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December 11, 2020

Kevin Williams
Director, Division of Materials Safety, Security, State, and Tribal Programs
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Delivered via email

Dear Mr. Williams,

I write to express concern about statements made by Advisory Committee on the Medical Uses of Isotopes (ACMUI) members Dr. Robert Schleipman and Dr. Hossein Jadvar during the public comment portion of the December 8 meeting to discuss radiopharmaceutical extravasations and medical event reporting. Specifically, Dr. Schleipman cited a study by Edward Silberstein to support the proposition that adverse events involving radiopharmaceuticals are exceedingly rare.[1] Dr. Jadvar cited a study by van der Pol et al. to support the proposition that extravasations of radiopharmaceuticals are exceedingly rare.[2] For the reasons set out below, the way these articles were cited is misleading and undermines the credibility of the ACMUI.

Edward Silberstein examined patterns of radiopharmaceutical use and adverse events in nuclear medicine from 2007-2011. While Silberstein did, indeed, conclude that the incidence of adverse events remained stable and relatively low at 2.1-2.3/10^5 dosages, Silberstein excluded several types of adverse events from his analysis. Specifically, Silberstein excluded altered biodistribution, vasovagal responses, deterministic and stochastic effects from therapeutic radiopharmaceuticals, overdoses, poor injection technique, and false positive results from the definition of adverse event – that is, many of the precise adverse events that result from or relate to extravasated radiopharmaceuticals. As you know and as Lisa Dimmick explained during the December 8 meeting, extravasations do occur frequently, and the Silberstein article cited by Dr. Schleipman does nothing to contradict the ample medical evidence on that point. Citing this work for the proposition that radiopharmaceuticals are safe in the context of extravasation is disingenuous at best and deceptive at worst.

Jochem van der Pol, et al. did not report on the frequency of extravasation, instead they demonstrated the alarming lack of monitoring for extravasations in nuclear medicine. Per van der Pol, of the 3,016 diagnostic radiopharmaceutical extravasations reported in the literature, only three had dosimetry performed and resulted in meaningful follow-up. All three patients suffered adverse tissue reactions, occurring 20 days, 2 years, and 3 years after the extravasation. None of the remaining 3,013 diagnostic extravasations cited in van der Pol, et al. had dosimetry performed or included patient follow-up. Had any of these 3,013 extravasation cases had dosimetry performed and been followed, it is reasonable to expect other injuries would have been found. During the December 8 meeting and also during the November 18, 2020 ACMUI meeting with NRC Commissioners, Dr. Hossein Jadvar cited van der Pol, et al. to suggest the extravasations only occur in 0.1% of nuclear medicine procedures. Far from establishing the

[1] E.B. Silberstein. Prevalence of Adverse Events to Radiopharmaceuticals from 2007 to 2011. J Nucl Med 2014; 55:1308–1310.
[2] J. van der Pol, et al. Consequences of Radiopharmaceutical Extravasation and Therapeutic Interventions: A Systematic Review. Eur J Nucl Med Mol Imaging. 2017; 7:1234-1243.

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scarcity of harm due to extravasations, van der Pol, et al. demonstrates the need for NRC to require practitioners to improve nuclear medicine injection and infusion safety and quality. Citing this work to support propositions that extravasations rarely occur and rarely result in harm is a misrepresentation of the article.

It is unacceptable that ACMUI members continue to misinform the public and NRC leaders about the incidence and consequences of extravasations. The purpose of the ACMUI is to advise the NRC on policy and technical issues relating to the medical uses of radioactive material in diagnosis and therapy – not to act as an advocacy organization to advance their own self-interests. Misrepresentative statements, like those offered by Dr. Schleipman and Dr. Jadvar, reflect poorly on the ACMUI and the NRC by association. Misrepresentative statements also cast doubt on the legitimacy and accuracy of other ACMUI guidance on medical event reporting and nuclear medicine extravasations.

I urge you, as suggested by Commissioner Baran during the November 5, 2020 meeting on Strategic Programmatic Overview of Decommissioning and Low-Level Waste and Nuclear Materials Users Business Lines, to seek guidance from sources outside of the ACMUI on this important policy matter. Most ACMUI members have years of experience in interpreting and authoring clinical articles. Deliberately misleading the NRC and the public by incorrectly citing publications discredits the ACMUI's evaluation of this issue and requires the NRC to seek more reliable sources of information. Furthermore, I request that the NRC address Dr. Schleipman's and Dr. Jadvar's misleading and incorrect remarks by either including this communication with the other public comments received during the December 8 public meeting or issue some other form of correction to ensure that the public is aware that these comments were inappropriate.

Sincerely,

DocuSigned by:
Ron Lattanze
0C2FCDBE78A7435...

Ronald Lattanze
Chief Executive Officer

Attachments: two articles referenced in this letter

Cc: Chris Einberg
Lisa Dimmick

Prevalence of Adverse Events to Radiopharmaceuticals from 2007 to 2011

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We studied the changing patterns of radiopharmaceutical use and the incidence of adverse events (AEs) to PET radiopharmaceuticals, non-PET radiopharmaceuticals, and adjunctive nonradioactive pharmaceuticals in nuclear medicine from 2007 to 2011. **Methods:** Fifteen academic institutions submitted quarterly reports of radiopharmaceutical use and AEs covering 2007–2011. **Results:** 1,024,177 radiopharmaceutical administrations were monitored: 207,281 diagnostic PET, 803,696 diagnostic non-PET, and 13,200 therapeutic. In addition, 112,830 adjunctive nonradioactive pharmaceutical administrations were monitored. The annual use of bone scintigraphy and radiotracer therapies was unchanged. PET radiopharmaceutical use increased from 17% to 26% of diagnostic procedures ($P < 0.01$). The incidence of radiopharmaceutical AEs was 2.1/10^5 administrations, with no hospitalizations or deaths. **Conclusion:** From 2007 to 2011, PET studies increased, and therapeutic radiopharmaceutical use and bone scintigraphy were unchanged. Over 2 decades, the incidence of AEs has remained stable at 2.1–2.3/10^5 dosages.

Key Words: radiopharmaceuticals; adverse events; nuclear medicine safety

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It is important to continuously monitor the use and adverse events (AEs) of radiopharmaceuticals to oversee, for our patients, our peers, and governmental regulators, the impressive safety record of our procedures (*1–6*), especially as new radiopharmaceuticals appear. We also inquired if there were changing patterns of use of radiopharmaceuticals for bone scintigraphy, PET, and radiolabeled antibody therapy for lymphoma.

MATERIALS AND METHODS

A group of nuclear pharmacists and physicians volunteered to join this unsponsored prospective study. These professionals are listed in the "Acknowledgments" section. The Institutional Review Board of the University of Cincinnati Medical Center ruled the study exempt from Institutional Review Board review according to title 45 of *Code of Federal Regulations* part 46.101 (b) (*4*). Nevertheless, some institutions involved in the study did require Institutional Review Board review of the protocol, and approval was always granted.

To avoid the quandary of requiring strict proof of causality, we used the Food and Drug Administration definition of an AE: "Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related" (*7–9*). An AE algorithm relating to the probability of causation was carefully reviewed by all participants, who agreed to its use to establish the triple classification of AEs as probable, possible, or unlikely for radiopharmaceuticals and nonradioactive pharmaceuticals (*5*). All allergic, noxious, or unintended outcomes, signs, symptoms, and laboratory abnormalities were reported for radiopharmaceuticals. For nonradioactive pharmaceuticals, only AEs not previously reported in the medical literature—or those so serious that they led to hospitalization, were life-threatening, or were lethal—were to be reported, because tabulating well-documented AEs from nonradioactive pharmaceuticals would provide no new information. Types of AEs not within the scope of this study were excluded: altered biodistribution, vasovagal responses, deterministic and stochastic effects from therapeutic radiopharmaceuticals, overdoses, poor injection technique, or false-positive results (*5*). This AE algorithm has also been adopted by the Radiopharmacy Committee of the European Association of Nuclear Medicine (*10*).

The participants sent a quarterly report to the study coordinator over a 5-y period, 2007–2011, for all radiopharmaceuticals and nonradioactive pharmaceuticals used at their institutions, including those under a new drug application, investigational new drug application, or Radioactive Drug Research Committee supervision, and any radiopharmaceutical compounded on site. Any report of an AE was followed by a conversation with the coordinator, with joint agreement being achieved on the likelihood of causality for all AEs reported. Linear regression analysis was used to determine the significance of changes in the data points over time (Data Disk, version 6.3; Data Description, Inc.).

RESULTS

Fifteen institutions participated in the planning of this study, but only 13, and finally 11, could continue to contribute data for all 5 y, as a few institutions dropped out if the career or personal path of the reporter changed. From 2007 through 2011 the group reported on 1,010,977 diagnostic studies, of which 20.5% (207,281) represented PET studies and 79.5% (803,696) were studies with single-photon–emitting radiopharmaceuticals, whether used for planar or SPECT scintigraphy. There were 13,200 therapeutic procedures, only 1.3% of the total of 1,024,177 nuclear medicine procedures monitored for AEs. The percentage of therapeutic procedures per year ranged from 1.2% (2007) to 1.5% (2010) of the total, but there was no trend suggesting significantly increasing or decreasing numbers of therapies ($P > 0.05$). In addition, 112,830 adjunctive procedures with nonradioactive pharmaceuticals, comprising 11% of procedures with radiopharmaceuticals, were reported.

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TABLE 1
AE Results for 2007–2011

Year	Centers (*n*)	All AEs (probable, possible, unlikely*)	Doses/y	AEs/10^5 doses
2007	13	7	214,930	3.2
2008	13	5	223,522	2.2
2009	13	4	208,535	1.9
2010	12	2	192,908	1.0
2011	11	3	184,282	1.6
5-y total		21	1,024,177	2.1 ± 0.6

*Five of these 21 AEs received a causality classification of unlikely.

Trends in Radiopharmaceutical Use from 2007 to 2011

There was a significant increase in PET studies as a percentage of the total over the 5 y of the study, moving from 17% to 26% of all diagnostic studies ($P < 0.01$). The decrease in ^{18}F-FDG studies as a percentage of total PET scans from 85% to 80% was not statistically significant.

Labeled anti-CD20 antilymphoma antibodies have produced impressive levels of remission in refractory lymphoma and had been expected to have wide use, but this did not occur, as they represented 4.5% of therapies in 2007 and 4.0% in 2011 ($P > 0.05$), with a 5-y average of 3.3% of all therapies and no trend toward increasing or decreasing. The volume of single-photon bone scintigraphy, almost always with ^{99m}Tc-methylene diphosphonate, also remained constant, averaging 11.9% of all diagnostic nuclear medicine studies.

AEs from Radiopharmaceuticals and Adjunctive Pharmaceuticals

In Table 1, we have documented the annual number of AEs due to radiopharmaceuticals from 2007 to 2011. The apparent decrease per 10^5 administrations per year was not statistically significant. The decrease in absolute numbers of dosages reported per year (Table 1) was caused by the loss of some investigators because of career or personal changes. Table 1 also provides the incidence of AEs (probable, possible, unlikely) per year from radiopharmaceuticals during the study, and the 21 AEs (including 5 deemed unlikely but that could not be excluded) are listed by symptom complex in Table 2. No AEs requiring hospitalization, deemed life-threatening, or lethal occurred.

DISCUSSION

The data collected in this study permit an examination of trends in nuclear medicine that might lead to a different pattern of radiopharmaceutical use, which had the potential to change for several reasons. Radiolabeled anti-CD20 antibodies have yielded unequivocal therapeutic advances (*11,12*) but increased use did not occur, because of adequate results from the unlabeled antibody rituximab (*13*) and oncologist referral patterns.

PET has become an important diagnostic modality, and it was deemed possible that bone scintigraphic studies would diminish as a percentage of the total of diagnostic studies, since ^{18}F-FDG can detect tumor in marrow before the cortex is invaded (*14*). However, the number of bone scintigraphy procedures was stable over the study period. The volume of PET studies did rise. Other ^{18}F-labeled radiopharmaceuticals came into use (e.g., ^{18}F-sodium fluoride), potentially reducing the percentage of PET studies performed with ^{18}F-FDG PET, but the occurrence of this small change was not statistically significant. Although the estimated number of nuclear medicine procedures in the United States over the 5 y of this study declined by about 9% (*15*), the number of procedures per institution in our study was essentially unchanged (16,533 in 2007 vs. 16,753 in 2011). Because we could not track changes in the use of over 40 radiopharmaceuticals, we do not have data that can more fully explain the use patterns observed.

Our primary goal was to document the incidence of AEs in the practice of nuclear medicine using prospective data collection by nuclear medicine scientists, clear definitions of AEs, (*16,17*), and a known denominator (*16,17*). With this approach, we believe we have overcome the problem of underreporting of AEs because of the transient nature of these events, confusion in the terminology of AEs, anxiety about potential liability, the time to complete a report form, and the lack of relevant reporting forms (*16–19*), although

TABLE 2
AEs Noted from Radiopharmaceuticals

Event	Radiopharmaceutical
Cutaneous (rash, flush)	^{99m}Tc-DMSA†, ^{18}F-FDG, ^{111}In-WBC*, ^{111}In-WBC/^{99m}Tc-SC/^{99m}Tc-MDP, ^{99m}Tc-MAG3/furosemide, ^{99m}Tc-MDP, ^{99m}Tc-MDP/^{99m}Tc-SC, ^{123}I-MIBG (2 patients)†, cold pyp†, ^{99m}Tc-sestamibi, ^{131}I-tositumomab
Nausea	^{123}I-MIBG (2 patients)†, ^{99m}Tc-DMSA†
Cardiovascular (anaphylactoid, hypotension, cardiac arrest)	^{99m}Tc-MDP (2 patients)*, ^{99m}Tc-SC, ^{18}F-FDG*, ^{99m}Tc-MAG3/furosemide
Neurologic (pain, hypesthesia, paresthesia)	Cold pyp†, ^{99m}Tc-sestamibi*, ^{99m}Tc-tetrofosmin (2 patients)*

*Judged as unlikely by study criteria, totaling 5 AEs; if 2 patients are noted as having had AEs, only one was deemed unlikely in this study.
†Three patients (1 each from ^{99m}Tc-DMSA, ^{123}I-MIBG, cold pyp) had 2 symptoms or signs from radiopharmaceuticals, but these were counted as 1 AE from 1 radiopharmaceutical that caused 2 symptoms.
DMSA = dimercaptosuccinic acid; WBC = white blood cells; SC = sulfur colloid; MDP = methylene diphosphonate; MAG3 = mercaptoacetyltriglycine; MIBG = metaiodobenzylguanidine; pyp = pyrophosphate.

MedWatch, the Safety Information and Adverse Event Reporting Program of the Food and Drug Administration, is available online at www.fda.gov/Safety/MedWatch/.

Because diagnostic radiopharmaceuticals are, by definition, not given for therapeutic purposes, one would expect few physiologic effects or AEs from them if the specific activity of these radiotracers is sufficiently high. Therefore, it is hardly surprising that such AEs are quite uncommon. In 1996 a survey study (covering 1989–1994) showed an AE incidence of $2.3/10^5$ dosages (*5*), and in this current study we have reported a virtually identical finding, 2.1 AEs/10^5administrations. Deterministic effects of therapeutic radiopharmaceuticals are not infrequent because of the activity of radiation deposited at sites of their normal physiologic distribution (e.g., ^{131}I gastritis, sialadenitis, oral mucositis), but no therapeutic radiopharmaceutical (13,200 administrations) or interventional nonradioactive drug (112,830 administrations) in this study caused hospitalization, a life-threatening AE, or death.

Outside our study, 2 deaths and 15 life-threatening AEs followed administration of the anti-CD15 antibody ^{99m}Tc-fanolesomab (NeutroSpec; Palatin Technologies), introduced in 2004 and withdrawn from the market in December 2005. No other deaths from radiopharmaceuticals have been reported since 1975 except for two from an albumin colloid and one from diethylenetriaminepentaacetic acid briefly mentioned and undated in a 1993 review (*20*).

In the current study, we report the first (to our knowledge) AEs from ^{18}F-FDG, flushing of the face and trunk occurring within minutes of administration and lasting less than 2 h after injection. Other AEs not previously reported occurred with ^{99m}Tc-labeled dimercaptosuccinic acid, sestamibi, and tetrofosmin (Table 2).

There are potential weaknesses of this study. The institutions in this study may not represent the practice of nuclear medicine elsewhere, although most radiopharmaceuticals should be the same. Also, minor AEs could have been missed or ignored by the nuclear medicine technologist. We chose to include in our report all AEs, including those believed to be unlikely, since, importantly, the "unlikely" label also fits any AE on its first occurrence. Nevertheless, the results from this and our previous studies (*5,6*) are virtually identical and support the credibility of these results, using the definitions and methodology described above.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. No potential conflict of interest relevant to this article was reported.

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REVIEW ARTICLE

Consequences of radiopharmaceutical extravasation and therapeutic interventions: a systematic review

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Abstract
Purpose Radiopharmaceutical extravasation can potentially lead to severe soft tissue damage, but little is known about incidence, medical consequences, possible interventions, and effectiveness of these. The aims of this study are to estimate the incidence of extravasation of diagnostic and therapeutic radiopharmaceuticals, to evaluate medical consequences, and to evaluate medical treatment applied subsequently to those incidents.
Methods A sensitive and elaborate literature search was performed in Embase and PubMed using the keywords "misadministration", "extravasation", "paravascular infiltration", combined with "tracer", "radionuclide", "radiopharmaceutical", and a list of keywords referring to clinically used tracers (i.e. "Technetium-99m", "Yttrium-90"). Reported data on radiopharmaceutical extravasation and applied interventions was extracted and summarised.
Results Thirty-seven publications reported 3016 cases of diagnostic radiopharmaceutical extravasation, of which three cases reported symptoms after extravasation. Eight publications reported 10 cases of therapeutic tracer extravasation. The most severe symptom was ulceration. Thirty-four different intervention and prevention strategies were performed or proposed in literature.
Conclusions Extravasation of diagnostic radiopharmaceuticals is common. ^{99m}Tc, ^{123}I, ^{18}F, and ^{68}Ga labelled tracers do not require specific intervention. Extravasation of therapeutic radiopharmaceuticals can give severe soft tissue lesions. Although not evidence based, surgical intervention should be considered. Furthermore, dispersive intervention, dosimetry and follow up is advised. Pharmaceutical intervention has no place yet in the immediate care of radiopharmaceutical extravasation.

Keywords Extravasation · Dose infiltration · Radiopharmaceuticals · Radiation ulcer

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Introduction

High doses of radiation exposure can potentially cause severe tissue damage, such as skin desquamation and necrosis. Extravasation of radionuclides used in nuclear medicine practice results in localized tissue retention of the radiopharmaceutical and subsequently in an unintended extended local radiation exposure. Because of the character of the radiation, extravasation of therapeutic radiopharmaceuticals has the highest tendency to result in tissue damage, although some cases of tissue damage following the extravasation of diagnostic radiopharmaceuticals have been reported [1].

Knowledge of possible consequences and interventions to prevent tissue damage are vital for an adequate risk-adapted management after extravasation of radiopharmaceuticals. The EANM procedure guideline for 90Y-radiolabeled ibritumomab tiuxetan (Zevalin®) is the only guideline that gives limited practical advice in case of extravasation, advising local hyperthermia, elevation of the extremity and gentle massage [2]. The SNMMI procedure standard for palliative treatment for painful bone metastases advises local heat to promote reabsorption [3]. Other EANM and SNMMI guidelines covering radionuclide

therapy do not give any practical information in case of extravasation, regardless of the potential complications [4–7].

To our knowledge, no previous study or literature review has been performed to summarize the effects of the extravasation of commonly applied diagnostic or therapeutic radiopharmaceuticals. Knowledge of the incidence of extravasation, the severity of these effects, and about the effectivity of interventions is necessary for adequate clinical response in case of extravasation, as well as in development of guidelines covering radiopharmaceutical extravasation. The purpose of this study was, therefore, to review systematically previously published data on the incidence and clinical outcome of radioactive extravasations and to summarize the reported incidences of events of most of the clinically used radiopharmaceuticals, the applied interventions, as well as the reported clinical outcomes.

Materials and methods

Search strategy

A computer-aided search of the PubMed/MEDLINE and Embase databases was conducted to find relevant published articles on extravasation of radiopharmaceuticals. No start date limit was used. No language limitation was applied in the initial search strategy. The search string was composed of several synonymous keywords for extravasation combined as a group using the "AND" operator with a combination of the keywords "radiopharmaceutical" and an extensive list of clinically used isotopes in five different notations (i.e. "I-131", "I131", "131I", "Iodine 131", "131 iodine"). In PubMed, all keywords were combined with a MESH equivalent when available, as well as an equivalent with the "Pharmaceutical action" tag. The used search strings are shown in Table 1. The search was updated until November 2016.

Studies reporting radiopharmaceutical extravasation in humans were eligible for inclusion. Only studies written in the languages mastered by the authors were included: English, Spanish, French, Italian, German, Hungarian, Romanian, or Dutch. No other limits were imposed. Animal studies were excluded.

Two reviewers (J.P. and S.V.) independently reviewed titles and abstracts to find articles reporting cases of extravasation, or to find literature otherwise relevant to the subject. In case of disagreement on relevance, the full text was retrieved. To expand our search, bibliographies of articles that finally remained after the selection process were screened for potentially relevant references. Subsequently, the corresponding full text articles were retrieved for further reading and selection.

Data extraction

The following data were extracted whenever available from eligible studies: first author, journal and year of publication, population studied, number of reported extravasations, radiopharmaceutical, injection place, estimated administered volume, estimated extravasated activity and tissue dose, description of tissue damage and delay since injection, duration of follow-up, and applied medical interventions.

Data analysis

Reported incidents were categorized and pooled according to radiopharmaceutical that was administered. Ratios were calculated between the pooled reported incidence of extravasation versus the number of reported incidences of adverse soft tissue effects. Cases were grouped and displayed in tables sorted by radiopharmaceutical separately for diagnostic and therapeutic radiopharmaceuticals. Furthermore, literature references that described interventions were organised in three categories: 1) advised by reference, 2) applied in case report, and 3) discouraged by reference.

Table 1 Search strings applied in PubMed/MEDLINE and Embase with search results specified to search engine and search strings

No.	Search strings[a]	Pubmed/MEDLINE	Embase
1	"Extravasation of Diagnostic and Therapeutic Materials" [Mesh] OR "Extravasation of Diagnostic and Therapeutic Materials" OR "extravasation" OR "infiltration" OR "misadministration"	110.807	171.853
2	"I-123" OR "I-124" OR "I-125" OR "I-131" OR "Tc-99m" OR "F18" OR "Ga-68" OR "In-111" OR "Tl-201" OR "Rb-82" OR "N-13" OR "O-15" OR "C-11" OR "Er-169" OR "Re-186" OR "Sr89" OR "Sm-153" OR "Y-90" OR "Ra-223" OR "P-32" OR Lu177	213.922	361.049
3	"Radiopharmaceuticals"[Mesh] OR "Radiopharmaceuticals" OR "Radioisotopes"[Mesh] OR "Radioisotopes"	301.588	15.949
4	1 AND (2 OR 3)	2.153	3.493

Search strategy with number of yielded results in PubMed/MEDLINE and Embase.

The "Mesh" tag was omitted for the Embase search strings

[a] In the actual search strings used, all radionuclides were spelled using five different conventions, i.e. the keyword "I-123" was accompanied by "I123", "123I", "Iodine 123", and "123 Iodine", grouped together with the "OR" operand

Results

The searches performed using Pubmed and Embase resulted in 2153 and 3493 publications respectively (Table 1). Of these, 1123 search results were found using both search engines yielding a total of 4523 abstracts after subtraction. Rejected abstracts described irrelevant animal studies (1012), reported extravasation of other agents than radionuclides (198), mentioned infiltration of other nature than infiltration of radiopharmaceuticals (2424), described lymph drainage studies or other nuclear medicine studies in which extravasation is a pathological finding, i.e. urinary extravasation in ^{99m}Tc-mercaptoacetyltriglycine (MAG3) (196), or publications about radionuclide use for other purposes than nuclear medicine studies (603), such as radioimmunoassays. The full text was retrieved for the remaining 81 publications. The references of relevant publications were screened, of which the full text was retrieved. In total, 108 full text articles or conference abstracts were retrieved for further evaluation. Radiopharmaceutical extravasation was reported in 44 publications, of which 37 about diagnostic and eight about therapeutic radiopharmaceuticals. Another 10 publications contained information on extravasation based on expert opinion or cited work.

Cases of diagnostic extravasation are summarised in Table 2. In total, 37 publications reported 3016 cases of radiopharmaceutical extravasation. For three cases symptoms and follow up was reported (0,1%) [42–44]. When grouped together, a total of 3003 cases described extravasation without reported symptoms after extravasation of 18F-fluorodeoxyglucose (FDG) (332) and 99mTc-labelled tracers (2671) [8–41]. Radiation ulcers in two patients following extravasation of 201Tl-thallous chloride were the most severe injuries reported [43, 44]. In one case a radiation ulcus was diagnosed 2 years. The injected activity and estimated tissue dose were 74 MBq and 200 Gy, respectively [43]. In the second case the diagnosis radiation ulcus was made after 3 years. The injected activity was 111 MBq and the worst case estimate of tissue dose was 250 Gy [44]. A pruritic and erythematous patch was described following the extravasation of 34 MBq of 131I-iodocholesterol, with a worst case tissue dose estimate of 490 Gy [42]. Other reported cases of diagnostic extravasation cases did not describe dosimetric parameters or follow-up.

Eight publications reported a total of 10 cases of therapeutic radiopharmaceutical extravasation [46–53]. Radionecrosis was the most severe symptom reported in five cases [47, 49, 50], although three cases reported needle track necrosis that resolved spontaneously [47]. The results and references are summarised in Table 3. Table 4 summarises a total of 34 interventions that are advised or, contrarily, discouraged in literature and those which are applied in reported cases.

Discussion

Multiple retrospective case series on bone scintigraphy, as well as 18F-FDG positron emission tomography (PET) report a large proportion of at least partial tracer extravasation [18–31]. Although there was no clinical follow-up after extravasation reported in these publications, no adverse reactions have

Table 2 Summary of reported cases of diagnostic radiopharmaceutical extravasation

References	Total reported cases	Radiopharmaceutical	No. of patients with reported radiation injury	No. of patients with reported follow-up	Most severe injury reported
[8–17]	332	18F-FDG	0	0	
[18–31]	2584	^{99m}Tc bone tracers	0	0	
[32]	3	^{99m}Tc-MAA	0	0	
[33]	1	^{99m}Tc-DMSA	0	0	
[34, 35]	10	^{99m}Tc-DTPA	0	0	
[36]	1	^{99m}Tc-HMPAO	0	0	
[37]	1	^{99m}Tc-MAG3	0	0	
[19, 38, 39]	15	^{99m}Tc-pertechnetate	0	0	
[40, 41]	2	^{99m}Tc-sestamibi	0	0	
[19]	38	^{99m}Tc-sulfurcolloid	0	0	
[19]	16	^{99m}Tc-microspheres	0	0	
[42]	1	^{131}I-iodocholesterol	1	1	Erythematous plaque and pruritus.
[43–45]	12	^{201}Tl-thallous chloride	2	2	Radiation ulcer
Total	3016		3	3	

Table 3 Summary of reported cases of therapeutic radiopharmaceutical extravasation

Reference	No. of patients with extravasation	Radiopharmaceutical	Reported extravasated activity [GBq]	Reported administered volume [ml]	Reported estimated tissue dose [Gy]	Symptoms after radiopharmaceutical extravasation[a]
Williams 2006 [52]	1	^{90}Y-ibritumomab tiuxetan	0,068–0,136	60	10–20 worst case	Erythema (1d), tenderness (14d), bulla (26d), moist desquamation (29d)
Siebeneck 2008 [50]	1	^{90}Y-ibritumomab tiuxetan	Not reported	Not reported	Not reported	Small erythematous area (1w). Progression to 15 × 25 cm erythematous area (4w). Moist desquamation (5w). No healing progression after 8-15w. Skin graft was advised. After 4m start of tissue granulation, with greyish necrotic in the centre size of dime.
Erken 1991 [47]	3	^{90}Y-colloid (radiosynovectomy)	Not reported	Not reported	Not reported	Needle track necrosis. Spontaneous healing (3m)
Terwinghe 2012 [51]	1	^{90}Y-DOTATOC	3,5 (worst case)	Not reported	Not reported	Painful and swollen arm (p.i.). No symptoms arose during follow-up (no time indication).
Minsky 1987 [48]	1	^{32}P-sodium phosphate	0,086	76	5,02	Raised area at infusion site (p.i.).
Patton 1950 [49]	1	^{90}Y-hydroxy citrate complex	Not reported	0,2	1000	Ulceration, 2cm in diameter.
Bonta 2011 [46]	1	^{131}I-metaiodobenzylguanidine	11,1 (worst case)	60	20–40	Forearm swelling (7d). Rash at injection site, 10x5cm (4w). Lesion still “angry looking” (7w), lesion appearance evolved to dry and scaly after corticosteroid cream.
Kawabe 2013 [53]	1	^{89}Sr-Strontium chloride	0.00296	30	1.78	Slight burning pain, slight reddening and small circular swelling. No symptoms reported during follow up.

[a] Whenever available, the time of symptom presentation and other events is printed between brackets, the following abbreviations are used: *d* days, *w* weeks, *m* months, *p.i.* post injection

Table 4 Summary of interventions advised in literature or applied in reported cases

Category	Intervention	Advised by references			Reported to have been applied	Discouraged by reference
		Diagnostic	Therapeutic	N.S.[a]		
General	Immediate cessation of the administration	[1, 34]	[1, 2, 34, 46, 51, 52, 54]	[55]	[52]	
	Aspiration of venous IV-catheter	[1, 34]	[1, 34]			
Concentrating	Cooling extravasated region			[1]		
Dispersive	Warming extravasated region	[1, 34, 56]	[1–3, 34, 46, 52]	[55, 57, 58]	[48, 53]	[59]
	Arm elevation	[34]	[2, 34, 46, 54]		[51]	
	Massage	[1]	[1, 2, 54]	[55, 58]	[51, 53]	
	Compression stockings	[46]	[46]			
	Pressure application				[48]	
	Squeezing a stress ball				[51]	
Surgical	Saline flushing	[1]	[1, 34, 52]			
	Local puncture				[51]	
	Early excision and skin grafting		[49, 52]		[49]	
Pharmacotherapeutic	Intralesional steroids		[52]			
	Topical steroid application	[1]	[1]	[58]	[46, 53]	
	Diphenhydramine iv				[46]	
	Local penicillin application				[49]	
	Hyaluronidase	[1]	[1]	[55]	[45]	[52]
	Amifostine		[46]			
	Silver sulfadiazine				[50, 52]	
Organizational	Contain syringe	[34]	[34]			
	Clearance evaluation and dosimetry	[1, 34, 43, 57, 60]	[1, 34, 43, 57, 60]		[12, 42–44, 46, 48–53, 61]	
	Follow up	[43]	[1, 59]		[46, 47, 49–53]	
	Delineation	[1, 34]	[1, 34]			
	Report event	[1, 34]	[1, 2, 34]			
Preventive	Use of intravenous catheter,					
Port–a-cath or midline venous catheter	[56, 57]	[1, 2, 4, 46, 50, 51, 55–57]	[34]	[46, 51, 52]		
Measures	Dilution of radiopharmaceutical		[46]		[51, 53]	
	Administration under gamma camera		[59, 62, 63]		[59]	
	Catheter placement by Experienced technician		[1, 49, 52]			
	Choose a large vein between wrist and antecubital fossa for intravenous access		[51, 52]			
	Place intravenous access proximal to any venipuncture site established within 24h		[50–52]			
	Avoid antecubital fossa to minimize damage to vital structures		[1]			
	Check of patency	[1, 34]	[1–3, 34, 46, 52, 55]		[50, 53]	
	Dose rate ratio between injection site and corresponding contralateral site		[51]	[55]	[51]	
	Slow needle retraction while infusing anti-inflammatory agent[b]		[64]			

[a] Not specified

[b] Reported as preventive measure for needle track necrosis following radiosynovectomy

been reported following extravasation of widely and frequently used ^{99m}Tc labelled radiopharmaceuticals. Similarly, no cases have been found with any symptoms after extravasation of ^{99m}Tc, ^{123}I, ^{18}F, and ^{68}Ga labelled radiopharmaceuticals. These radiopharmaceuticals together comprise a great majority of radiopharmaceuticals in use on a daily basis in general nuclear medicine practices. Lack of clinical follow-up after diagnostic nuclear medicine scans, but also a conservative attitude towards reporting and publishing of complications may have possibly lead to under-reporting of skin lesions. Nevertheless, given the long history of frequent usage of these agents and even in case of significant under-reporting, we would have expected that at least a few cases had been reported. Therefore, we consider it safe to be conservative in treatment of extravasation of these tracers. Attention should only be focused on early complications of the extravasation that are not attributable to the radioactivity, such as skin necrosis and compartment syndrome [65, 66]. Other diagnostic radiopharmaceuticals were reported to cause at least mild skin lesions, notably ^{201}Th-thallous chloride and ^{131}I-iodine-iodocholesterol. Only a few publications report these cases, which are further elucidated by only limited provided data on dosimetric data, follow-up of the patients, etc. [42–44]. Particularly the long period of 2 and 3 years after ^{201}Th-thallous chloride raise questions whether the skin lesions were radiation induced. Furthermore, it should be mentioned that ^{131}I-iodine-iodocholesterol is used only sporadically nowadays. Nevertheless, in our opinion this warrants at least minimal preventive measures and follow-up after extravasation of these tracers.

Few complications following therapeutic extravasation were reported, yet some causing severe soft tissue damage. Considering the high prevalence of extravasation in diagnostic procedures, the same could be true for therapeutic radiopharmaceuticals. Nevertheless, it is plausible that generally more care is taken in preventing extravasation.

Therapeutic options

Applied and advised interventions are mostly derived from treatment regimens of extravasation of non-radioactive agents. Only few were applied in reported cases. Dispersive actions can be effective in extravasation non-radiopharmaceutic agents [65, 66]. It can be debated if all listed dispersive interventions can be applied to radiopharmaceuticals. For instance, DeNardo argues that hyperthermia can ameliorate success of radiotherapy, similarly it might do more harm in case of extravasation [59]. On the other hand, it is plausible that warming up the tissue to promote hyperaemia and lymphatic flow might reduce the time of exposition enough to at least compensate this radiosensitising effect. Terwinghe et al. showed fast tissue wash out of 90Y-DOTATOC after arm elevation, warming the infiltrated area and squeezing a stress ball. This patient had no soft tissue symptoms during follow-up. Moreover they argue that the relatively low molecular weight contributes to faster tissue wash out, in comparison to radiopharmaceuticals with higher molecular weight, particularly in case of 90Y-ibritumomab tiuxetan [51]. Concentrating the radiopharmaceutical by cooling the tissue can be applied in anticipation of surgical interventions. Only two cases report the use of surgical techniques. Local puncture was not considered successful after extravasation of ^{90}Y-dotatate [51]. In one report from 1950 the ulceration was excised [49]. Other surgical treatments have not been described or advised in literature. Pharmacotherapeutical interventions have been reported in sporadic case reports. Ulcers were treated with antibiotics and discomfort was treated with topical steroids [46, 49, 50, 52, 53]. Intralesional corticosteroid therapy is advised by Williams, based on results after chemotherapy extravasation, but has not been reported in radiopharmaceutical extravasation [52]. Hyaluronidase use is based on results in extravasation of other agents [1, 55], and applied in one case report of 201Tl-thallous chloride extravasation [45]. Williams et al. discourage any use, because of the experimental status [52]. Amifostine might be effective in radiopharmaceutical extravasation for its proven radioprotective properties in radiotherapy [46]. Despite, it remains unknown how it performs in the high linear energy transfer radiation environment of radiopharmaceutical extravasation, while having considerable side effects.

Clearance evaluation and dosimetry are often advised to be part of extravasation management. Different methods have been used, yielding a large range of tissue doses, due to uncertainties such as retained activity and the volume of the infiltrated tissue, as well as the use of worse case scenarios [44, 46, 48, 49, 52, 53, 60, 61]. Sequential activity measurements with probes or gamma-camera can give useful insight in biological half-life, as well as effectiveness of applied interventions [42, 51, 52]. Furthermore, it might be helpful to also estimate the amount, meaning the volume, of extravasation as one can assume, that larger volumes of radioactive extravasation might cause more pronounced side effects than smaller amounts. However, the volume of an extravasation is hardly measurable, at least in the clinical setting and, consequently, to define. This is not only because of the “real time” setting, but it is even more difficult based on a retrospective literature search and analyses. Furthermore, preventive measures are reported, such as the use of an intravenous catheter (IV-catheter) and adequate check of patency for both diagnostic as well as therapeutic extravasation [1, 2, 4, 46, 50, 51, 55–57].

Limitations

A substantial number of publications reporting on extravasation, or which were otherwise relevant, were found by screening bibliographies and not in the initial search, despite the sensitive elaborate search strategy. This can be at least partially explained by mismatches in searched keywords and the

subject of the publication. For instance, a number of publications about pitfalls in image interpretation contained a brief case report of extravasation as an example for false positive lymph node visualisation. These publications were filtered out in our initial search because they did not contain the right keywords in title, abstract or keyword index. Similarly, some patient studies investigating a particular tracer for evaluation of a specific pathology also report extravasation, but were also filtered out because no keywords relevant for our search were matched. Others were brief case reports or "image of the month"-type of publications without an abstract, but contained some relevant information in image captions. Finally, we found several congress abstracts for oral or poster presentations that were not indexed in PubMed or Embase. This is a minor shortcoming in our literature search, although the publications that were found this way only reported minimal information on tracer extravasation. Moreover, it is challenging to avoid such difficulties.

We did not analyse the effect of extravasation on the image quality of diagnostic nuclear medicine scans. It is obvious that image quality might significantly be hampered by at least large extravasation leading to a lower degree of tracer uptake in the target tissue (organ) and to the potential need for a new scan. However, as we, in this review, are focusing on clinical consequences for the patients, we do not address this issue in detail. Furthermore, because of the design of the study, gaining more insights into this topic is not possible within the context of this review.

Future perspectives

The lack of data on interventions underlines the need for further scientific exploration on this subject. Future research is required to establish definite conclusions for all used radiopharmaceuticals, by retrospective or preferably prospective studies of extravasation cases with detailed clinical description, activity measurements, as well as serial scans to assess dynamic behaviour of the tracer in the time after extravasation. Furthermore, similar studies can be performed to evaluate the different therapies possible after extravasation. Alternatively, detailed case reports can proof to be helpful, especially for less used and probably less common extravasation of therapeutic radiopharmaceuticals. Nevertheless, trials performed in centres that treat large numbers of patients with nuclear medicine therapies are preferable.

Local protocol

In our clinic, every injection of diagnostic and therapeutic radiopharmaceutical is performed via an IV-catheter, preceded

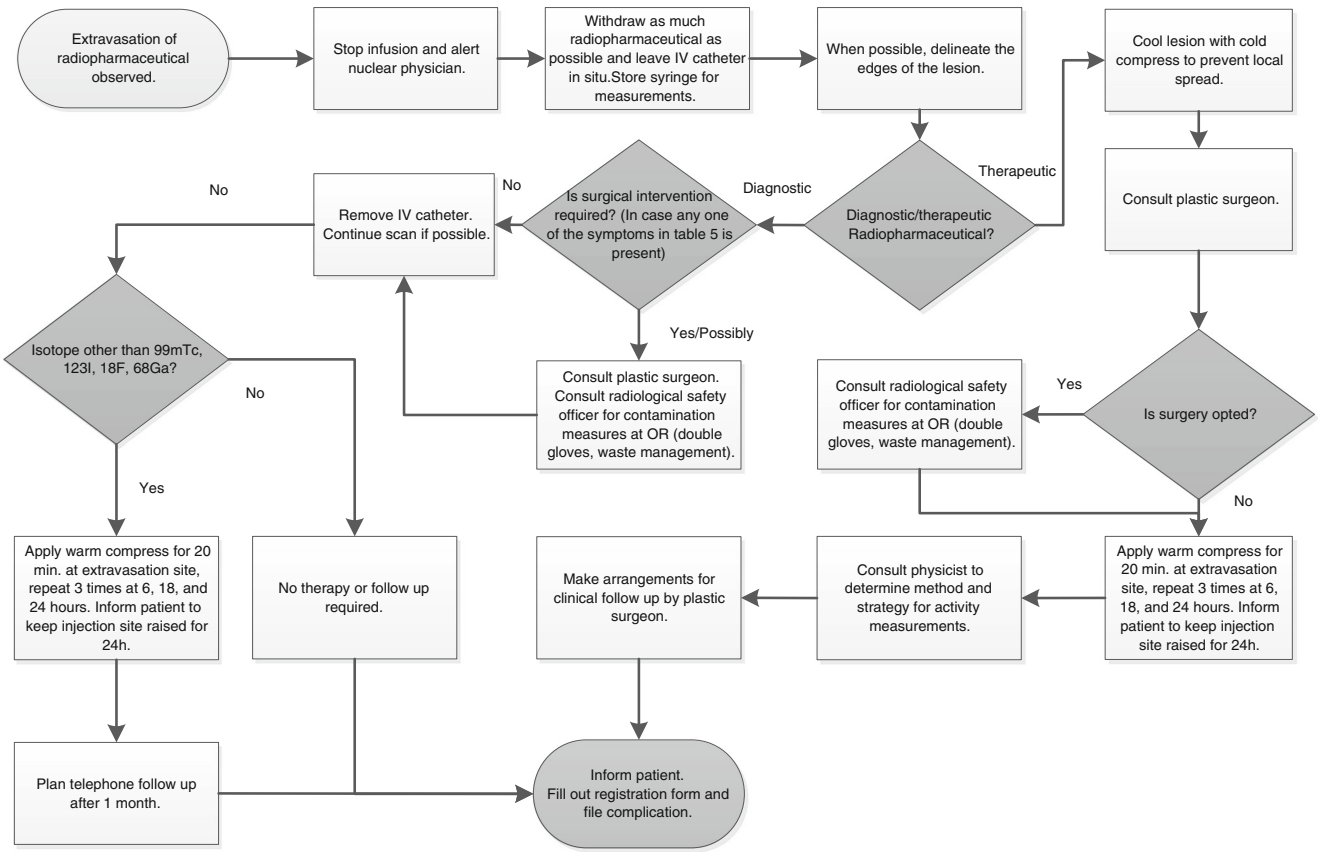

Fig. 1 Flowchart describing the protocol in use in Maastricht University Medical Center for management of radiopharmaceutical extravasation

by a check of patency that includes flushing the IV-catheter with saline solution, while visually inspecting if swelling occurs and asking the patient if he experiences discomfort during injection. Furthermore, some blood is drawn. When patency is doubtful, a second IV-catheter is inserted and checked for patency. Alternatively, in patients with difficult venous access, this step can be preceded by injecting ^{99m}Tc-pertechnetate with the patient's thorax positioned under a gamma camera, to visually confirm systemic spread. For therapeutic administrations, patency is always checked under supervision of the nuclear physician.

Figure 1 shows the protocol that is in use in our hospital for management of radiopharmaceutical extravasation. It is based on the findings of this review. It reflects the negligible probability of adverse events in frequently used ^{99m}Tc, ^{123}I, ^{18}F and ^{68}Ga labelled tracers by a conservative approach. A more careful approach has been chosen with relatively harmless preventive measures for diagnostic tracers combined with follow-up, in case of tracers for which adverse events have been reported, notably ^{201}Tl-thallous chloride, and for tracers no literature of extravasation was found at all. Although in general radiopharmaceutical administration volume is limited, severe consequences have been reported in non-radiopharmaceutical extravasation, such as tissue necrosis and compartment syndrome [65, 66]. Therefore, in case of any of the symptoms listed in Table 5, the plastic surgeon is consulted. For therapeutic extravasation a plastic surgeon is always consulted to discuss the usefulness of surgery. Until the decision for surgical intervention is made, the lesion is cooled to spare surrounding tissue by preventing spread of the radiopharmaceutical. If no surgical intervention is opted, frequently warming the extravasation area and elevation of the arm are advised to promote spreading of the radiopharmaceutical. Repetitive gamma camera measurements are performed in case of therapeutic extravasation in consultation with the physicist. The patient should always be informed about treatment and potential complications. All cases of extravasation in our hospital are being recorded using a standard form containing detailed information, such as symptoms, the location of extravasation, injected volume and activity, as well as treatment. Furthermore, the incident is documented for the local complication committee. The strategy applied in this protocol ensures an efficient workflow, by minimizing the effort needed for the most frequently used tracers.

Table 5 List of symptoms requiring consultation of a plastic surgeon

Symptom
Swelling > 2.5cm in longest axis
Numbness
Blanched, translucent skin
Tight skin, leaking
Discolored, bruised skin
Circulatory or nervous impairment
Moderate-severe pain

Adapted from Amjad et al. [65]

Conclusions

Extravasation of diagnostic radiopharmaceuticals is common. Often used ^{99m}Tc, ^{123}I, ^{18}F, and ^{68}Ga labelled tracers do not require specific intervention. Sporadic reports of extravasation of other diagnostic radiopharmaceuticals, however, have described soft tissue lesions. Dispersive intervention and follow-up is, therefore, advised in other diagnostic radiopharmaceuticals. Extravasation of therapeutic radiopharmaceuticals can lead to severe soft tissue lesions. Although not evidence based, surgical intervention should be considered. Furthermore, dispersive intervention, dosimetry and follow-up is advised. Pharmaceutical intervention has no place yet in the immediate care of radiopharmaceutical extravasation.

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