical proficiency make it a valuable addition to the toolkit for assessing radiation doses from extravasated radiopharmaceuticals.

Radiating Model

An inherent issue with the model previously discussed in the literature is the assumption that the sphere essentially radiates itself rather than radiating the surrounding tissue. Another method for dose assessment involves disregarding the extravasated volume and instead assessing the dose to the average particle range from the outer edges of the sphere.

The extravasated volume is still assumed to be spherical, but the calculation now factors in some distance around the sphere rather than focusing internally.

The aspects of this model that require calculation include the volume of tissue within the beta particle range of the extravasated sphere and the volume of extravasated radiopharmaceutical from which beta particles can escape. A significant degree of self-shielding by the radiopharmaceutical is anticipated. For instance, a sphere of 20cc will have a radius of 1.68 cm, but the average range of a Lu-177 beta particle is approximately 0.03 cm. This implies that only the outer 0.03 cm of the extravasated sphere of radiopharmaceutical can contribute to tissue dose, while the majority of the beta particles are absorbed within the radiopharmaceutical itself. Given that the depth of commonly used veins ranges from 2-3 mm (Mukai et al. 2020), significantly more than the average range of Lu-177 beta particles, it can be assumed that all beta radiation emanating from the sphere is absorbed.

To find the volume of tissue, V_t, being irradiated by the extravasated radiopharmaceutical, the total volume irradiated must be calculated and the volume of extravasated liquid, V_e, subtracted from it, as illustrated in the figure below.

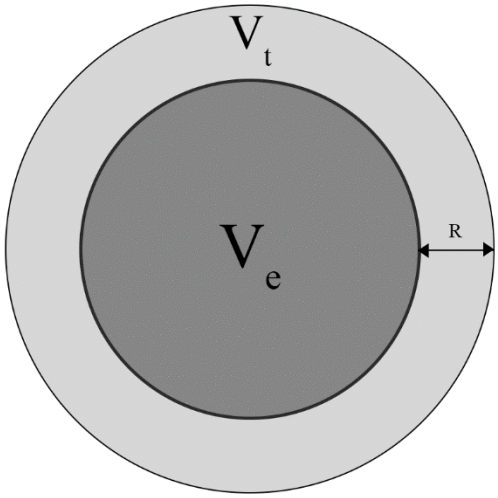

Figure 2. Example of Radiating Model. V_t represents the irradiated tissue being assessed, while V_e denotes the volume of the sphere of extravasated radiopharmaceuticals.

First, the volume of V_t is equated:

$$V_t = V_{total} - V_e$$

To find V_{total}, the average beta range must be calculated. Given that the average beta energy of most radiopharmaceuticals is less than 800 keV, the rule of thumb to determine the average range of beta particles less than 800 keV will be applied:

$$R_{avg}\left[\frac{\mathrm{cm}^2}{\mathrm{g}}\right] = 0.407 \cdot E_{avg}^{1.38}[\mathrm{MeV}]$$

Considering the density of affected tissue is 1.00 g/cc, which also matches the density of water, this simplifies the calculation, equating the result directly to the average range of the beta particle in centimeters, R. If other densities are considered, then the chosen density, in g/cc, must be factored into the range equation to obtain a range in centimeters.

$$R = R_{avg} \cdot \rho$$

With the range determined, both the volume of the affected tissue and the volume of extravasation containing the activity contributing to the dose can be calculated. The extravasated volume, V_e, is predetermined, but the radius of the sphere, r_e, must be calculated.

$$r_e = \left(\frac{3V_e}{4\pi}\right)^{\frac{1}{3}}$$

With r_e calculated, V_{total} can now be determined by adding the range, R, to the radius of the extravasation, r_e.

$$V_{total} = \frac{4}{3}\pi(r_e + R)^3$$

The percent of activity contributing to tissue dose is also determined using the range. The volume of the sphere where 100% self-shielding is assumed, V_s, is calculated by subtracting the determined range from the radius of the extravasated sphere. This provides the volume of radiopharmaceutical contributing to the activity, V_a.

$$V_s = \frac{4}{3}\pi(r_e - R)^3$$

$$V_a = V_e - V_s$$

By dividing the contributing volume, V_a, by the extravasated volume, V_e, percent activity contributing to dose, F, can be determined.

$$F = \frac{V_a}{V_e} \quad \text{or} \quad F = 1 - \frac{V_s}{V_e}$$

Adapting the derivation from the spheres model with the modifications introduced here, the calculation of the dose to surrounding tissue incorporates an adjustment to account for the partial self-shielding from the volume of V_a. This adjustment involves dividing the calculated dose by two. This acknowledges and assumes that the intensity of beta radiation will decrease linearly with distance from the extravasated volume.

$$D[\mathrm{Gy}] = \frac{1.602x10^{-4}\left[\frac{\mathrm{J}\cdot\mathrm{g}}{\mathrm{MeV}\cdot\mathrm{kg}}\right](F\cdot A_0[\mathrm{MBq}])\; I\; E_{avg}[\mathrm{MeV}]}{2\cdot\lambda[\mathrm{s}^{-1}]\;\rho\left[\frac{\mathrm{g}}{\mathrm{cm}^3}\right]V_t[\mathrm{mL}]}$$

Monte-Carlo Simulations

Monte-Carlo simulations represent a sophisticated approach to performing dose assessments. Leveraging the same foundational assumptions outlined in the manual calculation section, such as the negligible impact of photon interactions and the uniform distribution of radiation within a homogenous sphere, Monte-Carlo simulations offer a powerful tool for simulating the complex interactions of radiation with matter. This method's effectiveness hinges on its ability to model stochastic processes, thereby providing detailed insights into the radiation dose distribution within the extravasated area.

One of the primary strengths of Monte-Carlo simulations lies in their accuracy and utility when equipped with an appropriate model. By simulating thousands or even millions of individual radiation interaction events, these simulations can yield accurate estimates of radiation doses. This level of detail and accuracy is particularly beneficial when assessing the potential impact of radiation on surrounding tissues, considering the specific characteristics of the radiopharmaceutical and the medium it interacts with.

However, the implementation of Monte-Carlo simulations faces significant challenges, including the time-intensive process of creating appropriate models and performing computations, which stands as the primary barrier to their widespread use for rapid dose assessments. Additionally, accessing the necessary software poses a considerable obstacle. The software required for these simulations is not always readily available or affordable for all research groups or medical institutions, which can restrict its use. The complexity of the software further requires a level of proficiency and experience, rendering it less user-friendly for newcomers. This steep learning curve, combined with the extensive time required for model creation and computation, can significantly impede its adoption and effectiveness in immediate dose assessment scenarios.

Accuracy, while one of the method's advantages, is contingent upon the quality of the model provided to the simulation. The process of modeling, crucial to the success of Monte-Carlo simulations, is inherently susceptible to errors. Inaccuracies in the model, whether in the assumptions about the physical properties of the tissue, the geometry of the extravasated area, or the characteristics of the radiopharmaceutical, can lead to significant

discrepancies in the dose estimates. Therefore, meticulous attention to detail and a deep understanding of the modeling process are imperative to leverage the full potential of Monte-Carlo simulations for dose assessments.

Monte-Carlo simulations offer a highly accurate and detailed method for dose assessments in the context of extravasated radiopharmaceuticals, provided that a well-constructed model guides them. While the method's complexity and the need for specialized software may pose challenges, its potential for precise dose estimation makes it a valuable tool in the field of radiopharmaceutical safety and dosimetry. Careful modeling and an understanding of the simulation process are essential to minimize errors and fully realize the benefits of this advanced computational technique.

Internal Dose Assessment by Computer (IDAC)

The Internal Dose Assessment by Computer (IDAC) (Andersson et al. 2017) tool, particularly its spheres function, presents a convenient approach for performing dose assessments in cases of extravasation involving radiopharmaceuticals. A standout feature of IDAC is its accessibility; being free and available to all, it provides the ability to perform sophisticated dose calculations without the barrier of high costs associated with other software tools. Additionally, IDAC's interface is user-friendly, although newcomers to the software may experience a slight learning curve before they can use it with confidence (Andersson et al. 2013).

One of the standout features of IDAC for extravasation dose assessments is its spheres function, which simplifies the modeling process by allowing users to simulate the distribution of radiopharmaceuticals within a spherical volume. This is particularly relevant in the context of extravasations, where the leaked radiopharmaceutical can be approximated as a homogenous spherical deposit in the tissue.

However, potential users should be aware of certain limitations inherent to IDAC's spheres function. The software is designed to work with one homogenous material or tissue type for the sphere at a time, and it can only accommodate one radionuclide per calculation. This limitation necessitates a straightforward approach to dose assessment, aligning with the same foundational assumptions about uniform radiation distribution and negligible photon interaction that underpin manual calculations. Additionally, these constraints mean that IDAC, while powerful, may not capture the full complexity of scenarios involving multiple radionuclides or heterogeneous tissue compositions.

Despite these limitations, IDAC stands out as potentially the best option currently available for rapid dose assessment in the event of an extravasation. Its ease of use, combined with the lack of financial barriers to access, makes it a practical choice for healthcare providers and researchers alike. In my research through the literature, IDAC's performance in extravasation dose assessments has shown to closely align with results obtained from manual calculations, Monte-Carlo simulations, and even a modified version of VARSKIN+ (Wilson et al. 2022, Tsorxe and Hayes 2023). This alignment underscores IDAC's

reliability and accuracy in estimating radiation doses, making it an invaluable tool in the field of radiopharmaceutical safety and dosimetry.

While acknowledging its limitations, the use of IDAC's spheres function for extravasation dose assessment offers a blend of accessibility, ease of use, and accuracy. This balance makes it a highly attractive option for rapid response scenarios, providing healthcare professionals with a reliable method to assess potential radiation exposure and mitigate the potential risks associated with extravasated radiopharmaceuticals.

VARSKIN+

VARSKIN+ (USNRC 2021) stands out for its intuitive interface and accessibility, primarily designed for rapid dose assessments in scenarios involving skin contamination from external sources or contaminated wounds. This tool provides a straightforward approach for users needing to quickly evaluate potential radiation doses, highlighting its utility in rapid response situations.

However, its direct application to extravasation dose assessments presents a challenge, as the literature references the effectiveness of a modified version of VARSKIN+ specifically adapted for such purposes (Osborne et al. 2021). This modification, not widely available for general use, raises considerations regarding its accessibility and the extent of testing across various use cases. The native version of VARSKIN+, while invaluable for its intended applications, thus encounters limitations when directly applied to the complexities of extravasation scenarios without specific modifications.

While VARSKIN+ offers rapid and user-friendly dose assessment capabilities, its application in extravasation dose assessments is primarily noted through a specialized, modified version. This limitation points to the necessity of further development and validation to fully harness VARSKIN+'s potential in this specific context, reflecting the ongoing evolution of tools available for radiopharmaceutical safety and dosimetry.

Comparative Analysis of Dose Assessment Models for Lu-177 Extravasation

A comparative analysis is conducted using data from various hypothetical Lu-177 extravasation scenarios derived from the literature (Tsorxe and Hayes 2023), aiming to visually underscore the concordance among the Monte Carlo simulations, IDAC, and spheres model manual calculations. This examination also brings to light the notable divergences presented by the radiating model method, highlighting the differences between approaches to dose assessment.

Tables 1 and 2 below showcase the alignment between the Monte Carlo simulations, IDAC, and spheres model manual calculations for different extravasation scenarios involving Lu-177. This alignment reinforces the reliability and consistency of the manual calculations presented within the framework of the spheres model.

A comparison involving the VARSKIN model is absent due to the lack of sufficient data within the literature to accurately recreate the calculations, particularly regarding the initial activity levels of the extravasated radiopharmaceutical (Osborne et al. 2021).

The radiating model and the spheres model approach dose assessment from fundamentally different perspectives, leading to notable variations in their outcomes. Contrary to the spheres model, which does not consider the self-shielding effect and assumes that the radiopharmaceutical primarily irradiates itself within the sphere, potentially leading to an overestimation of the absorbed dose, the radiation model incorporates self-shielding of the radiopharmaceutical pocket. It specifically assesses the dose to surrounding tissue within the beta particle range, thereby providing a more nuanced estimation of the absorbed dose to the tissue.

Scenario	Isotope	Average Weighted Energy Emission (MeV)	Physical Half-Life (min)	Biological Clearance (min)	Effective Half-Life (min)	Initial Activity (MBq)	Sphere Volume (cc)
1	Lu-177	0.1349	9572	60	59.6	1850	20
2	Lu-177	0.1349	9572	60	59.6	1850	40
3	Lu-177	0.1349	9572	60	59.6	3700	20
4	Lu-177	0.1349	9572	60	59.6	3700	40

Table 1 Lu-177 Extravasation Scenario Parameters for Comparison

Scenario	Isotope	Initial Activity (MBq)	Monte Carlo Simulation Absorbed Dose (Gy)	IDAC-Dose Absorbed Dose (Gy)	Spheres Model Manual Calculation Dose (Gy)	Radiating Model Manual Calculation (Gy)
1	Lu-177	1850	12.1	10.9	10.3	5.0
2	Lu-177	1850	5.9	5.5	5.2	2.5
3	Lu-177	3700	23.5	21.8	20.6	10.0
4	Lu-177	3700	11.6	11	10.3	5.0

Table 2 Lu-177 Extravasation Dose Assessment Results for Comparitive Analysis

The data presented in Table 2 illustrates the consistency in dose estimations across the Monte Carlo simulations, IDAC, and spheres model manual calculations, suggesting a high degree of reliability and reproducibility within these models. Conversely, the Radiating Model's estimates for the absorbed dose are notably lower, underscoring a fundamental disparity in methodological assumptions about radiopharmaceutical behavior following extravasation.

This comparative analysis highlights the critical need for a standardized approach to dose assessment following radiopharmaceutical extravasation. The stark contrast in the outcomes from the Radiating Model method points to the potential risks of overestimating or underestimating patient exposure, underscoring the importance of methodological accuracy and the adoption of models grounded in empirical evidence and clinical relevance. Further research and validation of these models are imperative to ensure accurate, reliable, and standardized dose assessments that can inform clinical decision-making and regulatory compliance.

STANDARD CLINICAL EXTRAVASATION RESPONSE

The effective management of extravasations in oncology and other non-radiopharmaceutical fields hinge on the pillars of early detection and prompt, comprehensive response, complemented by rigorous prevention strategies. The process begins with the vigilant monitoring of patients receiving IV therapies for any alterations in sensation around the IV site, such as tingling, burning, or discomfort. These symptoms often serve as the first indications of potential extravasation, signaling the leakage of therapeutic agents into the surrounding tissues. Healthcare professionals also look for visible signs, including redness, swelling, or a palpable fluid collection, indicative of extravasation. Furthermore, patient-reported discomfort or pain, particularly descriptions of sharp or searing sensations, are taken seriously as corroborative evidence of extravasation. Routine inspection and palpation of the IV site, especially during the administration of vesicants known for their tissue-damaging potential, are critical for early identification (Boschi and Rostagno 2012, Nicola et al. 2016, Jackson-Rose 2017, Hwang et al. 2018, Kim et al. 2020, Roditi et al. 2022, Tarpey et al. 2023).

Upon identifying signs of extravasation, immediate action is taken to mitigate tissue damage and manage the condition effectively. The first step involves stopping the IV administration immediately to halt the further influx of the agent into the tissue. Following this, the IV line is carefully disconnected, and efforts are made to aspirate any remaining

drug from the cannula, minimizing the amount of the agent present in the tissue. If an extravasation occurs, the administration of a drug-specific antidote, if available, is crucial. This step requires knowledge of the specific agent involved and its corresponding antidote. Notification of a physician is imperative to assess the extravasation's severity and to plan further management, which may include medical or surgical interventions, if necessary (Boschi and Rostagno 2012, Nicola et al. 2016, Kim et al. 2020, Roditi et al. 2022, Tarpey et al. 2023).

Thermal treatments, employing cold or warm compresses, are applied based on the type of agent extravasated. Cold compresses are typically recommended for DNA-binding vesicants to induce vasoconstriction, theoretically limiting the spread of the agent. Conversely, warm compresses are used for non-DNA-binding vesicants to promote vasodilation, facilitating the dispersion and absorption of the agent away from the site of extravasation. The application of these compresses follows a specific regiment, usually 15 to 20 minutes every four hours for 24 to 48 hours, to maximize their therapeutic benefit (Boschi and Rostagno 2012, Nicola et al. 2016, Kim et al. 2020, Roditi et al. 2022, Tarpey et al. 2023).

Prevention strategies focus on minimizing the risk of extravasation through meticulous IV site selection, using the smallest gauge catheter suitable for the therapy, and ensuring robust site security. Education plays a pivotal role in prevention, with both patients and healthcare providers informed about the risks and signs of extravasation. Regular training sessions for healthcare providers on extravasation management protocols ensure preparedness, and

maintaining a readily available extravasation kit equipped with necessary supplies, including specific antidotes, ensures a swift response (Boschi and Rostagno 2012, Nicola et al. 2016, Kim et al. 2020, Roditi et al. 2022, Tarpey et al. 2023).

Together, these detailed steps in the detection, management, and prevention of extravasation form a comprehensive approach aimed at safeguarding patient well-being, minimizing the potential for tissue damage, and enhancing the overall quality of care in clinical settings where IV therapies are administered.

PROPOSED RADIOPHARMACEUTICAL EXTRAVASATION PROTOCOL

While managing radiopharmaceutical extravasations parallels the approach in non-radiopharmaceutical settings, focusing on prevention, early detection, and a comprehensive response to minimize patient harm and account for the unique properties of radioactive materials, it is recognized that extravasations cannot be completely eliminated. However, the implementation of this protocol aims not only to assist in developing procedures and protocols within radiation safety programs in anticipation of potential NRC regulations but also to reduce and improve the incidence of extravasations to a level that is As Low As Reasonably Achievable (ALARA). Although ALARA is typically applied to radiation doses, its principles are equally pertinent in minimizing the occurrence of extravasations, underscoring a commitment to enhancing patient safety and optimizing clinical outcomes in nuclear medicine practices.

Prevention Techniques

The prevention of radiopharmaceutical extravasation starts with meticulous IV site selection, prioritizing areas with robust vein integrity and avoiding sites prone to movement or where venous access might be compromised. The selection of the appropriate catheter is critical, with a preference for the smallest gauge that meets the infusion's requirements, minimizing the risk of vein injury. Secure cannulation is essential, ensuring that the cannula

remains fixed in place to prevent dislodgement. Education and training for healthcare professionals and patients about the risks, signs, and the critical importance of immediate reporting of any extravasation symptoms are foundational. Pre-infusion checks for correct catheter placement and patency, and a saline flush prior to administration form the last line of defense in prevention efforts.

Detection Techniques

Early detection relies on vigilant monitoring for any unexpected or unusual changes in sensation, such as tingling, burning, or discomfort at the IV site, and close observation for physical signs like redness, swelling, or fluid collection. Patient complaints of discomfort or pain are taken seriously as early indicators of potential extravasation. Regular inspection and palpation of the IV site are complemented by post-administration saline flush. Post-administration nuclear medicine scans, such as SPECT, can detect pockets of activity that signify an extravasation. Monitoring the IV infusion rate for any unusual changes serves as an additional detection method.

Response Techniques

Upon detecting an extravasation, the immediate cessation of the infusion is critical. The IV line is then disconnected carefully, with specific precautions to prevent the spillage of radiopharmaceuticals which can lead to gross contamination of the area and individuals. Immediate notification of the physician and Radiation Safety Officer is crucial for a coordinated response, considering the potential for radiation injury and contamination. The

application of warm compresses is recommended to promote vasodilation, facilitating the dispersion and absorption of the radiopharmaceutical away from the site of extravasation. Comprehensive documentation of the incident and thorough follow-up, including further nuclear medicine imaging or portable radiation instrumentation measurements, are essential for assessing the biological clearance rate of the extravasated dose. Dose assessments, using nuclear imaging and portable radiation instrumentation measurements, are undertaken to understand the extent of the extravasation and its implications, as well as being general good practice. Accurate recording of all time measurements associated with the response steps is vital for effective management and documentation.

Comparison to Current Clinical Protocols

The management strategies for radiopharmaceuticals and non-radiopharmaceutical extravasations share foundational similarities, particularly in the emphasis on prevention, detection, and the initial steps of the response process. However, key differences emerge in the response, most notably the absence of antidotes for radiopharmaceuticals, which necessitates the focus on minimizing radiation exposure and contamination rather than counteracting the agent itself. The involvement of the Radiation Safety Officer, specific to radiopharmaceuticals, underscores the unique safety and regulatory considerations in managing radioactive materials. Additionally, the exclusive use of warm compresses for radiopharmaceuticals contrasts with the variable thermal treatments (cold or warm) in non-radiopharmaceutical cases, reflecting the goal of promoting dispersion and absorption of the radiopharmaceutical. Dose assessments, including detailed imaging and radiation

measurements, highlight the specialized approach required to understand and mitigate the impact of radiopharmaceutical extravasations.

Extravasation Protocol Checklist

Prevention Techniques

- Select IV sites with good vein integrity.
- Use the smallest gauge catheter.
- Secure the cannulation effectively.
- Provide appropriate training to healthcare professionals and educate the patients on extravasation risks.
- Perform pre-infusion checks for catheter placement and patency.
- Perform pre-administration saline flush.

Detection Techniques

- Monitor for changes in sensation at the IV site.
- Observe for physical signs like redness and swelling.
- Take patient complaints of discomfort seriously.
- Inspect and palpate the IV site regularly.
- Consider post-administration nuclear medicine scans for detection.
- Monitor IV infusion rate for unusual changes.
- Perform post-administration saline flush.

Response Techniques

- Immediately cease the infusion at the first sign of extravasation.
- Disconnect the IV line carefully to prevent spillage.
- Notify the physician and Radiation Safety Officer.
- Apply warm compresses to the affected area.
- Document the incident thoroughly and follow up.
- Perform dose assessments, including imaging and radiation measurements.
- Accurately record all times related to the event and response.

OUTSTANDING ISSUES AND ISSUES IN EXISTING LITERATURE

Validity of Assumptions

The existing body of literature on dose assessments for therapeutic radiopharmaceuticals reveals significant variability in outcomes. Despite employing similar methodologies, studies report markedly diverse results, raising concerns about the accuracy and reliability of dose measurements, particularly in cases of extravasation. Some studies highlight alarmingly high levels of radiation dose, which could pose serious health risks, underscoring the need for a deeper understanding and standardization in dose assessment protocols (Shapiro et al. 1987, Bonta et al. 2011, van der Pol et al. 2017, Tylski et al. 2018, Osborne et al. 2021, Berry and Kendrick 2022, Fisher and Liverett 2022, Wilson et al. 2022, Tsorxe and Hayes 2023).

A key factor contributing to the discrepancies observed across various studies is the selection of parameters such as tissue density, volume, mass, and clearance rates. Notably, studies reporting higher dose levels often rely on calculations using minimal volumes, which can lead to a disproportionate increase in the estimated dose (Wilson et al. 2022, Tsorxe and Hayes 2023). However, the rationale behind choosing these specific volumes remains largely unexplained in the literature, suggesting a lack of standardized criteria for such determinations (Wilson et al. 2022).

The lack of biokinetic data on the clearance rates of extravasated radiopharmaceuticals significantly complicates the accuracy of dose assessments. Few studies have tracked the clearance of radioactivity at extravasation sites over time, creating a substantial gap in our understanding of radiopharmaceutical clearance dynamics. The variability in extravasation sites complicates dose assessments further; extravasations can affect both skin and muscle tissues. While the risk of beta radiation to skin is well-documented, radiation can also be absorbed by muscle tissue, which is traditionally not considered highly radiosensitive. Nevertheless, data on the deterministic effects of radiation on muscle tissue are scarce, indicating a critical need for further research in this area. Additionally, it may seem trivial but is important to acknowledge that most of our established deterministic thresholds for skin exposure are based on whole-body and external exposure, not from an internal source as encountered in extravasation scenarios.

Moreover, the unique biokinetic properties of each radiopharmaceutical, tailored to target specific molecular characteristics of cancerous and diseased cells, suggest that clearance rates and, consequently, dose assessments may vary significantly across different agents. This variability underscores the necessity for more comprehensive biokinetic studies to enable accurate dose assessments and to fully understand the risks associated with extravasation of radiopharmaceuticals. Only through targeted research and the accumulation of more robust data can we hope to mitigate the risks associated with therapeutic radiopharmaceuticals and enhance the safety and efficacy of nuclear medicine treatments.

Small, Localized Area Affected

In the ongoing debate surrounding radiopharmaceutical extravasations, a critical aspect often seems to be overlooked: the fact that these incidents affect small, localized areas of tissue. Despite this, the doses calculated in such scenarios are frequently treated as if they were distributed over a larger area. This oversight raises significant questions about the actual risk posed by these exposures and challenges the applicability of existing regulatory thresholds, such as the 50 rem (0.5 Sv) limit intended to prevent tissue reactions. The rarity of deterministic effects in cases of extravasation further complicates the discussion, suggesting that the regulatory framework may not fully capture the nuances of radiopharmaceutical administration, particularly when it involves highly localized exposure (Parihar et al. 2023).

This regulatory limit, while serving as a guideline for broader radiation safety measures, may not accurately reflect the nuances of radiopharmaceutical administration, particularly when the exposure is confined to very small volumes of tissue. The conventional dose metrics used in regulatory contexts, such as Committed Dose Equivalent (CDE), Committed Effective Dose Equivalent (CEDE), and Total Effective Dose Equivalent (TEDE), are designed to assess risk based on an abstract, averaged dose over large volumes or whole organs. This approach, however, is not suitable for evaluating the impact of radiation in cases of extravasation, where the affected area is significantly smaller.

The fields of microdosimetry and nanodosimetry offer more refined lens through which to view the effects of radiation at the cellular or sub-cellular level. Unlike macroscopic dose

assessments, microdosimetry considers the stochastic nature of energy deposition events within very small volumes, akin to the scale of biological structures like DNA or cell membranes. This perspective is crucial for understanding the localized biological effects of radiation, which can deviate significantly from the expectations set by macroscopic dose calculations (Hall and Giaccia 2006, Bushberg et al. 2020).

For example, the average beta range of F-18 in skin is approximately 0.6 mm, a distance that underscores the localized nature of potential radiation damage. This scenario can be likened to the "hot particle" issue encountered in nuclear reactor safety, where localized deposits of radioactive material produce intense radiation fields over minuscule areas. However, regulations concerning hot particles primarily address external exposures and calculate doses over defined areas, a contiguous 10 square centimeters (USNRC 2015). This approach contrasts starkly with the real-world scenarios encountered in radiopharmaceutical extravasations, where the volumes affected are often much smaller and the biological effects more localized.

As previously noted, the choice of volume can significantly influence the calculated dose and, by extension, the perceived risk. This discrepancy between calculated doses and observed deterministic effects (with very few radiation injuries reported) further complicates the matter. It suggests that the current methods for assessing radiation exposure in the context of radiopharmaceutical extravasations may not accurately reflect the actual risk to patients, particularly when the exposure is confined to small, localized areas.

The conventional frameworks for dose assessment, rooted in regulatory abstractions like CDE, CEDE, and TEDE, may not be entirely appropriate for evaluating the risks associated with radiopharmaceutical extravasations. Radiation biology concepts of microdosimetry and nanodosimetry offer valuable insights into the localized effects of radiation, challenging the assumptions underpinning macroscopic dose calculations (Li et al. 2018, Sato et al. 2022).

Diagnostic vs. Therapeutic

The landscape of radiopharmaceutical applications has undergone significant transformation since the NRC established guidelines for patient intervention in the event of radiopharmaceutical extravasations. Historically, these guidelines were formulated during an era when diagnostic procedures predominated the use of radiopharmaceuticals, with therapeutic applications being relatively rare or in their nascent stages. At that time, the perceived risks associated with extravasations were considerably lower, largely because diagnostic procedures typically involve lower doses of radiation compared to therapeutic applications (ACMUI 2020).

However, the current trend in the medical field sees a burgeoning expansion of therapeutic uses of radiopharmaceuticals. This shift towards therapeutic applications, which inherently involve higher doses of radiation, necessitates a reevaluation of the existing NRC guidelines. The escalation in dose levels associated with therapeutic radiopharmaceuticals elevates the potential risk of tissue damage in the event of an extravasation, challenging the adequacy of guidelines crafted in an era dominated by diagnostic procedures.

Given the distinct differences in risk profiles between diagnostic and therapeutic radiopharmaceuticals, there is a compelling argument for the NRC to consider separating the regulatory oversight for these two applications. Such a bifurcation would allow for more nuanced and appropriate risk management strategies tailored to the specific characteristics and risks of each type of application. If diagnostic dose levels have remained largely unchanged since the original NRC ruling, then it could be argued that the existing regulatory framework remains suitable for these types of procedures. In contrast, the emergent and rapidly evolving field of therapeutic radiopharmaceuticals presents new challenges and considerations that were not accounted for in the original guidelines.

The differentiation between diagnostic and therapeutic applications is not merely a matter of regulatory convenience but a reflection of the evolving understanding of risk, efficacy, and patient safety in the use of radiopharmaceuticals. As therapeutic uses of radiopharmaceuticals continue to grow and diversify, revisiting and potentially revising the regulatory approach to account for these developments becomes increasingly imperative. Doing so would not only address the current and future needs of patient care but also ensure that the regulatory framework keeps pace with the advancements and innovations in radiopharmaceutical therapy. This proactive approach would facilitate the safe and effective use of radiopharmaceuticals, ensuring that patient safety remains at the forefront of regulatory considerations.

Difficulty in Patient Follow Up

The issue of patient follow-up in the context of radiopharmaceutical extravasation presents a multifaceted challenge, compounded by the variability in opinions regarding whose responsibility it is to identify and manage such incidents. The necessity of patient cooperation following an extravasation is a critical yet often unpredictable element in the overall management strategy. This cooperation is pivotal not only for the initial identification of the extravasation but also for the subsequent monitoring and assessment of potential radiation-induced effects.

However, securing patient cooperation for follow-up can be fraught with difficulties. Patients may exhibit reluctance or outright refusal to participate in follow-up examinations, driven by various factors. For some, the experience of an extravasation may engender distrust or dissatisfaction with the facility, dissuading them from returning for further assessment or treatment. In other cases, patients may be physically unable to return due to the progression of their underlying condition or may even pass away from unrelated causes before a follow-up examination can be conducted. Such scenarios significantly hinder the ability of healthcare providers to effectively monitor and mitigate the consequences of extravasation incidents.

The challenge of ensuring patient follow-up is not unique to the administration of radiopharmaceuticals. Similar issues are encountered in the use of fluoroscopy, where facilities require patients to return for follow-up after receiving a certain threshold of radiation dose during procedures. The experiences of these facilities highlight the wide

range of patient responses, from diligent compliance to complete non-cooperation. This variability underscores the complexity of managing patient care in procedures involving significant radiation exposure and the need for effective strategies to enhance patient engagement and follow-up compliance.

Addressing the difficulty in patient follow-up requires a multifaceted approach, emphasizing clear communication, patient education, and the establishment of trust between patients and healthcare providers. By informing patients about the importance of follow-up in detecting and managing potential complications from extravasations, healthcare providers can foster a collaborative relationship that encourages patient participation in their own care. Additionally, exploring alternative follow-up methods, such as remote monitoring or telehealth consultations, may offer viable solutions for patients unable or unwilling to return to the facility. Ultimately, enhancing patient cooperation in the follow-up process is essential for the effective management of radiopharmaceutical extravasations, ensuring that potential adverse effects are identified and addressed promptly to safeguard patient health and well-being.

Difficulty in Detecting Some Radionuclides

The advancement of radiopharmaceuticals has introduced the exploration into alpha-emitting radionuclides, marking a significant shift from the traditionally utilized beta emitters. This transition towards alpha emitters introduces notable challenges, especially in the context of extravasation detection. Alpha particles, characterized by their high linear energy transfer (LET), offer therapeutic benefits through their capacity to deliver

concentrated doses of radiation with minimal tissue penetration beyond the target area. However, these properties also present complications in their detection following an extravasation event.

A pivotal challenge posed by alpha-emitting radiopharmaceuticals is the potential lack or weakness of gamma emission. Gamma rays, due to their penetrative capabilities, are crucial for the non-invasive monitoring of radiopharmaceutical dispersion, including the identification of extravasations. Current detection methodologies, such as those employed by Lucerno's Lara® system, are designed to detect gamma or beta emissions, which may not be effective for alpha emitters that either do not emit gamma rays or emit them at energies too low for external detection.

The absence or insufficient gamma emission from some alpha-emitting radionuclides underscores a critical gap in our current capability to non-invasively detect and assess extravasation events. This limitation poses significant risks, as the detection of extravasations is crucial for timely intervention and the prevention of localized tissue damage. The high LET of alpha particles means that undetected extravasations can result in considerable radiotoxic effects, emphasizing the need for attention in this area.

As the radiopharmaceutical industry continues to evolve with the incorporation of alpha-emitting radionuclides, the challenge of detecting extravasations without the aid of gamma emissions highlights an area that requires further research and guidance. The development of new strategies for the detection and management of such events is crucial to ensuring

the safety and efficacy of these novel therapeutic agents. The potential issues presented by the detection of alpha-emitting radionuclides in the event of an extravasation call for a concerted effort within the industry to address these challenges, ensuring that patient care and safety remain paramount as the field advances.

Side-Effects of Co-administered Agents

The NRC's proposed language, focusing on the responsibility of healthcare providers to detect and report radiation injuries following radiopharmaceutical extravasation, introduces a complex challenge in the therapeutic use of radiopharmaceuticals. This complexity is significantly amplified in treatments involving co-administered agents, such as amino acids or other pharmaceuticals, that are used in conjunction with radiopharmaceuticals to enhance efficacy or reduce toxicity. The core issue at hand is the potential difficulty in accurately determining whether adverse reactions observed in patients are a result of radiation injury from the extravasation or the side effects of the co-administered agents, or even the extravasation of a co-administered agent (Park et al. 2022).

This distinction is crucial for several reasons. First, the accurate identification of the cause of an adverse reaction is essential for providing appropriate patient care and mitigating any potential harm. Second, it plays a significant role in the regulatory reporting and documentation of radiopharmaceutical extravasations and their outcomes. The NRC's emphasis on the facility's responsibility to report radiation injuries necessitates a clear

understanding and identification of these injuries, a task made more complex by the presence of co-administered agents.

The potential for co-administered agents to cause reactions that mimic or overlap with the symptoms of radiation injury complicates the diagnostic process. Symptoms such as inflammation, redness, or tissue damage, which could be indicative of radiation exposure, might also align with known side effects of the co-administered agents (Hall and Giaccia 2006, Johnson and Birky 2012, Bushberg et al. 2020, Kim et al. 2020, Park et al. 2022). This overlap not only challenges the healthcare provider's ability to accurately diagnose the cause of the symptoms but also complicates the process of reporting and managing radiation injuries as proposed by the NRC.

Furthermore, the proposed NRC language (USNRC 2022, USNRC 2023) implies a level of diagnostic certainty that may be difficult to achieve in practice, given the variables introduced by co-administered agents. The responsibility placed on healthcare providers to discern the origin of adverse reactions requires a nuanced understanding of the potential side effects of all substances involved in the treatment, as well as sophisticated diagnostic tools and methodologies that may not always be readily available.

Lack of Available Tools for Quick Dose Determination

The selection of tools for rapid dose determination is fraught with limitations. Among the available options, VARSKIN+ and IDAC stand out, each with their own set of strengths and weaknesses that impact their utility in these specific scenarios.

VARSKIN+ emerges as a user-friendly and intuitive tool, widely accessible and designed with a focus on calculating skin doses. Its primary application has been in assessing skin doses from external contamination, as well as incorporating models for contaminated wounds. Despite its potential utility in extravasation scenarios, VARSKIN+ is not specifically tailored for this purpose. Literature examples show the use of a heavily modified version of VARSKIN+ to accommodate extravasations, yet such adaptations are not widely available or extensively tested across the spectrum of possible use cases. This gap underscores a significant limitation in applying VARSKIN+ directly to extravasation assessments without substantial modifications.

On the other hand, IDAC presents itself as a more technically sophisticated option, boasting accuracy, particularly when utilizing its spheres function for dose assessments. Despite its availability, IDAC's interface may pose challenges for those without prior experience, detracting from its ease of use. The necessity to input custom assumptions for modeling purposes—especially in the absence of a clear industry consensus on these parameters—introduces potential inaccuracies. These assumptions, which can significantly vary in their scientific justification, highlight the precarious nature of relying on IDAC for swift and accurate dose assessments in the context of radiopharmaceutical extravasations (Andersson et al. 2013).

The juxtaposition of VARSKIN+ and IDAC illuminates the broader issue at hand: the absence of a universally accessible, intuitive, and specifically designed tool for rapid dose assessment following an extravasation. While IDAC offers a closer approximation of such

a tool in terms of availability and accuracy, its utility is hampered by the need for accurate assumptions. As the common saying in computer science goes, “garbage in, garbage out.”

The ideal solution would combine the accessibility and user-friendliness of VARSKIN+ with the accuracy and detailed modeling capabilities of IDAC. Achieving this goal necessitates a consensus within the industry on the appropriate model for dose assessment in extravasation scenarios. A unified approach would not only enhance the accuracy and reliability of dose determinations but also make the process more accessible to healthcare providers, thereby improving patient care and safety in the management of radiopharmaceutical extravasations.

Lack of Industry Collaboration, Information, and Guidance

The management and assessment of radiopharmaceutical extravasations are at a pivotal juncture, with the NRC currently engaged in a rulemaking process poised to shape the future regulatory landscape (USNRC 2022). As stakeholders await the finalization of this process, anticipation grows regarding the comprehensiveness of the regulatory guides expected to be provided to licensees (USNRC 2023). These guides are crucial for offering a clear framework for adhering to regulations.

A critical issue is the scarcity of reliable data on the clearance rates and biokinetics of radiopharmaceuticals once they are deposited into soft tissue. This gap in knowledge complicates the ability of healthcare professionals to accurately assess and mitigate the risks associated with extravasations. The variability among radiopharmaceuticals, each

with its unique properties and behaviors, exacerbates the challenge of establishing standardized procedures for handling such events.

Further complicating the landscape is the emergence of partisan divisions within the academic and professional discourse. The rulemaking process has sparked debates that are often reflected in the literature, with some publications potentially leaning towards presenting data or conclusions that support specific viewpoints. This polarization adds an additional layer of complexity for practitioners seeking to navigate the information landscape, making it challenging to discern unbiased, evidence-based insights from those that may be influenced by underlying agendas.

Moreover, there is a notable lack of guidance from leading radiological protection bodies such as the National Council on Radiation Protection and Measurements (NCRP) and the International Commission on Radiological Protection (ICRP) regarding the management of extravasations. While these organizations acknowledge extravasation as a consideration in radiation safety planning for radiopharmaceutical procedures, the mention often resembles a footnote rather than detailed guidance (NCRP 2007, NCRP 2018, ICRP 2019). The absence of specific recommendations leaves a significant void in terms of operationalizing safety protocols and ensuring that potential risks are adequately managed.

The current state of industry collaboration, information availability, and regulatory guidance presents a multifaceted challenge. Without a concerted effort to bridge these gaps, healthcare providers may continue to face uncertainties in managing radiopharmaceutical

extravasations effectively. The need for comprehensive, unbiased data and clear, actionable guidelines has never been more critical, underscoring the importance of fostering industry-wide collaboration and advancing research to support evidence-based practices. As the NRC moves forward with its rulemaking process, the development of regulatory guides that address these issues could play a pivotal role in enhancing patient safety and ensuring regulatory compliance across the field.

Public Perception

Public perception is particularly susceptible to manipulation concerning adverse events within any segment of the nuclear industry, including the realm of radiopharmaceutical extravasations. This sensitivity often complicates efforts to maintain a balanced and factual discussion about the actual risks involved. Misconceptions and heightened fears can overshadow reasoned, evidence-based dialogue, making it challenging to convey the nuances of radiopharmaceutical safety and the real implications of extravasation incidents. Moreover, the potential for public opinion to be influenced can hinder the advancement of scientifically sound regulations, management strategies, and responses. Recognizing the power of public perception is essential, as it highlights the need for transparent, accurate, and effective communication strategies. Such strategies are vital for aligning public understanding with scientific realities, thereby facilitating a more informed and constructive discourse on the safe use of radiopharmaceuticals and the management of associated risks.

CONCLUSION

The management of radiopharmaceutical extravasations represents a complex and multifaceted challenge within the field of nuclear medicine, necessitating a nuanced approach to ensure patient safety and optimize therapeutic outcomes. This thesis has critically explored the current understanding, methodologies, and regulatory considerations surrounding extravasation events, highlighting the need for standardization in dose assessment protocols, adaptation to the evolving landscape of therapeutic radiopharmaceutical applications, and the development of strategies to improve patient follow-up and detection of extravasations. It also underscores the importance of differentiating between the effects of radiopharmaceuticals and co-administered agents, the limitations of existing tools for rapid dose determination, and the imperative for enhanced industry collaboration and clear regulatory guidance.

Addressing these challenges requires a concerted effort from healthcare providers, researchers, regulatory bodies, and the industry at large to foster innovation, collaboration, and education. By establishing standardized protocols, embracing advancements in detection and assessment methodologies, and ensuring transparent communication and education, the field can move towards more effective management of extravasation events. Moreover, the development of comprehensive guidelines and regulatory frameworks, informed by robust scientific evidence and clinical practice, will be crucial in mitigating

the risks associated with radiopharmaceutical extravasations. Ultimately, the goal is to enhance the safety and efficacy of nuclear medicine treatments, ensuring that the benefits of radiopharmaceuticals are maximized for patients while minimizing potential adverse effects.

Future Work

Future research and development are crucial for enhancing the management of radiopharmaceutical extravasations, with a focus on improving patient safety, regulatory compliance, and optimizing treatment approaches in response to the evolving landscape of nuclear medicine. Key areas include standardizing dose estimation protocols, developing advanced detection methods for alpha-emitting or other hard to detect radiopharmaceuticals, and conducting comprehensive biokinetic studies for a better understanding of radiopharmaceutical clearance. Additionally, a focus should be placed on the development of accessible tools for rapid dose determination tailored for healthcare professionals. The industry must remain agile, adapting to new advances and work towards ensuring that existing regulatory frameworks do not hinder innovation. Importantly, any regulatory adjustment by the NRC should also respect the significant level of responsibility and authority vested in Authorized Users as delineated in 10 CFR 35, ensuring that the critical roles these professionals play in patient care are acknowledged and maintained. Effective strategies for patient follow-up care, possibly leveraging new avenues like telehealth, are essential for maintaining patient engagement in the process. Public education efforts are also needed to accurately communicate the risks and benefits of nuclear medicine treatments. Addressing these areas will

significantly help to advance the field, making radiopharmaceutical therapies safer, more effective, and adaptable to industry changes.

Diagnostic vs. Therapeutic

The dichotomy between diagnostic and therapeutic radiopharmaceuticals necessitates a more nuanced regulatory approach than currently proposed. For decades, diagnostic radiopharmaceuticals have been an integral part of nuclear medicine, with extravasations occurring but often deemed exempt from stringent reporting due to their inevitability and the minimal risk they pose. This longstanding perspective aligns with the practical experiences and historical data which have consistently shown a lack of excessive risk associated with diagnostic extravasations.

However, the burgeoning field of theranostic and therapeutic radiopharmaceuticals presents new challenges that merit reevaluation of the current regulatory framework. While it is reasonable to scrutinize the exemptions for extravasations amidst the rise of therapeutic uses, it is important that this reassessment does not inadvertently undermine decades of established precedent for diagnostic radiopharmaceuticals. The NRC's attempt to umbrella both diagnostic and therapeutic radiopharmaceuticals under a single regulatory framework may not only be seen as an oversight but also as a misstep that disregards the fundamental differences between these applications. Labeling such an approach as somewhat irresponsible may seem harsh, yet it underscores the need to craft regulations that are both precise and appropriate to the distinct nature of each application, following the science and not necessarily uninformed public and corporate pressures.

Additionally, the lack of an accepted model within the industry to accurately assess dose following extravasations further complicates the potential for any effective regulation. Without a standardized dose model, the industry is left navigating a landscape filled with uncertainties ranging from the evaluation of patient risk to the formulation of response strategies. Crafting regulations without sufficiently understanding the consequences is simply irresponsible and potentially more dangerous than following current precedent. The absence of consensus not only hampers the development of informed regulatory policies but also impedes the advancement of safe and effective practices within nuclear medicine.

Model Standardization

The accurate assessment of dose following a radiopharmaceutical extravasation is foundational to patient safety and effective clinical response. However, the current approach to dose calculation is hampered by a lack of standardization in the critical inputs required for these calculations, notably in the assumptions or estimations used for biokinetics, clearance rates, and volume considerations. This inconsistency not only introduces uncertainty into dose assessments but also undermines the reliability of clinical decisions made in response to extravasation events.

A primary concern is the variability of inputs used in dose calculations. The selection of volume, for instance, is pivotal whether it involves estimating the dose imparted by the radiopharmaceutical to itself in the spheres method, or assessing the radiation emitted to surrounding tissues in the radiating model. Current methodologies rely on assumptions

and best-guess estimates, which can significantly skew dose assessments. The lack of a unified, evidence-based standard for determining these parameters leads to discrepancies in calculated doses and, by extension, in the management strategies for extravasations.

Accurately determining the clearance rate of extravasated radiopharmaceuticals is critical to assessing the resulting dose. This rate significantly influences the duration and intensity of radiation exposure to tissue. Without comprehensive biokinetic studies that provide a deeper understanding of how differently radiopharmaceuticals behave once extravasated, dose calculations remain speculative at best. Such studies are essential to developing standardized clearance rates that can be universally applied, enhancing the precision of dose assessments across the board.

Determining the appropriate volume for dose calculations, regardless of whether we use the self-irradiating or outwardly irradiating models, is a major area requiring standardization. Questions about how much dose is imparted as the radiopharmaceutical clears from the area, and how to account for the radiation dose delivered to skin tissue through vascular and lymphatic migration, remain unanswered. Additionally, distinguishing between the excess dose attributable to extravasation and the dose inherent to the procedural use of the radiopharmaceutical necessitates a clear, standardized approach.

While computational models like Monte-Carlo simulations, IDAC, and VARSKIN+ have shown agreement in dose assessments within the spheres model, agreement among these

models does not inherently validate their accuracy. The fundamental issue is not the internal consistency of these models but their correspondence to the real-world behavior of radiopharmaceuticals following an extravasation. Without empirical evidence to support the assumptions underlying these models, there remains a significant gap in our ability to confidently assert that they reflect the true dose received by patients. The lack of expected deterministic effects observed in patients estimated to receive well above the thresholds for the worst effects of radiation skin doses further supports the need to refine these models for accuracy.

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