LUCERNO DYNAMICS, LLC
140 Towerview Court
Cary, NC 27513
919-371-6800

June 23, 2022

Christopher Hanson, Chairman
Jeff Baran, Commissioner
David Wright, Commissioner
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Subject: Petition for Rulemaking (PRM)-35-22

Dear Chairman Hanson, Commissioner Wright, and Commission Baran,

It is my understanding that the Commission is reviewing the medical staff's recommendation regarding radiopharmaceutical extravasations. While this recommendation has not been made public, information in the 12/21/2021 Organization of Agreement States letter to NRC and the content from a Society of Nuclear Medicine and Molecular Imaging (SNMMI) presentation to CORAR suggest that the medical staff have recommended a patient injury threshold for reporting extravasations. This recommendation includes modifications proposed by SNMMI.

As the Commission knows, routine medical event reporting criteria has not required patient injury since misadministration reporting was initiated in 1980. Furthermore, use of a clinical assessment of adverse effects (i.e., patient injury as determined by a physician) as a threshold for reporting was determined to be a "moving target" and abandoned by the Commission in 1980 (May 14, 1980 Federal Register, page 31703) for good reasons:

- lack of clear definition for "clinically detectable adverse effect" and variability in the symptoms from patient to patient,
- too much physician leeway in making the determination,
- too difficult to make a determination without guidelines,
- and adverse effects may be delayed in time.

These reasons not only remain valid today, but the characteristics of the energy emission of isotopes used in nuclear medicine procedures now versus 1980 provide an additional reason why an injury reporting threshold will not provide patients adequate radiation protection. An examination of recent literature provides additional support for using existing dose thresholds, rather than patient injury, as a medical event reporting threshold. I have attached four highlighted papers and one abstract for the Commission's review.

The first article, *Underreporting of Patient Safety Incidents Reduces Health Care's Ability to Quantify and Accurately Measure Harm Reduction*, by Noble and Pronovost in 2010 echoes the Commission's 1980 view on physician leeway in reporting. The authors contend that physicians want voluntary reporting but are poor reporters of incidents, due to the unique lens through which they view healthcare. This hesitancy to report results in bias on the nature of the problems and hinders patient safety efforts. Noble and Pronovost state that reporting from all physicians needs to be equally weighted, which is especially important in understanding diagnostic errors.

The authors conclude that mandatory reporting offers certain advantages to the government and public, including provider accountability and bringing information to the public domain. Again, they echo the Commission's 1980 determination that a well-defined reporting threshold is necessary to benchmark and measure progress.

The abstract *Avoidance of radiation injuries from medical interventional procedures, ICRP Publication 85* is focused on radiation injuries caused during fluoroscopy-guided interventions. However, the parallels of this abstract from the year 2000 to nuclear medicine in 2022 are noteworthy:

- Like some nuclear medicine clinicians today, interventional cardiologists in 2000 were not adequately trained in radiation biology, were not aware of the potential for injury from their procedures nor the simple measures that could be taken to protect patients.
- Operational technique varied by clinicians, with poor technique leading to high doses, subsequent patient injury, and increased risk of future cancer for younger patients.
- Patients were not counselled on the radiation risks associated with fluoroscopy and not clinically followed when they received doses that could lead to injury.
- Absorbed doses could be high, with doses >2 Gy leading to erythema, > 7 Gy leading to permanent epilation, and > 12 Gy leading to delayed necrosis.
- Recommendations to reduce frequency of events and to improve radiation protection included:
    - Establishing protocols,
    - performing dosimetry and including results in the patient's record,
    - informing the patient and their physician of the excessive radiation dose,
    - and following the patient to ensure they received proper care.

The paper *Cutaneous Radiation Injuries: Models, Assessment and Treatments*, by DiCarlo et al. from 2020 summarized a meeting of 28 subject matter experts in radiation-induced skin injuries and medical counter measures. The paper's relevant topics include Cutaneous Radiation Injuries (CRI), the underlying soft tissue injury, medical counter measures for immediate mitigation, available tools to quantitatively assess tissue damage, and the inadequacy of clinical assessments for radiation injuries. Interestingly, the authors point out that radiation injuries resulting from fluoroscopy-guided interventions had been curtailed since more focus had been put on the issue in recent years. Highlights from this paper that support the inadequacy of using patient injury as a reporting threshold include:

- Since soft tissue injuries can be delayed months or years after exposure/irradiation, estimations of dose and dose rates are required as prognostic indicators to help guide early intervention and to adequately evaluate the skin and underlying tissue.
- Particle-based (positron, alpha, beta, and electron) energy can cause more damage at lower doses than photons.
- Irradiation damages the skin and the underlying tissue via dynamic, successive inflammatory waves, making prognosis difficult because visible lesion development is often delayed. Radiation necrosis can re-appear even years after the initial exposure, reinforcing the need for long-term monitoring.
- Clinical interpretation of an injury is not sufficient. More quantifiable information is needed. Patients will often seek help from dermatologists, who are not necessarily prepared to diagnose radiation injury.
- Often, tissue can be damaged and the skin does not show it.
- Patients experiencing high absorbed doses to tissue should have medical counter measures done immediately and should be followed with tissue assessment.

- Tools are available today to assess damage to underlying tissue.

The authors concluded: "In summary - assessment of what lies beneath the skin surface is required to inform medical-decision making in humans. This evaluation may include radiological surveys, ultrasound imaging and thermography."

The paper *Management of Ionizing Radiation Injuries and Illnesses, Part 5: Local Radiation Injury,* by Goans et. al. from 2014 also focuses on the effects of ionizing radiation on skin and underlying tissue. Nuclear medicine procedures are specifically cited as one source of Local Radiation Injury (LRI). Like the CRI paper, this paper discusses several topics that reinforce why patient injury as a reporting threshold is inadequate for protecting patients:

- Adverse tissue effects occur past a certain dose threshold, which are highlighted in a table in the paper.
- Adverse tissue effects are latent. Further delayed effects may occur from months to years after the injury and are the result of damage to the microvasculature. Much is still unknown about the pathophysiology of LRI, but injury comes in waves.
- Injury may not manifest until weeks later, which may delay patients seeking care.
- Because many patients do not really know they are being exposed to radiation or understand the risk and the latent effects of LRI, they may not attribute LRI to the procedure.
- Local radiation injuries are difficult to diagnose without known ionizing radiation exposures and are difficult to manage.
- Diagnosis requires a detailed recent history and physical exam. A health or medical physicist should estimate the dose. Delayed presentation may make the history and dose estimation difficult to impossible.
- Tools are now available to assess the effects of radiation to tissue.
- Management techniques are provided to minimize the dose if clinicians are immediately aware of the irradiation.

Lucerno has provided several dozen examples of tissues doses from radiopharmaceutical extravasations at the levels that this paper suggests lead to adverse tissue effects.

The last attached paper, *Adverse Events of Diagnostic Radiopharmaceuticals: A Systematic Review* by Schreuder et. al., from 2019 provides evidence that extravasations do represent patient risks worth improvement efforts. This systematic review paper provides an overview of the most common diagnostic radiopharmaceutical adverse events and their characteristics as reported in literature. Here are some relevant findings:

- Diagnostic radiopharmaceutical adverse events had a low reported frequency compared to therapeutic drugs. The author suggested several possible reasons.
    - All of the reviewed studies relied on voluntary reporting.
    - Inconsistency in the level of awareness of adverse events and need to report across institutions.
    - Adverse events may happen after patients leave the nuclear medicine centers.
    - Many studies excluded reporting of specific events, such as extravasations or administration site issues.
- Adverse event reporting to the relevant regulatory authorities or marketing authorization holder could detect hitherto unknown adverse events."

The authors screened over 20,000 papers, reviewed 101 publications that met inclusion criteria, and documented all reported adverse events. Despite a focus on the pharmaceutical aspects of

the diagnostic drugs and the exclusion of extravasations or administration site issues in some reviewed studies, the authors report the majority of the 2,447 adverse events were related to "skin and subcutaneous tissue disorders" and "general disorders and administration site conditions," suggestive of radiation induced adverse tissue effects. Descriptions include:

- Injection site erythema
- Dermatitis exfoliative
- Injection site necrosis
- Skin necrosis
- Injection site inflammation
- Injection site swelling
- Injection site rash
- Injection site irritation
- Administrative site reaction
- Injection site pain

The authors concluded that nuclear medicine departments should be prepared to manage adverse events and the need for vigilance is higher than ever with the increasing use of PET/CT and the introduction of new radiopharmaceuticals.

For all the reasons provided in these papers, patient injury as a reporting threshold will not adequately protect patients and will not lead to a reduction of extravasations in the future. NRC has received numerous public comments from medical societies suggesting that radiopharmaceutical extravasations are not of concern or do not represent a patient risk that warrants extra efforts on their part. These comments echo those from 2008-2009 ACMUI members who felt minimizing administrative burden was more important than an effective safety framework. Just last week, at the NRC presentation at the SNMMI Annual Meeting, a past president of SNMMI stated that since he has never seen patient harmed by radiopharmaceutical extravasations, NRC should not require reporting.

All of these comments reveal a general misunderstanding about the purpose of medical event reporting, the importance of protecting patients from inadvertent irradiation, and inadequate radiation safety competency concerning the energy emissions of routinely used radioisotopes and how ionizing radiation affects healthy tissue.

Many nuclear medicine centers administer radiopharmaceuticals with great care, but even in these centers some patients are significantly extravasated. Some centers routinely extravasate patients. Ionizing radiation is known to lead to adverse tissue reactions when doses exceed certain thresholds. If clinicians are adequately trained in the safe use of radioactive materials, they can take immediate actions to minimize adverse tissue reactions if extravasations are identified soon after they occur. Extravasations are the result of human error, lack of training and tools, or lack of quality policies—they can and should be avoided. Using patient injury as the threshold for reporting of these medical events will not adequately protect extravasated patients nor will they help reduce the number of future patients who are extravasated.

Removing the incorrect 1980 reporting exemption and using the existing dose threshold will identify which licensees are routinely extravasating patients to such a degree that requires reporting. Providing an adequate reporting grace period will allow licensees time to improve the quality of their radiopharmaceutical delivery and reduce the need to report. Smart rulemaking can minimize reporting burdens further. All of these changes will improve how significant

LUCERNO DYNAMICS, LLC
140 Towerview Court
Cary, NC 27513
919-371-6800

extravasations are managed to minimize absorbed dose to patient tissue and will lead to quality improvement efforts and improved patient protection.

Sincerely,

Ronald K. Lattanze

Digitally signed by Ronald K. Lattanze
DN: cn=Ronald K. Lattanze, o, ou, email=rlattanze@lucerno.com, c=US
Date: 2022.06.23 11:52:39 -04'00'

Ronald K. Lattanze

Cc: Marian Zobler
Bernice Ammon
Kevin Williams

Attached Publications:

1. *Underreporting of Patient Safety Incidents Reduces Health Care's Ability to Quantify and Accurately Measure Harm Reduction*
2. *Avoidance of radiation injuries from medical interventional procedures*
3. *Cutaneous Radiation Injuries: Models, Assessment and Treatments*
4. *Management of Ionizing Radiation Injuries and Illnesses, Part 5: Local Radiation Injury*
5. *Adverse Events of Diagnostic Radiopharmaceuticals: A Systematic Review*

Underreporting of Patient Safety Incidents Reduces Health Care's Ability to Quantify and Accurately Measure Harm Reduction

Douglas J. Noble, BSc, BMBCh, MRCS, MPH and Peter J. Pronovost, MD, PhD, FCCM*†*

Abstract: Underreporting of patient safety incidents creates a reservoir of information that is plagued with epidemiological bias. These include systematic biases such as the practice of reporting minor incidents at the expense of more serious ones. This leads to inaccurate rates of errors and an inability to generalize results to whole patient populations. It leaves reporting incidents, in epidemiological terms, comparable to nonrandom samples from an unknown universe of events.

These epidemiological problems lead to a situation where priorities are skewed toward what "we know we know." As "we know what we do not know," for example, gaps in knowledge about serious incidents due to low reporting rates, due caution must be applied in making policy based on biased underreporting.

Barriers to reporting contribute to low participation rates and further bias information. Lack of feedback and fear of personal consequences are common barriers.

Evaluation of reporting systems indicates reports can be used as tools for learning, but it is not yet possible to monitor improvement in patient safety or measurably prove reduction in harm. Mandatory reporting makes sense from an epidemiological point of view, but there are legitimate fears that it could further reduce reporting rates due to fear of reprisal.

Underreporting and the associated biases are a significant problem in realizing the epidemiological potential of incident reporting in health care.

Key Words: reporting, bias, health policy, diagnostic errors, risk

(*J Patient Saf* 2010;6: 247–250)

Systems that report patient safety incidents are widely used.[1] Yet, underreporting of patient safety incidents is common,[2–4] and incident reports may only account for 4% to 50% of events that occur in the United States each year.[1,5] In the United Kingdom, at least 22% to 39% of errors go unreported and more serious errors are often not reported.[6]

When reports are cumulatively analyzed at a hospital, regional, national, or international level, underreporting creates a systematic bias toward or away from certain errors. This severely constrains monitoring trends and progress in patient safety. Instead, these data play an important role in identifying hazards to focus improvement efforts.

The variation in reporting rates by different health care professionals, event type, and degree of harm further limit the usefulness of an epidemiological approach to reporting systems.

This analysis reviews barriers to reporting, biases in reporting systems, how underreporting confounds evaluation, and the controversy between voluntary and mandatory reporting systems. We argue that underreporting of patient safety incidents contributes to health care's inability to accurately identify and measurably reduce risks to patients.

BARRIERS TO REPORTING

Adverse event and near-miss reporting should preferably elicit all relevant information from incidents,[7] be subjected to suitable analysis by skilled personnel,[8] publicize findings in a way that benefits both the local institution and the wider health care community, and make efforts to reduce risk of harm to future patients. Underreporting make the latter 2 less likely.

Common barriers leading to underreporting are classified in 2 ways in Figure 1[1,9–11]: first, according to *Donebedians* structure, process, and outcome model of health care[12]; and second, by considering the attitudes and fears of individual professionals. Lack of feedback to the reporter and fear associated with reporting are common themes.

An anonymous survey of approximately 800 health care professionals highlighted that lack of feedback to the reporter was among the most significant barrier to reporting. Approximately 60% of physicians and nurses felt this to be the case.[11] Failing to feedback to the reporter demoralizes their efforts and, coupled with lack of support and fear of reprisal, decreases their likelihood of reporting again. A voluntary questionnaire study of 315 health care professionals revealed that reporting was most common to a colleague. Involving senior colleagues was not routine, more so for physicians than nurses.[4]

EPIDEMIOLOGICAL PROBLEMS

In addition to individual barriers, incident reporting has been plagued by epidemiological problems in 3 principal areas (Table 1). Paradoxically, establishing a reporting system creates a false impression of increasing levels of error within health care systems: the *Reporting Paradox*. As systems develop, professionals become more comfortable with reporting, and the systems are used more frequently. Error rates stay the same but are observed more frequently (Fig. 2). This has significant ramifications especially when such information is used by the media.

Second, underreporting of incidents and preference for incident type affects the generalizability of cumulative information. With at least half of all incidents going unreported,[1,5] and a trend to omitting serious incidents,[6] samples of reports are systematically biased.

Third, reporting is heavily skewed toward nursing professionals leading to a participation bias. This not only affects the generalizablility of samples to the whole patient populations, but also leads to incident reporting being perceived as owned by nursing professionals.

Participation Bias

Physicians are poor reporters of incidents. In a review of 5 health care centers in California, only 1.7% of reports were

From the *Johns Hopkins Bloomberg School of Public Health and †Johns Hopkins University School of Medicine, Baltimore, Maryland.
Correspondence: Douglas J. Noble, BSc, BMBCh, MRCS, MPH, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (e-mail: douglas.noble@doctors.org.uk; nobled@who.int).
Douglas J. Noble was a WHO Patient Safety scholar.

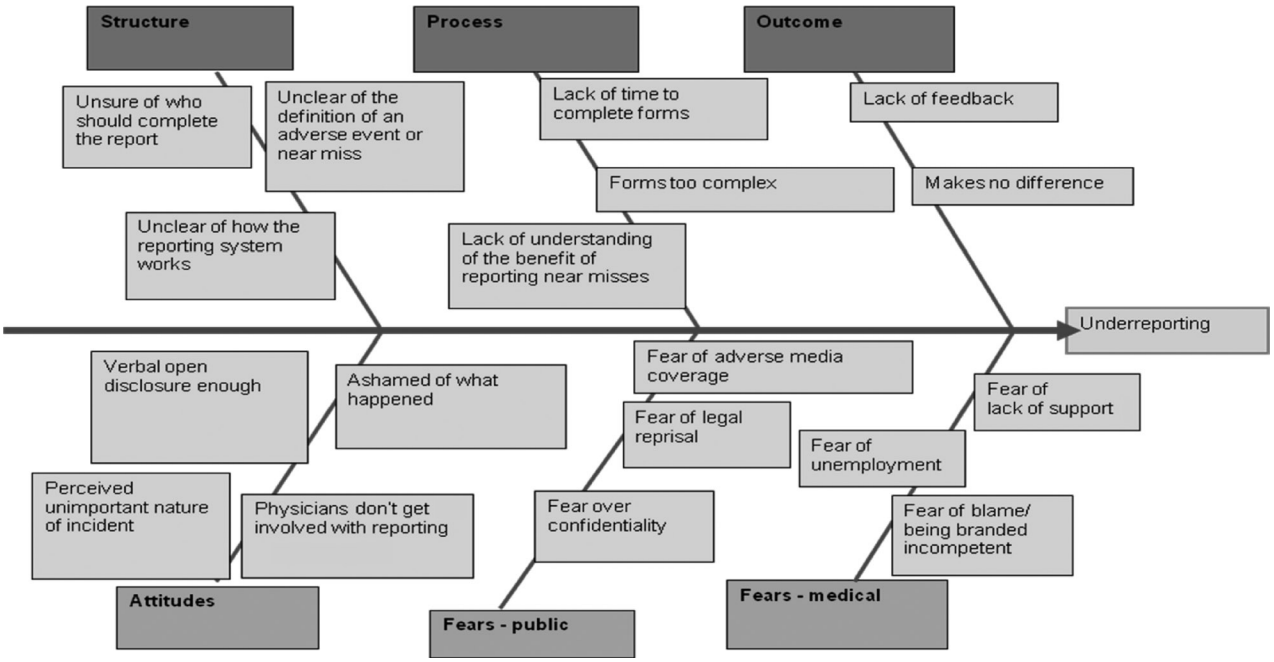

FIGURE 1. Barriers to incident reporting.

completed by physicians.[13] A survey of 120 physicians at the University of Virginia Hospital revealed that despite 65% having made no reports, 60% had observed 3 adverse events (or near misses) or more.[9] A similar finding was reported by the Australian Incident Monitoring System—physicians contributed 2% of reports versus nurses who submitted 88% of reports.[1]

In a descriptive study of 92,547 adverse events and near misses, representing 26 hospitals across the United States, there was a vast variation in reporting rates (9–95 reports per 1000 inpatient days), indicating underreporting in many sites. Physicians were identified as particularly poor reporters supplying 1.4% of reports. By contrast, nurses submitted 47% of reports.[14]

Low physician reporting is problematic because it hinders health care's ability to identify and mitigate risks. Each type of physician views health care through a unique lens, which allows them to identify certain types of hazards and certain contributing factors better than others. For example, an oncologist may be more likely to identify risks and errors in the process of care for radiotherapy. As such, lack of reporting hinders patient safety improvement efforts. It also has consequences for patients. A recent review of orthopedic implants suggested that underreporting of adverse events led to a delay in product recall and increased revision operations.[15]

INCORRECT PRIORITIZATION

Participation bias misdirects prioritization of solution development. Predominantly determining the frequency of error from reports from nurses creates an impression that certain errors are more of a problem than others. Until reports from all health care professionals are equally weighted, the possibility of using information to prove error reduction is not possible. This is particularly significant in the area of diagnostic errors (almost universally the role of a physician), especially as diagnostic errors are estimated to account for an unknown but likely high number of errors.[16]

Falls in hospital are frequently and consistently reported by nurses, whereas other more serious events go unreported. Falls accounted for 32.3% of all patient safety incident reports in the United Kingdom's National Patient Safety Agencies' National Reporting and Learning System between September 2005 and August 2006.[17] The United Kingdom's National Health Service has also suffered participation bias. It is countercultural for nurses not to fill in incident reports for falls out of bed; yet, physicians routinely fail to report serious untoward incidents.

Understanding the culture change that led to nurses filling in incident reports on falls out of bed is a mystery in British health care. It has been suggested that these incidents are frequently reported as there is no fear of personal consequences as the incidents are not felt to be due to individual mistakes.[6] There is a risk that if certain areas of reporting are disproportionately reported compared with other areas that these become routine and cease to be taken seriously. Yet, despite this, with increasing reporting rates, safety culture has improved.[18]

EVALUATING ERROR REDUCTION

At least 8 countries have national reporting systems.[19] Yet, few systems have been subjected to rigorous evaluation. Although ease of use is regularly reviewed, reduction of unsafe outcomes is rarely proved—confounded by the inherent bias' present in most data sources. A recent review of the National

TABLE 1. Underreporting Confounds an Epidemiological Approach to Reporting Systems

Epidemiological Weaknesses of Reporting Systems
The *Reporting Paradox*
Underreporting leading to systematic bias:
1. Of all incidents
2. Of incident type
Lack of generalizability to whole patient populations
Participation bias

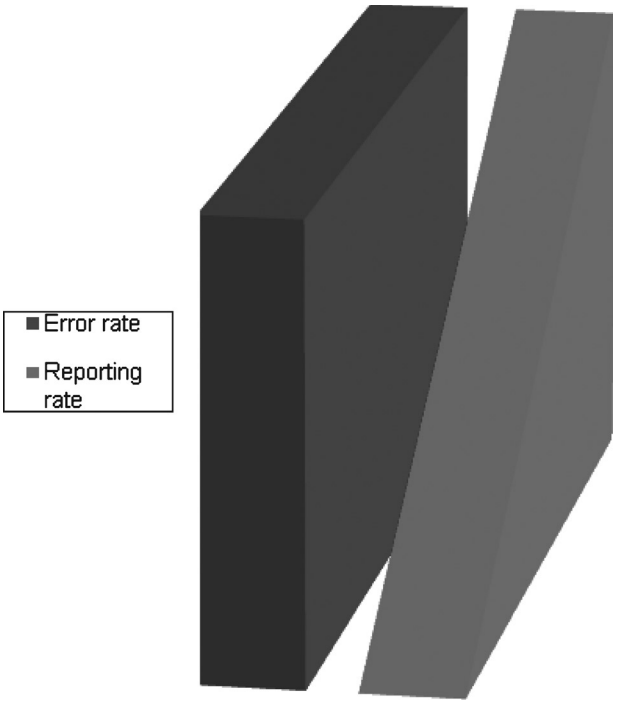

FIGURE 2. After the introduction of incident reporting, it appears as if the static error rate is increasing.

Patient Safety Agency National Reporting and Learning System, which exposed such bias in the data collection, concluded that[20]

"we believe that [reporting systems] such as the [National Reporting and Learning System] are tools for learning (identifying and mitigating hazards), not for monitoring progress toward improving patient safety"

CURRENT CONTROVERSIES

Physicians have tended to prefer a voluntary model of reporting,[10] although opponents argue this hinders progress in various ways. For example, it potentiates participation bias. In addition, collecting epidemiologically meaningful data, as described above, is stifled by a voluntary model and makes it difficult to get a clear picture of the magnitude and type of error,[21] simply because the sample may not reflect the population in a generalizable way. Proponents of a voluntary system argue that it provides more scope for depth of analysis, as reporters are free from fear of repercussion and more likely to report near misses.[22] It is unclear whether any self-reported system will ever yield enough valid information to monitor progress.

Anonymity is similar to a voluntary approach. Critics argue that it impedes objective independent enquiry,[23] but this partly misunderstands the role of incident reporting. Parallel to any incident there is often a recognized legal process that may result in individual or corporate prosecution. In a purist sense, reporting should only seek to improve safety and reduce risks to patients and not offer a method of legal reprisal.

Although voluntary systems have been favored by health care professionals, mandatory systems offer certain advantages to government (and perhaps the public) in provider accountability, including statutory responsibility, independent inquiry, mandated change, bringing information into the public domain, and having a mechanism to take legal action to enforce change.[24]

CONCLUSIONS

Underreporting is a significant problem in realizing the epidemiological potential of incident reporting in health care internationally. Systems are too complex and too numerous to yield accurate cumulative information about patient safety and suffer systematic bias that confounds proving a reduction in error.

Future challenges include taking a public health approach to reporting system design and analysis, improving physician reporting rates, reducing bureaucracy allowing translatability across geographical lines, and determining the extent to which different models of reporting (such as mandatory reporting) will allow accurate benchmarking of levels of harm and facilitate measurable improvement in safety.

Those managing incident reporting systems need to better understand, reduce, and make transparent biases in reporting and to create a situation whereby progress can be benchmarked and measured. Mandatory reporting of well-defined reportable events may be 1 step to achieving this goal. In addition, if systems are simple to use, easy to understand, and have built-in user feedback, success is more likely. Lack of uniformity across reporting systems locally, regionally, nationally, and internationally is a major system weakness[2] and may also contribute to underreporting, although this is hard to prove.

The problem of unsafe care and the need for fully functioning reporting systems is well understood, and it is undisputed that reporting systems should be a cornerstone of overall patient safety system reform. Yet, so far, underreporting is common place, physicians fail to be fully engaged and multiple biases prevent monitoring of progress.

REFERENCES

1. Kingston MJ, Evans SM. Attitudes of doctors and nurses towards incident reporting: a qualitative analysis. *Med J Aust*. 2004;181:36–39.
2. Arah OA, Klazinga NS. How safe is the safety paradigm? *Qual Saf Health Care*. 2004;13:226–232.
3. Weingart SN, Wilson RM, Gibberd RW, et al. Epidemiology of medical error. *BMJ*. 2000;320:774–777.
4. Lawton R, Parker D. Barriers to incident reporting in a healthcare system. *Qual Saf Health Care*. 2002;11:15–18.
5. Barach P, Small SD. Reporting and preventing medical mishaps; lessons from non-medical near miss reporting systems. *BMJ*. 2000;320:759–763.
6. Leigh E. Chairman. Great Britain Parliament House of Commons Committee of Public Accounts. *A Safer Place for Patients: Learning to Improve Patient Safety. Fifty-first Report of Session 2005–06 Report, Together With Formal Minutes, Oral and Written Evidence*. London, UK: House of Commons Papers. 2006.
7. Vincent C. Incident reporting and patient safety. *BMJ*. 2007;334:51.
8. Vincent C. Analysis of clinical incidents: a window on the system not a search for root causes. *Qual Saf Health Care*. 2004;13:242–243.
9. Schectman JM, Plews-Ogan ML. Doctor perception of hospital safety and barriers to incident reporting. *Jt Comm J Qual Improv*. 2006;32:337–343.

10. White J. *Adverse Event Reporting and Learning Systems: A Review of the Relevant Literature*. Alberta, Canada: Canadian Patient Safety Institute (CPSI). 2007.
11. Evans S, Berry JG, Smith BJ, et al. Attitudes and barriers to incident reporting: a collaborative hospital study. *Qual Saf Health Care*. 2006;15:39–43.
12. Donabedian A. Evaluating the quality of medical care. *Milbank Mem Fund Q*. 1966;44:166–206.
13. Nguyen QT, Weinberg J, Hillborne LH, et al. Physician event reporting: training the next generation of physicians. Available at: http://www.ahrq.gov/downloads/pub/advances/vol4/Nguyen.pdf Accessed April 21, 2009.
14. Milch CE, Deeb NS, Pauker SG, et al. Voluntary reporting of medical errors and adverse events. An analysis of 92,547 reports from 26 acute care hospitals. *J Gen Intern Med*. 2006;21:165–170.
15. Tanner M, Bradley G. Increasing patient safety and orthopaedic device quality via adverse event reporting mechanisms. *J Bone Joint Surg Am*. 2004;86:33–34.
16. Newman-Toker DE, Pronovost P. Diagnostic errors—the next frontier for patient safety. *JAMA*. 2009;301:1060–1062.
17. Healey F, Scobie S, Oliver D, et al. Falls in English and Welsh hospitals: a national observational study based on retrospective analysis of 12 months of patient safety incident reports. *Qual Saf Health Care*. 2008;17:424–430.
18. Hutchison A, Young TA, Cooper KL, et al. Trends in healthcare incident reporting and relationship to safety and quality data in acute hospitals: results from the National Reporting and Learning System. *Qual Saf Health Care*. 2009;18:5–10.
19. Farley DO, Haviland A, Champagne S, et al. Adverse-event–reporting practices by US hospitals: results of a national survey. *Qual Saf Health Care*. 2008;17:416–423.
20. Pronovost P. 2007 Final Project Report to The World Health Organization Analysis of Safety Issues: National Reporting and Learning System (NRLS).
21. Morrissey J. Patient safety proves elusive. *Mod Healthc*. 2004;34:6–32.
22. Cohen M. Why error reporting systems should be voluntary. *BMJ*. 2000;320:728–729.
23. Runciman B, Merry A, Smith AM, et al. Improving patients' safety by gathering information. *BMJ*. 2001;323:298.
24. Flowers L, Riley T. *State-Based Mandatory Reporting of Medical Errors: An Analysis of the Legal and Policy Issues*. Portland, ME: National Academy for State Health Policy; 2001.

PERGAMON

ICRP Publication 85

Annals of the ICRP

Avoidance of radiation injuries from medical interventional procedures

ICRP Publication 85

Approved by the Commission in September 2000

Abstract-Interventional radiology (fluoroscopically-guided) techniques are being used by an increasing number of clinicians not adequately trained in radiation safety or radiobiology. Many of these interventionists are not aware of the potential for injury from these procedures or the simple methods for decreasing their incidence. Many patients are not being counselled on the radiation risks, nor followed up when radiation doses from difficult procedures may lead to injury. Some patients are suffering radiation-induced skin injuries and younger patients may face an increased risk of future cancer. Interventionists are having their practice limited or suffering injury, and are exposing their staff to high doses.

In some interventional procedures, skin doses to patients approach those experienced in some cancer radiotherapy fractions. Radiation-induced skin injuries are occurring in patients due to the use of inappropriate equipment and, more often, poor operational technique. Injuries to physicians and staff performing interventional procedures have also been observed. Acute radiation doses (to patients) may cause erythema at 2 Gy, cataract at 2 Gy, permanent epilation at 7 Gy, and delayed skin necrosis at 12 Gy. Protracted (occupational) exposures to the eye may cause cataract at 4 Gy if the dose is received in less than 3 months, at 5.5 Gy if received over a period exceeding 3 months.

Practical actions to control dose to the patient and to the staff are listed. The absorbed dose to the patient in the area of skin that receives the maximum dose is of priority concern. Each local clinical protocol should include, for each type of interventional procedure, a statement on the cumulative skin doses and skin sites associated with the various parts of the procedure. Interventionists should be trained to use information on skin dose and on practical techniques to control dose. Maximum cumulative absorbed doses that appear to approach or exceed 1 Gy (for procedures that may be repeated) or 3 Gy (for any procedure) should be recorded in the patient record, and there should be a patient follow-up procedure for such cases. Patients should be counselled if there is a significant risk of radiation-induced injury, and the patient's personal physician should be informed of the possibility of radiation effects. Training in radiological protection for patients and staff should be an integral part of the education for those using interventional techniques. All interventionists should audit and review the outcomes of their procedures for radiation injury. Risks and benefits, including radiation risks, should be taken into account when new interventional techniques are introduced.

A concluding list of recommendations is given. Annexes list procedures, patient and staff doses, a sample local clinical protocol, dose quantities used, and a procurement checklist.

Keywords: Interventional radiology; Radiation protection; Erythema; Necrosis; Cataract

Cutaneous Radiation Injuries: Models, Assessment and Treatments

Authors: DiCarlo, Andrea L., Bandremer, Aaron C., Hollingsworth, Brynn A., Kasim, Suhail, Laniyonu, Adebayo, et al.

Source: Radiation Research, 194(3) : 315-344

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RADE-20-00120.1

RADIATION RESEARCH **194**, 315–344 (2020)
0033-7587/20 $15.00

DOI: 10.1667/RADE-20-00120.1

WORKSHOP REPORT

Cutaneous Radiation Injuries: Models, Assessment and Treatments

Andrea L. DiCarlo,[a,1] Aaron C. Bandremer,[b] Brynn A. Hollingsworth,[a] Suhail Kasim,[c] Adebayo Laniyonu,[c] Nushin F. Todd,[c] Sue-Jane Wang,[c] Ellen R. Wertheimer[d] and Carmen I. Rios[a]

[a] *Radiation and Nuclear Countermeasures Program (RNCP), Division of Allergy, Immunology and Transplantation (DAIT), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Rockville, Maryland;* [b] *Biomedical Advanced Research and Development Authority (BARDA), Department of Health and Human Services (HHS), Washington, DC;* [c] *U.S. Food and Drug Administration (FDA), White Oak, Maryland; and* [d] *DRT Strategies, Arlington, Virginia*

DiCarlo, A. L., Bandremer, A. C., Hollingsworth, B. A., Kasim, S., Laniyonu, A., Todd, N. F., Wang, S-J., Wertheimer, E. R. and Rios, C. I. Cutaneous Radiation Injuries: Models, Assessment and Treatments. *Radiat. Res.* 194, 315–344 (2020).

Many cases of human exposures to high-dose radiation have been documented, including individuals exposed during the detonation of atomic bombs in Hiroshima and Nagasaki, nuclear power plant disasters (e.g., Chernobyl), as well as industrial and medical accidents. For many of these exposures, injuries to the skin have been present and have played a significant role in the progression of the injuries and survivability from the radiation exposure. There are also instances of radiation-induced skin complications in routine clinical radiotherapy and radiation diagnostic imaging procedures. In response to the threat of a radiological or nuclear mass casualty incident, the U.S. Department of Health and Human Services tasked the National Institute of Allergy and Infectious Diseases (NIAID) with identifying and funding early- to mid-stage medical countermeasure (MCM) development to treat radiation-induced injuries, including those to the skin. To appropriately assess the severity of radiation-induced skin injuries and determine efficacy of different approaches to mitigate/treat them, it is necessary to develop animal models that appropriately simulate what is seen in humans who have been exposed. In addition, it is important to understand the techniques that are used in other clinical indications (e.g., thermal burns, diabetic ulcers, etc.) to accurately assess the extent of skin injury and progression of healing. For these reasons, the NIAID partnered with two other U.S. Government funding and regulatory agencies, the Biomedical Advanced Research and Development Authority (BARDA) and the Food and Drug Administration (FDA), to identify state-of-the-art methods in assessment of skin injuries, explore animal models to better understand radiation-induced cutaneous damage and investigate treatment approaches. A two-day workshop was convened in May 2019 highlighting talks from 28 subject matter experts across five scientific sessions. This report provides an overview of information that was presented and the subsequent guided discussions.

INTRODUCTION

In the wake of the terrorist attacks on September 11, 2001, the U.S. Government re-focused attention on the potential threat from a radiological or nuclear incident on U.S. soil. In response to growing concerns about the ability of the Government to mount a medical response to such a disaster, several agencies were tasked with the mission to support research to develop medical countermeasures (MCMs) to diagnose (biodosimetry) and treat radiation injuries in the wake of a mass casualty, public health emergency. One of these organizations was the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), within the Department of Health and Human Services (HHS). Since 2004, the NIAID has supported countermeasure development across the entire spectrum of radiation research: development of animal models, basic research to identify and target biological pathways involved in the radiation damage response, and advanced development of approaches needed to obtain approval[2] for marketing by the U.S. Food and Drug Administration (FDA). The Biomedical Advanced Research and Development Authority (BARDA), also a part of HHS, supports late-stage activities needed for product approval and is responsible for procurement of products to be placed in the U.S. Strategic National Stockpile (SNS). In parallel, the FDA provides guidance to drug developers seeking approval of products for a radiation countermeasures indication, for which efficacy studies in humans cannot be feasibly or ethically obtained. Referred to as the

[1] Address for correspondence: DAIT, NIAID, NIH, 5601 Fishers Lane, Room 7B13, Rockville, MD 20852; email: cohena@niaid.nih.gov.

[2] As per FDA nomenclature, drugs are approved, biological products are licensed, and devices are cleared.

TABLE 1
Workshop Speakers and Areas of Expertise[a]

Name	Affiliation	Areas of expertise
Christopher Abularrage, MD	Johns Hopkins Medicine, Baltimore, MD	Ulcer and wound care, peripheral vascular injury
Peter Antinozzi, PhD	Argentum Medical, Geneva, IL	Wound care and dressings, product development
David J. Barillo, MD	Disaster Response/Critical Care Consultants, Mount Pleasant, SC	Mass casualty response/management, burn and wound care
J. Daniel Bourland, PhD	Wake Forest University, Winston-Salem, NC	Medical physics, oncology imaging, radiation oncology
Luke Burnett, PhD	KeraNetics, Winston-Salem, NC	Product development model development
Darrell Carney, PhD	Chrysalis, Galveston, TX	Radiation mitigators, product development
Deborah Citrin, MD	National Cancer Institute, Bethesda, MD	Radiation oncology, radiation injury
Nicholas Dainiak, MD	Yale University School of Medicine, New Haven, CT	Medical management of radiation injury
Andrea DiCarlo, PhD	RNCP, NIAID, NIH, Rockville, MD	Radiobiology, product development, MCM testing
Alexis Gabard, MS, MBA	Technical Project Solutions, Winston-Salem, NC	Product development, model development
Jorg Gerlach, MD, PhD	McGowan Institute for Regenerative Medicine, Pittsburgh, PA	Cellular therapies, devices for burn and radiation injury
Gautam Ghatnekar, PhD	FirstString Research, Mount Pleasant, SC	MCM development, wound therapies, product development
Ronald Honchel, PhD	CDER, FDA, White Oak, MD	Pharmacology, toxicology, Animal Rule, MCMs
Narayan Iyer, PhD	BARDA, HHS, Washington, DC	Radiation MCM development, thermal burn and CRI
Juliann Kiang, PhD	AFRRI, DoD,[b] Bethesda, MD	Animal models, MCM testing, RCI
Adebayo Laniyonu, PhD	CDER, FDA, White Oak, MD	Pharmacology, toxicology, Animal Rule, MCMs
Lixin Liu, PhD	CDRH,[c] FDA, White Oak, MD	Animal models, MCM development
William McBride, PhD, DSc	University of California, Los Angeles, Los Angeles, CA	Radiobiology, immunology, radiation mitigation
Maria Moroni, PhD	AFRRI, DoD, Bethesda, MD	Porcine models, MCMs for cutaneous radiation injuries
Neil Ogden, MS	CDRH, FDA, White Oak, MD	Device evaluation, imaging, MCM development
Kathleen Rodgers, PhD	University of Arizona, Tucson, AZ	Small molecule discovery, product development
Julie Ryan Wolf, PhD, MPH	University of Rochester Medical School, Rochester, NY	Pathology, dermatology, radiation-induced skin injury
Alla Shapiro, MD, PhD	CDER, FDA, White Oak, MD	Radiation, MCM development
Stanley Stern, PhD	CDER, FDA, White Oak, MD	Health physics, Animal Rule, MCM development
Radia Tamarat, PhD	Institut de Radioprotection et de Sûreté Nucléaire (IRSN), Fontenay-aux-Roses, France	Radiation biology, surgery, radiation burn wound care
Nushin Todd, MD, PhD	CDER, FDA, White Oak, MD	Medical affairs, Animal Rule, MCM development
Sue Jane Wang, PhD	CDER, FDA, White Oak, MD	Animal Rule, MCM development
Waylon Weber, PhD	Lovelace Biomedical Research Institute, Albuquerque, NM	Animal models, MCMs testing, product development

[a] All speakers had the opportunity to review this meeting report prior to journal submission.
[b] Armed Forces Radiobiology Research Institute, Department of Defense.
[c] Center for Devices for Radiological Health.

''Animal Rule'' (*1*), the FDA created a pathway that has been used to obtain approval for three MCMs to treat hematopoietic complications resulting from radiation exposure: filgrastim (Neupogen®, FDA approved March 2015);[3] pegfilgrastim (Neulasta®, FDA approved November 2015);[4] and sargramostim (Leukine®, FDA approved March 2018).[5]

Although there are now products approved to address radiation-induced hematopoietic complications, there are still other injuries for which no treatment options specific to radiation exposure are approved. These injuries include damage to the gastrointestinal (GI) tract, lungs, kidneys, cardiovascular systems and skin. There are products in development for all of these radiation sub-syndromes; however, the skin represents the organ system that historically has been most affected in human cases of radiation exposure. For this reason, the Radiation and Nuclear Countermeasures Program (RNCP), within the NIAID, NIH convened a workshop with other agencies within HHS to address cutaneous radiation injuries, partnering with the FDA's Center for Drug Evaluation and Research (CDER) and Center for Devices and Radiological Health (CDRH), BARDA and the NIH National Institute of General Medical Sciences (NIGMS). Held in Rockville, MD on May 6 and 7, 2019, the target audience for the workshop included U.S. Government planning and funding entities, healthcare providers, hospital-based emergency management professionals, agencies involved with emergency preparedness, and industry and academic researchers engaged in assessing biomarkers for radiation-induced skin injuries and developing MCM treatment approaches. The workshop highlighted talks from 28 subject matter experts (Table 1) across five scientific sessions.

[3] https://bit.ly/2ZJO9KH.
[4] https://bit.ly/2U8OwdE.
[5] https://bit.ly/30ASp1M.

The purpose of the meeting was to: 1. discuss what is known about the clinical manifestations of cutaneous radiation injuries (CRI) in humans; 2. review current diagnostic and medical management of skin injuries (from radiation and other causes or complications, e.g., burns, diabetic ulcers and other wounds) in the clinic; 3. consider *in vitro* and *in vivo* human and animal models for radiation-induced skin injuries, including natural history, end points and medical management; 4. examine available radiation exposure devices and methods to induce injuries that simulate CRI in preclinical studies; 5. review MCMs currently under development to treat CRI; and 6. discuss whether current rodent and large animal models satisfy the requirements of the FDA Animal Rule, including relevance to injuries that could result from a radiation mass casualty incident. The agenda included presentations in many areas of preclinical development and clinical use of treatments. Participants and clinical experts provided context for methods to assess severity of skin injuries and progression of healing through a series of talks and guided discussions at the conclusion of each session. Other investigators with experience in preclinical modeling of these injuries, and in determining efficacy of MCMs to treat radiation-induced skin complications, presented and were part of the discussion. Together, the gathered medical, scientific and regulatory communities contributed to a greater understanding of CRI, available models and their use to advance MCM research. An overview of these presentations and discussions is provided below.

BACKGROUND

Radiation can be especially damaging, due to its impact on multiple tissues. These effects, when combined, can lead to severe morbidities and even death from multi-organ dysfunction and failure. Although CRI alone is not often life threatening, it can lead to complications including those that affect quality of life, such as chronic pain, fibrosis and disfigurement, which can translate into a lifetime need for medical interventions. In addition, when skin injuries are coupled with total-body irradiation [TBI; radiation combined injury (RCI)], skin injuries (in the form of thermal or radiation injuries and/or wounds) can reduce chances of survival. For example, after the Chernobyl accident, of the 115 patients presenting with acute radiation syndrome, most patients had injuries to more than one organ system, and 56 (48.6%) also had thermal burns (*2*). Early assessment of the severity and extent of CRI is often difficult, since clinical signs and symptoms develop over days to weeks after exposure to ionizing radiation. Erythema is the earliest sign of CRI and may be followed by skin ulceration. Delayed effects of injury to the soft tissue may manifest months or years after radiation exposure. Thus, for medical, and particularly surgical decision-making, clinical assessment of CRI must include consideration of co-morbidities (e.g., diabetes, hypertension, smoking, etc.), and estimates of radiation dose and dose rates, in addition to evaluation of surface area and depth of injury (skin only, versus muscle involvement), interaction with concomitant injuries, and systemic effects of radiation (*3*). In the context of CRI, dosimetry broadly refers to physical and biological modeling, measurement, computational simulation, quantitative estimation, and characterization of the radiation dose and resulting skin injury. Radiation dose and dose rate are used as prognostic indicators (*4*) to help guide early intervention. In industrial accidents where exposure parameters were known, biodosimetry along with dosimetric maps and models have informed the surgical boundaries for early excision of non-viable skin and soft tissues to minimize extension of injury to viable tissue (*5*). The effects of radiation dose can vary due to differences in intrinsic radiosensitivity of different cell types. Radiosensitive organs are characterized by highly proliferative and adequately oxygenated tissue. Within the skin, the melanocytes, hair follicle stem cells and the basal keratinocyte layer are most radiosensitive and are affected by deep dermal injury (*6*).

The challenge in developing models and methods specific to CRI is the need to consider exposure scenarios anticipated during a radiation public health emergency, and end points to be measured must be based on existing best practice of medicine. Animal studies of CRI have employed various radiation sources (e.g., X rays, beta rays and gamma rays, and neutrons) (*7–13*). Use of any of these modalities to simulate CRI in animals is generally considered reasonable, because the mechanisms of cell injury, necrosis and other downstream effects are similar between them and are consistent with the radiobiology of CRI. Dosimetric models of CRI are largely informed by experiences with radiotherapy patients and by animal studies conducted under controlled irradiation conditions. However, a scenario of concern is that of a ground detonation of an improvised nuclear device yielding, for example, a 10-kiloton TNT-equivalent blast (*16*). The medical exigencies ensuing from such a blast would include multiple, systemic insults and physiological responses such as ruptured eardrums and damaged lungs, blunt injuries from flying debris, and thermal burns (*14, 15*). A primary cause of CRI could be beta-particle emissions of radioactive fallout in prolonged contact with unprotected skin (*16*). Within 20 miles of the blast, dose rates from beta particle ''ground shine'' are estimated at approximately 1 mGy/h, while gamma-ray dose rates are estimated at 0.1 mGy/h (*14, 16, 17*). Gamma rays with an average energy of approximately 0.6 MeV would penetrate more than 30 cm in soft tissue (*18*), whereas beta particles with an average energy of approximately 0.4 MeV would penetrate approximately 0.1–0.2 cm of skin (*16, 19*). For skin doses ranging greater than 2 Gy, reactions range from transient erythema, epilation, moist desquamation, edema and acute ulceration, to dermal atrophy, induration and necrosis over timeframes of less than two weeks to 52 weeks, with severe injury

TABLE 2
Topics Addressed During the Discussion Sessions

Session	Topic
Session 1	
	Common pathophysiologic mechanisms that can be modeled from the clinical setting to the animal
	Standard methods to evaluate extent and depth of skin injury to define severity and progression
	Standards of care to be applied to the animal model
Session 2	
	Strengths and weaknesses of each available model and how wound assessment is best conducted in each
	Impact of euthanasia and other IACUC criteria on animal models
	Gaps in appropriate modeling of drug efficacy with different mechanisms of action
	Species most suitable for small and large animal pivotal efficacy studies
	Usefulness of rodent models and their ability to reflect findings that extrapolate well to humans
Session 3	
	Commonly used methods for assessing CRI and their mapping to end points
	Standardization of wound placements if multiple per animal and their systemic interaction
	Appropriate end points for use in animal models
Session 4	
	Considerations for animal models of CRI (animal care, euthanasia criteria)
	Methods for verifying depth or grade of injury
	Study design and data quality issues (reproducibility, single versus multiple labs)
	Statistical issues surrounding multiple wounds in the same animal
	Clinical outcomes for burn wounds and chronic cutaneous ulcers: incidence of complete wound closure, time to complete closure, facilitation of surgical closure, quality of closure
	Appropriateness of end points for a CRI product using the Animal Rule
	Consideration of additional end points for a successful CRI product, e.g., meaningful reduction compared to the untreated group in the development of full- or partial-thickness injury
	Appropriateness of survival end point, e.g., in combined injuries
	Appropriate methods for assessing these end points for CRI
	Utility of repurposing approaches for other related conditions in CRI studies
Session 5	
	Impact of selection of a model for MCM testing on findings of efficacy
	Impact of infection and sepsis derived from radiation-induced chronic cutaneous wounds on animal models
	Key elements to successfully developing new therapies for CRI

requiring surgical intervention (*20*). Severe CRI can extend into the subcutaneous fat and muscle; its pathophysiology has been reviewed in detail elsewhere (*20–22*). A more in-depth discussion of these factors, as well as other considerations for creating, assessing and treating radiation-induced skin injuries is provided below.

MEETING PROGRAM OVERVIEW[6]

The two-day meeting was structured with the following scientific sessions.

Session 1: Skin Injuries from Radiation and Other Clinical Conditions. Here, clinical manifestations and assessment of cutaneous radiation and other injuries, and standard of care considerations were addressed.
Session 2: Radiation Sources and Animal Models of Cutaneous Radiation Injury
Session 3: Assessment Methods to Determine Extent of Skin Injuries
Session 4: Regulatory Considerations for Development of Products for CRI
Session 5: Medical Countermeasures to Treat CRI.

All sessions included a discussion, during which participants were provided with prompts to address issues of concern (Table 2). Common elements of these discussions are captured in the Discussion section below.

Session 1: Skin Injuries from Radiation and Other Clinical Conditions

In the first session of day 1, the intent was to set the stage on the current understanding of radiation injuries to the skin. This involved a historical look at human exposures resulting from radiation incidents, such as those observed in atomic bomb survivors, as well as victims of nuclear energy accidents, nuclear testing, and industrial or medical over-exposures. In addition, subject matter experts from different dermatologic and vascular disciplines shared best medical practices in their fields of thermal burn and diabetic foot ulcers, to highlight established assessment and care protocols in those areas.

Historical experience from large-scale human exposures to radiation. Beginning with an exploration of the 1945 bombings in Japan, an overview of three major incidents involving cutaneous radiation exposures was presented. These included the U.S. bombings of Hiroshima and

[6] Where pre-publication data are discussed, the first initial and the last name of the presenter who provided the information is shown in parentheses.

Nagasaki, Marshall Islands nuclear testing, and the Chernobyl Nuclear Power Plant accident. The goal of this overview was to learn about the types of skin injuries that resulted from these radiation exposures and understand the outcome of medical treatments used for the injuries. As a physician first responder during the Chernobyl accident, the speaker focused on her experience treating patients after the incident (A. Shapiro).

Perhaps the most significant human radiological incident was the large-scale exposure and resulting devastation from the dropping of the atomic bombs on Japan in August of 1945. Although the majority of all deaths occurred immediately after the explosion, reports estimate that over 50% of the deaths were due to thermal burns, as the resulting fireball temperature reached one million degrees Celsius (*23*). In addition, ~65% of the casualties had combined radiation injuries (i.e., radiation exposure combined with another trauma such as burns or other wounds) (*24, 25*). Patients with burns at Hiroshima were all less than ~1.4 miles from the hypocenter of the explosion at the time of the bombing, and in Nagasaki, patients with burns were observed out to the remarkable distance of ~2.6 miles. Several types of burns were noted in the survivors, including those resulting from direct exposure to fire, and also flash-burns, which presented with different pathologies than the fire burns. Flash burns showed immediate erythema, and skin that was covered by clothing appeared to be protected dependent on the color of the fabric.[7] At the time, burn treatments were very crude, and included topical applications of cooking oil, potato or cucumber slices, and tomato juice.[8]

Less than ten years later, there was another atomic incident that resulted in unanticipated human exposures, with both systemic radiation damage and also skin injuries. The Marshall Islands in the Pacific were an important test site for the U.S. military. Although there were 67 nuclear tests carried out there by the U.S. between 1946 and 1958,[9] problems developed with the March 1, 1954 detonation. This particular testing led to fallout for the atolls of the Marshall Islands, and in particular, crewmembers on a Japanese fishing boat were exposed to fallout and sustained severe radiation skin injuries.[10] Although the detonation that day initially went as planned, testing of a larger and more potent bomb design led to an unexpected reaction, which meant the explosion was much larger than predicted. In addition, the prevailing winds were stronger than meteorologists had forecasted and went in unanticipated directions. These factors resulted in widespread fallout contamination to islands hundreds of miles downwind from the test site, and consequently high radiation exposures to the Marshall Islanders (*26*). These exposures of nearby populations (~250 persons) to radioactive fallout resulted in nausea, vomiting, and skin beta burns associated with large external doses (up to 1.9 Gy).[11]

Although inadvertent radiation exposures continued to be documented in the intervening years between 1954 and 1986, most of these were limited in terms of number of individuals affected, and tended to occur in Russian and U.S. research and industrial settings.[12] However, on April 26, 1986, as a treating physician in Kiev, Ukraine, Dr. Alla Shapiro had first-hand experience in managing the care of employees and first responders after the fire and explosion that occurred at the Chernobyl Nuclear Power Station. There were fatalities and injuries at the site, and changing winds allowed for dissemination of dangerous radionuclides across many parts of world. Triage care provided to casualties within the first 36 h included antiemetics, symptomatic treatments, sedatives and potassium iodide (*27*). Twenty-two patients died 14–34 days after exposure and in twenty of those fatalities, beta burns were the main cause of death. An additional five patients succumbed from 48–99 days postirradiation, which is after the bone marrow recovery stage. Although 13 patients received bone marrow transplants, 11 of them died. Concomitant skin burns were thought to be a contributing factor as to why the transplants were seemingly ineffective. Both early and late skin lesions were noted in patients, which included erythema, edema, blisters and ulcers (early) as well as pigment alterations, atrophy, keratosis, non-healing ulcers and fibrosis (A. Shapiro). In addition, basal cell carcinomas were noted in some patients years after the initial radiation exposure.[13]

There were some interesting skin pathologies noted in those with radiation skin injuries. For example, the face and wrists were found to be the first areas affected, followed by the neck and feet, and then torso. Presence of wrinkling in those areas is thought to be the cause of the early reaction after the burn was produced. Also, burn severity was found to be worse for those individuals who worked the night shift at the plant. Because the accident occurred at 1:23 am, night shift employees, without access to locker room keys, could not obtain clean and dry uniforms, and therefore spent significant time in uniforms drenched in radioactive water (A. Shapiro). The most severe skin lesions were observed in patients who also had severe radiation-induced myelosuppression and GI syndrome.

Early skin injuries led to chronic skin syndromes in several patients (A. Shapiro). Skin ulcers were found to be progressive and often complicated with infections. Late manifestations included keratosis and fibrosis as well as hyperpigmentation and telangiectases (even after 15 years had passed). Although significantly more advanced than the crude remedies that were used in Japan in 1945, there were still many aspects of the treatment of the Chernobyl

[7] https://bit.ly/2AuB0NJ.
[8] https://bit.ly/3cXPl29.
[9] https://bit.ly/3hiMHYq.
[10] https://bit.ly/2XT01ek.
[11] https://bit.ly/2XUwTTO.
[12] https://bit.ly/3fj5alV.
[13] https://bit.ly/2MSVmTa.

accident victims that were experimental. Systemic treatments to address the radiation and thermal burns included hemoperfusion, plasmapheresis, continuous heparinization, and administration of fresh frozen plasma. Local treatment of skin injuries consisted primarily of combutec-2 (a polymer formulation based on soluble collagen with antibacterial elements to promote skin regeneration) (*28, 29*). Lioxazol, an approved spray that was composed of a combination of hydrocortisone and topical antibiotic, was also applied. Pain management was challenging and not effective due to a scarcity of local anesthetics, and in some cases, there was a need for early-stage surgical interventions (*2, 27, 30, 31*). Although not used at the time of the Chernobyl incident, Indralin, an α1-adrenomimetic radioprotector (*32–34*) is also now approved in Russia for the treatment of radiation victims, and alongside Lioxazol, is part of a standard, anti-radiation first aid kit on hand at the site (*30*). There were many lessons learned in Chernobyl about the nature and progression of CRI. What was unexpected was the diversity of clinical manifestations of skin lesions and unrecognized course of clinical stages of radiation injury to skin. Because of the significant severity of injuries that were noted, there was a pronounced influence of skin burns on the general state of a patient. Finally, more surgical operations than anticipated were required at an early stage of the injury. The take-home message is that a nuclear accident anywhere has the potential to be a nuclear accident everywhere, as evidenced by the Chernobyl experience, which also revealed that safety culture at radiation/nuclear facilities requires constant assessment to prevent equipment malfunction and human errors. It is also important to note that the presentation and manifestation of radiation skin burns differ from thermal burns, and that novel, multidisciplinary therapeutic approaches for treating victims of radiation accidents open new prospects in the field of medical care for future radiation casualties.

Radiation cutaneous injuries resulting from industrial accidents. The Institute for Radiological Protection and Nuclear Safety (IRSN), under the joint authority of the Ministries of Defense, the Environment, Industry, Research, and Health in France is the nation's public service resource for nuclear and radiation scientific and technical activities. The IRSN, together with the Hôpital d'Instruction des Armées Percy (Percy Hospital) in Paris have a broad and unique experience working together to address CRI in humans. Radiation accidents present certain distinctive characteristics, which explains why healthcare management is so complex, and harmonization of the methods of diagnosis and treatment is needed (R. Tamarat). In 2001, a manual was published by expert scientists evaluating worldwide victims of radiation accidents (*35*). Several of the case studies highlighted in that publication, as well as a few cases that have occurred since that time, were presented to demonstrate the severity of cutaneous injuries that might be observed after a radiological or nuclear incident. In general, radiation burns are not thermal burns, and therefore, standard clinical burn treatments may not be appropriate to radiation-induced lesions (R. Tamarat). For example, radiation burns are a dynamic process: they evolve over time in successive inflammatory waves, making prognosis difficult because the development of lesions is often delayed. Further, wound healing takes a long time, and closed wounds are often fragile and unpredictable. Perhaps the most challenging difference is that the pain resulting from a radiation skin wound is often resistant to opiates, which can lead to psychological crises for the patients.

The first case study presented involved a radiation exposure at the Yanango Hydroelectric Power Plant in Peru on February 20, 1999 (*36*). During a gammagraphy assessment of a pipe being repaired, a source pigtail became detached from the equipment. The welder placed the iridium (Ir)-192 source in his pocket and began to experience pain at the end of the day. Preliminary dose estimates showed high localized doses to the welder and low doses to his family and other persons. Persistent complications ensued, along with moderate to severe lumbar pain and necrosis by day 72. Unfortunately, that patient continues to suffer skin complications and chronic pain, even 20 years later (R. Tamarat). In the second radiation exposure case, which occurred after an incident in Lilo, Georgia in 1997, soldiers found a sealed radiation source in the forest, which was then placed into a jacket pocket (*37*). As a result, one patient was hospitalized in France on the 25th day after exposure. After four excision procedures, five skin autografts and one omentum flap, the wound finally closed; however, due to the chronic and latent nature of radiation wounds to the skin, the patient returned to France 22 years later, and was treated again (*38*).

The third radiation accident that was documented occurred at a building site for a cellulose manufacturing plant in Nueva Aldea, Chile on December 4, 2005 (*39*). In that incident, involving arc welding quality control, an Ir-192 source was found outside its storage container. A worker held the source in his hand then transferred it to his pocket, with the total time of exposure estimated at 40 min (1,900 Gy skin surface exposure) (*40*). The patient was transferred to the burn treatment department of Percy Hospital, and a new dosimetry-guided surgical approach was used to examine the pathology of the lesion after removal (*41*). Although the victim continued to experience superficial erosions on occasion, years after the exposure, the skin was essentially fully-healed in the exposed area. Significant in the Chile case was that a new treatment approach was tested involving mesenchymal stem cells (MSCs) derived from autologous bone marrow expanded *ex vivo*, that were then re-injected into the site of the irradiated wound (*42*). These highly proliferative stem cells have the capacity to acquire the morphology and function of damaged resident cells, as well as the capacity for growth factor production, immunotolerance and multipotentiality (they can become bone cartilage, muscle, stroma, tendon or

adipocytes). Using a cell therapy unit for clinical-grade MSC production approved by the French regulatory agency (CTSA, Percy Hospital), cells are harvested and cultured for ten days, and are then selected for MSC differentiation and amplified for injection. These cells have been used along with other treatment modalities such as wound dressings or skin autografts (R. Tamarat). Improved progression of healing was observed in patients given these cells, as evidenced by their successful use in the treatment of a hand injury, which resulted in complete functional recovery and a dramatic decrease in pain for the patient (*5*).

In the fourth human radiation accident case considered, another Ir-192 source for arc welding quality control was found outside a storage container in Francisco de Orellana, Ecuador on April 12, 2009. Three spots appeared on the leg of the victim after exposure, and he was hospitalized in France later that month. Dosimetry-guided surgery and phantom reconstructions were also used to treat this patient; however, additional lesions continued to appear, and the initial injury was not improving. For this reason, at day 38 after exposure, physicians pursued more excisions, skin grafts and ultimately MSC injections into the wound site, which were repeated on day 51. Additional skin transplants on day 65 finally led to healing of the CRI.

In the final case report presented, involving an Ir-192 source accident in Dakar, Senegal in 2006, a patient was sent to Percy Hospital for assessment (including dose reconstruction) and treatment 29 days after radiation exposure (*43*). His hematopoietic acute radiation syndrome was successfully treated with cytokines, which led to recovery of his bone marrow (*44*); however, he had also suffered radiation burns that led to moist desquamation on his left arm (*45*). By day 63 postirradiation, the wound had extended from his shoulder to elbow, and was associated with intense pain. Treatments were initiated using a standard surgical approach that included use of a dermal substitute and skin autograft. The spontaneous evolution of the wound was marked by whole dry necrosis involving the underlying muscles. The patient was also treated with the autologous MSC therapy that had been successful with the patient from Chile detailed above (*5*) as well as conservative surgery. Dose reconstruction estimated 70 Gy at the surface of the skin. Multiple treatment attempts also included a skin flap that eventually became ischemic and necrotic. Finally, after multiple MSC therapies and skin grafting, the lesion finally healed, and the pain disappeared.

Although the above case histories represent small-scale exposures, they are informative in that they provide insight into the predictable complexity of a mass casualty incident. In addition, follow-up with some of the patients suggests that radiation necrosis can re-appear even years after the initial exposure, reinforcing the need for long-term monitoring. For this reason, it is critically important to prepare, conduct and evaluate exercises to test preparedness for response to nuclear and radiological emergency, and be prepared to spend many years engaged in medical follow-up.

Radiotherapy and fluoroscopy-induced cutaneous injuries. Skin injuries from radiotherapy continue to be a problem despite technological advances in these kinds of cancer treatments, and there are currently no effective treatments to prevent or reduce radiotherapy-associated skin reactions (J. Ryan Wolf). Acute skin reactions (radiation dermatitis) are a commonly observed toxicity from radiation therapy (*46*); however, there is larger variation in late effects such as fibrosis, with incidence ranging from 6–85% (*47*). Treatment- (dose, body location, fractionation) and patient- (age, gender, obesity) related factors contribute to severe radiation-induced skin injuries. Skin reactions from radiotherapy are most common in patients receiving radiation to the neck, face, upper chest or back, or extremities. The clinical rating scale most commonly used for radiation dermatitis is the NIH Common Terminology Criteria for Adverse Events (CTCAE), which has five grades of severity, ranging from light erythema (grade 1) up to ulceration/skin necrosis (grade 4) and death (grade 5). Approximately 20–25% of radiotherapy patients experience grade 3 or 4 skin reactions. A major need in this field is a more objective and quantitative way to measure severity of radiation dermatitis rather than multiple, subjective clinical rating scales (*46*). Radiation skin injury presents in various stages depending on the dose to the skin and length of time exposed, with hair loss, erythema or hyperpigmentation, dry and moist desquamation, weeping, and ulceration possible (*48*). After fractionated radiation doses >45 Gy, late or chronic radiation skin effects such as continued ulceration, atrophy, fibrosis, and telangiectasia may be noted even years after exposure. Radiation-induced skin fibrosis results from overproduction of connective tissue and can also be caused from infections, implants, autoimmune disease and tumors (*49*). In 2001, Schmuth *et al.* (*50*) showed that trans-epidermal water loss, a functional measure for epidermal integrity, increases as the severity of radiation dermatitis increases. These increases are temporary, and the skin barrier is often able to recover. Radiation burns are not thermal burns in that they have a dose-dependent clinical pattern in skin breakdown, and inflammatory waves can occur for weeks to years after exposure. Radiation recall is another skin complication seen in radiotherapy. It is an uncommon and unpredictable inflammatory reaction that is confined to a previously irradiated area that is triggered by a systemic medication, such as chemotherapy or antibiotics (*51*).

Radiation skin injury can also occur from fluoroscopy procedures that use X rays. In fluoroscopy, such as that used during cardiac catheterization procedures, an X-ray beam contributes its high dose at and within a few centimeters of the skin surface, with a normal initial presentation of a rash within a week of a procedure, which can then progress and persist. Within a year, patients have presented with non-healing ulcers diagnosed as fluoroscopy-induced chronic

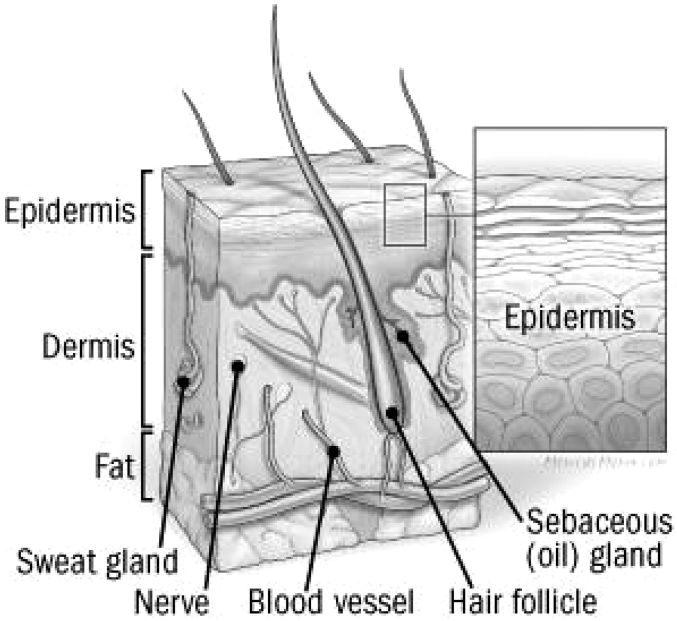

FIG. 1. Cross-section representation of the skin.[19] The three major layers of the skin are shown, along with underlying structures.

radiation dermatitis. Standard care is often in the form of topical steroids and surgical debridement, with or without skin graft. Fortunately, these kinds of adverse fluoroscopy reactions are now uncommon, due to limitations on the length of time for fluoroscopy procedures or repeated procedures in the same area (*52, 53*).

In terms of mechanism, radiation skin injury is a complicated process involving an imbalance of antioxidant status and redox control of wound healing, as well as chronic inflammation (Fig. 2). Radiation skin fibrosis is a result of chronic inflammation from tissue injury in which there is an immune imbalance that causes release of profibrotic cytokines (*54, 55*). Overall, an effective therapeutic would be one that targets more than one aspect of the immune system (*48, 56, 57*).

Until recently, standard medical management for radiation therapy-associated dermatitis has consisted of washing the area and applying water-based moisturizing creams. In a recent clinical trial, 16 different topical, standard-of-care treatments were utilized at six different cancer sites (J. Ryan Wolf). The most commonly used topicals were Aquaphor®, Silvadene®, and topical steroids, based on the results of a study addressing high-grade dermatitis in patients who received radiation therapy after a mastectomy (*58*). To date, there is little consensus on topical agents that could provide alleviation of symptoms, although a few approaches have been studied, including pentoxifylline and alpha-tocopherol in combination (*59, 60*); silver nylon dressings (*61*); hyaluronic acid (*61*); Silvadene (*62*); epidermal growth factor (EGF) (*63*); and statins (*64*). Another novel treatment for skin fibrosis is visible red light, which decreases

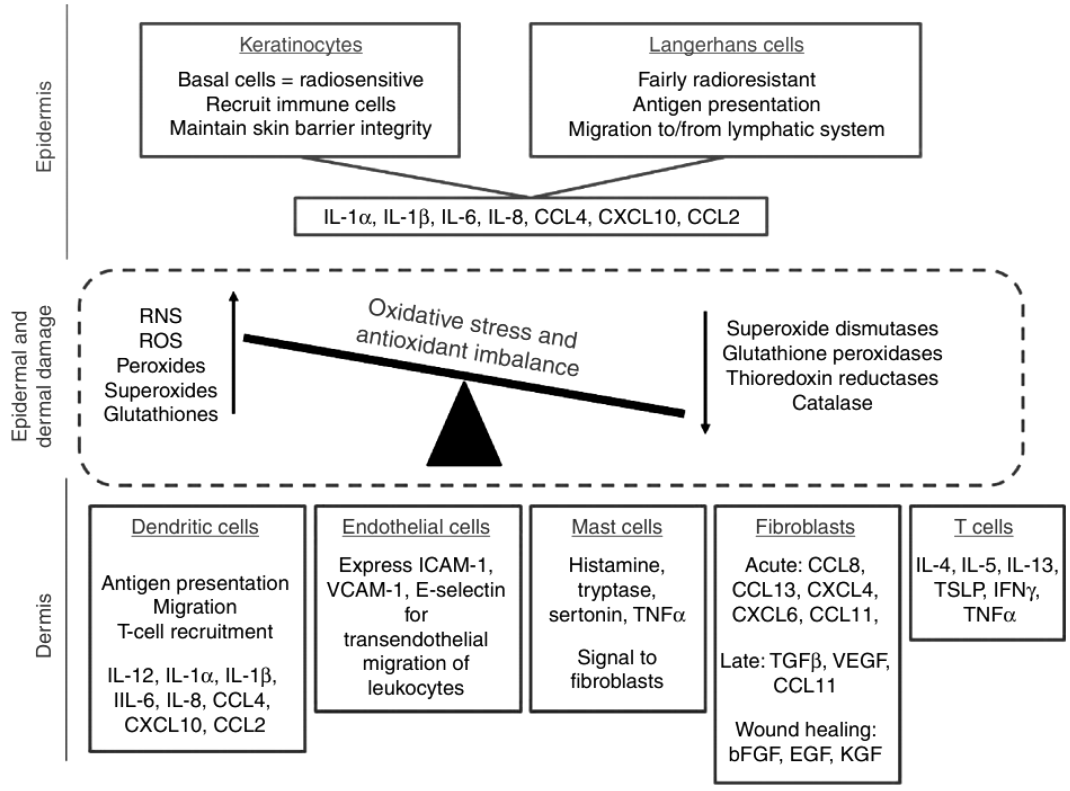

FIG. 2. Tissue mediators of radiation skin effects. Shown is a schematic identifying the key cells and mediators involved in radiation skin injury. (Reprinted with permission, J Invest Dermatol 2012; 132/3, part 2:985–93; Ryan JL. ''Ionizing Radiation: The Good, the Bad, and the Ugly'')

collagen production and fibroblast proliferation (*65*), and is cleared by the FDA for acne and herpes infections. Further development of therapeutics addressing the skin microbiome could be beneficial, since microbiota and immune cells both respond to skin damage, and harnessing both could lead to accelerated and scarless healing (*66*). Given the similarities in injuries that occur in human cancer patients and some low-level CRI reactions, radiotherapy-induced dermatitis in the clinic could potentially provide insight into developing models for CRI. In addition, more studies on the skin microbiome, wound healing of other clinical complications (e.g., diabetic ulcers) and chronic skin diseases such as psoriasis may help identify effective therapeutics.

Clinical experience in thermal burn. Autologous keratinocyte spray-grafting represents an innovative investigational approach for potential use in the treatment of radiation skin burns in humans (J. Gerlach). Skin anatomy is made up of the epidermis, dermis, with underlying fat, and lower levels of muscle and bone (Fig. 1). Radiation burns are most problematic in the lower layers because cells in the upper layers are either dead or viable but not dividing. Because the basal layer (stratum basale) contains stem and progenitor cells, it represents the greatest interest for radiation burns (*67*). Standard therapeutic options to address skin wounds include full-thickness skin grafting, split skin or mesh-split skin (allows for stretching of the graft), micrografting skin cubes (1 mm), and more recently, single-cell spray-grafting. Culturing keratinocytes in sheets and then applying to the wound is also an approach, but these grafts do not always take, and the closure can be thin and vulnerable (*68*). In addition, keratinocytes have a high division rate, but during culture, stemness of the cells can be lost, resulting in transplantation of primarily more mature keratinocytes. In contrast, epidermal stem/progenitor cells from the regenerative basal keratinocyte layer can be isolated and sprayed onto the wound where they can then increase in size, divide, and differentiate within the site of injury. To achieve this, cells for spray-grafting are isolated by enzymatic digestion and then sprayed onto the wound bed (*69*). Current investigational work has focused on the development of the stem cell spray devices. Although this approach might work well for first- and second-degree burns, third-degree injuries require mesh grafting.

It is important to note that the source of the cells is defined by different patterns of surface markers. Ideally, cells should be isolated from the dermis as an autologous source (J. Gerlach). These cells behave *in vitro* in the same way as MSCs from other sources, in that they differentiate into adipocytes, chondrocytes and osteocytes. Case studies have been published describing the experience with spray grafting in over 71 patients (*70, 71*), and the treatment has been evaluated in a number of different burn etiologies, including flame, scald, grease, chemical and electrical, among others. Experimental results were successful independent of the cause of the injury, suggesting that spray grafting might be extrapolated for use in the treatment of radiation burns. Another approach for potential skin wound treatments is the use of active wound dressings (with inflow and outflow fluids) to enable tissue engineering in the wound. These technologies could be brought to bear in healing of mild first- and second-degree radiation burns. These novel dressings regulate the chemical environment of the wound (e.g., pH, electrolytes, nutrition), remove debris, and allow for the provision of regenerative factors and local antibiotics (*72*). In summary, there are a number of innovative investigational technologies that are being developed to address thermal burns that could have applicability in the treatment of radiation-induced skin injuries.

Clinical experience in chronic wounds. There exists overlap between studies of chronic wounds resulting from disease states, such as diabetes, because radiation burns often involve the vasculature, as do diabetic foot ulcers. There are a number of underlying factors in the development and progression of diabetic foot complications, which involve neuropathy and local trauma, and can lead to skin ulceration in ~25% of cases. These ulcers often become chronic wounds that do not heal normally because of poor blood flow, structural imbalance, infection, edema and poor glycemic control. In some instances, the failure of these wounds to heal is a risk for limb loss. In diabetic wounds, vascular disease of both the macro- and microvasculature is predominant. Involvement of major blood vessels bringing blood to the site of injury is classified by angiosomes (specific areas of the skin supplied by a single vessel; direct perfusion). Radiation is known to cause macrovascular diseases through activation of cytokines and recruitment of inflammatory cells and can also lead to stenosis in the larger blood vessels. Clinically, it is important to define wound healing, which is commonly referred to as complete epithelialization and restoration of sustained functional and anatomical continuity for six weeks after healing (*73, 74*). Chronic wounds have multiple risk factors that can be affected by radiation exposure, including poor perfusion to specific arteries and impaired microcirculatory reactivity to stimuli, which can make it difficult to predict which wounds will heal. Other factors include narrowing of larger arteries and structural deformity due to scarring and edema.

There are several classification systems commonly used for assessing wounds resulting from diabetic complications, with the wound, ischemia, and foot infection (WIfI) model being preferred by clinicians as an accurate predictor of wound healing. In this scoring system, all three individual components of the skin complication are individually graded on a scale of 0–3 to generate a composite score and clinical staging (*75*). Wounds are graded based on ulcer, gangrene and clinical description; ischemia is graded 0–3 based on perfusion and ankle and toe pressures, and infection is graded 0–3 (none to systemic inflammatory response). This system has been used by other researchers to accurately predict the probability of wound healing (*76*–

79). In summary, there is a wealth of knowledge that can be accessed from both the human radiation experience of accidental and clinical exposures, as well as from existing practice of medicine for other types of skin injuries, such as thermal burns, and chronic, non-healing wounds. Learning more about how wounds are assessed and treated in these other situations can help guide the selection of the best approaches to address CRI.

Session 2: Radiation Sources and Animal Models of Cutaneous Radiation Injury

When embarking on studies to look at mechanisms of radiation-induced skin injuries, biomarkers for severity of damage as well as testing of MCMs, it is critical to select animal models that both match the proposed action of the approach to be tested and represent anticipated human responses. As discussed above, data from human exposures has its limitations, in terms of dose of radiation received and inter-individual variabilities in response. Animal models, however, represent a means of studying radiation-induced skin damage that can be closely monitored, and damage is more uniform than that seen in humans due to the fact that the radiation exposure is closely controlled. In this session, different species of animal and human skin models, both *in vivo* and *in vitro*, are considered, as well as different means of creating radiation-induced injuries.

Cutaneous radiation injuries created using different radiation sources. Before embarking on a new study to investigate cutaneous radiation injuries, it is important to first consider how the radiation-induced skin damage will be generated. There are many ways to induce radiation skin injury. For example, sunburns are a simple case study that can manifest injuries ranging from first degree (erythema) to second degree (blistering) and third degree (necrosis). Although ozone blocks some of the ultraviolet light that reaches Earth, and application of sunscreen can block even more, radiation from a weak energy source (like the sun) can still create burns of concern. There are other, more powerful radiation emissions from sources such as Co-60 and Cs-137, which are gamma-emitters but also emit beta radiation at different energies. Similarly, radiation exposure devices can have different energies. For example, Grenz irradiators (20 kV), orthovoltage radiotherapy units (200–300 kV), and linear accelerators (LINACs) (6–20 MV) cover a large range of X-ray energies. Whereas lower-energy photons have long wavelengths and lower penetration, higher energies have shorter wavelength and higher penetration. All of these details must be considered when designing a model for radiation-induced skin injury.

Researchers at Lovelace Biomedical Research Institute have used a Grenz machine to deliver a dose of 150 Gy of X rays to produce injuries in Göttingen minipigs (W. Weber). Animals were photographed at day 60 postirradiation, and although very little effect of the exposure was seen early on, profound necrosis was noted at later time points for some dose levels. This is because the Grenz device provides a more superficial, surface dose, depositing most of the dose in the outer layers of the skin. In contrast, when a 250 kVp X-ray machine was used, which possesses a ten-fold higher energy, less damage was noted on the surface, but injuries were seen deeper within the skin layers. In fact, pigs exposed to X rays from the 250 kVp irradiator died because of underlying, systemic radiation effects. Similarly, irradiation with a 6 MV LINAC resulted in the need to euthanize animals due to hematopoietic complications within the first nine days, although there were no dermal wounds (W. Weber).

Particles can also be used to create radiation skin wounds, which might better approximate radiation injuries resulting from fallout. Unlike photons, they have a physical mass, and are grouped into alpha (helium nuclei, α) or beta (electron, β) particles. An alpha particle is not likely to result in a full-thickness wound because the particles do not penetrate beyond the top layer, which protects the underlying tissue. However, this kind of particle can be very damaging if it is internalized (e.g., through inhalation, ingestion or wound contamination). Beta particles deposit their energy in the first several layers of tissue, resulting in more external damage compared to photons; however, there is also deeper tissue damage resulting in complex wounds. The presence of particles creates more damage at lower doses compared to photons. The linear energy transfer (LET), or the amount of energy deposited per unit distance, explains why the severity of skin injuries is not always proportional to dose.

In summary, it is important to understand the source that will be used for the radiation exposure. Pure gamma rays will require a large dose to create a dermal wound, while alpha particles as an external beam directed at the surface are less likely to result in a significant dermal wound (for intact skin, alphas do not penetrate the outer dead layer, and thus, do not reach living tissue). Beta particles, which would be the biggest concern in a fallout exposure, have penetration at all dermal levels. Lower doses can result in dermal injuries similar to high gamma doses. In terms of isotopes with multiple routes of decay (beta and gamma), exposure will result in wounds from either of these radiation emissions; however, the beta injuries will be more pronounced due to dermal interactions. The radiation exposure should be relevant to the desired skin injury model (e.g., full- or partial-thickness or combined injury).

Radiation combined injuries. Radiation combined injury (RCI) has been previously defined as an injury that involves both radiation exposure and other trauma. (*80, 81*). RCI can result from a radiological dispersal device (RDD) or a nuclear detonation event. Both the Hiroshima and Nagasaki atomic bombings resulted in many combined injuries, comprising upwards of 39–42% of the injuries noted in victims (*82*). In animal models of burns or wounds combined with TBI, combined injuries reduce survival (*83*). This was demonstrated in a mouse model of skin

wound or burn, combined with photons alone, or a combination of gamma rays and neutrons, in which animals were irradiated and then wounded 1 h later. Survival was assessed at day 30 postirradiation; photon radiation was found to delay the wound-healing rate and skin thickness, a finding that was worse when neutrons were involved (*84–86*). Rodent models may be reasonable for early studies to screen MCMs for RCI. For example, wound areas in the rat correlate well with blood vessel regeneration (*87*), and the use of mouse models of radiation skin injury to determine MCM efficacy by survival and wound healing have been demonstrated (*84, 88*).

Wounding enhances radiation injury-induced biomarker signals from hours to days after exposure (*86*). For example, wounds increase iNOS protein levels in the skin and also the level of some circulating cytokines, primarily pro-inflammatory interleukins and chemokines, and in animals exposed to combined wound and radiation, systemic bacterial infection increased (*85*). Combined injuries were also found to alter blood cell counts in a manner different from radiation or wounding alone. Levels of other serum biomarkers such as c-reactive protein (a marker of chronic inflammation), C3, prostaglandin E_2 and Ig, although variable based on the nature of the injury (wounding, burning or combinations), may represent good biomarkers for these injuries (*89*). A number of drugs have been screened at the Armed Forces Radiobiology Research Institute (AFRRI) for their ability to improve wound healing and survival in an established mouse model for combined radiation injury (J. Kiang). Only a few drug approaches were shown to be successful in accelerating wound healing in the RCI mouse model; these include ciprofloxacin, ghrelin, and bone marrow-derived mesenchymal stem cells (J. Kiang). In summary, wound-induced alterations in levels of circulation blood cells, platelets, cytokines, c-reactive protein, complement C3, IgM, and prostaglandin E2 cause homeostatic imbalances. Clinically, evidence of elevated levels of these factors in blood, taken together with skin biopsy, could be a reliable measure of wound healing prognosis, and agents that target these pathways could be therapeutic for addressing wound healing postirradiation.

Guinea pig model of cutaneous radiation injury. Several companies have approached the FDA for consideration of both their drugs and animal models for approval to treat CRI. US Biotest (San Luis Obispo, CA) has received U.S. Government funding to develop a guinea pig model for CRI, to test their MCM candidate, DSC127 (also called USB001) (*90*). It was important to identify appropriate, large animal models to simulate human CRI and the impact of drug treatments, since rodents are known to have skin properties that differ from humans and can lead to dissimilar permeation of drugs across the skin (*91*). There are a number of reasons that the guinea pig model is a preferred choice for radiation-induced skin injury studies. This rodent species has a skin architecture and thickness that is similar to humans (*92*), in that its hair growth cycle has follicles that grow independently in time (*93*), they are tight-skinned, and therefore have contracture similar to humans (*94*), and their metabolism and bacterial responses are also similar to humans (*95*). The company has used the Dunkin-Hartley guinea pig, an albino strain derived from the short-haired English guinea pig, as their animal model to assess MCMs for radiation skin injuries under the Animal Rule (K. Rodgers).

The device in use for US Biotest radiation exposures is a 50 kVp X-ray machine (*90*), which is optimized to administer low-penetrating radiation (50% of the radiation energy deposits at 3 mm) (K. Rodgers). Lead shielding is used to restrict radiation to a specific area of the skin. Prior to irradiation, fur is removed by shaving and then the skin is depilated using Nair™. During the study described, it became clear that it is of the utmost importance to be mindful of how the wounds will be cared for in any animal model of skin injuries. For example, guinea pigs are known to scratch their wounds if they are unbandaged, and therefore, hygiene must be carefully considered. Great effort was devoted to designing the bandages used for the wounds. Given the nature of these experiments, animal care concerns need to be incorporated into the study design, along with humane end points for euthanasia (if applicable).

Among the available visual scoring scales (Table 3), U.S. Biotest scientists selected the Kumar scale to assess the extent of injury in the guinea pigs, ranging from a score of 1.0 (no effect) to 5.0 (full-thickness, open wound), with scoring increments of 0.5. This scoring system has been used historically in animal models of skin wounds (*96*). In addition to the Kumar scale, the Radiation Therapy Oncology Group (RTOG®) Clinical Assessment System for Cutaneous Radiation Injury (*97*) was also utilized to assess severity of damage in the guinea pigs, to more closely align with scoring used clinically. Unlike the Kumar scale, the RTOG system has a six-point-range scoring scale (0–5); however, it has a more compressed scale with only integer scoring and includes death as a score of 5. US Biotest researchers established a natural history of their CRI model by exposing animals to localized radiation doses ranging from 23–79 Gy. They found they could achieve severe radiation-induced skin ulcerations in the model and observed improvements in healing when wounds were treated with their product, USB001, when initiated either at start of erythema or at loss of dermal integrity (*90*). They also established an in-house histology scoring system, which incorporates aspects of epithelial integrity, blood vessel presence, depth of collagen damage, inflammation and quality of adipose tissue. Using these end points, the group established the ability to treat irradiated skin with USB001 to reduce inflammation in the upper dermis (*90*). The company has developed a severe CRI guinea pig model and has shown efficacy of their drug by visual and histologic assessment, and reduced expression of inflammatory cytokines. Researchers concluded that this full-

TABLE 3
Different Skin Injury Scoring Scales Discussed at the Meeting

Scale name	Preclinical or clinical	Features	Ref.
Common Terminology Criteria for Adverse Events (CTCAE)	Clinical	Scoring ranges from grade 1 (light erythema) to 5 (death)	(*47*)
Wake Forest University (JD Bourland)	Clinical	Scoring ranges from grade I–IV; correlates in-person and pictorial scoring; measured features are erythema 0–6, and moist desquamation 0–3.	(*107*)
Erythema and moist desquamation	Clinical	Scoring ranges from 0–4 based primarily on redness, swelling and peeling of the skin	(*99*)
Acute Phase Skin Scoring (Dion)	Preclinical	Scoring ranges from 1.0 to 5.0 (0.5 increments) based on erythema, desquamation (dry and moist), necrosis and loss of dermis	(*148*)
Kumar	Preclinical	Scoring ranges from 1.0 (no effect) to 5.0 (full-thickness, open wound), with scoring increments of 0.5	(*96*)
METREPOL	Clinical	Scoring ranges C1–C4; based on erythema, sensation, swelling, blistering, desquamation, ulcer, hair loss, and onycholysis. Does not incorporate pain assessment	(*127*)
Radiation Therapy Oncology Group (RTOG)	Clinical	6-point range scale; 0 = no injury to 5 = death. Scoring on atrophy, pigmentation, telangiectasia, hair loss, ulceration	(*97*)
University of Texas San Antonio Diabetic Wound Classification System	Clinical	Wounds graded by depth (0–III). Divides based on vascular complications or infections and dept of necrosis. Four stages within each grade (non-ischemic clean, non-ischemic infected, ischemic, infected ischemic	(*170*)
Visual Analog Scale (VAS)	Clinical	Scale based on erythema, dry and moist desquamation and ulceration	(*100*)
Wound Ischemia and foot Infection (WIfI)	Clinical	Scores from 0–3 in each assessment area in patients with diabetic foot ulcers; Vascular assessments are wounds (ulcer, gangrene) ischemia (perfusion), and infection (none to systemic)	(*75*)

thickness ulceration model provided a replicable injury for which clinical and histological assessment of severe CRI was possible.

Porcine (minipig) skin radiation injuries. In animal model development conducted at AFRRI, large animal species have been studied as potential models for human skin injuries caused by radiation (M. Moroni). Specifically, CRI in the Göttingen minipig strain was modeled on a documented human radiation accident involving skin injuries, which occurred in Maryland in 1991 (*98*). In this accident, while conducting maintenance on an accelerator, a technician received radiation exposure to his hands, feet and head from the beam. This exposure led to severe damage to the hands, resulting in amputation of affected fingers. In designing the minipig model, researchers attempted to recreate injuries that paralleled those observed clinically, through delivery of 50 Gy to the back of the animals, resulting in non-healing, partial- to full-thickness CRI. The use of 4 MeV electrons generated by a LINAC, in conjunction with a 1 cm bolus material, limited the damage to the epidermal and dermal layers. Six sites per animal were irradiated, and animals were monitored for 90 days, with clinical observations and wound scoring, blood samples and histopathology conducted. The lesions that formed in the minipig were compared to the lesions suffered by the Maryland accident victim and were found to correlate closely in terms of severity and timeline. During model development, lessons learned included the need to produce a level of injury from which recovery was possible, to understand the nature of the lesions, including predictability from experiment to experiment. There were several sources of variability identified, which included the cells affected in the pig skin and the immunological status of the animal,[14] as well as radiation quality and radiation scatter from nearby bones underlying the skin. To move beyond a clinical description of the injury toward a more quantifiable outcome, a combination of imaging, histology and other novel methods (e.g., planimetry, color image analysis, ultrasound, thermography, MRI, etc.) were employed. Kumar scoring and other methods, such as an adapted Visual Analog Scale (VAS, based on erythema, dry and moist desquamation and ulceration) were also considered (*96, 99, 100*). Common pathologies in the Göttingen minipig included erythema, edema, inflammation, vascular damage, tissue necrosis, alopecia, fibrosis, thinning of the epithelial layer, and loss of hair follicles.

In working with this model, it became clear that extra care was needed when obtaining skin biopsies and that more non-invasive methods would be preferred. Furthermore, progress of wound healing needs to be determined across

[14] https://bit.ly/3cV2XLQ.

various depths of skin to ensure stable healing. In discovering appropriate biomarkers to use as a determinant of healing, some cytokines, including TGF-β1, appeared to be upregulated after injury, which is known to lead to delayed healing (*101*). In summary, the Göttingen minipig appears to be suitable to study CRI, since the lesions generated by radiation exposure are similar to those seen in humans. Development of this model has established end points that may be applicable to assessing the severity of skin injury and studying the efficacy of MCMs to mitigate CRS.

Porcine (Yorkshire) skin radiation injuries. White pigs are relatively well-characterized in terms of the similarity of their skin to humans and are easily trained for handling (*102*). They are frequently used for study of drug efficacy for many dermatologic indications including vitiligo, necrosis, burns, wounds and melanoma (*103*). Several strains of these animals have been used in radiation skin research dating back to the 1980s (*104, 105*). More recently, the Yorkshire pig has been studied for its ability to demonstrate significant improvements in skin healing with MCM administration after exposure to a beta radiation source (J/D. Bourland). Researchers at Wake Forest University using this animal model have developed a unique beta irradiation device that is composed of an array of Sr-90 sources (*106*). Radiation emissions from this novel device, tested using ionizing chambers and film dosimetry methods, show good uniformity, with a dose rate of ~2.64 Gy/min. Dose profiles were found to have acceptable homogeneity, flatness and symmetry.

In this model, animals are irradiated in ten circular areas (five per side, 10 cm^2) and then treated at day +35 postirradiation with an MCM (*107*). Radiation doses evaluated have ranged from 16 to 42 Gy. Evaluations are done until day +70, at which time strip biopsies are collected, images are scored, and histology is conducted. CRI symptoms progress reliably from epidermal degradation to moist desquamation with exposure to doses in excess of 24 Gy. The progression of CRI is most pronounced at the highest radiation doses, with scabbing noted between +35 and +46 days postirradiation (*107*). A unique, on-screen image-scoring technique is conducted using both an erythema and moist desquamation scale, with a consensus score then derived. This method, conducted in a single laboratory, reduces bias, allows for more independent scorers to be utilized, and shows good correlation when compared to in-person scoring. Other scoring modalities have also contributed to the overall assessment of the wound, including histopathology and planimetry. The Wake Forest University research group is currently working toward development of Good Laboratory Practice (GLP) capabilities to continue to carry out this work, in the hopes of making the model the basis for advanced development of an MCM for CRI.

Alternative skin models. Although a number of appropriate animal models for the study of CRI have been published, they are still just models of the human situation. Therefore, there is still knowledge to be gained by using alternative human skin models (e.g., *in vitro* constructs), to more fully understand radiation responses in human skin. More than 50 different kinds of cells make up the complex structure of human skin, in addition to other components such as vascular, neuronal and immune (*108*). Advances in tissue engineering have provided additional models for the study of the human skin radiation response (D. Citrin). Several models that were considered included human and animal cell lines, organoids, full-thickness skin, tissue chips, 2-D and 3-D models and dermal equivalents. As with *in vivo* models, the goal of these alternatives is to more closely simulate human skin, minimize animal use, and allow for less expensive screening of potential MCMs. Epidermal models, such as one in which a bed of cells is scratched to simulate injury, are able to discern decreased wound healing capacity (*109*), and other 2-D cell models assess wound healing by measuring contraction of a gel in which the cells are grown (*110*).

There exist several commercially-available, 3-D tissue products, which usually have both a dermal and epidermal layer, along with an air/liquid interface. These include EpiDermFT™, Phenion® FT Model, StrataTest®, Hyalagraft 3D, Apligraf and Tissue Tech Autograft. In addition, one study on how matrices can be used to heal wounds used a biopsy punch of human skin, which was injured and then used to test different dermal substitutes (*111*). One of the problems with these *in vitro* models is that they often lack supporting cells (e.g., dendritic, Langerhans, endothelial, mast, and T cells as well as the skin microbiome) that play a critical role as mediators of radiation-induced tissue injury and repair (Fig. 1). Although many alternative *in vitro* platforms allow for evaluation of histologic outcomes like collagen accumulation and fibroblast proliferation (*112*), it is difficult to reproduce other skin responses commonly observed in patients, such as vascular leakage, hemorrhage and infiltration of immune elements (*113*). To address these potential confounders, tissue engineering using human constructs has led to the development of 3-D printed models, in which the various structural elements can be layered (*114*). Using induced pluripotent stem (iPS) cells to create both animal and human skin organoids also provides models that more closely resemble human skin and its niche elements; however, these models lack the influence of the immune system. Although these alternative approaches do have limitations, they are nonetheless useful in understanding aspects of CRI, especially those dealing with structural damage.

There currently exist many *in vitro*, *in vivo* and *ex vivo* surrogate models that are available to conduct preclinical studies on different aspects of CRI. Some of these models are more appropriate for determining a mechanism of action of the radiation-induced injury, whereas other models may be better used to pursue studies for MCM efficacy that could provide necessary data for drug approval.

Session 3: Assessment Methods to Determine Extent of Skin Injuries

Moving beyond scoring paradigms to determine the depth and severity of CRI, talks in this session focused on other novel means of assessing skin wounds, with presentations and discussions focusing on imaging modalities, clinical grading and histopathological assays, as well as functional outcomes, such as mechanical means of determining strength of healing.

Overview of wound imaging methods. In bringing a skin imaging device to the market, it is important to establish a consistent regulatory strategy. This necessitates an understanding of how the device will be used (e.g., systemic versus topical; invasive versus non-contact) and if it will mimic an existing clinical or pathological assessment or a new measurement (N. Ogden). In addition, one must determine in what setting (e.g., in the field or in the lab) use is anticipated, since the regulatory pathways can vary based on these factors. There have been a number of technologies for general skin imaging that have been reviewed by the FDA, including optical approaches, Raman, OCT, laser doppler, laser spectral, hyperspectral, near infrared, spatial frequency domain, fluorescence and photoacoustic. Although there are numerous steps associated with clearance of a device for CRI, demonstration of ''levels of evidence'', typically stand-alone clinical data showing performance, is at the center of any effort.

Data requirements that need to be addressed for a device to be reviewed by the FDA include device labeling, performance specifications, an understanding of any tissue effects (e.g., increased temperature or blood flow), clinical validation of detection and valid scientific evidence. The latter requirement has been defined in 21 CFR 860.7, which states ''Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.'' [15] There are a number of devices that have been cleared for wound imaging to date,[16] including:

1. Old Tech Verge Videometer provides 3-D volume measurements for wounds.
2. moorLDl Laser Doppler Imager is used for blood flow studies in a range of clinical research applications.
3. Visitrak™ System (Smith and Nephew) uses a template to calculate wound area and can also determine wound depth.
4. Silhouette® (ARANZ Medical) is used for wound measurement and documentation.
5. Aimago Easy LDI is used for blood flow measurements in the microcirculation.
6. SpectralMD™ DeepView™ Wound Imaging System (Spectral MD) is used for studies of blood flow in the microcirculation.
7. WoundVision Wound Measuring and Monitoring System is a combination digital and infrared camera that provides a measure of wound and body surface data.

Optical imaging technology for wounds represents an emerging field in many medical applications, particularly coupled with dermatology diagnostics (*115*); however, no devices have yet been cleared for imaging of CRI or radiation dermatitis.

Radiation effects on skin wound tensile strength. Scientific studies to determine the effects of radiation on the skin began in the early 1940s, when Strandquist determined that the effect of radiation on the skin depends on the dose and time of exposure and that fractionation was an important component (*4*). These findings were further supported by work using pig skin that demonstrated the effect of number of fractions of radiation on skin-related radiotherapy complications (*116*). Later, others generated plots to derive injuries resulting from alpha and beta in pig skin (*117*), and Withers (*118*), who developed the first *in situ* clonogenic assay, showed that skin will remain intact (no evolution to moist desquamation) if postirradiation clonogen survival in the skin is approximately 10^{-6} per cm^2. In full-thickness wound healing, the dermis is considered to be a slow-proliferating, late-responding tissue (*119*). Complex tissue responses that occur in CRI are the reason that the dermal tissue is so different from typical acute responses (W. McBride).

A murine model has been developed in which a full-thickness incision is made in the skin and then allowed to heal. Skin from the healed wound is then removed and cut into thin strips. When placed in a device called a tensiometer that applies pressure to and stretches the strip, it is possible to determine the applied force needed to break the wounded skin open again, referred to as the wound tensile strength (WTS). This technique is reproducible (*120–123*) and can measure the strength of healing of the wound in the presence or absence of radiation and MCM treatments. Using this approach, it has been shown that for animals irradiated prior to wounding, WTS (at day-14 after wounding) was 40% lower. In a partial-shielded model (hemi-body irradiation in which only the bottom half of the animal is irradiated), wound healing was found to be impaired. Furthermore, the resulting radiation injury varied depending on whether the radiation exposure was localized to a part of the skin or to the entire body. At lower doses, TBI decreased WTS. Even if more than three months elapsed between irradiation and incision, skin did not recover its tensile strength, despite appearing visually

[15] https://bit.ly/2XUxAg5.

[16] Any reference in this publication to any person, organization, product or service does not constitute or imply endorsement, recommendation or favoring by the U.S. Government.

normal. For this reason, clinicians are often hesitant to perform surgery on preirradiated sites (*124*).

In the progression of wound healing over a five-week period, there are several phases of repair, with inflammation occurring from one to two weeks, tissue formation from two to three weeks, followed by remodeling from three to four weeks. RNA-Seq analysis suggests a complex wound signature with different cell types, and genes expressed (high within the first week, but declining by the end of the second week). There are also processes that occur during healing (e.g., lymphocyte activation, phagocytosis and chemotaxis, vasculature development). Bone marrow-derived mesenchymal stromal cells (MSCs, which are multipotent progenitor cells that can differentiate into fibroblasts, osteoblasts, chondrocytes, adipocytes, myocytes, stromal cells, and may transdifferentiate into vascular/perivascular cells at sites of injury) can home in on damaged tissues. MSCs placed directly into the wound site are under study as a means of correcting radiation-reduced WTS. Use of this cellular treatment approach improves healing of wounds caused after TBI, but for optimal effects, a structure to deliver sufficient cells to the wound site is needed. Research suggests that culturing the MSCs on fibrin microbeads (FMBs) delivered to the wound promotes *in situ* cell proliferation and survival and has also been shown to benefit hair follicle re-growth (*123*). These FMBs are biodegradable and can last two to four weeks *in vivo*. These MSC-FMB constructs are being evaluated to correct wound healing deficits caused by TBI and skin-only irradiation, but they are better at compensating the former, which compromises the bone-marrow derived cellular infiltration. Whereas FMBs are applicable for use in smaller wounds, the technology can be adapted to larger wounds using collagen sheets, which can be fabricated to allow MSCs to be delivered to a larger surface area (*123*). In addition to MSC use for radiation-induced skin wounds, research has focused on a B-Raf enzyme inhibitor, vemurafenib (marketed as Zelboraf® for treatment of late-stage melanoma). The agent causes hyperproliferative responses in the skin, and when added to a radiation wound, might increase healing (as measured by a gain in WTS) via a MAP kinase pathway (*125*).

Diagnosis and medical management of cutaneous injury after accidental exposure to ionizing radiation. In addition to other scoring systems in use to assess skin injuries, METREPOL (MEdical TREatment ProtocOLs for Radiation Accident Victims) grading, which includes scoring for other radiation injuries as well as skin, can be helpful to determine the course of treatment for injured patients during a mass casualty incident (*126–128*). Signs and symptoms for skin injuries are rated from 1 to 4, based on a number of diverse criteria. Classification of skin injuries by colleagues in the METREPOL project provided the first objective system to compare cutaneous injuries observed among different radiological incidents; it is used today with minor modification by clinicians worldwide (N. Dainiak). As a follow-on to the establishment of this scoring system, in 2009, the World Health Organization (WHO) convened a panel of 37 experts (from 13 countries) to rank the evidence for medical countermeasures for management of acute radiation syndrome (ARS) in a hypothetical scenario involving the hospitalization of 100 to 200 victims. The goal of this panel was to achieve consensus on optimal management of ARS affecting nonhematopoietic organ systems based on evidence in the published literature (*129*). The WHO Consultancy discussed approaches for clinical management of radiation injuries, including specific suggestions for treatment of CRI based on an evidence-based review, and made treatment recommendations for radiation-induced skin wounds:

1. Topical class II–III steroids, antibiotics and antihistamines;
2. Silver sulfadiazine cream with non-adherent dressings;
3. Surgical excision of necrotic tissue and skin grafts/flaps/amputation.

Interestingly, systemic steroids were not recommended, unless there is another medical reason for their use, and the panel noted that some products with limited data (e.g., pentoxifylline, α-tocopherol, transforming growth factor-β, fibroblast growth factor, interferon-γ and estradiol) could be viable treatment options. As for the use of cellular therapies such as MSCs, the group found controlled clinical trials were needed to assess their efficacy. One anecdotal report supporting their possible use involved the treatment of an industrial skin wound with adipose-derived MSC. That patient, after receiving hyperbaric oxygen treatments, still experienced wound recurrence and pain, which was resolved (healed lesion and pain decreased) at four months postirradiation after MSC therapy (*130*).

Several human exposures were presented for consideration, which involved internal contamination with radionuclides. The first was the poisoning of Alexander Litvinenko, in which he was determined to have ingested 1,800 Bq of ^{210}Po radiation per gram of skin tissue (*131*). The second was a nuclear worker who experienced skin contamination with ^{238}Pu from an industrial procedure. In that case study, contaminated tissue was excised to remove the isotope (*132*). These human exposures highlight the fact that skin complications arising from radiation are not limited to high-dose, external X-ray or gamma exposures. In summary, assessment of what lies beneath the skin surface is required to inform medical decision-making in humans; this evaluation may include radiological surveys, ultrasound imaging and thermography. Radiation injury to the skin and surrounding tissues may be localized, but a systemic effect may be observed.

Histopathology assessments of cutaneous radiation injury. The skin is not considered to be especially radiosensitive; however, as it is the largest organ, it can be more affected than other areas of the body (D. Barillo). In addition, localized radiation therapy has to transit the skin

layers to be deposited in the deep organs, thus there are inadvertent skin injuries in human patients undergoing cancer treatments. Unlike thermal burns, radiation injury creates a chronic wound that has a large effect on the vasculature, creating ischemia in the tissues and making the damage difficult to address. There have been documented human exposures to radiation fallout that have resulted in beta burns to the skin. For example, beta burns of the feet and neck were noted in one patient one month after fallout exposure from the Castle Bravo 15 megaton thermonuclear test (*133, 134*). In addition, there were beta burns noted in victims of the Chernobyl Nuclear Power Plant accident (*31*).

Generally, histopathology is considered the gold standard for characterizing CRI. In irradiated minipigs, quantifiable measures of CRI include the presence of subepidermal edema, ulceration, collagen thickness, hypodermal changes, presence of vascular damage, and number of hair follicles and sebaceous glands. In pig skin, only a very small proportion of basal cells are stem cells. By giving a sufficient radiation dose to produce moist desquamation in the minipig, at day 21 postirradiation, the number of visible layers in the epidermis is reduced and the dermal ridges that lead to stronger skin are lost. Damage consisting of epidermal hyperplasia and dermis cell infiltration can be revealed with immunostaining (*118*), and biomarkers such as TGF-β1 have been proposed as indicators of inflammatory response and delayed wound healing (*119*). In a Göttingen minipig model of gamma-radiation-induced skin injury, erythema presents in waves. Onset of the first wave tends to occur within 24 h of exposure and lasts several days; the second wave begins between 10 and 14 days postirradiation. This is typically the only presentation for exposures in the range of 2–5 Gy. At higher radiation doses, erythema can be followed by dry (12–20 Gy) and/or moist desquamation (acute dose exceeding 25 Gy or cumulative dose over 40 Gy) at later time points. Ulcerations are also possible in exposures higher than 30 Gy, with necrosis a possibility at doses above 35 Gy. To assess wound severity, there are a number of different modalities that can be considered:

1. Clinical assessment, including photography and documentation of wound size;
2. Planimetry, which relies on digital color photography followed by computer analysis to determine the progression of injury or of healing;
3. Thermography, which is useful as both a research tool and for pre-operative planning;
4. Ultrasound, which is widely available and allows assessment of deeper tissue injury;
5. Histopathology, which is the gold standard, although accessing tissue for staining can be challenging.

The above methods have different situations in which they are most useful. For example, planimetry is objective, quantitative, and can measure the wound area, but assesses only the skin surface. It is useful both in research and in the clinic to document re-epithelialization and wound closure. However, assessment of deeper tissue and microvascular damage may require techniques such as ultrasound, thermography, and light-based imaging. A combination of ultrasound and thermography to image skin lesions has been used to evaluate subcutaneous changes in irradiated animals and human patients (*135*). Optical imaging devices have been used to quantify the 3-D volume of wounds and blood flow in the microcirculation (*115*). Areas of continued research include the use of magnetic resonance spectroscopy and fusion imaging to evaluate skin function (e.g., metabolic changes) rather than structure. Finally, point-of-care ultrasound devices are now widely available, and some versions are now very compact (portable, battery-operated, and hand-held, built on smartphone and iPad formats). Because of the low risk associated with many of these approaches, these devices, which facilitate serial examination, should be further investigated for evaluation of CRI.

Session 4: Regulatory Considerations for Development of Products for CRI

The fourth session of the meeting comprised presentations from FDA staff. To provide consistent information that the FDA considers important to the development of CRI product advancement, the talks are presented here as an integrated narrative. Included in this session were talks on: 1. dosimetry considerations for skin irradiation; 2. study designs and statistical considerations, difficult experimentation for cutaneous radiation injury drug development; 3. non-clinical considerations for drug development under the Animal Rule; and 4. regulation of wound dressing devices and considerations for development of medical devices used for cutaneous radiation injury.

Development of drug products for CRI should include studies of the natural history of disease, radiation dose-response curve, and pharmacokinetics of therapeutic product in animals. The safety of MCM products designed to counter radiological threats is evaluated in healthy volunteers; however, where human efficacy studies of MCMs are unethical or not feasible, the ''Animal Rule'' allows the FDA to grant approval of new drugs or biologics based on efficacy studies in animals, provided that such studies are well controlled and establish the MCM product as reasonably likely to provide clinical benefit in humans (*136*). Generally, the efficacy of the drug product should be demonstrated in more than one animal species; however, it is not necessarily rodent and non-rodent, as the rule is silent on which species is selected. Understanding the natural history of CRI in the animal model is also essential to establishing clinically meaningful end points and the timing of end point measurement. Landmark timepoints include the manifestations of maximal injury, optimal wound healing in response to standard care and investigational treatment, and post-healing timepoints to show durability of treatment effect. Natural history studies should establish a reproduc-

ible injury model with well characterized documentation of the depth and area of the wound based on histological verification. Consideration should be given to supportive care, including adequate pain management, wound debridement when clinically indicated, and criteria for euthanasia.

For clinical studies of therapies for non-healing chronic wounds, the FDA recommends as the primary end point complete wound closure, defined as skin re-epithelization without drainage or dressing requirements confirmed at two consecutive study visits two weeks apart, and durable wound closure (based on follow-up evaluation at least three months after complete wound closure). Complete wound closure of a chronic, nonhealing wound is one of the most objective and clinically meaningful wound healing end points (*137*). The duration of efficacy studies should be long enough to establish the durability of treatment effect.

Desired clinical outcomes in CRI include improvement in survival, reduction in the depth and area of irradiated skin that undergoes necrosis, improvement in healing or ability to achieve durable skin coverage of the wound, and improvement in the quality and durability of the skin repair. Additional outcomes include facilitation of skin closure using surgical wound closure and grafting, reduced time to wound healing or surgical closure, decreased infection at the wound site, quality of healing (e.g., decreased scarring that may improve function, improved cosmesis), and improved wound care (e.g., decreased need for pain management). Examples of efficacy end points in animal models of CRI include the assessment of wound area and depth or the proportion of wounds meeting a minimal level of improvement (e.g., at least x% of the defined area improved); evidence of durability of treatment effect is also necessary.

While complete re-epithelization and durable wound closure is desired, wound healing demonstrated with a meaningful reduction in full-thickness CRI[17] may be considered for product development under the Animal Rule. The demonstration of a defined reduction in wound size may also be considered clinically meaningful, if it can facilitate additional interventions for wound closure. Partial-thickness CRI generally requires the demonstration of complete wound closure/healing. The incidence and time to full closure should be assessed in the animal model in the presence of standard wound care (surgical and nonsurgical). Descriptive end points that do not adequately characterize the depth and area of skin injury (e.g., moist desquamation) are not recommended. Efficacy determination may also include improvements in tissue histology of irradiated sites. Histologic characterization of the wound(s) in the animal model is recommended at pre-specified time intervals determined in natural history studies.

[17] Full-thickness cutaneous radiation injury is defined by the presence of an ulcer, as observed in the irradiated skin, along with the histological measures of loss of epidermis, reduced number of blood vessels, increased dermal inflammation, loss of adipose integrity and collagen necrosis in the dermis.

Efficacy of treatments for CRI may be assessed using either a two-arm parallel design (treatment animals and matched control animals, each with multiple injury sites) or a paired design in which a single animal has treated and control sites in bilaterally symmetrical locations. While the latter is generally more efficient, efficacy gains may be offset by two major drawbacks: blinding to the treatment allocation of skin sites in a single animal is challenging, and contamination of an animal's control sites with the treatment product is a risk for topical studies (*138*). Wound scoring and histopathological evaluation by personnel blinded to treatment are important to minimize bias in an adequate and well-controlled study for Animal Rule licensure. Statistical approaches to account for correlation among skin sites within an animal should be considered. The length of trials and the number of test animals required may be reduced via a two-stage adaptive design approach that uses the same end point for establishing dose response as well as for demonstrating efficacy with the selected dose. Design efficiency depends on how much learning can be gained in stage one, which may also include an improved investigation of the natural history of CRI, in addition to assessing dose-response relationship.

As of 2019, no wound dressing device for CRI has yet been cleared or approved for marketing by the FDA. Wound dressings cleared for radiation dermatitis may be an appropriate predicate device for the 510(k) review of a dressing indicated for the same signs and symptoms in patients with CRI, provided that there are similarities in the primary action of the device (i.e., to provide a moist wound healing environment) and in the health status of indicated patients. Dressing devices intended for severe CRI and comorbidities associated with CRI may not be appropriate for 510(k) review, and additionally, depending on the claims and mechanism of action, other regulatory paths may be appropriate. Wound healing studies in animals are recommended for 510(k) submission when a device is cytotoxic, which may have the potential to impair the natural wound healing process, or when the sponsor elects to evaluate local tissue response in lieu of an implantation study as part of the biocompatibility assessment. Note that the Animal Rule does not apply to devices, as it may be acceptable not to have clinical data for some marketed devices. As an animal model is being developed, it is important to have a conversation with the FDA and demonstrate what the study will look like in terms of model and end points. In closing, regulatory guidance from the FDA should be sought as early as possible, so that resources are not wasted in developing models that would not be acceptable to the agency for the Animal Rule, or another pathway to approval for marketing. Regulators are hoping to understand from scientists the current thinking in their area of research, and what should be incorporated into the regulatory process to make the path to drug approval more predictable and standardized.

TABLE 4
Skin MCM Studies Supported by the NIAID

MCM	Site (mechanism)	Model
Granexin gel (aCT1 peptide)[a]	AFRRI (IAA)	Minipig (CRI)
TP508 (thrombin peptide)[a]	University of Texas Medical Branch, Galveston (SBIR)	Mouse TBI[b] + wound
Nor Leu 3-A(1-7) (angiotensin analog)[a,b]	US Biotest (grant)	Guinea Pig and mouse RCI[b] (thermal)
Antibiotics (cipro, gentamicin)[a]	Multiple (IAA)	IR alone / RCI (burn or wound)
Mesenchymal stromal cells (MSCs)[a]	UCLA (grant)	Mouse
Curcumin (nutraceutical)[a]	University of Rochester (grant)	Mouse
Celecoxib (non-steroidal anti-inflammatory drug) (NSAID)	University of Rochester (grant)	Mouse RCI (wound)
Timolol (beta blocker)	University of California, Davis (grant)	*Ex vivo* human culture – RCI (burn)
Esculentoside-A (Chinese herbal)	University of Rochester (grant)	Mouse IR alone
Granulocyte-colony stimulating factor (G-CSF)	AFRRI (IAA)	RCI (wound)
Ghrelin (hormone)	AFRRI (IAA)	RCI (burn)
CpG-ODN (TLR9 receptor agonist)	Brigham and Women's Hospital (grant)	Mouse IR & RCI (burn)
Ex-RAD (chlorobenzylsulfone derivative)	AFRRI (IAA)	Mouse IR & RCI (wound)
Insulin-like growth factor-1 (IGF-1)	Duke University (grant)	Mouse RCI (wound)
Bone marrow cells	Duke University (grant)	Mouse RCI (wound)
ARA-290 (non-erythropoietic peptide from erythropoietin)	AFRRI (IAA)	Mouse RCI (wound)
ALXN-4100 (TPO mimetic)	AFRRI (IAA)	Mouse RCI (wound)
17-DMAG (Hsp90 inhibitor)	AFRRI (IAA)	Mouse RCI (wound)
Euk-189 (SOD/Catalase mimetic)	University of Rochester/MCW (grant)	Rat IR alone
Euk-207 (SOD/Catalase mimetic)	University of Rochester/MCW (grant	Rat IR alone
Meloxicam (NSAID)	AFRRI (IAA)	Mouse RCI (wound)
Recombinant IL-12	University of Rochester (grant)	Mouse IR alone
Bone marrow derived MSCs	AFRRI (IAA)	Mouse RCI (burn)
Hemjoba (cannabinoid derivative)	AFRRI (IAA)	RCI (wound)
Kineret (interleukin-1 receptor antagonist)	University of Massachusetts (grant)	Mouse IR alone
JP4-039 (mitochondrial-targeted gramicidin S (GS)-nitroxide)	University of Pittsburgh (grant)	Mouse IR only
Alpha-chemokine	AFRRI (IAA)	Mouse RCI (burn)

[a] Presented at the meeting.
[b] Also funded by BARDA.
Abbrevations: AFRRI = Armed Forces Radiobiology Research Institute; CRI = cutaneous radiation injury; IAA = inter-agency agreement; IR = ionizing radiation; MCW = Medical College of Wisconsin; MSC = mesenchymal stromal cell; NSAID = non-steroidal anti-inflammatory drug; ODN = oligodeoxynucleotide; RCI = radiation combined injury; SBIR = Small Business Innovative Research; TBI = total body irradiation.

Session 5: Medical Countermeasures to Treat CRI

The final session of the conference focused on medical countermeasures to address CRI. For the purposes of the meeting, MCMs for CRI included both physical barrier (e.g., wound dressings) and drug treatment approaches. Also included was additional information on appropriate animal models and metrics to assess MCM efficacy.

Overview of NIAID/BARDA portfolios and possible repurposing of approaches. The RNCP, NIAID has supported several funding mechanisms focused on skin research (A. DiCarlo). These mechanisms include RC1 challenge grants on radiation-induced skin injuries funded through the American Recovery and Reinvestment Act, combined injury R21/R33 grants, Small Business Innovation Research (SBIR) grants (R43/R44), an interagency agreement (IAA) with the Armed Forces Radiobiology Research Institute (AFFRI), and both pilot and full projects funded through the Centers for Medical Countermeasures against Radiation Consortium (CMCRC). The RNCP has categorized types of skin damage as either radiation-only injuries localized to the skin by gamma, beta and X-ray sources, or RCI. RCI is further categorized as irradiated wounds (incision or punch) or irradiated thermal burns. Such thermal burns are created in several ways, including contact with scalding water or a heated metal bar contact, flash exposure, or ignited ethanol. The RNCP has identified the following animal models that have been utilized since 2009 in studies in their funded portfolio: mice, guinea pigs, minipigs, domestic pigs and human *ex vivo* skin. Study model selection is based on availability of animals and equipment with oversight by IACUC. End points for studies commonly used are survival, time to full closure, percentage healing, histopathology, limb shortening, barrier function, wound tensile strength, and biomarkers of injury with impact of MCM intervention. Current approaches under study by the NIAID include many small molecules, antibodies, cellular therapies, antioxidants and growth factors regulated by the Center for Biologics Evaluation and Research (CBER), FDA and CDER, FDA as appropriate (Table 4). In addition, BARDA has supported the advanced development of approaches that are generally under CDRH regulatory purview, such as Silverlon® wound dressing (Argentum Medical LLC, Geneva, IL), and KeraStat® Cream (KeraNetics Inc., Winston-Salem, NC), both detailed below.

Cellular therapy approaches to treat cutaneous radiation injuries. IRSN's expertise in regenerative medicine has

focused on stem cell therapy and its impact on radiation-induced lesions involving skin, muscle and bone that lasts decades (R. Tamarat). It has been well established that tissue regeneration involves several major processes: 1 mobilization of bone marrow cells that pre-differentiate into inflammatory cells; 2. circulation of angiogenic cells to be recruited to the site of lesions for revascularization; and 3. participation of resident stem cells in the damaged tissue. As described in several studies, stem cells used for treatment originate from different sources such as the bone marrow (i.e., MSCs), blood (i.e., cord blood, somatic stem cells) and other organ-specific tissues such as the heart, brain and adipose tissue. Mechanisms of action driving cell homing and tissue regeneration span from endothelial cell to smooth muscle cell differentiation and paracrine effects, to intrinsic mechanisms and host-tissue effects. Together, the interaction of the pathways regulating these activities allow for the remodeling and regeneration of tissues. Percy Military Hospital has performed stem cell therapy in human patients, with technical support from IRSN scientists who developed experimental animal protocols (*139*). They have documented complete healing of radiological burns with functional recovery and rapid loss of pain during patient follow-up. To optimize the strategy based on stem cell therapy, researchers from IRSN showed that adipose-derived stem cells (ADSCs) participate in dermal wound healing by promoting re-epithelialization and angiogenesis (*140*). This work showed that adipose lineage cells could represent an alternative cell source for therapy in the context of wound healing. The study method involved delivery of a full-thickness wound made by punch application on the back of mice, and subsequent 20 Gy irradiation. To assess the ability of ADSCs to fuse with epithelial cells, ADSCs from female mice were transplanted into male recipients. Follow-up assessments included morphometric observations to determine wound closure, laser Doppler to measure cutaneous blood flow, a cutometer to determine viscoelasticity and immunohistochemistry. Stem cells were found to enhance vascular density, improve blood perfusion to the skin and have a positive effect on angiogenesis in the affected tissues. Furthermore, skin viscoelasticity was higher in animals treated with ADSCs, and wound closure was accelerated (*140*). Another study demonstrated the beneficial effect of bone marrow mononuclear cells on radiation-induced skin lesions, by preventing vascular dysfunction, permeability and unfavorable remodeling in the acute and late phases after radiation exposure (*141*).

The IRSN group later sought to determine the effect of stem cell therapy by combining MSC cells with ADSC cells and endothelial progenitors cells to stimulate tissue regeneration after irradiation. MSCs with the ability to secrete paracrine factors were delivered for immunomodulation, which demonstrated a dose-dependent effect of the cells. More importantly, the neovascularization process was investigated by different approaches, including micro-angiography, cutaneous blood flow assessment with laser Doppler for perfusion imaging, and capillary density analysis in frozen sections of gastrocnemius muscles. Finally, based on a strategy of improved treatment in a mass casualty scenario, another therapeutic approach that has been explored by IRSN teams over the past ten years is to treat CRI with extracellular vesicles (EVs). Known to be involved in the regulation of biological processes (*142, 143*), EVs play an important role in intercellular communication. Recently published studies show a role for EVs in radiation injuries to multiple organ systems (*144, 145*), including the skin (*146*), suggesting their use as a therapeutic. In summary, bench-to-bedside advancements in cellular therapies to treat radiation skin injuries are ongoing, with outcomes observed in patients informing research. This paradigm of a partnership between clinicians and investigators represents an effective means of accelerating the advancement of these valuable therapies.

Repurposing burn dressings to address radiation skin injuries. Argentum Medical, LLC is funded by BARDA to advance development of their Silverlon burn contact dressing for a radiation indication (P. Antinozzi). Silverlon consists of a single layer of knitted nylon fiber substrate coated with metallic silver and is currently cleared for the management of a wide variety of wounds including partial-thickness wounds and 1st and 2nd degree burns.[18] The goal of the company is to obtain clearance for Silverlon dressings for both radiation therapy-induced dermatitis as well as CRI. To do this, the company has devised a two-stage regulatory strategy. Stage one seeks clearance for indications in lower-severity radiation injuries leading up through dry desquamation with clinical data in radiotherapy patients. Stage two seeks a submission for higher-severity indications leading up through moist desquamation and necrosis. Preclinical studies utilizing a Yorkshire swine model and beta-irradiation devices with highly reproducible single radiation doses per site are planned in stage two. Assessments will include visual observations weekly and end of study, and histopathology at necropsy. Three independent scorers will perform visual assessments at the time of bandage change, based on Erythema and Moist Desquamation scales (discussed above). For computational scoring, an image analysis pipeline is used to process study images. On-image color patches are used for image scaling with respect to color and lighting quality measures. Every image is assigned a computational score and a longitudinal analysis is established for each wound site. In a similar fashion, histopathology-scoring bias is also being addressed with further development of such computational strategies. This scoring platform is scalable and can be distributed for remote scoring of both clinical and preclinical studies. It is the company's hope that this assessment method, which avoids bias and incorporates computer learning, will be acceptable to the FDA in terms of determining degree of

[18] https://bit.ly/2UwZRXN.

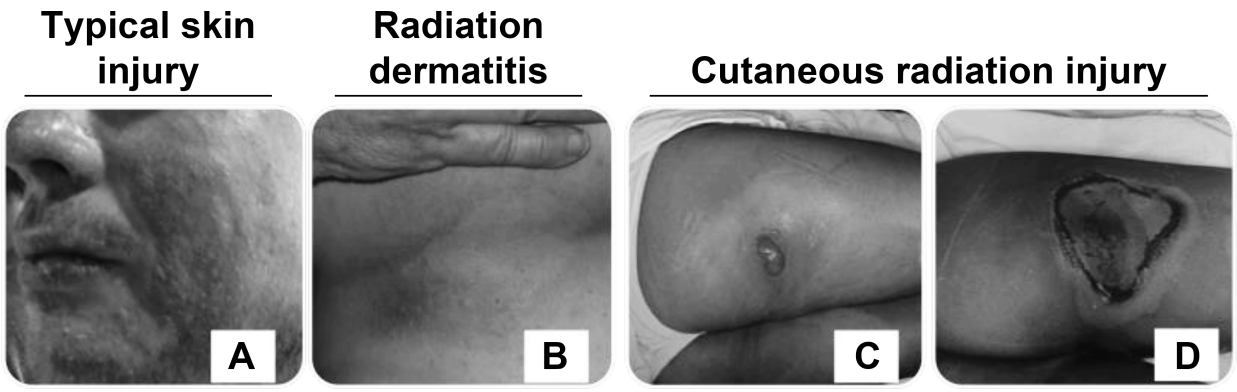

FIG. 3. Reactions observed from radiation exposure of the skin.[19] Panel A: Typical mild skin injury in a radiation therapy patient. Panel B: Radiation dermatitis in a patient after a skin reaction to radiation therapy. Panels C and D: Acute ulceration in a patient who inadvertently placed an Ir-192 source in his back pocket, at 3 and 10 days, respectively, after exposure (*36*).

injury, and amelioration of damage by application of the dressings.

Approaches targeting skin structural components. KeraNetics presented on MCM approaches under development that target skin structural components to retain barrier function. Skin injuries presented were characterized as typical, radiation dermatitis or CRI (Fig. 3). Typical skin injuries (Fig. 3A) such as abrasions and thermal/chemical burns are immediately evident and have a known course of healing. Radiation dermatitis (Fig. 3B) has an unpredictable course of healing with evidence of injury that progresses over time. Much like radiation dermatitis, CRI (Fig. 3C) also exhibits evidence of injury that progresses over time (A. Gabard). The visible effects to the skin are dependent on the magnitude and penetration depth of the radiation dose with lesions appearing hours to days after exposure. Profiling injuries resulting from diagnostic radiation procedures can further characterize the nature of radiotherapy-induced skin reactions. For example, a patient with a radiation-induced skin injury resulting from a fluoroscopy procedure displayed prolonged erythema at 6–8 weeks postirradiation imaging (*20*). The injury during this timeframe had a distinctive mauve central area suggestive of ischemia. At 16–21 weeks later, the skin injury was depigmented with a central area of necrosis. Onset of deep necrosis with atrophic borders developed 18–21 months after exposure. In another case, a radiation oncology patient developed radiation dermatitis four weeks into the course of radiotherapy (*147*). The skin injury displayed erythema associated with cutaneous necrosis, pain and fever, and the patient developed a wound-based *Staphylococcus aureus* infection. At five weeks postirradiation, an escharotomy of the dead tissue was performed and by 7–8 weeks, the patient's infection was resolved, and re-epithelialization was observed at the site of injury. A patient with cutaneous radiation injuries was profiled as well.[19] This patient developed a skin wound that advanced from mild erythema to confluent moist desquamation by 26 days after irradiation. The wound progressed to the point of necrosis, fibrosis and telangiectasia at two years postirradiation (see similar wound in Fig. 3C and D).

It is important to standardize terminology used by the medical and scientific communities to describe radiation skin injuries. Scoring that aligns with terminology needs to be established to allow for measurement of individual symptoms of injury across the full spectrum of skin pigments (L. Burnett). Current systems for grading skin damage vary on how they score injuries. For example, the scales differ somewhat in their grading of symptoms such as edema, blistering, desquamation and ulceration/necrosis (Table 3). These inconsistencies could best be addressed by stakeholders in the field, including clinicians, researchers, FDA product reviewers, and other government agencies. In addition to the vital human data available, animal models are tools that can be used to assess dose-dependent injury over time and across multiple skin pigments. Data from well-established animal models can be translated to better understand similar injuries in humans. One such animal model, the Yorkshire swine [presented in Session 2 (*107*)], was administered radiation at multiple doses using beta, orthovoltage X-ray or linear accelerator. As described above, observations and histological data show radiation dose-dependent evolution of skin pathology over time, including the diminishing, then absent, basal cell population by day 70 (*107*). The severity of skin reactions was assessed using a modified methodology and acute skin injury scale (*148*). In addition, given the fact that skin comes in many different shades, CRI studies using the red Duroc pig, a dark-skinned animal, are also important to properly assess injuries in darker skin shades (*149*).

Since ionizing radiation causes disruption of skin barrier function leading to trans-epidermal water loss, it was suggested that preservation of the epidermal permeability barrier function with topical treatment could reduce the negative effects of radiation dermatitis (*50*). Interacting molecular partners that maintain skin barrier are potential targets for development of treatments; therefore, alpha-

[19] https://bit.ly/2MMnojv.

catenin and its many molecular partners were investigated (*150*). Alpha-catenin sits at the junction of intercellular adhesion, coordinating activity between cells. Electron microscopy of the intercellular components of the skin shows the major cellular junctions and desmosomes (*150*), which are known to be adversely affected by ionizing radiation (*107*). For this reason, KeraStat Cream (containing purified, human-derived keratin) has been tested for its ability to manage both porcine and human skin injuries, in the hopes that the application of human-derived keratin, the main skin protein, will create an environment supportive of healing. In a large white pig model, wounds dressed with the cream showed improvement by four weeks postirradiation, and in a human skin wound, skin dressed with the cream showed less injury (as assessed by RTOG scoring) by four weeks, compared to skin treated with standard of care (L. Burnett).

Focusing on future directions, drug development for radiation-induced skin injury should include a ''multi-omic'' approach with biomarker pathway analysis. This is necessary to correlate animal model data with human skin biopsies after radiation oncology procedures. For example, in the large swine model of irradiated skin, metabolomic analysis revealed dose- and time-dependent changes in several metabolites not previously shown to be associated with CRI. These changes occurred in pathways reflecting protein degradation, oxidative stress, eicosanoid production, collagen matrix remodeling, mitochondrial stress, cell membrane composition and vascular disruption (*107*).

Alpha connexin carboxyl-terminal (ACT1) peptide to mitigate the progression of CRI. FirstString Research (Mount Pleasant, SC) is focused on developing and bringing therapies to market based on inflammation and injury-focused medical conditions. FirstString has developed a first-in-class new chemical entity called Granexin® gel that has demonstrated activity in multiple non-clinical and clinical studies (G. Ghatnekar). Granexin has been studied to enhance tissue regeneration (*151*), promote faster healing (*152*), reduce inflammation, and attenuate scarring (*153, 154*) in several clinical and non-clinical models of injury. FirstString has advanced Granexin into late-stage clinical trials for cutaneous radiation injury, cutaneous scarring and thermal burns (*153, 155, 156*). Preclinical development is also ongoing in ophthalmology indications (*157*). Cell-cell communication is a key aspect of injury response with cells communicating with each other to effectively bring about fast and efficient healing. The connexin 43 protein is a key component of cellular junctions that are essential for mediating cell-cell communication and inflammatory responses as well as maintaining tissue integrity. The aCT1 peptide, the active pharmaceutical ingredient in Granexin, tempers damaging inflammatory responses and helps preserve and restore the coordinated cellular activity that is compromised after injury, thus preventing the spread of the damage and acting to reboot the healing and regenerative process.

As described previously, pigs represent the gold standard to evaluate cutaneous disorders; however, not all pigs are created equal. A comparison study performed using Göttingen, Sinclair and Yorkshire pigs showed consistent development of CRI symptoms by day 35 postirradiation only in the Yorkshire strain. For this reason, the natural history of CRI in the Yorkshire pig was studied further for the determination of clinically meaningful end points, quantitative methodology for assessment of radiation injury, concept of operations, and an indication statement. Animals were exposed at eight separate circular sites on the back to a single fraction of 60 Gy with 6-MeV electrons from a LINAC. For 120 days, clinical parameters and skin healing were assessed using four scoring scales to analyze the progression of CRI phenotypes. The study used the Kumar, Erythema and Desquamation, RTOG, and an adapted VAS system (Table 3). All four metrics revealed consistent progression of CRI across all irradiated sites that followed a similar time course as that seen for CRI progression in humans (*98*). By day 50, the majority of sites showed clinically meaningful levels of injury, and at day 90, all irradiated sites showed clinically significant dermal necrosis and ulceration. In response to 60 Gy doses of acute ionizing radiation, Yorkshire pigs showed a controlled, reproducible full-thickness cutaneous radiation injury. A proof-of-concept pig study was performed using Granexin as the test article. Treatment of radiation sites with Granexin mitigated CRI progression and reduced injury severity over time compared to vehicle control treatment (G. Ghatnekar). The gel was applied once daily upon observation of erythema (Kumar score >1.0). In conclusion, FirstString's novel connexin-based peptide has shown promise in modulating injury response. Their Granexin compound has successfully demonstrated activity in both Göttingen and Yorkshire pig models of CRI. These studies have laid a solid foundation to advance Granexin gel into a pivotal GLP efficacy study in the Yorkshire pig model of CRI.

Using regenerative medicine to mitigate effects of radiation combined injury. Chrysalis BioTherapeutics (Galveston, TX) has developed novel thrombin peptide regenerative drugs to address skin injuries. The company's lead product, thrombin peptide 508 (TP508), is a clinical-stage, investigational peptide drug with demonstrated safety and activity in human clinical trials for topical and local delivery to diabetic foot ulcers and bone fractures (D. Carney). The company has been funded by the NIAID to develop TP508 as a radiation MCM, which is also under development for clinical use to protect normal tissues from damage caused by radiation therapy. Normal wound healing is a complex network of processes involving the interaction of multiple cell types such as keratinocytes, fibroblasts and endothelial cells. However, radiation-impaired wound healing is disrupted, leading to inflammation and ongoing cellular regeneration (*158, 159*). This type of wound healing represents a major problem for radiation therapy patients and for survivors of nuclear

exposure. Chrysalis has shown that a single topical application of TP508 accelerates normal revascularization and healing of injured tissue in rats after full-thickness excisional wounding. Histological sections from wounds treated with TP508 showed more advanced healing with larger functioning blood vessels, fewer inflammatory cells and more mature granulation of tissue by day 7 (*160*). In clinical studies, TP508 has been shown to be effective for treating diabetic foot ulcers; TP508 shortens time to closure and doubles the number of completely healed ulcers on the foot and heel by day 60 (*161*). TP508 has been found to be especially active in the treatment of complex ischemic heel ulcers that are known to be the most difficult ulcers to treat effectively. Heel ulcers are more ischemic and prone to infection, leading to the highest percentage of amputation. It is believed that diabetic ulcers may be representative of ulcers resulting from radiation exposure. In one study, TP508-treated ulcers closed more completely compared to saline controls, and treatment more than doubled the rate of healing (*161*). TP508 stimulates cell signaling and endothelial cell nitric oxide (NO) production to activate progenitor stem cells, stimulate regeneration and revascularization, and mitigate effects of radiation. Its mode of action includes restoration of endothelial function and vascular epidermal growth factor, NO-dependent signaling, reducing ischemia and decreasing inflammation (*162, 163*), stimulation of progenitor stem cell proliferation (*164*), and increasing survival and maintenance of GI crypt integrity (*165, 166*). An RCI animal model was also developed by Chrysalis, in which mice received either 3 or 8 Gy of gamma radiation, followed by full-dermal excisional wounds 24 h later. Radiation exposure decreased the rate of wound closure. By day 16, nonirradiated control wounds were closed ~97% (3% open) while only 75% of irradiated wounds were closed (25% open). In contrast, TP508 treatment resulted in closure of 91% of wounds when the drug was administered 24 h after wounding. In other studies, intravenous injection of TP508 at 24 h postirradiation also restored normal healing and minimized RCI-induced increases in lethality.

Chrysalis held a pre-investigational new drug (Pre-IND) meeting, which led to the FDA's recommendation that survival be the primary end point for the proposed animal efficacy studies and that end points related to major morbidities (e.g., wound healing) could be supportive. It was also suggested that TP508 efficacy in the setting of acute radiation syndrome be clearly shown before pursuing a combined radiation injury indication (e.g., radiation injury plus traumatic wound or burn). To date, TP508 has demonstrated a survival benefit in rodent models of hematopoietic and gastrointestinal radiation injuries and is undergoing testing in survival models in large animals (minipig/nonhuman primate) for both acute and delayed radiation sub-syndromes.

MEETING DISCUSSION

To direct comments to the areas of greatest interest to both the funding and regulatory agencies, questions were developed by the meeting planners for each session, to more readily gain expert responses from the presenters and other participants. Although conversations were held at the end of each session, content from all the discussions has been grouped together, and is further divided by topic area below.

Animal Models

Because the FDA Animal Rule is so important in the development of MCM approaches to address CRI, the development of animal models to simulate human injuries is central to moving approaches toward approval for marketing. Because human exposures could result from industrial or radiotherapy accidents, multiple animal models could be employed to generate data that could be extrapolated to clinical patients. Issues with clinical assessments of CRI are that they are often subjective, not reproducible, do not define well the depth of the skin area involved, and do not discriminate well between the types of injuries to the skin (CRI versus chronic diabetic ulcer versus thermal burn). Animal modeling may help bridge clinical scales with histopathology to make clinical assessments more quantitative and objective. To this end, there are a number of factors that must be considered when selecting the appropriate model:

1. Anatomical and physiological similarity between humans and the animal species under consideration:
   - The anatomy and physiology of large pig models seem to most closely resemble that of humans, with similar skin thickness, hair and sweat glands.
   - The cost of a large pig and the inability to house these animals can be limiting.
   - For preliminary studies, guinea pig or minipig models may be appropriate as a rodent species for testing.
2. Human and animal heterogeneity in terms of skin tissue distribution and impact on radiation dose distribution:
   - In humans, subcutaneous skin thickness and body fat vary as a function of age, sex and ethnicity. Fat tissue thickness can lead to wound variability, especially in the case of beta radiation, and the presence of MSCs in the adipose tissue could alter the response. Therefore, care must be used in selecting a model that minimizes these variables.
   - In pig and mouse models, there can be different healing rates based on what part of the skin is irradiated. For example, in the pig, thicker dorsal skin heals differently than the thinner ventral skin. Mice also have similar skin location differences, in that radiation-induced damage can be very different in that of leg skin compared with that of ear skin.

- Proximity of the radiation exposure to bone can play a role in the extent of damage.

3. Effect of skin melanization in view of possible differential radiation responses due to higher levels of melanin, as well as challenges involved in scoring erythema in pigmented skin:
   - Concerning the use of a pig such as the Duroc, which is more heavily melanized, differential sensitivity to high-energy radiation may be observed due to the presence of melanin (*167*).
4. Humane and ethical challenges encountered in these studies:
   - Partial-thickness burns in animals raise concerns due to humane considerations surrounding pain.
   - Full-thickness wounds are better tolerated, because the nerves are killed, and the animal is no longer sensing the pain.
   - Use of a fentanyl patch should be considered.
   - Because pain in animal models can be difficult to evaluate, a test or tool is needed to be better quantify the pain, especially in rodents (*168*).
   - Euthanasia criteria must also be carefully designed and closely monitored.
5. Radiation type selected for the study:
   - The main issue is the penetration depth of the radiation that is being used.
   - Different structures within the skin may receive different radiation doses, for example, if exposed to beta (which goes up to ~5 mm), or X rays/gamma, which penetrate farther and can therefore cause damage to deeper structures like the vasculature.
6. Statistical considerations:
   - Planning for the use of appropriate statistical approaches is important when embarking on any animal study. It is critical to power studies properly, and it is necessary to justify these experiments.
   - Pilot studies may be a precursor to designing a fully-powered study.
7. Consideration of the number of areas per animal that will be wounded:
   - It is possible that radiation exposure can affect the animal's response to an adjacent wound (via a bystander effect involving biological signaling), as there is likely a systemic component to the lesion that depends on the area of the wound as well as the dose of radiation administered.
   - It is advisable to irradiate small areas that are as far away from each other as possible, while remaining in the same general area of the animal (e.g., in the pig, the back).
   - For mouse studies, their small size limits the number of wounds per animal. Furthermore, since the body surface area of a wound can have a dramatic effect on the outcome in studies that use TBI combined with a skin injury, it is important to confine that exposure to ~15% (J. Kiang).

Standards of Wound Care that Could be Applied to an Animal Model

Once an appropriate animal model has been selected, it is important to determine how that model will be treated, to mimic expected human care as accurately as possible. In humans, there is a high level of variability in how the patient will be treated; however, in an animal model, the care provided needs to be standardized to achieve comparable outcomes across studies. Nonetheless, there are standard clinical practices involved in the care of wounds that could be translated into animal models:

1. Maintain a clean wound bed and be diligent in looking for signs of infection, while understanding that the native cutaneous microbiome can play a role in the progression of healing.
   - Remove necrotic tissues (debridement); this is a common standard of care in the clinic that is not often used in animal models (although there has been limited use in pigs) due to challenges with assessing animal pain.
   - Consider antimicrobial therapy; however, given the low incidence of infections in caged rodent models, it is assumed that they are robust in their ability to fight off infection.
2. Keep the wound area moist with a dressing.

Assessment Methods to Evaluate Extent of Skin Injury

After decisions have been made concerning selection of an animal model and its treatment during the study, a determination of how the wound and any healing will be evaluated must also be considered. One of the most common methods to assess these end points are scoring scales (Table 3); however, no current consensus exists in research or clinical communities:

1. Many researchers use the Kumar scale, although there are some challenges with the method, because CRI lesions are not homogeneous; for example:
   - It is possible to have erythema and desquamation with an overlying blister.
   - There have been cases where an irradiated animal with skin that appeared normal was scored as a ''0'' using this scale; however, after histological assessment, that skin was found to be severely damaged in the lower layers.
   - There could be lesions that exhibit primarily desquamation, but with a small area of necrosis. That wound would receive a higher score that may not be representative of the whole lesion.
   - Recommendation is to combine some form of visual scoring with histopathology.
2. Similarly, using photography to assess skin injuries can be challenging:
   - Amount of light in the room is critical when assessing erythema.

- Positioning of the animal, and the animal's position within the room must be exactly replicated using the same camera for all images.
- Every detail must be carefully documented, to compare between photographs taken over time and between subjects.

For these reasons, a system that quantifies damage and eliminates subjectivity is needed. To address this shortfall, computer programs have been developed to enable unbiased scoring; however, a computer-learning algorithm is only as good as its training. Although there may still be systematic bias in computerized systems, these approaches could still improve on individual or group scoring.

Other methodologies that may be useful in determining the extent of injury and progression of healing, which have already been used for CRI, include the following.

1. Ultrasound allows for a full-thickness view of the skin, but depending on the nature of the radiation exposure, there may be other damaged tissues beneath the skin layer that will not be detected.
2. Infra-red imaging cameras have also been used to get a better look at deeper radiation dose injuries.
3. Optical coherent tomography is under development; however, this methodology may not be as reliable as a histology sample.
4. Fluorescein dye with a spy camera can be useful.
5. Laser Dopple is available, but not necessarily amenable to a mass casualty assessment.
6. Photography-based apps may be useful to determine if tissue is healthy or damaged in an open wound.
7. Thermography is a useful tool to assess local injury, which can present as elevated skin temperature (*135*).
8. CT scans and MRI (better for soft tissue than CT) have been used. MRI is good for bone and general structures, but there are no known studies of MR images of CRI or radiation dermatitis.
9. Assessment of the vasculature to look at long-term viability of the closure, which can be accomplished via dye injection and imaging to assess vascularization, is the gold standard for assessing vascularization clinically (i.e., routinely done pre-operatively for reconstructive surgery), but has not been used for CRI.

Other end points that are used clinically include epithelial integrity, extent of blood vessel involvement or proliferation in the dermis, depth of collagen necrosis, extent of inflammation, infection rates, adipose integrity, and pain.

Clinical Presentations

Although radiation skin injuries are not commonly encountered from a public health emergency perspective, it may be possible to leverage injuries encountered in existing clinical populations to learn more about possible assessment and treatment approaches:

1. Relatively few overexposures result from fluoroscopy procedures (standards limit the length of time and repeated procedures in the same area, so they are not as common).
2. Skin reactions from fractionated radiation therapy exposures are seen in patients irradiated for breast, lung, or head and neck cancers.
3. Patients undergoing combined chemotherapy and radiation protocols often have more severe skin reactions; the exposures are often fractionated, making it difficult to compare to victims of a prompt radiation exposure.
4. Irradiated patients may have skin injuries that are unmasked after a second radiation exposure. Patients with TBI conditioning for bone marrow transplant are more prone to developing graft versus host disease (GvHD).
5. After radiotherapy, it is possible to see vascular effects in patients 20–30 years later. The healed wound looks fine, but the patient develops toxicity decades later due to vascular atrophy.

Because radiation burns can result from normal tissue radiotherapy complications or some diagnostic procedures, it is informative to also study thermal burns to better understand how medical professionals assess these kinds of wounds. From a regulatory perspective, it may be appropriate to conduct therapeutic studies for radiation dermatitis in humans, but CRI studies in animals, given that it is difficult to identify clinical damage consistent with CRI outside of rare, accidental exposures.

Clinicians would appreciate products that allow for more rapid and accurate diagnosis and better assessment, especially of layers beneath the skin and other aspects of cutaneous injury that are not easily visible. Surgeons need as much objective information about the depth, breadth and severity of injury including evaluation of blood supply to understand the injury and plan resection. Histopathology, which is the gold standard for animals, cannot be easily done for human injury, and needs to be linked to human skin lesions observed with imaging modalities such as ultrasonography, thermography or MRI, or molecular signatures such as biomarkers or chromosomal abnormalities, to accurately map out the extent of a lesion. Some suggested end points used in other skin injuries such as 100% re-epithelialization, defined as complete epithelialization observed at two visits two weeks apart, may be too ambitious in the context of CRI, though this could represent an appropriate regulatory and clinical end point. It is important that durable skin stays closed, and that sufficient blood supply is available to the wound to support tissue remodeling in the years after injury. While a functional, desirable outcome for diabetic foot ulcer care may be 100% wound closure, radiation injuries are more complex, making it difficult to achieve similar outcomes. The following end points could be alternatives:

1. decrease in skin necrosis,

2. facilitation of surgical closure,
3. accelerating time to autograft,
4. cosmesis,
5. reduction in pain,
6. other parameters that affect patient quality of life.

Wound closure should still be assessed as a safety end point to ensure the treatment being studied does not interfere with or delay the wound-healing process. In the clinic, there are a few functional outcomes that can be assessed to determine if skin will remain durable or a wound will remain closed/healed, such as blood flow assessment via laser doppler. In the burn field, physicians utilize different scoring scales to assess for fibrotic outcomes such as scarring and to look for vascularization, which often utilizes the Vancouver Scar Scale (*169*). This assessment method uses the color and pliability of a scar to provide some indications concerning the expected duration of healing. In chronic diabetic foot ulcers, edema of the extremity must be managed for wound healing to be long-term. The inter-center FDA guidance document on burns and chronic cutaneous ulcers is an excellent resource for other potential end points (*138*).

It is clear that a team approach is needed to appropriately address CRI, including well-established relationships between trauma clinicians, radiation oncologists, radiation physicists, dermatologists and others. For example, in the case of radiation dermatitis, dermatologists will often be sought for treatment, but may not know that patient's history well enough to understand the cause of the rash. Often, the presence of a grid pattern of a delineated field edge from the collimator may be the only indication of a radiation burn. It is critical to have all care providers working together to best diagnose and treat patients with suspected skin radiation injuries.

Medical Countermeasures

Medical countermeasures (MCMs) under study to address CRI have ranged from small molecules and growth factors to cellular therapies. In developing these various approaches, it is important to note that it is not reasonable to expect that a single product will be able to address the heterogeneity of the lesions observed after radiation exposure of the skin. When to initiate treatment with a MCM for CRI depends on the agent's mechanism of action. For example:

1. Antioxidants might be best initiated prior to irradiation.
2. Anti-inflammatories could yield greatest efficacy when administered postirradiation.
3. For some approaches, equal efficacy has been observed whether the drug is started at erythema or moist desquamation; however, if treatment was initiated only at time of moist desquamation, with an equal outcome, an argument could be made to wait until that time in a scarce-resources setting.
4. Some topicals could work better if given at the time of moist desquamation because the skin would be more open to accept the drug.
5. Bone marrow stromal cells as mitigators of radiation fibrosis provided improvement when administration was delayed until macrophages accumulated at the site, up to 6 weeks postirradiation. It is notable that cellular approaches such as MSCs could also address intractable pain known to accompany CRI.

An understanding of the mechanism of action of the drug and the end point it will modify allow researchers to determine the appropriate time point for intervention in the process.

SUMMARY AND CONCLUSIONS

As demonstrated through the presentations and discussions held during this meeting, CRI represents damage that must be considered when discussing injuries anticipated from a radiation mass casualty incident. Development of animal models to address this damage has lagged behind those for other radiation syndromes; however, there are several approaches currently under study that utilize both small and large animals generally believed to approximate a human response to radiation exposure. Standardization of methods to assess the severity of the injury and its amelioration by treatment is also needed. It is, nonetheless, promising that several repurposed MCMs (e.g., skin wound dressings for thermal burn), or drugs for which clinical data are being gathered for another indication (e.g., diabetic foot ulcers), are undergoing testing. This approach could accelerate the clearance/approval/licensure of these MCMs. It is, therefore, important for funding agencies to continue to support basic-through-advanced development of all of these aspects of CRI.

ACKNOWLEDGMENTS

We thank the meeting speakers (Table 1) and conference attendees for providing their expertise and insight during both the presentations and discussion sessions. We would also like to acknowledge the conference moderators (Session 1: Scott Somers, NIGMS and Betsy Ballard, FDA; Session 2: Andrea DiCarlo, NIAID and Adebayo Laniyonu, FDA; Session 3: Nushin Todd, FDA and Narayan Iyer, BARDA; Session 4: Sue Jane Wang, FDA and Cynthia Chang, FDA; and Session 5: Carmen Rios, NIAID and Aaron Bandremer, BARDA). We recognize the efforts of other FDA members of the planning committee (Heather Agler, Frank Lutterodt, Lisa Skarupa, Cynthia Welsh, Kunyi Wu, and Zishan Zhao), and the strong guidance and support of Libero Marzella (FDA). Finally, we thank DAIT, NIAID colleagues (David Cassatt, Merriline Satyamitra, Lanyn Taliaferro and Thomas Winters) for their critical review of the manuscript prior to submission.

Received: May 2, 2020; accepted: June 11, 2020; published online: August 28, 2020

REFERENCES

1. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evalu-

ation and Research (CBER) Product Development Under the Animal Rule. Guidance for Industry. 2015.

2. Barabanova A. Acute radiation syndrome with cutaneous syndrome. In: Ricks R, Berger, ME, Ohara FM Jr., editor. Medical basis for radiation accident preparedness: The clinical care of victims. New York: Parthenon Publishing Group; 2002.
3. Hirsch E, Oliveira A, Browne D, et al. Consensus statement on the cutaneous radiation syndrome. In: MacVittie TJ, Weiss JF, Browne D, editors. Advances in the treatment of radiation injuries. Proceedings of the Second Consensus Development Conference on the Management of Radiation Injuries, Bethesda, MD, April 12–14, 1993. New York: Pergamon Elsevier; 1996.
4. Strandquist M. A study of the cumulative effects of fractionated X-ray treatment based on the experience gained at Radiumhemmet with the treatment of 280 cases of carcinoma of skin and lip. Acta Radiol 1944; 55:300.
5. Lataillade J, Doucet C, Bey E, Carsin H, Huet C, Clairand I, et al. New approach to radiation burn treatment by dosimetry-guided surgery combined with autologous mesenchymal stem cell therapy. Regen Med 2007; 2:785–94.
6. Rachidi W, Harfourche G, Lemaitre G, Amiot F, Vaigot P, Martin MT. Sensing radiosensitivity of human epidermal stem cells. Radiother Oncol 2007; 83:267–76.
7. Agay D, Scherthan H, Forcheron F, Grenier N, Herodin F, Meineke V, et al. Multipotent mesenchymal stem cell grafting to treat cutaneous radiation syndrome: development of a new minipig model. Exp Hematol 2010; 38:945–56.
8. Archambeau J, Mathieu G, Brenneis H, Thompson K, Fairchild R. The response of the skin of swine to increasing single exposures of 250-KVP X-rays. Radiat Res 1968; 36:299–326.
9. Forcheron F, Agay D, Scherthan H, Riccobono D, Herodin F, Meineke V, et al. Autologous adipocyte derived stem cells favour healing in a minipig model of cutaneous radiation syndrome. PLoS One 2012; 7:e31694.
10. Hadad I, Johnstone BH, Brabham JG, Blanton MW, Rogers PI, Fellers C, et al. Development of a porcine delayed wound-healing model and its use in testing a novel cell-based therapy. Int J Radiat Oncol Biol Phys 2010; 78:888–96.
11. Hopewell J. The skin: its structure and response to ionizing radiation. Int J Radiat Biol 1990; 57:751–73.
12. Riccobono D, Agay D, Scherthan H, Forcheron F, Vivier M, Ballester B, et al. Application of adipocyte-derived stem cells in treatment of cutaneous radiation syndrome. Health Phys 2012; 103:120–6.
13. Sieber V, Wells J, Rezvani M, Hopewell J. Radiation induced damage to the cells of pig hairs: a biological indicator of radiation dose and dose distribution in skin. Radiat Prot Dosimetry 1986; 16:301–6.
14. National Security Staff, Interagency Policy Coordination Subcommittee for Preparedness and Response to Radiological and Nuclear Threats. Planning guidance for response to a nuclear detonation. 2nd ed. Homeland Security Council Interagency Policy Coordination Subcommittee for Preparedness and Response to Radiological and Nuclear Threats. 2010.
15. Tsipis K. Understanding nuclear weapons. London: Wildwood House; 1985.
16. Barss NM, Weitz RL. Reconstruction of external dose from beta radiation sources of nuclear weapon origin. Health Phys 2006; 91:379–89.
17. Adams TG, Yeddanapudi N, Clay M, Asher J, Appler J, Casagrande R. Modeling cutaneous radiation injury from fallout. Disaster Med Public Health Prep 2019; 13:463–9.
18. Hubbell J, Seltzer S. Tables of X-ray mass attenuation coefficients and mass energy-absorption coefficients 1 keV to 20 MeV for elements Z=1 to 92 and 48 additional substances of dosimetric interest. Gaithersburg, MD: National Institute of Standards and Technology; 1995.
19. Berger MJ, Coursey J, Zucker M, Chang J. ESTAR, PSTAR, and ASTAR: Computer programs for calculating stopping-power and range tables for electrons, protons, and helium ions, v1.2.3. Gaithersburg, MD: National Institute of Standards and Technology; 2005.
20. Balter S, Hopewell JW, Miller DL, Wagner LK, Zelefsky MJ. Fluoroscopically guided interventional procedures: a review of radiation effects on patients' skin and hair. Radiology 2010; 254:326–41.
21. Bolderston A, Lloyd NS, Wong RK, Holden L, Robb-Blenderman L. Supportive Care Guidelines Group of Cancer Care Ontario Program in Evidence-Based Care. The prevention and management of acute skin reactions related to radiation therapy: a systematic review and practice guideline. Support Care Cancer 2006; 14:802.
22. Jacobson LK, Johnson MB, Dedhia RD, Niknam-Bienia S, Wong AK. Impaired wound healing after radiation therapy: A systematic review of pathogenesis and treatment. JPRAS Open 2017; 13:92–105.
23. Iijima S. Pathology of atomic bomb casualties. Acta Pathol Jpn 1982; 32:S237–70.
24. Report of the United Nations Scientific Committee on the Effects of Atomic Radiation to the General Assembly. Annex G: Early effects in man of high doses of radiation. New York: United Nations; 1988. p. 545–65.
25. Kishi HS. Effects of the ''special bomb'': recollections of a neurosurgeon in Hiroshima, August 8–15, 1945. Neurosurgery 2000; 47:441–46.
26. Abella M, Molina MR, Nikolic-Hughes I, Hughes EW, Ruderman MA. Background gamma radiation and soil activity measurements in the northern Marshall Islands. Proc Natl Acad Sci U S A 2019; 116:15425–34.
27. Guskova AK, Baranov AE, Barabanova AV, Gruzdev GP, K. PE, Nadezhina NM. Acute radiation effects in exposed persons at the Chernobyl Atomic Power Station accident. Med Radiol 1986; 477:3–18.
28. Potentials of polyhydroxyalkanoates for repair of skin defects In: Volova TG, Vinnik YS, Shishatskaya EI, Markelova NM, Zaikov GE, editors. Natural-based polymers for biomedical applications. 1st ed. Palm Bay, FL: Apple Academic Press; 2017.
29. Selezneva LG, Barabanova AV, Adamian AA, Drobysh SV, Kochergina LD, Chechetkin PI, et al. The use of kombutek 2 in treating patients with radiation damages to the skin. Med Radiol (Mosk) 1990; 35:33–4. (Article in Russian)
30. Baranov AE, Gus'kova AK, Protasova TG. [Experience in treating the victims of the accident at the Chernobyl Atomic Electric Power Station and the immediate disease outcomes. Med Radiol (Mosk). 1991; 36:29–32. (Article in Russian)
31. Barabanova AV. Significance of beta-radiation skin burns in Chernobyl patients for the theory and practice of radiopathology. Vojnosanit Pregl 2006; 63:477–80.
32. Vasin MM, Ushakov IB, Kovtun VY. Radioprotector indralin at early and late manifestations of local radiation injuries. Vopr Onkol 2016; 62:406–12.
33. Vasin MV, Antipov VV, Chernov GA, Abramov MM, Gavriliuk DN, L'Vova TS, et al. The role of the vasoconstrictor effect in realizing the radioprotective properties of indralin in experiments on dogs. Radiats Biol Radioecol 1997; 37:46–55. (Article in Russian)
34. Vasin MV, Chernov GA, Antipov VV. Width of radiation protective effects of indralin in comparative studies using different animal species. Radiats Biol Radioecol. 1997;37(6):896–904. (Article in Russian)
35. Gusev IA, Guskova AK, Mettler FA. Medical management of radiation accidents. 2nd ed. Boca Raton, FL: CRC Press; 2001.
36. Barriga LE, Zaharia M, Pinillos L, Moscol A, Heredia A, Sarria G, et al. Long–term follow-up of radiation accident patients in

Peru: review of two cases. Radiat Prot Dosimetry 2012; 151:652–5.

37. International Atomic Energy Agency. The radiological accident in Lilo. Vienna, Austria: IAEA; 2000.
38. Jikia D. Long-term follow-up of the patients injured in the Lilo radiological accident. Health Phys 2010; 98:872–5.
39. International Atomic Energy Agency. The radiological accident in Nueva Aldea. Vienna, Austria: IAEA; 2009.
40. Lima CM, Lima AR, Degenhardt AL, Valverde NJ, Silva FC. Reconstructive dosimetry for cutaneous radiation syndrome. Braz J Med Biol Res 2015; 48:895–901.
41. Jose de Lima Valverde N, Ferreira da Silva J, Tantalean OB. An update on three radiation accidents in South America. Health Phys 2010; 98:868–71.
42. Tamarat R, Lataillade JJ, Bey E, Gourmelon P, Benderitter M. Stem cell therapy: from bench to bedside. Radiat Prot Dosimetry 2012; 151:633–9.
43. Clairand I, Huet C, Trompier F, Bottollier-Depois JF. Physical dosimetric reconstruction of a radiological accident due to gammagraphy equipment that occurred in Dakar and Abidjan in summer 2006. Radiat Meas 2008; 43:698–703.
44. Bertho JM, Roy L, Souidi M, Benderitter M, Bey E, Racine R, et al. Initial evaluation and follow-up of acute radiation syndrome in two patients from the Dakar accident. Biomarkers 2009; 14:94–102.
45. Gourmelon P, Benderitter M, Bertho JM, Huet C, Gorin NC, De Revel P. European consensus on the medical management of acute radiation syndrome and analysis of the radiation accidents in Belgium and Senegal. Health Phys 2010; 98:825–32.
46. Zenda S, Ota Y, Tachibana H, Ogawa H, Ishii S, Hashiguchi C, et al. A prospective picture collection study for a grading atlas of radiation dermatitis for clinical trials in head-and-neck cancer patients. J Radiat Res 2016; 57:301–6.
47. Leventhal J, Young MR. Radiation dermatitis: recognition, prevention, and management. Oncology 2017; 31:885–7, 94–9.
48. Ryan JL. Ionizing radiation: the good, the bad, and the ugly. J Invest Dermatol 2012; 132:985–93.
49. Hegedus F, Mathew LM, Schwartz RA. Radiation dermatitis: an overview. Int J Dermatol 2017; 56:909–14.
50. Schmuth M, Sztankay A, Weinlich G, Linder DM, Wimmer MA, Fritsch PO, et al. Permeability barrier function of skin exposed to ionizing radiation. Arch Dermatol 2001; 137:1019–23.
51. Lamoureux C, Gerard E, Ouhabrache N, Toukal F, Pham-Ledard A, Beylot-Barry M. A case of potential radiation recall dermatitis induced by chemotherapy, following low-dose total-skin electron beam therapy. Eur J Dermatol 2019; 29:671–2.
52. Reichman EF. Fluoroscopy-induced radiation dermatitis. J Emerg Med 2014; 47:e117–9.
53. Lyons AB, Harvey VM, Gusev J. Fluoroscopy-induced chronic radiation dermatitis (FICRD) after endovascular abdominal aortic aneurysm endoleak repair. JAAD Case Rep 2015; 1:403–5.
54. Wick G, Grundtman C, Mayerl C, Wimpissinger TF, Feichtinger J, Zelger B, et al. The immunology of fibrosis. Annu Rev Immunol 2013; 31:107–35.
55. Straub JM, New J, Hamilton CD, Lominska C, Shnayder Y, Thomas SM. Radiation-induced fibrosis: mechanisms and implications for therapy. J Cancer Res Clin Oncol 2015; 141:1985–94.
56. Gremy O, Benderitter M, Linard C. Acute and persisting Th2-like immune response after fractionated colorectal gamma-irradiation. World J Gastroenterol 2008; 14:7075–85.
57. Liao W, Hei TK, Cheng SK. Radiation-induced dermatitis is mediated by IL17-expressing gammadelta T cells. Radiat Res 2017; 187:454–64.
58. Ho AY, Olm-Shipman M, Zhang Z, Siu CT, Wilgucki M, Phung A, et al. A randomized trial of mometasone furoate 0.1% to reduce high-grade acute radiation dermatitis in breast cancer patients receiving postmastectomy radiation. Int J Radiat Oncol Biol Phys 2018; 101:325–33.
59. Delanian S, Porcher R, Balla-Mekias S, Lefaix JL. Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. J Clin Oncol 2003; 21:2545–50.
60. Delanian S, Lefaix JL. Current management for late normal tissue injury: radiation-induced fibrosis and necrosis. Semin Radiat Oncol 2007; 17:99–107.
61. Fernandez-Castro M, Martin-Gil B, Pena-Garcia I, Lopez-Vallecillo M, Garcia-Puig ME. Effectiveness of semi-permeable dressings to treat radiation-induced skin reactions. A systematic review. Eur J Cancer Care (Engl) 2017; 26.
62. Hemati S, Asnaashari O, Sarvizadeh M, Motlagh BN, Akbari M, Tajvidi M, et al. Topical silver sulfadiazine for the prevention of acute dermatitis during irradiation for breast cancer. Support Care Cancer 2012; 20:1613–8.
63. Lee J, Lee SW, Hong JP, Shon MW, Ryu SH, Ahn SD. Foam dressing with epidermal growth factor for severe radiation dermatitis in head and neck cancer patients. Int Wound J 2016; 13:390–3.
64. Ghasemi A, Ghashghai Z, Akbari J, Yazdani-Charati J, Salehifar E, Hosseinimehr SJ. Topical atorvastatin 1% for prevention of skin toxicity in patients receiving radiation therapy for breast cancer: a randomized, double-blind, placebo-controlled trial. Eur J Clin Pharmacol 2019; 75:171–8.
65. Mamalis A, Siegel D, Jagdeo J. Visible red light emitting diode photobiomodulation for skin fibrosis: key molecular pathways. Curr Dermatol Rep 2016; 5:121–8.
66. Canesso MC, Vieira AT, Castro TB, Schirmer BG, Cisalpino D, Martins FS, et al. Skin wound healing is accelerated and scarless in the absence of commensal microbiota. J Immunol 2014; 193:5171–80.
67. Esteban-Vives R, Young M, Over P, Schmelzer E, Corcos A, Ziembicki J, et al. In vitro keratinocyte expansion for cell transplantation therapy is associated with differentiation and loss of basal layer derived progenitor population. Differentiation 2015; 89:137–45.
68. Harris PA, Leigh IM, Navsaria HA. Pre-confluent keratinocyte grafting: the future for cultured skin replacements? Burns 1998; 24:591–3.
69. Gerlach JC, Johnen C, Ottomann C, Brautigam K, Plettig J, Belfekroun C, et al. Method for autologous single skin cell isolation for regenerative cell spray transplantation with non-cultured cells. Int J Artif Organs 2011; 34:271–9.
70. Gerlach JC, Johnen C, McCoy E, Brautigam K, Plettig J, Corcos A. Autologous skin cell spray-transplantation for a deep dermal burn patient in an ambulant treatment room setting. Burns 2011; 37:e19–23.
71. Esteban-Vives R, Corcos A, Choi MS, Young MT, Over P, Ziembicki J, et al. Cell-spray auto-grafting technology for deep partial-thickness burns: Problems and solutions during clinical implementation. Burns 2018; 44:549–59.
72. Esteban-Vives R, Young MT, Ziembicki J, Corcos A, Gerlach JC. Effects of wound dressings on cultured primary keratinocytes. Burns 2016; 42:81–90.
73. Margolis DJ, Berlin JA, Strom BL. Interobserver agreement, sensitivity, and specificity of a ''healed'' chronic wound. Wound Repair Regen 1996; 4:335–8.
74. Lazarus GS, Cooper DM, Knighton DR, Percoraro RE, Rodeheaver G, Robson MC. Definitions and guidelines for assessment of wounds and evaluation of healing. Wound Repair Regen 1994; 2:165–70.
75. Mills JL, Sr., Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery lower extremity threatened limb classification system: risk

stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg 2014; 59:220–34 e1–2.

76. Weaver ML, Hicks CW, Canner JK, Sherman RL, Hines KF, Mathioudakis N, et al. The Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification system predicts wound healing better than direct angiosome perfusion in diabetic foot wounds. J Vasc Surg 2018; 68:1473–81.

77. Hicks CW, Canner JK, Mathioudakis N, Sherman R, Malas MB, Black JH 3rd, et al. The Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification independently predicts wound healing in diabetic foot ulcers. J Vasc Surg 2018; 68:1096–103.

78. Hicks CW, Canner JK, Karagozlu H, Mathioudakis N, Sherman RL, Black JH 3rd, et al. The Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification system correlates with cost of care for diabetic foot ulcers treated in a multidisciplinary setting. J Vasc Surg 2018; 67:1455–62.

79. Mathioudakis N, Hicks CW, Canner JK, Sherman RL, Hines KF, Lum YW, et al. The Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification system predicts wound healing but not major amputation in patients with diabetic foot ulcers treated in a multidisciplinary setting. J Vasc Surg 2017; 65:1698–705 e1.

80. Messerschmidt O, Birkenmayer E, Bomer H, Koslowski L. Radiation sickness combined with burn. Vienna, Austria: International Atomic Energy Agency; 1970.

81. Wintz H. Injuries from roentgen rays in deep therapy. AJR Am J Roentgenol 1923; 10:140–7.

82. United Nations Scientific Committee of the Effects of Atomic Radiation (UNSCEAR). Sources and effects of ionizing radiation; 2006 Report to the General Assembly with Annexes. New York: United Nations; 2006.

83. Ledney GD, Elliott TB. Combined injury: Factors with potential to impact radiation dose assessments. Health Phys 2010; 98:145–52.

84. Kiang JG, Garrison BR, Burns TM, Zhai M, Dews IC, Ney PH, et al. Wound trauma alters ionizing radiation dose assessment. Cell Biosci 2012; 2:20.

85. Kiang JG, Jiao W, Cary LH, Mog SR, Elliott TB, Pellmar TC, et al. Wound trauma increases radiation-induced mortality by activation of iNOS pathway and elevation of cytokine concentrations and bacterial infection. Radiat Res 2010; 173:319–32.

86. Kiang JG, Olabisi AO. Radiation: a poly-traumatic hit leading to multi-organ injury. Cell Biosci 2019; 9:25.

87. Doctrow SR, Lopez A, Schock AM, Duncan NE, Jourdan MM, Olasz EB, et al. A synthetic superoxide dismutase/catalase mimetic EUK-207 mitigates radiation dermatitis and promotes wound healing in irradiated rat skin. J Invest Dermatol 2013; 133:1088–96.

88. Kiang JG, Fukumoto R. Ciprofloxacin increases survival after ionizing irradiation combined injury: gamma-H2AX formation, cytokine/chemokine, and red blood cells. Health Phys 2014; 106:720–6.

89. Kiang JG, Ledney GD. Skin injuries reduce survival and modulate corticosterone, C-reactive protein, complement component 3, IgM, and prostagladin E2 after whole-body-reactor-produced mixed field irradiation. Oxid Med Cell Longev 2013; 2013.

90. Rodgers KE, Tan A, Kim L, Espinoza T, Meeks C, Johnston W, et al. Development of a guinea pig cutaneous radiation injury model using low penetrating X-rays. Int J Radiat Biol 2016; 92:434–43.

91. Todo H. Transdermal permeation of drugs in various animal species. Pharmaceutics 2017; 9.

92. Nicolai JP, Goris RJ. A guinea-pig model in burn research. Eur Surg Res 1980; 12:22–9.

93. Zawacki BE, Jones RJ. Standard depth burns in the rat: the importance of the hair growth cycle. Br J Plast Surg 1967; 20:347–54.

94. Gross J, Farinelli W, Sadow P, Anderson R, Bruns R. On the mechanism of skin wound ''contraction'': A granulation tissue ''knockout'' with a normal phenotype. Proc Natl Acad Sci U S A 1995; 92:5982–6.

95. Bjornson AB, Bjornson HS, Knippenberg RW, Cardone JS. Temporal relationships among immunologic alterations in a guinea pig model of thermal injury. J Infect Dis 1986; 153:1098–107.

96. Kumar S, Kolozsvary A, Kohl R, Lu M, Brown S, Kim JH. Radiation-induced skin injury in the animal model of scleroderma: implications for post-radiotherapy fibrosis. Radiat Oncol 2008; 3:40.

97. Hoeller U, Tribius S, Kuhlmey A, Grader K, Fehlauer F, Alberti W. Increasing the rate of late toxicity by changing the score? A comparison of RTOG/EORTC and LENT/SOMA scores. Int J Radiat Oncol Biol Phys 2003; 55:1013–8.

98. Schauer DA, Coursey BM, Dick CE, McLaughlin WL, Puhl JM, Desrosiers MF, et al. A radiation accident at an industrial accelerator facility. Health Phys 1993; 65:131–40.

99. Babaee N, Mansourian A, Momen-Heravi F, Moghadamnia A, Momen-Beitollahi J. The efficacy of a paste containing Myrtus communis (Myrtle) in the management of recurrent aphthous stomatitis: a randomized controlled trial. Clin Oral Investig 2010; 14:65–70.

100. Szepietowski JC, Sikora M, Kusztal M, Salomon J, Magott M, Szepietowski T. Uremic pruritus: a clinical study of maintenance hemodialysis patients. J Dermatol 2002; 29:621–7.

101. Anscher MS. Targeting the TGF-beta1 pathway to prevent normal tissue injury after cancer therapy. Oncologist 2010; 15:350–9.

102. Meyer W, Schwarz R, Neurand K. The skin of domestic mammals as a model for the human skin, with special reference to the domestic pig. Curr Probl Dermatol 1978; 7:39–52.

103. Herron AJ. Pigs as dermatologic models of human skin disease. 60th Annual Meeting of the American College of Veterinary Pathologists; Monterey, CA: International Veterinary Information Service; 2009.

104. Peel DM, Hopewell JW, Wells J, Charles MW. Nonstochastic effects of different energy beta emitters on pig skin. Radiat Res 1984; 99:372–82.

105. Peel DM, Hopewell JW, Wells J, Charles MW. Late non-stochastic changes in pig skin after beta irradiation. Radiat Res 1985; 101:491–6.

106. Dorand JE, Burnett LR, Tytell M, Bourland JD. A Sr-90 irradiation device for the study of cutaneous radiation injury. Med Phys 2014; 41:493.

107. Burnett LR, Gabard AR, Robinson M, Bourland JD, Dorand JE, Dozier S, et al. Biomolecular analysis of beta dose-dependent cutaneous radiation injury in a porcine model. Radiat Res 2019; 192:145–58.

108. Fuchs E. Skin stem cells: rising to the surface. J Cell Biol 2008; 180:273–84.

109. Jourdan MM, Lopez A, Olasz EB, Duncan NE, Demara M, Kittipongdaja W, et al. Laminin 332 deposition is diminished in irradiated skin in an animal model of combined radiation and wound skin injury. Radiat Res 2011; 176:636–48.

110. Horton JA, Li F, Chung EJ, Hudak K, White A, Krausz K, et al. Quercetin inhibits radiation-induced skin fibrosis. Radiat Res 2013; 180:205–15.

111. van Kilsdonk JW, van den Bogaard EH, Jansen PA, Bos C, Bergers M, Schalkwijk J. An in vitro wound healing model for evaluation of dermal substitutes. Wound Repair Regen 2013; 21:890–6.

112. Horton JA, Chung EJ, Hudak KE, Sowers A, Thetford A, White

AO, et al. Inhibition of radiation-induced skin fibrosis with imatinib. Int J Radiat Biol 2013; 89:162–70.

113. Bernier J, Russi EG, Homey B, Merlano MC, Mesia R, Peyrade F, et al. Management of radiation dermatitis in patients receiving cetuximab and radiotherapy for locally advanced squamous cell carcinoma of the head and neck: proposals for a revised grading system and consensus management guidelines. Ann Oncol 2011; 22:2191–200.

114. Abaci HE, Coffman A, Doucet Y, Chen J, Jackow J, Wang E, et al. Tissue engineering of human hair follicles using a biomimetic developmental approach. Nat Commun 2018; 9:5301.

115. Jayachandran M, Rodriguez S, Solis E, Lei J, Godavarty A. Critical review of noninvasive optical technologies for wound imaging. Adv Wound Care 2016; 5:349–59.

116. Fowler JF, Bewley DK, Morgan RL, Silvester JA, Alper T, Hornsey S. Dose-effect relationships for radiation damage to organized tissues. Nature 1963; 199:253–5.

117. Douglas BG, Fowler JF. The effect of multiple small doses of X rays on skin reactions in the mouse and a basic interpretation. Radiat Res 1976; 66:401–26.

118. Withers HR. The dose-response relationship for epithelial cells of skin. Radiology 1966; 86:1110–1.

119. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. Nature 2008; 453:314–21.

120. Vegesna V, McBride WH, Taylor JM, Withers HR. Effect of low-dose radiation on mouse dermal tissue using wound strength as an endpoint. Int J Radiat Biol 1997; 72:645–52.

121. Vegesna V, McBride WH, Taylor JM, Withers HR. The effect of interleukin-1 beta or transforming growth factor-beta on radiation-impaired murine skin wound healing. J Surg Res 1995; 59:699–704.

122. Vegesna V, Withers HR, Holly FE, McBride WH. The effect of local and systemic irradiation on impairment of wound healing in mice. Radiat Res 1993; 135:431–3.

123. Xie MW, Gorodetsky R, Micewicz ED, Mackenzie NC, Gaberman E, Levdansky L, et al. Marrow-derived stromal cell delivery on fibrin microbeads can correct radiation-induced wound-healing deficits. J Invest Dermatol 2013; 133:553–61.

124. Vegesna V, McBride WH, Withers HR. Postoperative irradiation impairs or enhances wound strength depending on time of administration. Radiat Res 1995; 143:224–8.

125. Escuin-Ordinas H, Li S, Xie MW, Sun L, Hugo W, Huang RR, et al. Cutaneous wound healing through paradoxical MAPK activation by BRAF inhibitors. Nat Commun 2016; 7:12348.

126. Fliedner TM. Medical management of radiation accidents-manual on the acute radiation syndrome. London: British Institute of Radiology; 2009.

127. Fliedner TM, Powles R, Sirohi B, Niederwieser D. European Group for Blood Marrow Transplantation Nuclear Accident Committee. Radiologic and nuclear events: the METREPOL severity of effect grading system. Blood 2008; 111:5757–8.

128. Waselenko JK, MacVittie TJ, Blakely WF, Pesik N, Wiley AL, Dickerson WE, et al. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. Ann Intern Med 2004; 140:1037–51.

129. Dainiak N, Gent RN, Carr Z, Schneider R, Bader J, Buglova E, et al. Literature review and global consensus on management of acute radiation syndrome affecting nonhematopoietic organ systems. Disaster Med Public Health Prep 2011; 5:183–201.

130. Iddins CJ, Cohen SR, Goans RE, Wanat R, Jenkins M, Christensen DM, et al. Case report: Industrial X-ray injury treated with non-cultured autologous adipose-derived stromal vascular fraction (SVF). Health Phys 2016; 111:112–6.

131. Nathwani AC, Down JF, Goldstone J, Yassin J, Dargan PI, Virchis A, et al. Polonium-210 poisoning: a first-hand account. Lancet 2016; 388:1075–80.

132. Sugarman SL, Findley WM, Toohey RE, Dainiak N. Rapid response, dose assessment, and clinical management of a plutonium-contaminated puncture wound. Health Phys 2018; 115:57–64.

133. Glasstone S, Dolan PJ, United States Department of Defense, United States Department of Energy, United States. Defense Atomic Support Agency. The effects of nuclear weapons. 3d ed. Washington, DC: U.S. Dept. of Defense; 1977.

134. National Research Council (US), Committee on Fire Research, Office of Civil Defense. Mass burns: Proceedings of a workshop, 13–14 March 1968. In: Walter CW, Phillips AW, editors. Washington, DC: National Academy of Sciences; 1969. p. 248.

135. Goans R, Iddins C, Christensen D. Ultrasound and thermography for diagnosis of extent and magnitude of acute local radiation injury (LRI). Proceedings of the 5th International REAC/TS Symposium: The Medical Basis for Radiation Accident Preparedness and the Biodosimetry Workshop. Oak Ridge, TN: REAC/TS; 2013.

136. New drug and biological drug products; evidence needed to demonstrate effectiveness of new drugs when human efficacy studies are not ethical or feasible. Final rule. Fed Regist 2002; 67:37988–98.

137. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). Guidance for industry. Chronic cutaneous ulcer and burn wounds–developing products for treatment. Rockville, MD: Food and Drug Administration; 2006.

138. Willard-Mack C, Ramani T, Auletta C. Dermatotoxicology: Safety evaluation of topical products in minipigs: Study designs and practical considerations. Toxicol Pathol 2016; 44:382–90.

139. DiCarlo AL, Tamarat R, Rios CI, Benderitter M, Czarniecki CW, Allio TC, et al. Cellular therapies for treatment of radiation injury: Report from a NIH/NIAID and IRSN workshop. Radiat Res 2017; 188:e54–e75.

140. Ebrahimian TG, Pouzoulet F, Squiban C, Buard V, Andre M, Cousin B, et al. Cell therapy based on adipose tissue-derived stromal cells promotes physiological and pathological wound healing. Arterioscler Thromb Vasc Biol 2009; 29:503–10.

141. Holler V, Buard V, Roque T, Squiban C, Benderitter M, Flamant S, et al. Early and late protective effect of bone marrow mononuclear cell transplantation on radiation-induced vascular dysfunction and skin lesions. Cell Transplant 2019; 28:116–28.

142. Anderson HC, Mulhall D, Garimella R. Role of extracellular membrane vesicles in the pathogenesis of various diseases, including cancer, renal diseases, atherosclerosis, and arthritis. Lab Invest 2010; 90:1549–57.

143. Thery C, Gho YS, Quesenberry P. Journal of extracellular vesicles: the seven year itch! J Extracell Vesicles 2019; 8:1654729.

144. Wen S, Dooner M, Papa E, Del Tatto M, Pereira M, Borgovan T, et al. Biodistribution of mesenchymal stem cell-derived extracellular vesicles in a radiation injury bone marrow murine model. Int J Mol Sci 2019; 20.

145. Szatmari T, Hargitai R, Safrany G, Lumniczky K. Extracellular vesicles in modifying the effects of ionizing radiation. Int J Mol Sci 2019; 20.

146. Flamant S, Tamarat R. Extracellular vesicles and vascular injury: New insights for radiation exposure. Radiat Res 2016; 186:203–18.

147. Martella S, Rietjens M, Lohsiriwat V, Lazzari R, Vavassori A, Jereczek B, et al. Acute radiation dermatitis in breast cancer: topical therapy with vitamin E acetate in lipophilic gel base. Ecancermedicalscience 2010; 4:190.

148. Dion MW, Hussey DH, Osborne JW. The effect of pentoxifylline on early and late radiation injury following fractionated irradiation in C3H mice. Int J Radiat Oncol Biol Phys 1989; 17:101–7.

149. Zhu KQ, Engrav LH, Gibran NS, Cole JK, Matsumura H, Piepkorn M, et al. The female, red Duroc pig as an animal model of hypertrophic scarring and the potential role of the cones of skin. Burns 2003; 29:649–64.

150. Kobielak A, Fuchs E. Alpha-catenin: at the junction of intercellular adhesion and actin dynamics. Nat Rev Mol Cell Biol 2004; 5:614–25.

151. Ghatnekar GS, O'Quinn MP, Jourdan LJ, Gurjarpadhye AA, Draughn RL, Gourdie RG. Connexin43 carboxyl-terminal peptides reduce scar progenitor and promote regenerative healing following skin wounding. Regen Med 2009; 4:205–23.

152. Montgomery J, Ghatnekar GS, Grek CL, Moyer KE, Gourdie RG. Connexin 43-based therapeutics for dermal wound healing. Int J Mol Sci 2018; 19.

153. Rhett JM, Ghatnekar GS, Palatinus JA, O'Quinn M, Yost MJ, Gourdie RG. Novel therapies for scar reduction and regenerative healing of skin wounds. Trends Biotechnol 2008; 26:173–80.

154. Grek CL, Montgomery J, Sharma M, Ravi A, Rajkumar JS, Moyer KE, et al. A multicenter randomized controlled trial evaluating a Cx43-mimetic peptide in cutaneous scarring. J Invest Dermatol 2017; 137:620–30.

155. Grek CL, Prasad GM, Viswanathan V, Armstrong DG, Gourdie RG, Ghatnekar GS. Topical administration of a connexin43-based peptide augments healing of chronic neuropathic diabetic foot ulcers: A multicenter, randomized trial. Wound Repair Regen 2015; 23:203–12.

156. Ghatnekar GS, Grek CL, Armstrong DG, Desai SC, Gourdie RG. The effect of a connexin43-based peptide on the healing of chronic venous leg ulcers: a multicenter, randomized trial. J Invest Dermatol 2015; 135:289–98.

157. Moore K, Bryant ZJ, Ghatnekar G, Singh UP, Gourdie RG, Potts JD. A synthetic connexin 43 mimetic peptide augments corneal wound healing. Exp Eye Res 2013; 115:178–88.

158. Hunt TK. The physiology of wound healing. Ann Emerg Med 1988; 17:1265–73.

159. Haubner F, Ohmann E, Pohl F, Strutz J, Gassner HG. Wound healing after radiation therapy: Review of the literature. Radiat Oncol 2012; 7:162.

160. Stiernberg J, Norfleet AM, Redin WR, Warner WS, Fritz RR, Carney DH. Acceleration of full-thickness wound healing in normal rats by the synthetic thrombin peptide, TP508. Wound Repair Regen 2000; 8:204–15.

161. Fife C, Mader JT, Stone J, Brill L, Satterfield K, Norfleet A, et al. Thrombin peptide Chrysalin stimulates healing of diabetic foot ulcers in a placebo-controlled phase I/II study. Wound Repair Regen 2007; 15:23–34.

162. Olszewska-Pazdrak B, Hart-Vantassell A, Carney DH. Thrombin peptide TP508 stimulates rapid nitric oxide production in human endothelial cells. J Vasc Res 2010; 47:203–13.

163. Olszewska-Pazdrak B, Carney DH. Systemic administration of thrombin peptide TP508 enhances VEGF-stimulated angiogenesis and attenuates effects of chronic hypoxia. J Vasc Res 2013; 50:186–96.

164. Freyberg S, Song YH, Muehlberg F, Alt E. Thrombin peptide (TP508) promotes adipose tissue-derived stem cell proliferation via PI3 kinase/Akt pathway. J Vasc Res 2009; 46:98–102.

165. Olszewska-Pazdrak B, McVicar SD, Rayavara K, Moya SM, Kantara C, Gammarano C, et al. Nuclear countermeasure activity of TP508 linked to restoration of endothelial function and acceleration of DNA repair. Radiat Res 2016; 186:162–74.

166. Kantara C, Moya SM, Houchen CW, Umar S, Ullrich RL, Singh P, et al. Novel regenerative peptide TP508 mitigates radiation-induced gastrointestinal damage by activating stem cells and preserving crypt integrity. Lab Invest 2015; 95:1222–33.

167. Ryan JL, Bole C, Hickok JT, Figueroa-Moseley C, Colman L, Khanna RC, et al. Post-treatment skin reactions reported by cancer patients differ by race, not by treatment or expectations. Br J Cancer 2007; 97:14–21.

168. Foley PL, Kendall LV, Turner PV. Clinical management of pain in rodents. Comp Med 2019; 69:468–89.

169. Baryza MJ, Baryza GA. The Vancouver Scar Scale: an administration tool and its interrater reliability. J Burn Care Rehabil 1995; 16:535–8.

170. Laver LA, Armstrong DG, Harkless LB. Classification of diabetic foot wounds. J Foot Ankle Surg 1996; 35:528031.

Management of Ionizing Radiation Injuries and Illnesses, Part 5: Local Radiation Injury

Carol J. Iddins, MD; Doran M. Christensen, DO; Steven J. Parrillo, DO; Erik S. Glassman, EMT-P, MS; and Ronald E. Goans, PhD, MD, MPH

From the Radiation Emergency Assistance Center/Training Site (REAC/TS), Oak Ridge Institute for Science and Education in Tennessee (Drs Iddins, Christensen, and Goans); the Division of Emergency Medicine at Einstein Medical Center in Elkins Park and Philadelphia University in Pennsylvania (Dr Parrillo); National Security and Emergency Management Programs at the Oak Ridge Institute for Science and Education in Tennessee (Mr Glassman); and the Division of Radiological Engineering at MJW Corporation in Oak Ridge, Tennessee (Dr Goans).

Financial Disclosures: None reported.

Support: This work was partly performed under Contract # DE-AC05-06OR23100 between ORAU and the US DOE. REAC/TS is a program of the Oak Ridge Institute for Science and Education, which is operated for the US DOE by ORAU.

Address correspondence to Erik S. Glassman, EMT-P, MS, Oak Ridge Institute for Science and Education, 4301 Wilson Blvd, Suite 300, Arlington, VA 22202-1867.

E-mail: erik.glassman@orise.orau.gov

Submitted May 13, 2013; revision received October 18, 2013; accepted November 13, 2013.

This final article in the series on the medical management of ionizing radiation injuries and illnesses focuses on the effects of acute ionizing radiation exposure to one of the largest organ systems of the body—the skin. These injuries may extend beyond the skin into deeper tissues and cause local radiation injury. There are numerous causes of these injuries, ranging from industrial incidents to medical procedures. In the present article, the authors characterize the clinical course, pathophysiologic process, sources of injury, diagnosis, and management of local radiation injury and describe a clinical scenario. This information is important for primary care physicians, to whom patients are likely to initially present with such injuries.

J Am Osteopath Assoc. 2014;114(11):840-848
doi:10.7556/jaoa.2014.170

The skin is usually defined as the epidermis, dermis, and appendages (sebaceous, sweat, apocrine, mammary glands, and hair follicles).[1,2] Injury to the skin due to ionizing radiation (IR) can result in local radiation injury (LRI), which is not limited to the skin. Local radiation injury can be sustained from fluoroscopy, nuclear medicine, and computed tomography in disciplines such as radiology, nuclear medicine, interventional radiology, and interventional cardiology.[3] As noted by Shope,[4] the US Food and Drug Administration (FDA) first brought attention to fluoroscopy-induced cutaneous radiation injuries with the Safe Medical Devices Act of 1990. Since that time, much attention has been paid to LRI sustained from these injuries.[4] However, it is primary care physicians who order these tests and follow up with patients after testing and, therefore, primary care physicians should be a patient's primary source for information on the risks of medical imaging. All clinicians should be aware of the signs and symptoms of cutaneous and deeper-tissue injuries caused by IR. Many other sources of LRI exist, resulting in pain, disability, and death.[5] Industrial or commercial sources, medical sources, nuclear accidents, and, potentially, terrorist events can lead to cutaneous and deeper-tissue exposure to high doses of IR.

To increase physician awareness of LRI, we review the terminology, clinical presentation, sources of injury, and evaluation and management of LRI, and conclude with a clinical scenario to illustrate the major concepts. Although these are not common injuries, they are difficult to diagnose without a known history of IR exposure, and they are difficult to manage. Similar to chemical and thermal burns, the extent of dermatologic injury has been shown to be a strong prognosticator of patient survival.[6,7] However, these injuries have some significant caveats in management compared with chemical and thermal burns, which are discussed in the Management section.

Terminology

The terms used to describe IR injury to the skin and deeper tissues vary. Some authorities classify damage to the skin as a subsyndrome of acute radiation syndrome (ARS) and generally use the term *cutaneous radiation syndrome* (CRS) to refer to this injury. Cutaneous radiation syndrome is also used to describe the classic, clinical picture of IR injuries to skin without another organ system component of ARS.[6,8] *Local radiation injury* (LRI) is sometimes used to refer to injury to tissues or organs deeper than the skin,[9-12] and this term will be used henceforth in this article to describe IR injuries to the skin and deeper tissues. *Beta burns* refer to injury to the skin by beta particles and may cause a partial or even a full-thickness burn, depending on the beta energy of the radionuclide.[13] *Radiodermatitis* is often used to refer to radiotherapy-induced skin changes.[14]

Clinical Course

Acute LRI often occurs when an individual handles or comes into close contact with a high-dose rate, sealed radiation source. Many of these accidents are reported to the Radiation Emergency Assistance Center/Training Site (REAC/TS) and managed in consultation with patients' primary care physicians.

The 3 isotopes that cause the most concern for these injuries are ^{192}iridium, ^{60}cobalt, and ^{137}cesium. Local radiation injury is a deterministic effect, or an effect that varies with dose and for which a threshold is believed to exist.[15] The *Table* presents the clinical dose thresholds for LRI as used at REAC/TS. It is important to note that this information serves as a guideline and that there is some variation among sources for dose threshold and timing of appearance.[10,12,16]

Pathophysiology

A prodrome of erythema may occur transiently within a few hours of exposure and reappear weeks later as a manifestation of the injury. The mechanism causing erythema includes arteriolar constriction with capillary dilation and increased vascular permeability. Early erythema is highly variable, however, and may not occur at all, although the incidence increases with dose. With dry desquamation, there is diminished mitotic activity in the cells of the basal and parabasal layers, with thinning of the epidermis and desquamation of large macroscopic flakes of skin. Moist desquamation exhibits intracellular edema, coalescence of vesicles to form bullae, and a moist dermal surface. With doses greater than 25 Gy, overt radionecrosis may occur.

The classic presentation of LRI during the weeks to months after injury follows. Within the first week, the patient may present with a prodrome of transient erythema (which, as above, is highly variable), pruritis, and paresthesias of the skin. In subsequent weeks, true erythema develops along with progressive epilation, suppression of sweating, and diminished sebaceous gland secretion. As the injury evolves, the patient exhibits edema, pruritus, and blister formation, and he or she may have severe pain. There may be a spectrum of changes in

Table.
Clinical Dose Estimation for Local Radiation Injury

Radiation Dose, Gy	Clinical Sign	Exposure to Presentation, Time
3	Epilation (temporary)	14-17 d
6	Erythema	Minutes to weeks
10-15	Dry desquamation	2-3 wk
15-20	Moist desquamation	2-3 wk
>25	Deep ulceration/ radionecrosis	>21 d

Source: *The Medical Aspects of Radiation Incidents.* Oak Ridge, TN: The Radiation Emergency Assistance Center/Training Site; 2013:21-22. http://orise.orau.gov/files/reacts/medical-aspects-of-radiation-incidents.pdf. Accessed September 24, 2014.

pigmentation, ranging from redness to bronzing and blackening if necrosis develops. A higher dose leads to an earlier and more severe presentation.

Delayed effects of LRI, which may occur from months to years after injury, include telangiectasia formation, atrophy, and fibrosis. Telangiectasias occur as a result of damage to the microvasculature and subsequent distortion of capillary loops. Fibrosis, one of the most consistent delayed effects, may occur in tissues and vessels. Fibroblasts are the main producers of extracellular matrix, which is necessary for normal wound healing and scar formation. Local radiation injury causes the fibroblasts to become atypical and enlarged, often called *radiation fibroblasts*. These atypical and dysfunctional fibroblasts may be responsible for the delayed fibrosis.[17] This delayed and progressive fibrosis is 1 factor that makes LRI so different from chemical or thermal burns.[18]

The pathophysiology of LRI is still not fully understood and seems to be multifactoral. There is agreement that part of the reason LRI continues evolving is secondary to waves of various interrelated physiologic cascades.[12,19] Inflammation is a major component. Many mediators are involved with and feed back to prolong these processes. Damage to the microvasculature consists of damage to endothelial cells and subsequent activation of many proinflammatory and proclotting cascades. In addition, IR induces free radical species that may lead to oxidative stress.

It is important to recognize that patients may have a high dose of radiation to the skin with little to no dose to the whole body or to the bone marrow. As noted above, with deeper tissue injury, other organ systems may become involved in the area of injury and present different subsyndromes of ARS. There may be enough damage to deeper tissues over enough area or even a whole-body distribution to cause ARS. Therefore, a suspicion of ARS is warranted in any case of radiation exposure, even if only LRI is initially evident. Ionizing radiation injury to more than 50% of the body surface area is a poor prognosticator for survival.[6] Multiorgan failure and death may result.[5,18]

Sources of Injury

Many LRI incidents occur in industrial settings. In the United States, most of these cases are known to be IR-related early in their course. However, given that the injury may not manifest until weeks later, patients may delay seeking care. Internationally, a number of "orphaned" sources have been handled by persons who did not know the devices were radioactive. These injuries are often misdiagnosed. For further reading on many of these cases, full reports can be downloaded from the International Atomic Energy Agency at http://www-pub.iaea.org/mtcd/publications/.

The nuclear power plant accident at Chernobyl in 1986 is a well-known incident in which many of the victims had severe CRS caused by a mixture of beta particles and gamma-emitting radionuclides. Sixteen of the 28 acute deaths after the incident were attributed to CRS.[5]

Another source of LRI that has attracted much attention over the past 20 years is radiologic imaging techniques that deliver a large dose of IR. The average radiation dose received by patients in the United States has roughly doubled over the past 20 years, and the increase is primarily attributed to medical exposure (radiography, fluoroscopy, computed tomography, nuclear medicine, and external beam radiotherapy).[20,21]

Physician and patient education along with safety features on newer equipment have helped reduce the dose of radiation exposure. In the past, a lack of education resulted in patients not knowing that they were being exposed to radiation during their procedures or understanding the risk associated with exposure. A latent LRI presentation may not have been attributed to the procedure by patient or physician.[4,22-25] Educational efforts among physicians are improving and are including many different disciplines.[21,26] Discussing with patients the nature of a radiologic procedure, the radiation dose involved, and the risks and benefits of the procedure is necessary, especially if the procedure is potentially lifesaving. Radiotherapy-induced LRI should be suspected if the wound has a grid-like pattern (*Figure*), if there are 2 locations of injury that correspond to the angles used in

the procedure, or if the wound resembles a burn without a history of thermal or chemical burn.

Diagnosis and Evaluation

The diagnosis of LRI depends on a detailed recent history and a complete physical examination. Physicians should collect incident histories, including what the patients were doing at the time of injury and for how long; whether they touched the source and if so with which fingers/hands; whether they held the source to their face to examine it closely (eye exposure); whether anyone else handled it or was exposed; whether the source was intact (some radiotherapy sources may be broken open); and whether they put it in a clothing pocket. Obviously, these questions will vary depending on the incident. A health or medical physicist should be enlisted to fully elucidate the details of an incident to estimate the dose. The health physicist may also recreate the incident to assist in dose estimation. For the physician, it is important to ask patients about their symptoms and the timeline of the onset, severity, and disappearance of symptoms. These symptoms may include erythema, hair loss, peeling, blistering, itching, tingling, burning, and pain.

Because ARS should be considered in any case of radiation exposure, blood chemistry should be analyzed as appropriate. Baseline and serial complete blood cell (CBC) counts with differentials should be obtained (ideally, every 8 hours) to assess for a decline in absolute lymphocyte count during the first 12 to 48 hours after LRI.[27,28] If it is determined that the patient has a severe local injury that could result in ARS, CBC counts with differentials will be needed to monitor for bone marrow suppression.[9,27,28] Other laboratory tests to consider include serum amylase (for head or neck exposure) and C-reactive protein (CRP), because CRP will be elevated in cases of significant partial body or total body irradiation. More information about the laboratory evaluation of ARS can be found in Christensen et al.[29]

Imaging studies should be performed as indicated and to detect the degree of tissue and microvascular damage. Magnetic resonance imaging and magnetic resonance angiography are helpful in determining the extent of tissue damage. There has been much research and some historical use of ultrasound with Doppler and thermography to evaluate the extent of tissue damage, but these modalities are not in widespread use for the evaluation of LRI.[30-32] Some additional studies to determine the margin of damage to the microvasculature include laser Doppler, blood perfusion imaging, radioisotope clearance, transcutaneous oxygen pressure, spectrophotometry, and photoplethysomography.[33-40]

Electron spin or electron paramagnetic resonance (EPR) may be a helpful tool for dose estimation in conjunction with other methods of dose estimation (eg, incident recreation and cytogenetic biodosimetry).[41-43] Electron paramagnetic resonance, which measures the radiation-induced free radical formation, can be performed on tissue, bone, teeth or tooth enamel, nails, and textiles. This specialized test is still considered primarily a research tool; it is not widely or commercially available. In the United States, EPR for radiation dose assessment is currently used in research activities at the National Institute of Standards and Technology, the US Naval Dosimetry Center, and the EPR Center for the Study of Viable Systems at the Geisel School of Medicine at Dartmouth.[41,42,44] The *Institut de Radioprotection et de Surete Nucleaire* (the French Institute for Radiological Protection and Nuclear Safety) and other institutions around the world are also actively performing research in EPR dosimetry.[41,42] An important clinical consideration for using this biodosimetry tool is that all tissue (from debridement, amputation, etc) must be preserved for study, as it may provide important dose information.

One of the best tools for evaluating LRI is serial, digital color photography. This format is ideal for electronic submission of photographs to subject matter experts for consultation and evaluation. These wounds do evolve over time, and keeping a photographic timeline captures the progression. As with any medical condition that changes with time, it is advantageous to show disease course, treatment response, and treatment progression or

regression. Many dermatologists use photo-mapping for skin surveillance of atypical nevi and in microscopically controlled surgery.[45]

Management

Most treatment regimens for patients with LRI have been derived from radiation oncology, traditional burn care, and past experiences with acute LRI. Acute LRI may differ dramatically from radiotherapy-induced injuries, because radiotherapy-induced skin injuries are the result of fractionated doses, not acute doses. Fractionation of a radiation dose allows for some tissue healing and repair to occur between treatments. Many of the incidents of accidental LRI are delivered much more rapidly or at high doses with little or no fractionation.

Local radiation injury is managed similarly to thermal burns—with a few important caveats. One is that LRI needs to be protected from temperature extremes and trauma from the moment of injury indefinitely, even after apparent healing. These injuries are prone to reactivation with even the mildest of trauma for years after the initial injury. As soon as the injury is known to be IR-induced, the patient needs to be counseled about ways to protect the area, including work restrictions. In the case of an occupational LRI, patient and employer need to understand the health risks involved. Like thermal burns, IR wounds are very painful. The difference is that the pain may continue, perhaps for years, until successful wound healing has occurred. Often, wound healing is achieved with skin grafting or amputation. Another caveat is the damage to the microvasculature, which may be too extensive for the skin grafting techniques used in burn surgery. There must be a well-vascularized flap for these wounds to heal.[41]

Inflammation plays a large role in LRI, and methods to reduce inflammation are beneficial. There is consensus for topical steroidal treatment; class II and III topical steroids have been used historically.[8,47,48] Some radiation oncologists have had success with intralesional steroids (A.L. Wiley, personal communication, September 2013). The World Health Organization consultancy was strongly against use of systemic steroids in the absence of a specific indication.[8] Nonsteroidal anti-inflammatory drugs may also be indicated, but their use for LRI has not been addressed by the World Health Organization consultancy. Further, they should only be used if no contraindication is present (eg, gastrointestinal ulcer or bleeding, thrombocytopenia, coagulopathy, or aspirin allergy).

Recommendations have been fairly consistent on the use of topical antibiotics for LRI.[9] The use of systemic antibiotics should be based on the clinical picture. Physicians should consider consulting with infectious disease specialists if there is suspicion of a high dose to deep tissues, a large percentage of affected body surface area, or another organ system is involved. The use of silver sulfadiazine and dressings may be helpful, as indicated. "Skin substitutes" and other dressing constructs should be used as indicated for thermal burns.

Combination treatment with 400 mg of pentoxifylline (not FDA-approved for this use) 3 times per day and α-tocopherol (a form of vitamin E) has shown success in decreasing radiofibrosis.[49-51] Pentoxifylline alone may also help to decrease pulmonary damage due to lung and breast radiotherapy.[52] Other antioxidants or antioxidant enzymes such as superoxide dismutase have been used to manage these injuries and are still areas with active research for further development.[53-55] Topical aloe vera seems to shorten healing time, has anti-inflammatory and antihistaminic properties, and is an excellent moisturizer.[56] Aloe vera is often recommended to patients undergoing radiotherapy; however, the literature about its efficacy is mixed.[57,58]

Reports have provided evidence that mast cells may play a role in LRI. Mast cells store 98% of our body's histamine.[59] They become activated and degranulate, releasing histamine and many other proinflammatory mediators. Historically, antihistamines have been used for symptomatic relief of pruritus and erythema.[8,59-62] Some animal studies support a treatment role for these medications.[62-64] Nonsedating antihistamines (fexofenadine or loratadine) have worked well in REAC/TS' experience.

Another treatment modality that may be helpful is hyperbaric oxygen therapy. This modality has been effective for delayed radiotherapy injuries, particularly osteoradionecrosis.[65] Hyperbaric oxygen therapy may result in improved quality of life, as exhibited in gynecologic oncology patients with delayed manifestation of radiotherapy-induced injuries, such as tissue necrosis and osteoradionecrosis.[66] The benefits of hyperbaric oxygen may include vasculoneogenesis, increased oxygenation of the tissues, and, possibly, increased production of various growth factors.[65]

Traditional surgical management of LRI may be indicated, but surgeons must be aware that the margin of injury and nonviable tissue will not be grossly visible or evident. Imaging modalities or radiation dose mapping should be used to delineate the margin of the damage to the microvasculature or margin for necrosis before surgical intervention. If the microvasculature and infrastructure are adequate, and the dose is below the threshold for necrosis, successful skin-grafting may be achieved. Consultation with experts in radiation-induced injuries should be done before definitive surgical therapy.

A newer treatment approach that shows promise is mesenchymal stem cell therapy or adipose-derived stem cells. Japanese investigators,[67] using adipose-derived stem cells injected into the wound and surgical debridement, showed good wound healing in a gynecologic oncology patient with late tissue and bone necrosis. French investigators[10] successfully used bone marrow mesenchymal stem cell wound injections, with and without skin grafting, in a small series of patients. They used dose mapping techniques to determine the margins for excision of all of the necrotic or potentially necrotic tissue and then injected the area with the mesenchymal stem cells.[10] Both aforementioned investigation teams are engaged in ongoing clinical trials of these methods, with continued success. Appropriate controlled studies need to be performed with long-term follow-up before these techniques can be recommended unequivocally. However, such results may be difficult to achieve with the relatively low incidence rate of LRI.

Clinical Scenario

A 62-year-old man had chest pain while traveling alone overseas. His medical history included diabetes, coronary artery disease, and 2 previous percutaneous coronary interventions, with 1 stent placed each time. In addition, he had a 40 pack-per-year history of tobacco abuse and was obese (height, 5'9"; weight, 240 lb). He was rushed into the interventional cardiology suite of a large metropolitan hospital and, after several hours, a successful percutaneous coronary intervention was accomplished. The patient returned home from his travels without further incident. Twelve days later, he experienced itching in his back, but it stopped. Twenty-five days after his return home, he began to have more itching, burning, and pain in his back. His primary care physician noted some erythema and desquamation on his left, lower scapular area and his right subscapular area (laterally) but was more concerned with establishing follow-up with his cardiologist. A month after the follow-up, his physician noted some blister formation in the left, lower scapular area and the right, subscapular area (laterally) (*Figure*). His primary care physician requested a consultation with a dermatologist, who tried conservative topical treatment without success. The dermatologist performed a punch biopsy, and the specimen showed morphea consistent with sclerosis or radiation injury. At that point, the primary care physician consulted REAC/TS. The patient was evaluated and started on a treatment protocol similar to the management recommendations outlined in the Management section in the current article. He received more than the standard recommended hyperbaric oxygen therapy (100 treatments). His wound care continued for 4 years, and then he underwent wide local excision of the nonhealing area of the lesion, with aggressive postoperative wound care (months of wound vacuum dressings, dressing changes, etc). He also had successful excision and skin grafting of the lesion on the left. One year after his surgical procedures and aggressive wound care, his wounds healed completely.

Discussion

Local radiation injury has a classic presentation with a somewhat predictable course. Presenting signs include transient erythema, itching, and edema, resulting in a nonhealing wound, possibly with a grid-like pattern, that may progress to necrosis. The additional presence of nausea, emesis, and diarrhea should put the physician on alert that such a patient may have ARS. Furthermore, immunologic compromise may result in a complex and potentially life-threatening situation that requires intensive therapy. Many cases of occupational LRI involve the hands. While not necessarily life-threatening, LRI can cause significant disability and psychosocial problems. On-the-job LRI is further complicated by the unapproved, "experimental" therapies that may be required in these cases but are not covered by worker's compensation insurance carriers. Mesenchymal stem cell wound injections are not approved by the FDA.

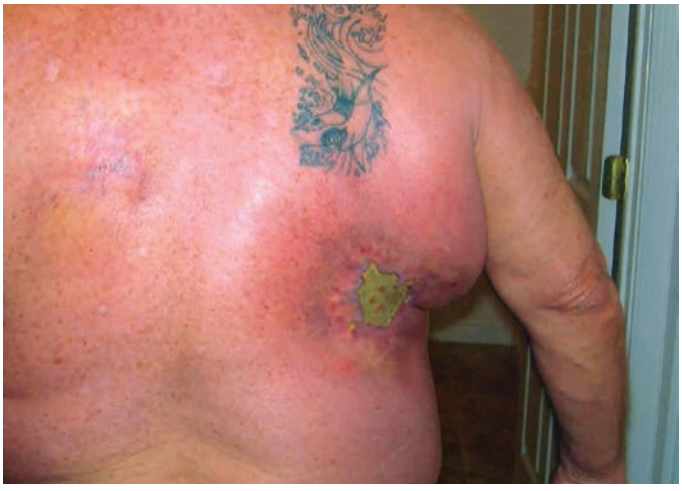

Figure.
Blister formation in the left lower scapular and right subscapular regions of a patient who underwent percutaneous coronary intervention a month earlier. The grid-like pattern is associated with ionizing radiation injury.

Conclusion

Although uncommon, LRI is difficult to diagnose without a known history of radiation exposure. These injuries often have a delayed presentation that may make the history and dose estimation difficult to impossible. They may initially present as minor but evolve into a critical stage and are often associated with a high degree of disability and morbidity. An evolving wound resembling a burn in the absence of a history of thermal or chemical exposure should alert physicians to the possibility of LRI. As with most complex medical cases, specialty consultation should be obtained when dealing with IR-induced injuries of all types. Specialties that may be helpful include radiation oncology, nuclear medicine/radiology, hematologic oncology, surgical oncology, dermatology, burn surgery, and infectious diseases. Other resources available for assistance are REAC/TS (emergency number, 865-576-1005; http://orise.orau.gov/reacts/), the Armed Forces Radiobiology Research Institute (301-295-0530; http://www.usuhs.mil/afrri/), the Radiation Treatment Injury Network (http://ritn.net), and public radiologic health departments.

References

1. MacKie RM. *Clinical Dermatology (Oxford Core Texts)*. 5th ed. New York, NY: Oxford University Press; 2003:19.
2. Marks JG Jr, Miller JJ. *Lookingbill and Marks' Principles of Dermatology*. 5th ed. Philadelphia, PA: Saunders; 2013:2.
3. Koenig TR, Mettler FA, Wagner LK. Skin injuries from fluoroscopically guided procedures: part 2, review of 73 cases and recommendations for minimizing dose delivered to patient. *AJR Am J Roentgenol*. 2001;177(1):3-20.
4. Shope TB. Radiation-induced skin injuries from fluoroscopy. *Radiographics*. 1996;16(5):1195-1199.
5. Gottlober P, Steinert M, Weiss M, et al. The outcome of local radiation injuries: 14 years of follow-up after the Chernobyl accident. *Radiat Res*. 2001;155(3):409-416.
6. Meineke V, van Bueningen D, Sohns T, Fliedner TM. Medical management principles for radiation accidents [review]. *Mil Med*. 2003;168(3):219-222.
7. Fliedner TM, Dörr HD, Meineke V. Multi-organ involvement as a pathogenetic principle of the radiation syndromes: a study involving 110 case histories documented in SEARCH and classified as the bases of haematopoietic indicators of effect. *BJR Suppl*. 2005;27:1-8.

8. Dainiak N, Gent RN, Carr Z, et al. Literature review and global consensus on management of acute radiation syndrome affecting nonhematopoietic organ systems. *Disaster Med Public Health Prep*. 2011;5(3):183-201. doi:10.1001/dmp.2011.73.

9. Oak Ridge Institute for Science and Education website. Guidance for Radiation Accident Management. Managing radiation emergencies: guidance for hospital medical management. http://www.orise.orau.gov/reacts/guide/syndrome.htm. Accessed July 8, 2014.

10. Benderitter M, Gourmelon P, Bey E, et al. New emerging concepts in the medical management of local radiation injury. *Health Phys*. 2010;98(6):851-857. doi:10.1097/HP.0b013e3181c9f79a.

11. Radiation Emergency Assistance Center/Training Site. *The Medical Aspects of Radiation Incidents*. Oak Ridge, Tennessee: Oak Ridge Institute for Science and Education; 2011. http://orise.orau.gov/files/reacts/medical-aspects-of-radiation-incidents.pdf. Accessed July 8, 2014.

12. Muller K, Meineke V. Advances in the management of localized radiation injuries. *Health Phys*. 2010;98(6):843-850. doi:10.1097/HP.0b013e3181adcba7.

13. Ansari A. *Radiation Threats and Your Safety: A Guide to Preparation and Response for Professionals and Community*. Boca Raton, FL: Chapman & Hall/CRC; 2009.

14. Dini D, Macchia R, Gozza A, et al. Management of acute radiodermatitis: pharmacological or nonpharmacological remedies? *Cancer Nurs*. 1993;16(5):366-370.

15. Radiation terms and definitions. Health Physics Society website. http://hps.org/publicinformation/radterms/. Accessed July 8, 2014.

16. National Council on Radiation Protection & Measurements. *NCRP Report No. 161, Management of Persons Contaminated With Radionuclides*. Bethesda, MD: NRCP; 2008:131.

17. Fajardo LF, Berthrong M, Anderson RE. *Radiation Pathology*. New York: Oxford University Press Inc; 2001:159.

18. Peter RU. Cutaneous radiation syndrome in multi-organ failure. *BJR Suppl*. 2005;27:180-184.

19. Benderitter M, Gourmelon P, Bey E, et al. New emerging concepts in the medical management of local radiation injury. *Health Phys*. 2010;98(6):851-857. doi:10.1097/HP.0b013e3181c9f79a.

20. National Council on Radiation Protection & Measurments. *NCRP Report No.160, Ionizing Radiation Exposure of the Population of the United States, National Council on Radiation Protection and Measurements*. Bethesda, MD: NCRP; 2009:4-5.

21. Balter S, Miller DL. Patient skin reactions from interventional fluoroscopy procedures [review]. *AJR Am J Roentgenol*. 2014;202(4):335-342. doi:10.2214/AJR.13.12029.

22. Frazier TH, Richardson JB, Fabre VC, Callen JP. Fluoroscopy-induced chronic radiation skin injury: a disease perhaps often overlooked. *Arch Dermatol*. 2007;143(5):637-640.

23. Otterburn D, Losken A. Iatrogenic fluoroscopy injury to the skin. *Ann Plast Surg*. 2010;65(5):462-465. doi:10.1097/SAP.0b013e3181d6e2d3.

24. Valentin J. Avoidance of radiation injuries from medical interventional procedures [review]. *Ann ICRP*. 2000;30(2):7-67.

25. Henry MF, Maender JL, Shen Y, et al. Fluoroscopy-induced chronic radiation dermatitis: a report of three cases. *Dermatol Online J*. 2009;15(1):3.

26. Boncher J, Bergfeld WF. Fluoroscopy-induced chronic radiation dermatitis: a report of two additional cases and a brief review of the literature. *J Cutan Pathol*. 2012;39(1):63-67. doi:10.1111/j.1600-0560.2011.01754.x.

27. Goans RE, Holloway EC, Berger ME, Ricks RC. Early dose assessment following severe radiation accidents. *Health Phys*. 1997;72(4):513-518.

28. Goans RE, Holloway EC, Berger ME, Ricks RC. Early dose assessment in criticality accidents. *Health Phys*. 2001;81(4):446-449.

29. Christensen DM, Iddins CJ, Parrillo SJ, Glassman ES, Goans RE. Management of ionizing radiation injuries and illnesses, part 4: acute radiation syndrome. *J Am Osteopath Assoc*. 2014;114(9):702-711. doi:10.7556/jaoa.2014.138.

30. Goans RE, Iddins CJ, Christensen DM. Ultrasound and thermography for diagnosis of extent and magnitude of acute local radiation injury (LRI). *Proceedings of the 5th International REAC/TS Symposium: The Medical Basis for Radiation Accident Preparedness and the Biodosimetry Workshop*. Oak Ridge, TN: Oak Ridge Associated Universities; 2013.

31. Jammet H, Gongora R, Jockey P, Zucker JM. The 1978 Algerian accident: acute local exposures of two children. In: Hubner KF, Fry SA. *The Medical Basis for Radiation Accident Preparedness*. Amsterdam, The Netherlands: Elsevier; 1980:229-245.

32. Goans RE, Goans RH, Goans RE Jr, Christensen DM. Ultrasonic analysis of acute thermal and radiation injury—a pilot study. *Radiat Meas*. 2007;42(6-7):1261-1264.

33. Allen J. Photoplethysmography and its application in clinical physiological measurement. *Physiol Meas*. 2007;28:R1-R39.

34. Swain ID, Grant LJ. Methods of measuring skin blood flow [review]. *Phys Med Biol*. 1989;34(2):151-175.

35. Schultz-Ehrenburg U, Blazek V. Value of quantitative photoplethysmography for functional vascular diagnostics: current status and prospects. *Skin Pharmacol Appl Skin Physiol*. 2001;14(5):316-323.

36. Malvezzi L, Castronuovo JJ Jr, Swayne LC, Cone D, Trivino JZ. The correlation between three methods of skin perfusion pressure measurement: radionuclide washout, laser Doppler flow, and photoplethysmography. *J Vasc Surg*. 1992;15(5):823-829.

37. Almond NE, Cooke ED. Observations on the photoplethysmograph pulse derived from a laser Doppler flowmeter. *Clin Phys Physiol Meas*. 1989;10(2):137-145.

38. Huelsbusch M, Blazek V. Contactless mapping of rhythmical phenomena in tissue perfusion using PPGI. In: Clough AV, Chen CT. *Medical Imaging 2002: Physiology and Function From Multidimensional Images*. Society of Photo Optical; 2002. doi:10.1117/12.463573. *Proceedings of Spie*; vol 4683.

39. Brumen V, Horvat D, Bonic I. Evaluation of serial application of capillaroscopy, photoplethysmography, and dermatothermometry in diagnosis and prevention of radiolesions of peripheral microvessles. *Microvasc Res*. 1994;47(2):270-278.

(continued)

40. Levitskaia TG, Bryan SA, Creim JA, et al. Optical spectroscopy and multivariate analysis for biodosimetry and monitoring of radiation injury to the skin. *Drug Develop Res*. 2012;73:252-273. doi:10.1002/ddr.21021.

41. Romanyukha A, Mitchell CA, Schauer DA, Romanyukha L, Swartz HM. Q-band EPR biodosimetry in tooth enamel microsamples: feasibility test and comparison with x-band. *Health Phys*. 2007;93(6):631-635.

42. Wieser A, Debuyst R, Fattibene P, et al. The 3rd international intercomparison on EPR tooth dosimetry: part 1, general analysis. *Appl Radiat Isot*. 2005;62(2):163-171.

43. Romanyukha A, Trompier F. Electron paramagnetic resonance retrospective dosimetry. *AIP Conf Proc*. 2011;1345(1):120-128.

44. Desrosiers M, Schauer DA. Electron paramagnetic resonance biodosimetry. *Nucl Instrum Methods Phys Res B*. 2001;184:219-228.

45. Koranda FC, Heffron ET, Modert CW, Perkins LL. Photo-mapping for microscopically controlled surgery. *J Dermatol Surg Oncol*. 1982;8(6):463-465.

46. Nenot JC. Medical and surgical management for localized radiation injuries [review]. *Int J Radiat Biol*. 1990;57(4):783-795.

47. Flynn DF, Goans RE. Nuclear terrorism: triage and medical management of radiation and combined-injury casualties. *Surg Clin N Am*. 2006;86(3):601-636.

48. Berger ME, Christensen DM, Lowry PC, Jones OW, Wiley AL. Medical management of radiation injuries: current approaches. *Occup Med (Lond)*. 2006;56(3):162-172.

49. Delanian S, Porcher R, Balla-Mekias S, Lefaix J. Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. *J Clin Oncol*. 2003;21(13):2545-2550.

50. Delanian S, Porcher R, Rudant J, Lefaix JL. Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis. *J Clin Oncol*. 2005;23(34):8570-8579.

51. Magnusson M, Hoglund P, Johansson K, et al. Pentoxifylline and vitamin E treatment for prevention of radiation-induced side-effects in women with breast cancer: a phase two, double-blind, placebo-controlled randomised clinical trial (Ptx-5). *Eur J Cancer*. 2009;45(14):2488-2495. doi:10.1016/j.ejca.2009.05.015.

52. Ozturk B, Egehan I, Atavci S, Kitapci M. Pentoxifylline in prevention of radiation-induced lung toxicity in patients with breast and lung cancer: a double-blind randomized trial. *Int Rad Onc Biol Phys*. 2004;58(1):213-219.

53. Campana F, Zervoudis S, Perdereau B, et al. Topical superoxide dismutase reduces post-irradiation breast cancer fibrosis. *J Cell Mol Med*. 2004;8;(1):109-116.

54. Delanian S, Baillet F, Huart J, Lefaix JL, Maulard C, Housset M. Successful treatment of radiation-induced fibrosis using liposomal Cu/Zn superoxide dismutase: clinical trial. *Radiother Oncol*. 1994;32(1):12-20.

55. Esco R, Valencia J, Coronel P, Carceller JA, Gimeno M, Bascón N. Efficacy of orgotein in prevention of late side effects of pelvic irradiation: a randomized study. *Int J Radiat Oncol Biol Phys*. 2004;60:(4):1211-1219.

56. Maenthaisong R, Chaiyakunapruk N, Niruntraporn S, Kongkaew C. The efficacy of aloe vera used for burn wound healing: a systematic review. *Burns*. 2007;33(6):713-718.

57. Richardson J, Smith JE, McIntyre M, Thomas R, Pilkington K. Aloe vera for preventing radiation-induced skin reactions: a systematic literature review. *Clin Oncol (R Coll Radiol)*. 2005;17(6):478-484.

58. Ahmadi A. Potential prevention: aloe vera mouthwash may reduce radiation-induced oral mucositis in head and neck cancer patients. *Chin J Integr Med*. 2012;18(8):635-640. doi:10.1007/s11655-012-1183-y.

59. Donlon MA. Role of mast cell mediators in radiation injury and protection. *Pharmacol Ther*. 1988;39(1-3):373-377.

60. Denham JW, Hauer-Jensen M. The radiotherapeutic injury—a complex 'wound.' *Radiother Oncol*. 2002;63(2):129-145.

61. Albrecht M, Muller K, Kohn FM, Meineke V, Mayerhofer A. Ionizing radiation induces degranulation of human mast cells and release of tryptase. *Int J Radiat Biol*. 2007;83(8):535-541.

62. Moriyasu S, Yamamoto K, Kureyama N, Okamura K, Ikeda T, Yamatodani A. Involvement of histamine released from mast cells in acute radiation dermatitis in mice. *J Pharmacol Sci*. 2007;104(2):187-190.

63. Doyle TF, Turns JE, Strike TA. Effect of antihistamine on early transient incapacitation of monkeys subjected to 4000 rads of mixed gamma-neutron radiation. *Aerosp Med*. 1971;42(4):400-403.

64. Alter WA, Hawkins RN, Catravas GN, Doyle T, Takenaga JK. Possible role of histamine in radiation-induced hypotension in the Rhesus monkey. *Radiat Res*. 1983;94:654.

65. Feldmeier JJ, Packard MW. Delayed radiation injuries (soft tissue and bony necrosis). In: Gesel LB, ed. *Hyaperbaric Oxygen Therapy Indications*. 12th ed. Durham, NC: Undersea and Hyperbaric Medical Society; 2008.

66. Craighead P, Shea-Budgell MA, Nation J, et al. Hyperbaric oxygen therapy for late radiation tissue injury in gynecologic malignancies. *Curr Oncol*. 2011;18(5):220-227.

67. Akita S, Akino K, Hirano A, Ohtsuru A, Yamashita S. Noncultured autologous adipose-derived stem cells therapy for chronic radiation injury. *Stem Cells Int*. 2010;532704. doi:10.4061/2010/532704.

ELSEVIER

Seminars in
NUCLEAR
MEDICINE

Adverse Events of Diagnostic Radiopharmaceuticals: A Systematic Review

Nanno Schreuder, PharmD,[*,†] Daniëlle Koopman, MSc,[‡,¶] Pieter L. Jager, MD, PhD,[‡] Jos G.W. Kosterink, PharmD, PhD,[*,#] and Eugène van Puijenbroek, MD, PhD[*,**]

Diagnostic radiopharmaceuticals used in nuclear medicine can cause adverse events. Information on these adverse events is available in case reports and databases but may not be readily accessible to healthcare professionals. This systematic review provides an overview of adverse events of diagnostical radiopharmaceuticals and their characteristics. A median frequency for adverse events in diagnostical radiopharmaceuticals of 1.63 (interquartile range: 1.09-2.29) per 100,000 is reported. Most common are skin and subcutaneous tissue disorders, and general disorders and administration site conditions. Many adverse events reported are minor in severity, although 6.7% can be classified as important. In rare cases, adverse events are serious and potentially life-threatening. With the introduction of new radiopharmaceuticals and the increasing use of positron emission tomography-computed tomography, previously unknown adverse events may be detected in daily practice. Future work should cover the experience of the patient with adverse events from diagnostic radiopharmaceuticals.

Semin Nucl Med 49:382-410

Radiopharmaceuticals are drugs containing a radioactive isotope used for diagnostic or therapeutic purposes,[1,2] with the radioactive isotopes emitting radiation that can be detected with imaging modalities, such as single-photon emission computed tomography (SPECT) or positron emission tomography (PET). Images and data allow for functional processes such as metabolism to be evaluated in the human body. Most diagnostic radiopharmaceuticals are used in very small quantities[3]—generally in the range of micrograms—and therefore do generally not have a pharmacologic effect, although adverse reactions may still occur. These adverse reactions can often not be explained by the known actions of the radiopharmaceutical, and are mostly unpredictable. The World Health Organization defines an adverse drug reaction as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" and an adverse event as "any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment."[4,5] "Adverse drug reaction" excludes events that do not have a proven relationship with a drug, although it may not be possible to establish a causal link at the moment the event occurs or is reported. Therefore, adverse events are still of interest in evaluating drug safety. For this reason, and for uniformity, the more general term "adverse event" is used here.

Assessment is needed to determine if a particular drug caused the adverse event, specifically looking at the probability of causality and including clinical judgment. Many systems have been developed to support this process; for radiopharmaceuticals, often-used causality methods are the Naranjo algorithm[6] and the method described by Silberstein.[7]

Adverse events related to diagnostic radiopharmaceuticals are considered rare. Detailed information on these adverse events is available in case reports or dedicated databases, although this information might not be readily available to

*Groningen Research Institute of Pharmacy, Pharmacotherapy, Epidemiology & Economics, University of Groningen, Groningen, the Netherlands.
†GE Healthcare Radiopharmacy Zwolle, Zwolle, the Netherlands.
‡Department of Nuclear Medicine, Isala Hospital, Zwolle, the Netherlands.
¶MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, the Netherlands.
#Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.
**Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, the Netherlands.
Address reprint requests to Nanno Schreuder, PharmD, Groningen Research Institute of Pharmacy, Pharmacotherapy, Epidemiology & Economics, University of Groningen, Antonius Deusinglaan 1, Groningen, the Netherlands. E-mail: n.schreuder@rug.nl

 https://doi.org/10.1053/j.semnuclmed.2019.06.006
0001-2998/

healthcare professionals when a patient experiences an adverse event. Information on these adverse events—including their severity, duration, and frequency—is needed for healthcare professionals to understand risk and management for patients.[8] For this reason, a comprehensive overview of adverse events related to diagnostic radiopharmaceuticals is essential. Several reviews have been conducted, some providing a narrative summary of adverse reactions[9-15] and others focusing on a specific topic or combination of topics with preparation errors or product defects[16]; one review, published as a letter to the editor, presents data on the prevalence of adverse events for radiopharmaceuticals.[17] Additionally, several information databases have been developed to provide information about adverse events related to radiopharmaceuticals, although 2 are currently inaccessible.[18-20] However, to our knowledge, a systematic review to describe adverse events related to diagnostic radiopharmaceuticals has not yet been published.

This review aims to provide an overview of the most common adverse events and their characteristics (such as frequency, severity, and proposed mechanism), for diagnostic radiopharmaceuticals as reported in literature.

Methods

This review process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[21] and the review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under number 42016042831.

Search Strategy

We performed a systematic search using the databases MEDLINE (PubMed) and Embase, applying no year limits and therefore extending as far back as the late 1940s. For each database, a University Medical Center Groningen staff member and one of the authors (N.S.) developed the search strategy. The search strategy for MEDLINE was: ("Radiopharmaceuticals" [MeSH] OR "Radiopharmaceutical*" [tiab] OR "Radioisotopes" [MeSH] OR "Radioisotope*" [tiab]) combined (AND) with ("adverse effects" [subheading] OR "adverse reactions" [tiab] OR "adverse effects"' [tiab] OR "adverse events" [tiab] OR "side effects" [tiab]). A filter for the search was applied—NOT (Animals NOT Humans)—to exclude animal-only studies. The search strategy for Embase was: ("Radiopharmaceutical agent"/exp OR "Radioisotope"/exp OR "Radiopharmaceutical*":ab,ti OR "Radioisotope*":ab,ti) combined (AND) with ("adverse reaction"/exp OR "adverse effect*":ab,ti OR "adverse reaction*":ab,ti OR "adverse event*":ab,ti OR "side effect*":ab,ti); a filter was applied to exclude articles available in MEDLINE, and a filter was applied—NOT (Animals NOT Humans)—to exclude animal-only studies. The articles selected were screened for relevant references, which were included in the selection process. The initial search was completed in September 2016 and updated with recent articles until July 10, 2018.

Study Selection

The first author (N.S.) assessed all titles obtained. For potentially relevant articles, the full text was obtained and 2 reviewers (D.K. and N.S.) assessed them independently for relevance. In cases where the reviewers' opinions differed, a third researcher (E.v.P.) was consulted to reach consensus. Selected articles met the following criteria: described adverse events that are possibly or likely attributed to radiopharmaceuticals as the main outcome parameter; only dealt with diagnostic radiopharmaceuticals; related to radiopharmaceuticals used in humans.

Assessment of Articles' Methodological Quality

Two reviewers (D.K. and N.S.) independently assessed the methodological quality of the included studies using the method described by Murad et al.[22] For each article, the reviewers scored 8 items with leading explanatory questions; scores were added to create an aggregate score and ranked as "low," "moderate," or "good." In cases of differing opinion on a score, a third researcher (E.v.P.) was consulted to reach consensus.

Data Collection

For studies meeting the selection criteria, data were extracted using a standardized approach. When available, data were extracted on: (1) study design; (2) name(s) of radiopharmaceutical(s); (3) verbatim record of each adverse event and standardized term; (4) number of patients with an adverse event per radiopharmaceutical; (5) total number of patients being studied and/or the calculated frequency; (6) the confidence interval given for a calculated frequency; (7) the method of causality assessment used; and (8) corresponding probability of the causality assessment.

Synthesis of Results

To compare the results, we handled the data in the following way:

The names of the radiopharmaceutical were standardized and categorized using the Anatomical Therapeutic Chemical (ATC) classification system.[23] The ATC system divides active substances into several groups according to the organ or system on which the substance acts and its therapeutic, pharmacologic, and chemical properties. Diagnostic radiopharmaceuticals are grouped into a specific group (V09) and subdivided into 10 subgroups depending on the site of action or organ system.

The adverse events were extracted from the articles exactly as written, with the Medical Dictionary for Regulatory Activities (MedDRA) terminology[24] used to code the verbatim record of the adverse event or, in cases for which the adverse events were not yet described, according to MedDRA-standardized terminology. MedDRA is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for

Registration of Pharmaceuticals for Human Use (ICH). The standardized terminology contains terms on 5 hierarchical levels. The highest level is the system organ class, of which there are 26; the lowest is the lowest level term, linked with a preferred term. Whereas lowest level terms may represent synonyms, preferred terms represent a unique medical concept and are therefore favored for data representation. Each preferred term is linked to a system organ class, making system organ class ideal for representing a large dataset with multiple preferred terms. Our study used preferred term and system organ class to present data. Adverse events with an unlikely causality as determined by the author of the particular study were excluded.

Adverse events were screened for important medical events (IMEs) using the IME list drafted by the EudraVigilance Expert Working Group.[25] This list relates to the MedDRA terms and provides guidance on whether an adverse event could be considered important; serious adverse events are occurrences that result in death, are life-threating, require hospitalization, result in disability, or are congenital defects, and IMEs are those that might jeopardize the patient or require intervention to prevent a serious adverse event.[26] Two researchers (D.K. and N.S.) independently conducted extraction, coding, and screening for severity. When the syntheses of the results were not in agreement, a third researcher (E.v.P.) was consulted to resolve discrepancies.

Results

Search Results

The initial search found 18,464 titles, and the second search (until July 10, 2018) found 1899 titles, for a total of 20,363 titles; another 24 articles were identified through references. Figure 1 outlines the selection process, and Table 1 provides an overview of the 101 articles meeting the inclusion criteria. From the included articles, 46 are case reports, 23 prospective studies, 16 retrospective studies, and 16 summaries of case reports collected by registries maintained in a country or continent. Thirty-seven of the articles describe adverse events in a population using various diagnostic radiopharmaceuticals, and the other 64 articles are related to one specific radiopharmaceutical. In one article, the author planned to study the frequency of adverse events in radiopharmaceuticals but found none[117]; this study was included, as it relates to the frequency of adverse events in radiopharmaceuticals. Some articles mention adverse events related to the

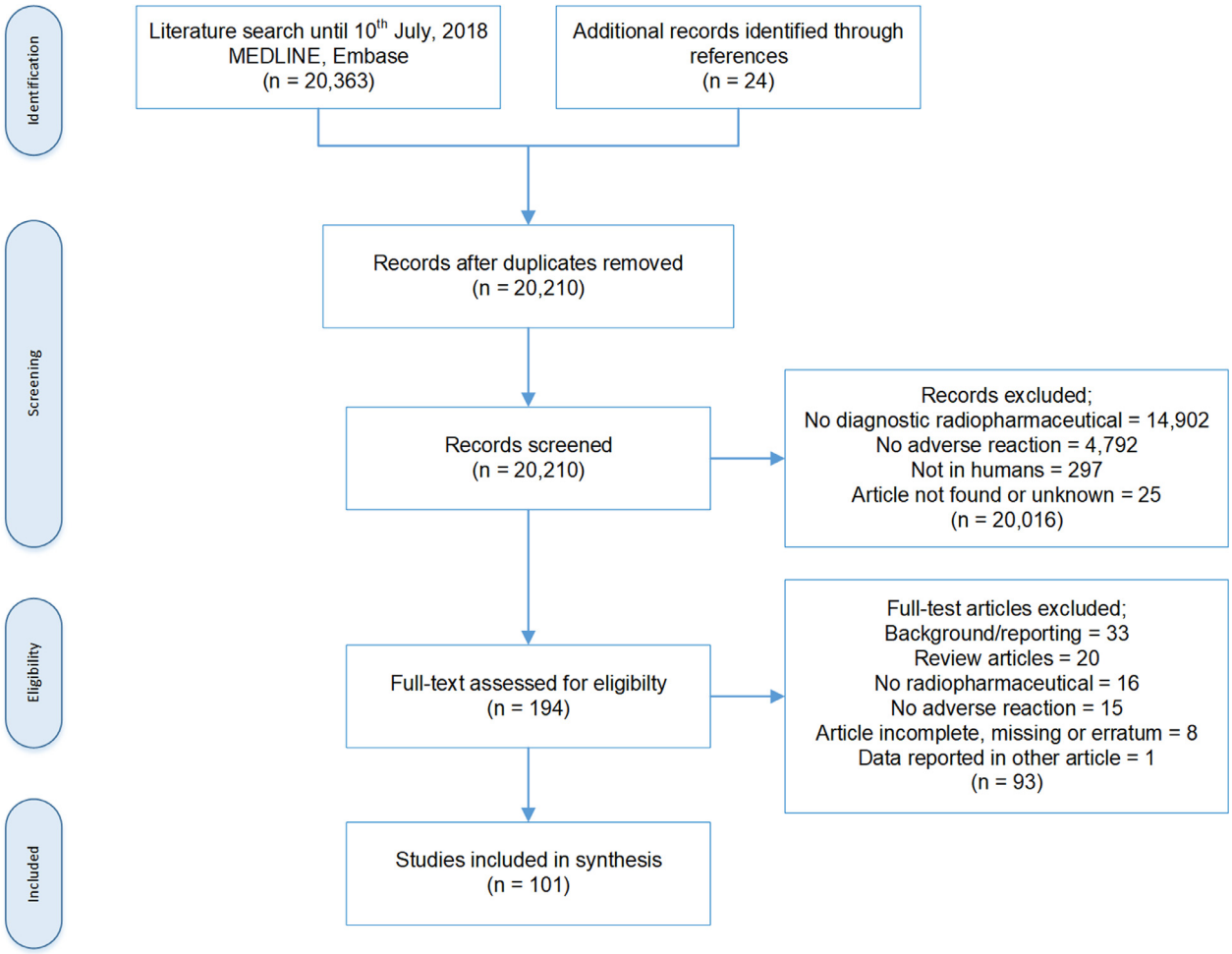

Figure 1 Selection of studies according to the PRISMA statement.[21]

Table 1 Overview of Included Articles Reporting Adverse Events as an Outcome of use of Diagnostic Radiopharmaceuticals

First Author [Reference]	Year	Study Design	Number of Patients	Radiopharmaceutical	Number With AE	Causality Method
Alderson[27]	1973	C	2	In-111 pentetic acid	2	ND
Atkins[28]	1972	PS	1,107,621*	Various	124	ND
Atkins[29]	1986	SC	NA	Various	21‡	ND
Aziz Jalali[30]	2004	C	1	Tl-201 chloride	1	ND
Bach-Gansmo[31]	2016	PS	714	F-18 fluciclovine	4	ND
Bagheri[32]	1996	PS	14,794	Various	3	B
Balan[33]	2003	C	1	Tc-99m medronic acid	1	ND
Banerji[34]	1972	RS	88	I-131 human albumin	36	ND
Barnes[35]	1972	C	5	I-131 human albumin	5	ND
Bliek[36]	1971	C	1	I-131 human albumin	1	ND
Block[37]	1970	C	1	Tc-99m sulfur colloid	1	ND
Bohdiewicz[38]	1998	PS	1041	In-111 satumomab pendetide	45	ND
Burton[39]	2003	C	1	Tc-99m nanocolloid	1	ND
Chicken[40]	2007	C	1	Tc-99m nanocolloid	1	ND
Child[41]	1975	C	1	Tc-99m macrosalb	1	ND
Codreanu[42]	2013	C	1	F-18 fludeoxyglucose	1	N
Collins[43]	1988	C	1	Tc-99m medronic acid	1	CO
Commandeur[44]	1992	C	1	Ga-67 citrate	1	ND
Cotrina-Monroy[45]	2010	C	1	Tc-99m nanocolloid	1	ND
Deppen[46]	2016	PS	97	Ga-68 DOTA-TATE	3	ND
Detmer[47]	1965	C	1	I-131 human albumin	1	ND
Doerr[48]	1991	PS	116	In-111 satumomab pendetide	7	ND
Dos Santos Almeida[49]	2013	PS	55	Tc-99m medronic acid	1	ND
Doukaki[50]	2010	C	1	Tc-99m sestamibi	1	ND
Dramov[51]	1971	C	2	I-131 human albumin	2	ND
Dworkin[52]	1966	C	1	I-131 macrosalb	1	ND
EANM†,[53]	1994	SC	62	Various	52‡	ND
EANM†,[54]	1995	SC	73	Various	73‡	ND
EANM†,[55]	1996	SC	64	Various	54‡	ND
ENMS†,[56]	1982	SC	51	Various	51	ND
ENMS†,[57]	1984	SC	24	Various	24	ND
ENMS[58]	1987	SC	62	Various	62‡	ND
ENMS†,[59]	1987	SC	24	Various	24‡	ND
FDA†,[60]	2005	SC	63	Tc-99m fanolesomab	63	ND
Ford[61]	1978	SC	57	Various	57‡	ND
Hart[62]	1989	C	1	Tc-99m oxidronic acid	1	ND
Hertel[63]	1990	PS	800	Various	1	ND
Hesse[64]	2011	C	1	Tc-99m sestamibi	1	ND
Hesslewood†,[65]	2002	SC	62	Various	38‡	S
Hesslewood†,[66]	2003	SC	61	Various	35‡	S
Hesslewood[67]	1997	PS	71,046	Various	8‡	S
Hirosawa[68]	1991	PS	981	I-123 iobenguane	4	ND
Hurman[69]	1982	C	1	Tc-99m pentetic acid	1	ND
Ishibashi[70]	2009	C	1	I-131 iobenguane	1	ND
James[71]	1992	PS	115	Various	17	ND
Jayabalan[72]	1975	C	3	In-111 pentetic acid	3	ND
Johnston[73]	2015	PS	60	Tc-99m sulfur colloid	11	PA
Jonas[74]	1972	C	1	I-131 human albumin	1	ND
JSNM[75]	2003	RS	1,390,843	Various	27	ND
JSNM[76]	2004	RS	1,395,928	Various	37	ND
JSNM[77]	2005	RS	1,357,419	Various	21	ND
Kennedy-Dixon†,[78]	2017	SC	191	Various	176	S
Koopmans[79]	2005	C	1	F-18 fluorodihydroxyphenylalanine (DOPA)	1	ND
Kusakabe[80]	2002	RS	1,401,962	Various	24	ND
Kusakabe[81]	2006	RS	1,277,906	Various	16	ND

Table 1 (*Continued*)

First Author [Reference]	Year	Study Design	Number of Patients	Radiopharmaceutical	Number With AE	Causality Method
Kusakabe[82]	2007	RS	1,264,098	Various	19	ND
Kusakabe[83]	2008	RS	1,189,127	Various	32	ND
Lai[84]	2016	PS	85	Tc-99m tilmanocept	6	ND
Laroche[†,85]	2015	SC	6,434,988[¶]	Various	256	ND
Lee[86]	2013	C	1	F-18 fludeoxyglucose	1	N
Line[87]	2004	PS	30	Tc-99m fanolesomab	12	ND
Littenberg[88]	1975	C	1	Tc-99m microspheres	1	ND
Makaryus[89]	2008	C	1	Tc-99m sestamibi	1	ND
Maltby[90]	2002	C	1	I-131 norcholesterol diagnostic	1	ND
Manoharan[91]	2017	PS	20	Ga-68 edotreotide (DOTA-TOC)	4	ND
Matsuda[92]	2009	RS	1,192,072	Various	11	ND
Matsuda[93]	2012	RS	1,046,243	Various	22	ND
Matsuda[94]	2013	RS	1,068,833	Various	14	ND
Matsuda[95]	2014	RS	1,060,526	Various	11	ND
Matsuda[96]	2015	RS	1,056,876	Various	8	ND
Matsuda[97]	2017	RS	1,056,828	Various	15	ND
Matsuda[98]	2018	RS	1,052,650	Various	9	ND
Mooser[99]	1998	C	1	Tc-99m medronic acid	1	ND
Mujtaba[100]	2007	C	1	Tc-99m sestamibi	1	ND
Nicol[101]	1967	C	1	I-131 human albumin	1	ND
Núñez[102]	2007	C	1	I-131 sodium iodine diagnostic	1	ND
O'Dorisio[103]	2018	PS	26	Ga-68 edotreotide (DOTA-TOC)	9	ND
Oldham[104]	1970	C	2	I-131 human albumin	2	ND
Oosterhuis[105]	1971	PS	83	I-131 human albumin	3	ND
Peller[106]	1994	C	1	Tc-99m mertiatide	1	ND
Pravettoni[107]	2009	C	1	Tc-99m sestamibi	1	ND
Ramos-Gabatin[108]	1986	C	1	Tc-99m medronic acid	1	ND
Rhodes[109]	1971	C	1	Tc-99m microspheres	1	ND
Rhodes[110]	1974	PS	30	In-111 pentetic acid	6	ND
Rhodes[111]	1976	C	66	In-111 pentetic acid	66	ND
Rhodes[†,112]	1980	SC	8,000,000[#]	Various	47[‡]	ND
Roberts[113]	1970	C	1	I-131 macrosalb	1	ND
Schafer[†,114]	2016	PS	52	Ga-68 edotreotide (DOTA-TOC)	NA	ND
Schaub[115]	1983	C	1	Tc-99m sulfur colloid	1	ND
Silberstein[116]	2014	PS	1,024,177	Various	21[‡]	S
Silberstein[117]	1998	PS	81,801	Various	0	S
Silberstein[7]	1996	PS	783,525	Various	18[‡]	S
Smith[†,118]	1967	RS	4775	Tc-99m sulfur colloid	15	ND
Sörensen[119]	2013	PS	6	F-18 fluciclovine	1	ND
Spicer[120]	1985	C	1	Tc-99m medronic acid	1	CO
Spyridonidis[121]	2008	C	2	I-131 norcholesterol diagnostic	2	ND
Støckel[122]	1983	C	1	I-131 iodohippurate	1	ND
Thomson[123]	2001	C	1	Tc-99m sestamibi	1	ND
Vincent[124]	1968	C	1	Tc-99m macrosalb	1	ND
Williams[125]	1974	SC	77	Various	77	ND
Williams[126]	1974	C	1	Tc-99m macrosalb	1	ND

AE, adverse event; B, Bégaud; C, case report; CO, Cordova; N, Naranjo; ND, not defined; PA, pain scale; PS, prospective study; RS, retrospective study; S, Silberstein; SC, summaries of case reports collected by registers maintained in a country or continent.

*Number of patients are totals over 3 years while number of cases is over 4 years.

†Number of events could not exactly be matched with number of patients.

‡Number of patients with AEs also include radiopharmaceuticals with therapeutic use.

¶Number of patients are totals over 8 years while number of cases is over 25 years.

#Estimation.

nonradioactive pharmaceuticals pyrophosphate and stannous agent, which are used in combination with radiopharmaceutical Tc-99m pertechnetate for blood pool scintigraphy; because of their clear use in a diagnostic procedure in nuclear medicine, these 2 agents were included in the results. Of the studies, 12 (12%) use a described method to determine causality: 7 use the method described by Silberstein,[7] 2 use the algorithm described by Naranjo,[6] 2 use a method developed for radiopharmaceuticals proposed by Cordova,[127] and 1 uses a method described by Bégaud.[128]

Assessed Methodological Quality of Included Studies

In terms of methodological quality, 23.0% (n = 23) were rated as good, 62.0% (n = 62) as moderate, and 15.0% (n = 15) as low; this excludes one article that could not be assessed in terms of quality because no adverse events were reported.[117] Table 2 provides a detailed overview of the assessment.

Frequency

Twenty-two studies present the frequency of adverse events for various radiopharmaceuticals in a population. Table 3 provides the frequency as reported or estimated by the authors and the method of reporting for each study. A median frequency of 1.63 adverse events per 100,000 administrations (0.0016%) was calculated. In 16 controlled studies, the frequency of adverse events was determined for specific radiopharmaceuticals; the frequency ranged from 0.125% to 40.9% and is discussed in the next subchapter ("Summary of findings").

Summary of Findings

In total, 2447 adverse events were reported in 1804 patients. We found that 84.4% of the reported adverse events with diagnostic radiopharmaceuticals were related to 6 system organ classes (Table 4), the most common being "skin and subcutaneous tissue disorders" (26.6%) and "general disorders and administration site conditions" (24.4%). Other adverse events were related to "gastrointestinal disorders" (9.8%), "nervous system disorders" (8.5%), "investigations (results of tests)" (7.9%), and "immune system disorders" (7.2%). For "skin and subcutaneous tissue disorders," the most frequently reported adverse events were rash (248), pruritus (150), erythema (61), urticaria (67), and hyperhidrosis (28). For "general disorders and administration site conditions," the adverse events most reported were fever (104), unspecified adverse events (43), and discomfort (35); for "gastrointestinal disorders," nausea (104) and vomiting (96); and for "nervous system disorders," dizziness (44), headache (38) and presyncope (32). For "investigations," the most reported adverse events were related to a change in blood pressure (45), and hypersensitivity (161) was most reported for "immune system disorders."

From the reported adverse events, 165 (6.7%) were considered to be an IME. Nine deaths were reported, 5 occurring with the use of I-131 or Tc-99m macrosalb for pulmonary scintigraphy in cases of severe reduction in pulmonary capacity[41,52,113,124,126]; although these deaths were related to the use of these radiopharmaceuticals, pulmonary vascular pathology was identified as an additional risk factor. Two deaths occurred with the radiopharmaceutical Tc-99m fanolesomab,[60] which was withdrawn from the market, and were attributed to cardiopulmonary failure in diabetic patients; 15 other patients experienced serious events within minutes after injection of the Tc-99m fanolesomab. Two deaths occurred with F-18 fluorodeoxyglucose[85]; 1 patient suffered from a convulsive seizure and cardiorespiratory distress, and the other patient suffered from septic shock 24 hours after injection (October 19, 2018 e-mail from Prof Laroche to N.S.; unreferenced).

A detailed overview of adverse events using standardized terminology for all radiopharmaceuticals and references to the articles can be found in Table 5. The following section presents a summary of findings for each commonly used radiopharmaceutical per ATC group. Data presented in this summary are: number of adverse events, characteristics of most reported adverse events, frequency when reported, number of IMEs and their main characteristics, and noteworthy adverse events.

Central Nervous System (ATC Group V09A)

Iodine Ioflupane (I-123). For I-123 ioflupane, we found 17 adverse events in 7 patients. The most reported were erythema, injection site pain, pruritus, and rash. No IMEs were reported.

Indium (In-111) Pentetic Acid. For In-111 pentetic acid (pentetate), we found 133 adverse events in 81 patients. In addition to 67 adverse events not further specified, the most reported adverse events were abnormal cerebrospinal fluid values, fever, and meningitis. From the adverse events reported, 21 were classified as IMEs in 5 patients, all suffering from meningitis after the use of In-111 pentetic acid. Some symptoms in these patients included fever, vomiting, chills, nuchal rigidity, Kernig's sign, Brudzinski's sign, generalized tonic-clonic seizures, and abnormal cerebrospinal fluid values.

In-111 pentetic acid is a diagnostic radiopharmaceutical used for cisternography and injected intrathecally, bypassing the blood-brain barrier. A 1974 study investigating patients' febrile response after In-111 pentetic acid injection found that 10% of patients had a temperature increase greater than 1°F within 8 hours of injection. It is now commonly accepted that pyrogens are involved in the pathogenesis.[110] Cases of meningitis with In-111 pentetic acid were reported between 1973 and 1982,[27,56,61,111] with no new reports on adverse events after 1982.

Technetium (Tc-99m) Exametazime. For Tc-99m exametazime, we found 13 adverse events in 7 patients. The most reported adverse event was erythema. No IMEs were reported.

Table 2 Methodological quality assessment of studies included.

First Author [Reference]	Q1*	Q2*	Q3*	Q4*	Q5*	Q6*	Q7*	Q8*	Assessment†
Alderson[27]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Atkins[28]	No	Yes	No	No	No	No	Yes	No	Low
Atkins[29]	No	Yes	Yes	No	No	No	Yes	No	Low
Aziz Jalali[30]	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Bach-Gansmo[31]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Bagheri[32]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Balan[33]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Banerji[34]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Barnes[35]	Yes	Yes	Yes	Yes	No	No	Yes	No	Moderate
Bliek[36]	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Block[37]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Bohdiewicz[38]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Burton[39]	Yes	Yes	Yes	Yes	No	No	Yes	No	Moderate
Chicken[40]	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Child[41]	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Codreanu[42]	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Collins[43]	No	Yes	Yes	Yes	No	No	Yes	No	Moderate
Commandeur[44]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Good
Cotrina-Monroy[45]	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Deppen[46]	Yes	Yes	Yes	No	No	No	Yes	Yes	Moderate
Detmer[47]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Doerr[48]	Yes	Yes	Yes	No	No	No	Yes	Yes	Moderate
Dos Santos Almeida[49]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Doukaki[50]	No	Yes	Yes	Yes	No	No	Yes	No	Moderate
Dramov[51]	No	Yes	Yes	No	No	No	Yes	Yes	Moderate
Dworkin[52]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
EANM[53]	No	Yes	Yes	No	No	No	Yes	No	Low
EANM[54]	No	Yes	Yes	No	No	No	Yes	No	Low
EANM[55]	No	Yes	Yes	No	No	No	Yes	No	Low
ENMS[56]	No	Yes	Yes	No	No	No	Yes	No	Low
ENMS[57]	No	Yes	Yes	No	No	No	Yes	No	Low
ENMS[58]	No	Yes	Yes	No	No	No	Yes	No	Low
ENMS[59]	No	Yes	Yes	No	No	No	Yes	No	Low
FDA[60]	Yes	Yes	Yes	Yes	No	No	Yes	No	Moderate
Ford[61]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Hart[62]	No	Yes	Yes	Yes	No	No	Yes	No	Moderate
Hertel[63]	Yes	Yes	Yes	No	No	No	Yes	Yes	Moderate
Hesse[64]	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Hesslewood[65]	No	Yes	Yes	No	No	No	Yes	No	Low
Hesslewood[66]	No	Yes	Yes	No	No	No	Yes	No	Low
Hesslewood[67]	Yes	Yes	Yes	Yes	No	No	Yes	No	Moderate
Hirosawa[68]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Hurman[69]	No	Yes	Yes	No	No	No	Yes	Yes	Moderate
Ishibashi[70]	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
James[71]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Jayabalan[72]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Johnston[73]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Jonas[74]	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
JSNM[75]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
JSNM[76]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
JSNM[77]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Kennedy-Dixon[78]	Yes	Yes	Yes	Yes	No	No	Yes	No	Moderate
Koopmans[79]	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Kusakabe[80]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Kusakabe[81]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Kusakabe[82]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Kusakabe[83]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Lai[84]	Yes	Yes	Yes	Yes	No	No	Yes	No	Moderate

Table 2 (*Continued*)

First Author [Reference]	Q1*	Q2*	Q3*	Q4*	Q5*	Q6*	Q7*	Q8*	Assessment†
Laroche[85]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Lee[86]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Line[87]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Good
Littenberg[88]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Makaryus[89]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Maltby[90]	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Manoharan[91]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Matsuda[92]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Matsuda[93]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Matsuda[94]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Matsuda[95]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Matsuda[96]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Matsuda[97]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Matsuda[98]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Mooser[99]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Mujtaba[100]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Nicol[101]	Yes	Yes	Yes	Yes	No	No	Yes	No	Moderate
Núñez[102]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
O'Dorisio[103]	Yes	Yes	Yes	No	No	No	Yes	Yes	Moderate
Oldham[104]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Good
Oosterhuis[105]	Yes	Yes	Yes	No	No	No	Yes	Yes	Moderate
Peller[106]	No	Yes	Yes	No	No	No	Yes	Yes	Moderate
Pravettoni[107]	No	Yes	Yes	Yes	No	No	Yes	No	Moderate
Ramos-Gabatin[108]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Rhodes[109]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Rhodes[110]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Rhodes[111]	No	Yes	Yes	No	No	No	Yes	No	Low
Rhodes[112]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Roberts[113]	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Schafer[114]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Schaub[115]	No	Yes	Yes	No	No	No	Yes	No	Low
Silberstein[116]	Yes	Yes	Yes	Yes	No	No	Yes	No	Moderate
Silberstein[117]	No cases were found								
Silberstein[7]	Yes	Yes	Yes	Yes	No	No	Yes	No	Moderate
Smith[118]	Yes	Yes	Yes	No	No	No	Yes	No	Moderate
Sörensen[119]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Spicer[120]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Good
Spyridonidis[121]	Yes	Yes	Yes	Yes	No	No	Yes	No	Moderate
Støckel[122]	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Thomson[123]	No	Yes	Yes	No	No	No	Yes	No	Low
Vincent[124]	No	Yes	Yes	No	No	No	Yes	Yes	Moderate
Williams[125]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Williams[126]	No	Yes	Yes	No	No	No	Yes	No	Low
Total score:									Good 23 (23%)
									Moderate 62 (62%)
									Low 15 (15%)

*Questions: Q1: Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?; Q2: Was the exposure adequately ascertained?; Q3: Was the outcome adequately ascertained?; Q4: Were other alternative causes that may explain the observation ruled out?; Q5: Was there a challenge/rechallenge phenomenon?; Q6: Was there a dose-response effect?; Q7: Was follow-up long enough for outcomes to occur?' Q8: Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?

†Score: ≤3 = low; >3-<6 = moderate; ≥6 = good.

Skeleton (ATC Group V09B)

Technetium (Tc-99m) Medronic Acid. For Tc-99m medronic acid (medronate), we found 104 adverse events in 82 patients. The most reported adverse events were hypersensitivity, nausea, and rash. One study with 55 patients receiving Tc-99m medronic acid found 1 patient reported an adverse event, for a frequency of adverse events of 1.8%.[49] Three IMEs were reported; 1 patient had an anaphylactic reaction described by the author as mild,[7] another developed erythema multiforme 48 hours after use,[120] and 1 involved respiratory distress.[80]

Table 3 Study Characteristics Relevant for Assessment of Frequency of Reported AEs

Reference	Year	Country	Duration of Study (y)	Number	Reported Number With AEs	Frequency per 100,000 Administrations	Method of Data Collection
Atkins	1972	USA	3	1,107,621	111	10.02	Surveys were sent out to institutions to look retrospectively at their data.
Bagheri	1996	France	1.5	14,794	3	20.28	Each week a report was sent in by the nuclear medicine department. The pediatric department provided information about AEs in their patients related to radiopharmaceuticals on a weekly basis.
Hesslewood	1997	Europe (8 countries)	1	71,046	8	11.26	Each month a report was sent in by participating institutions. AEs were assessed for causality using Silberstein.
JSNM	2003	Japan	1	1,390,843	27	1.94	Based on responses to questionnaires sent to institutions.
JSNM	2004	Japan	1	1,395,928	37	2.65	Based on responses to questionnaires sent to institutions.
JSNM	2005	Japan	1	1,357,419	21	1.55	Based on responses to questionnaires sent to institutions.
Kusakabe	2002	Japan	1	1,401,962	24	1.71	Based on responses to questionnaires sent to institutions.
Kusakabe	2006	Japan	1	1,277,906	16	1.25	Based on responses to questionnaires sent to institutions.
Kusakabe	2007	Japan	1	1,264,098	19	1.50	Based on responses to questionnaires sent to institutions.
Kusakabe	2008	Japan	1	1,189,127	32	2.69	Based on responses to questionnaires sent to institutions.
Laroche	2015	France	8	6,434,988	147	2.28	Search in database of spontaneous reporting. Data of number of diagnoses with SPECT or PET were retrieved from a French health data base.
Matsuda	2009	Japan	1	1,192,072	11	0.92	Based on responses to questionnaires sent to institutions.
Matsuda	2012	Japan	1	1,046,243	22	2.10	Based on responses to questionnaires sent to institutions.
Matsuda	2013	Japan	1	1,068,833	14	1.31	Based on responses to questionnaires sent to institutions.
Matsuda	2014	Japan	1	1,060,526	11	1.04	Based on responses to questionnaires sent to institutions.
Matsuda	2015	Japan	1	1,056,876	8	0.76	Based on responses to questionnaires sent to institutions.
Matsuda	2017	Japan	1	1,056,828	15	1.42	Based on responses to questionnaires sent to institutions.
Matsuda	2018	Japan	1	1,052,650	9	0.85	Based on responses to questionnaires sent to institutions.
Rhodes	1980	USA	1	8,000,000*	47	0.59	Based on forms sent to institutions approximately 3 times a year. Number of administrations is an estimation.
Silberstein	1996	USA	5	783,525	18	2.3	Participants sent in a monthly questionnaire. All AEs were assessed for causality.
Silberstein	1998	USA	4	81,801	0	0	Participation institutions looked retrospectively at their data and provided prospective monthly data. Only PET radiopharmaceuticals were included.
Silberstein	2014	USA	5	1,024,177	1	2.05	Participants sent a quarterly report. All AEs were assessed for causality.
Median and interquartile range (25th-75th percentile)						1.63 (1.09-2.29)	

*Estimation.

Table 4 Number of Reported AEs per SOC for Each ATC Group of Radiopharmaceuticals

	Skin and Subcutaneous Tissue Disorders	General Disorders and Administration Site Conditions	Gastrointestinal Disorders	Nervous System Disorders	Investigations	Immune System Disorders	Respiratory, Thoracic, and Mediastinal disorders	Vascular Disorders	Cardiac Disorders	Musculoskeletal and Connective Tissue Disorders	Psychiatric Disorders	Eye Disorders	Infections and Infestations	Injury, Poisoning and Procedural Complications	Renal and Urinary Disorders	Blood and Lymphatic System Disorders	Reproductive System and Breast Disorders	Hepatobiliary Disorders	Endocrine Disorders	Psychiatric Disorders	Ocular Infections, Irritations, and Inflammations	Metabolism and Nutrition Disorders	Ear and Labyrinth Disorders	Sub Total
V09A central nervous system	22	88	10	19 (2)	29 (14)		3	2	2	8	4	1	6 (5)				1							195 (21)
V09B skeleton	111 (2)	90	59	33 (6)	16	16 (3)	11 (3)	12	4	5	5	5	1		2			1						371 (14)
V09C renal system	47	34	37	38 (3)	8	15	7 (2)	9	4	2	5	5		1	1		1					1		215 (5)
V09D hepatic & reticulo endothelial system	26	90	9	9 (2)	6	59 (2)	7	6 (1)	6 (1)		1			10	1 (1)									230 (7)
V09E respiratory system	22 (3)	33 (5)	5	18 (2)	32	31 (2)	24 (6)	3 (1)	13 (5)		4				2 (1)	1								188(25)
V09F thyroid	10	8	4	8 (2)	4	9	1	9	1		1		1											56 (2)
V09G cardiovascular system	70 (4)	36 (1)	26	32 (3)	14	10 (4)	10	8	1 (1)	1	2	4			1	3					1			219 (13)
V09H inflammation and infection detection	49	19 (4)	9	9 (1)	11	3	8 (2)	5	6 (3)	2	2		3	2				1						129 (10)
V09I tumor detection	75 (9)	53 (2)	23	17 (2)	9	5 (1)	2	8	4 (1)	3	3			1		1 (1)			1 (1)	1				206 (17)
V09X other diagnostic radiopharmaceuticals	21	146	29	26 (1)	65 (41)	27 (2)	16	20	10 (1)	26	10	3	5 (5)	2	1 (1)								1	408 (51)
Radiopharmaceutical not specified	199	1	30																					230
Subtotal	652 (18)	598 (12)	241	209 (24)	194 (55)	175 (14)	89 (13)	82 (2)	51 (12)	47	37	18	16 (10)	16	8 (3)	5 (1)	2	2	1 (1)	1	1	1	1	2447 (165)
Percentage of total (%)	26.6	24.4	9.8	8.5	7.9	7.2	3.6	3.4	2.1	1.9	1.5	0.7	0.7	0.7	0.3	0.2	0.1	0.1	0.0	0.0	0.0	0.0	0.0	

Numbers in parentheses represent the number of important medical events.

Table 5 Overview of AEs per Radiopharmaceutical

Central Nervous System (ATC Group V09A)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
I-123 iofetamine (IMP)	57,75-77,81-83,94,95,98	13	*IME:* none reported	–
			Other AEs: erythema (3), nausea (3), affective disorder (2), pruritus (2), rash (2), vomiting (2), adverse reaction, blood pressure decreased, blood pressure increased, chills, cold sweat, conjunctival hyperemia, dyspnea, eczema, flushing, headache, heart rate increased, pallor, pyrexia, respiration abnormal, urticaria	29
I-123 ioflupane	66,96-98	7	*IME:* none reported	–
			Other AEs: erythema (2), injection site pain (2), pruritus (2), rash (2), abdominal pain, headache, heart rate increased, hyperhidrosis, influenza, muscular weakness, pyrexia, speech disorder, urticaria	17
In-111 pentetic acid	27,56,61,72,78,110-112	81	*IME:* CSF glucose increased (4), CSF protein increased (4), meningitis aseptic (4), CSF white blood cell count increased (3), CSF cell count increased (2), generalized tonic-clonic seizure (2), CSF test abnormal, meningitis	21
			Other AEs: adverse reaction (67), pyrexia (8), body temperature increased (6), headache (4), nuchal rigidity (4), vomiting (4), xanthochromia (3), musculoskeletal stiffness (3), chills (2), Kernig's sign (2), meningeal disorder (2), myoclonus (2), Brudzinski's sign, heart rate increased, hyperreflexia, irritability, vaginal hemorrhage	112
Tc-99m exametazime	55,76,81,93,96	7	*IME:* none reported	–
			Other AEs: erythema (2), anxiety, blood pressure increased, chills, cyanosis, headache, nasal congestion, palpitations, pruritus, pyrexia, rash, vasovagal symptoms	13
Yb-169 pentetic acid	56	3	*IME:* none reported	–
			Other AEs: Adverse reaction (3)	3

Skeleton (ATC Group V09B)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
Bisphosphonates (not specified)	53-55,61,65,66	68	*IME:* anaphylactoid reaction, unresponsive to stimuli	2
			Other AEs: dizziness (4), nausea (3), rash (3), vomiting (3), arthralgia (2), headache (2), hyperhidrosis (2), lethargy (2), pruritus (2), pruritus generalized (2), rash generalized (2), cyanosis, dyspnea, hypersensitivity, injection site pain, limb discomfort, mouth swelling, myalgia, edema	41

Table 5 (*Continued*)

Skeleton (ATC Group V09B)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
			peripheral, oral mucosal blistering, pyrexia, syncope, throat irritation, thrombophlebitis, vision blurred	
Tc-99m butedronic acid	55	2	*IME:* none reported	–
			Other AEs: adverse reactions not specified	–
Tc-99m medronic acid	7,29,33,43,49,55-59,75,76,80,82,83,92,93,96-99,108,112,116,120	82	*IME:* anaphylactic reaction, erythema multiforme, respiratory distress	3
			Other AEs: hypersensitivity (10), nausea (7), nonspecific reaction (7), rash (7), presyncope (5), blood pressure decreased (3), erythema (3), headache (3), pallor (3), pruritus (4), rash erythematous (3), adverse reaction (2), cardiovascular symptom (2), chest discomfort (2), chills (2), discomfort (2), local reaction (2), pruritic rash (2), pyrexia (2), vomiting (2), cold sweat, conjunctival hyperemia, conjunctivitis, cough, dizziness, dry mouth, general symptoms, hypertension, hypoesthesia, hypotension, injection site erythema, injection site pain, jaundice, liver function test abnormal, malaise, myalgia, nasal congestion, edema peripheral, oliguria, oropharyngeal pain, pharynx discomfort, rash maculopapular, renal function test abnormal, skin reaction, skin test positive, swelling face, tachycardia, throat irritation	101
Tc-99m oxidronic acid	7,55,57-59,62,75-77,80-83,85,92-94,96-98,108,112	61	*IME:* loss of consciousness (4), anaphylactic shock, angioedema, respiratory arrest, respiratory failure, seizure	9
			Other AEs: rash (26), edema (25), pruritus (18), nausea (13), discomfort (9), local reaction (9), not specified (9), urticaria (8), vomiting (6), adverse reaction (4), erythema (4), malaise (4), affective disorder (3), dermatitis allergic (3), dizziness (3), eyelid edema (3), hyperhidrosis (3), hypertension (4), blood pressure decreased (3), cold sweat (2), headache (2), hot flush (2), hypersensitivity (2), rash generalized (2), abdominal pain, acute generalized exanthematous pustulosis, asthenia, blood creatine phosphokinase increased, diarrhea, dyspnea, eczema, flushing, incontinence, injection site erythema, injection site pain, laziness, mood altered, mouth swelling, pallor (2), papule, presyncope, pruritus generalized, rash erythematous, rash pruritic, stomatitis, vasculitis, white blood cell count increased	191
Tc-99m pyrophosphate	58,61,76,77,80,83,93,112	18	*IME:* none reported	–
			Other AEs: adverse drug reaction (7), adverse reaction, defecation urgency, dizziness, erythema (2), flushing, injection site erythema, nausea (4), presyncope, pruritus, vomiting (4)	24

Table 5 (*Continued*)

Renal System (ATC Group V09C)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
Cr-51 edetate	54,56,59,78	5	*IME:* none reported	–
			Other AEs: adverse reaction, chromaturia, hypersensitivity, local reaction, retching, testicular swelling	6
I-123 iodohippurate	56,59	2	*IME:* none reported	–
			Other AEs: local reaction, presyncope	2
I-131 iodohippurate	28,56,57,122	18	*IME:* depressed level of consciousness	1
			Other AEs: hypersensitivity (11), nonspecific reaction (4), abdominal pain, dyspnea, flushing, hypotension, nausea, presyncope, pruritus generalized, sense of oppression, tachycardia, toxicity to various agents	25
Tc-99m ethylenedicysteine	75,80,81,83,92,94,95,96	10	*IME:* respiratory distress	1
			Other AEs: nausea (3), rash (3), erythema (2), pruritus (2), vomiting (2), abdominal pain lower, blood pressure increased, diarrhea, discomfort, dyspnea, flushing, heart rate increased, hypertension, laziness, palpitations, sneezing	23
Tc-99m gluceptate	29,58,61,112	6	*IME:* none reported	–
			Other AEs: presyncope (2), adverse drug reaction, chills, dizziness, nausea, nonspecific reaction, rash, urticaria	9
Tc-99m mertiatide	53-55,65,66,80,94,106,116	23	*IME:* none reported	–
			Other AEs: nausea (6), dizziness (4), rash (3), blood pressure decreased (2), cold sweat (2), hyperhidrosis (2), pallor (2), urticaria (2), affective disorder, blister rupture, cardiovascular symptom, chest pain, chills, discomfort, eye swelling, fluid retention, headache, malaise, pruritus generalized, skin reaction, somnolence, syncope, vomiting	38
Tc-99m pentetic acid	7,28,29,53-56,58,59,61,65,69, 76,77,80,81,82,112,125	50	*IME:* paralysis, respiratory distress, seizure	3
			Other AEs: presyncope (9), nausea (5), rash (5), vomiting (5), nonspecific reaction (4), syncope (3), adverse reaction (2), chest pain (2), erythema (2), hypersensitivity (2), urticaria (2), adverse drug reaction, agitation, arthralgia, asthenia, blood pressure decreased, blood pressure increased, conjunctival hyperemia, cyanosis, depressed mood, dizziness, dry eye, dysgeusia, dyspnea, emotional distress, eye disorder, flushing, grunting, headache, hypoesthesia, malaise, muscle twitching, pallor, pruritus, rash generalized, venous pressure jugular increased. For Tc-99m pentetic acid with Fe used in the preparation 6 AEs were found in 1 patient, being: adverse drug reaction, dizziness, erythema, hypotension, pruritus, swelling	72
Tc-99m succimer	29,53-55,59,61,65,66,75,76, 82,83,94,96,116	32	*IME:* none reported	–

Table 5 (*Continued*)

Renal System (ATC Group V09C)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
			Other AEs: rash (7), headache (4), nausea (4), erythema (3), vomiting (3), adverse drug reaction (2), dizziness (2), discomfort, erythema of eyelid, hypersensitivity, hypoesthesia oral, nonspecific reaction, pallor, pyrexia, rash macular, rash pruritic, swollen tongue	35

Hepatic and Reticuloendothelial System (ATC Group V09D)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
I-131 rose bengal	61,112	3	*IME:* none reported	–
			Other AEs: adverse drug reaction (2), adverse reaction	3
In-113m colloid	28	34	*IME:* none reported	–
			Other AEs: hypersensitivity (27), toxicity to various agents (6), pyrexia	34
Se-75 tauroselcholic acid (SehCAT)	54,57,59,78	5	*IME:* anaphylactic reaction	1
			Other AEs: hypersensitivity (3), pruritus (2), rash (2), burning sensation, dizziness, dyspepsia, dyspnea, flushing, local reaction, nausea, pain, swelling, throat tightness	17
Tc-99m albumin colloid	53,56,58	6	*IME:* none reported	–
			Other AEs: hypersensitivity (3), administration site reaction, urticaria	5
Tc-99m antimony sulfide colloid	56,57,59	6	*IME:* none reported	–
			Other AEs: hypersensitivity (6)	6
Tc-99m diethylenetriami-nepentaacetic acid-galactosyl human serum albumin (GSA)	76,80,83,94,96	5	*IME:* none reported	–
			Other AEs: pruritus (2), rash (2), vomiting (2), blood pressure increased, cough, pain, pyrexia, sneezing	11
Tc-99m nanocolloid	39,40,45,54,65-67	8	*IME:* none reported	–
			Other AEs: urticaria (4), headache, hypotension, mouth swelling, peripheral swelling, pruritus, pruritus generalized, rash, rash macular	12
Tc-99m phytate	58	2	*IME:* none reported	–
			Other AEs: adverse reaction (2)	2
Tc-99m rheniumsulfide colloid	56	1	*IME:* none reported	–
			Other AEs: hypersensitivity	1

Table 5 (*Continued*)

Hepatic and Reticuloendothelial System (ATC Group V09D)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
Tc-99m sulfur colloid	7,28,29,37,56,58,61,73,112,115,116,118,125	110	*IME:* loss of consciousness (2), acute kidney injury, anaphylactic reaction, atrial fibrillation, circulatory collapse	6
			Other AEs: adverse reaction (37), pyrexia (19), hypersensitivity (15), injection site pain (12), nonspecific reaction (5), toxicity to various agents (4), rash (3), adverse drug reaction (2), cyanosis (2), dizziness (2), erythema (2), flushing (2), nausea (2), pruritus (2), vomiting (2), arrhythmia supraventricular, blood creatinine increased, blood pressure decreased, blood urea increased, bronchospasm, cardiovascular symptom, feeling hot, headache, hypotension, not specified, presyncope, pulse absent, respiratory disorder, swelling, tachycardia, urine output decreased, urticaria, wheezing	129
Tc-99m tin colloid	57-59	3	*IME:* none reported	–
			Other AEs: hypersensitivity (2), adverse reaction	3

Respiratory System (ATC Group V09E)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
I-131 macrosalb	28,36,52,113	7	*IME:* death (2), anuria, hemorrhagic infarction, hypersensitivity vasculitis, pulmonary hemorrhage, skin necrosis	7
			Other AEs: body temperature increased (2), dyspnea (2), hemoptysis (2), heart rate increased (2), hypersensitivity (2), nonspecific reaction (2), agitation, anemia, blood pressure decreased, blood pressure immeasurable, blood urea increased, bundle branch block right, chest pain, cough, cyanosis, dizziness, hematuria, heart rate decreased, hyperhidrosis, lung consolidation, pleuritic pain, PO2 decreased, rash, rhinorrhea, sinus tachycardia, tachypnea, venous pressure increased	33
Tc-99m microspheres	29,56,58,61,88,109,112	48	*IME:* anaphylactic shock, anaphylactoid shock, choking, respiratory distress	4
			Other AEs: hypersensitivity (16), adverse drug reaction (7), presyncope (5), nonspecific reaction (3), bronchospasm (2), cyanosis (2), flushing (2), anxiety, blood pressure immeasurable, femoral pulse abnormal, pruritus, pyrexia, rash, urticaria	44
Tc-99m macrosalb	7,28,41,53-55,57,58,61,65,66,71,76,80,83,112,124-126	59	*IME:* death (3), apnea (2), cardiac arrest (2), angioedema, bradycardia, loss of consciousness, respiratory arrest, right ventricular failure, unresponsive to stimuli, ventricular arrhythmia	14
			Other AEs: hypersensitivity (11), adverse reaction (9), dyspnea (5), dizziness (4), rash (4), nausea (3), pruritus (3), urticaria (3), cyanosis (2),	70

Table 5 (*Continued*)

Respiratory System (ATC Group V09E)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
			erythema (2), headache (2), heart rate increased (2), oxygen saturation decreased (2), vomiting (2), adverse drug reaction, blood pressure immeasurable, chills, cold sweat, dysgeusia, emotional distress, face edema, local reaction, mood altered, edema, presyncope, rash generalized, respiratory disorder, syncope, tachycardia, wheezing	
Tc-99m technegas	71,78	15	*IME:* none reported	–
			Other AEs: oxygen saturation decreased (15), paresthesia	16

Thyroid (ATC Group V09F)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
I-123 sodium iodine	56,58,59	3	*IME:* none reported	–
			Other AEs: adverse reaction, hypersensitivity, presyncope	3
I-123 sodium iodine (capsule)	76,102	2	*IME:* none reported	–
			Other AEs: pruritus, rash, urticaria	3
I-131 sodium iodine diagnostic	28,56,75,76	7	*IME:* none reported	–
			Other AEs: discomfort (3), pallor (3), dizziness (2), hypersensitivity (2), hypotension (2), adverse reaction, affective disorder, asthenia, blood pressure increased, cold sweat, cyanosis, feeling abnormal, hot flush, hyperhidrosis, nausea, yawning	23
I-131 sodium iodine diagnostic (capsule)	102	*	*IME:* none reported	–
			Other AEs: urticaria	1
Tc-99m pertechnetate	28,53,54,57,58,61,76,80,82	17	*IME:* loss of consciousness (2)	2
			Other AEs: hypersensitivity (6), rash (3), nausea (2), adverse reaction, blood pressure decreased, dizziness, flushing, headache, heart rate decreased, hypertension, pallor, phlebitis, presyncope, sinusitis, urticaria, vomiting	24
Cr-51 chromate-labeled cells and I-125 human albumin	56	1	*IME:* none reported	–
			Other AEs: adverse reaction	1
I-123 iodofiltic acid (BMIPP)	57,81,83,95	5	*IME:* none reported	–
			Other AEs: erythema (2), rash (2), blood pressure decreased, dyspnea, headache, hypersensitivity, nausea, rash	10

Table 5 (*Continued*)

Thyroid (ATC Group V09F)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
Pyrophosphate (nonradioactive)	29,32,116	5	*IME:* injection site necrosis, loss of consciousness	2
			Other AEs: blood pressure immeasurable, injection site inflammation, malaise, neurologic symptom, nonspecific reaction, skin reaction, vomiting	7
Stannous agent (nonradioactive)	7	3	*IME:* anaphylactic reaction (2)	2
			Other AEs: dizziness	1
Tc-99m human albumin	57,61,95,112	6	*IME:* none reported	–
			Other AEs: hypersensitivity (2), adverse drug reaction, blood pressure decreased, flushing, heart rate increased, nausea, pyrexia, rash, respiratory disorder	10
Tc-99m human albumin—DTPA	75,80,81,92	5	*IME:* none reported	–
			Other AEs: rash (3), erythema (2), pruritus (2), dizziness, nausea, edema peripheral, pyrexia	11
Tc-99m stannous agent-labeled cells	29,58,59	6	*IME:* none reported	–
			Other AEs: adverse reaction (2), hypersensitivity (2), nonspecific reaction	5
Tc-99m sestamibi	7,50,53,54,64-67,76,80-83,89, 92-95,100,107,116,123	30	*IME:* dermatitis exfoliative (2), anaphylactic reaction, angioedema, erythema multiforme	5
			Other AEs: vomiting (5), malaise (4), dysgeusia (3), erythema (3), hypertension (3), nausea (3), pruritus (3), pruritus generalized, rash (3), dizziness (2), eosinophilia (2), feeling cold (2), flushing (2), swollen tongue (2), blood pressure increased, discomfort, drooling, dyspnea, dysstasia, eyelids pruritus, headache, hyperhidrosis, injection site pain, injection site swelling, neck pain, neurologic symptom, edema, paresthesia, rash generalized, rash macular, rash maculopapular, skin exfoliation, skin reaction, speech disorder, syncope, tachypnea, wheezing	61
Tc-99m tetrofosmin	54,55,65,66,77,78,82,83,93,97,116	21	*IME:* epilepsy	1
			Other AEs: rash (6), nausea (4), vomiting (3), dizziness (2), dysgeusia (2), injection site erythema (2), neurologic symptom (2), pruritus (2),, burning sensation, cough, discomfort, dyspnea, fatigue, flushing, hyperhidrosis, hypertension, induration, lacrimation increased, oropharyngeal pain, rash generalized, rhinorrhea, slow response to stimuli, swelling, thrombophlebitis	40
Tl-201 chloride	30,55,58,65,75-77,80-83,92,93,95,97,98	25	*IME:* anaphylactic reaction, bradycardia, loss of consciousness	3
			Other AEs: rash (10), erythema (6), blood pressure decreased (3), hyperhidrosis (3), nausea (2), pruritus (2), pyrexia (2), syncope (2), vomiting (2),	60

Table 5 (*Continued*)

Thyroid (ATC Group V09F)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
			acute generalized exanthematous pustulosis, adverse reaction, affective disorder, amnesia, asthenia, chills, claustrophobia, conjunctival hyperemia, discomfort, dizziness, dyspnea, eyelid edema, feeling hot, flushing, hypersensitivity, hypotension, incontinence, leukocytosis, local reaction, oral mucosa erosion, papule, presyncope, red blood cell sedimentation rate increased, respiration rate increased, skin burning sensation, skin irritation, urticaria, vision blurred	

Inflammation and Infection Detection (ATC Group V09H)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
Ga-67 citrate	7,44,54,56,57,59,61,65,75-77,81-83,92-94	39	*IME:* altered state of consciousness, bradycardia	2
			Other AEs: rash (15), pruritus (11), pyrexia (5), rash generalized (5), adverse reaction (3), erythema (3), nausea (3), urticaria (3), blood pressure decreased (2), dyspnea (2), hyperhidrosis (2), hypersensitivity (2), vomiting (2), affective disorder, arthralgia, asthenia, burning sensation, C-reactive protein increased, discomfort, dysgeusia, feeling cold, flushing, generalized erythema, heart rate increased, hepatic function abnormal, local reaction, palpitations, paresthesia, rash morbilliform, skin plaque, sneezing, syncope, tachycardia, thirst, viral upper respiratory tract infection	80
In-111 oxinate-labeled cells	53,58,116	3	*IME:* none reported	–
			Other AEs: headache, hypersensitivity, myalgia, nausea, skin reaction	5
Tc-99m fanolesomab	60,87	75	*IME:* cardiac arrest (2), cardio-respiratory arrest (2), sudden cardiac death (2), hypoxia	7
			Other AEs: human antimouse antibody positive (5), paresthesia (2), viral upper respiratory tract infection (2), ankle sprain, blood lactate dehydrogenase increased, contusion, dyspnea, flushing, hypotension, malaise, toothache, transaminase increased	18
Tc-99m human immunoglobulin (HIG)	54	1	*IME:* none reported	–
			Other AEs: nausea	1
Tc-99m exametazime-labeled cells	54,65,66	5	*IME:* none reported	–

Table 5 (*Continued*)

Inflammation and Infection Detection (ATC Group V09H)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
Tc-99m sulesomab	54,65	3	*Other AEs:* dyspnea (2), emotional distress, flushing, malaise, pruritus generalized, rash pruritic	7
			IME: pulmonary edema	1
			Other AEs: blister, cyanosis, dizziness, hyperhidrosis, hypertension, nausea, pruritus, rash erythematous	8

Tumor Detection (ATC Group V09I)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
F-18 fluciclovine	31,119	5	*IME:* none reported	–
			Other AEs: adverse event (4), injection site erythema	5
F-18 fludeoxyglucose	42,78,83,85,86,92-95,97,98,116	17	*IME:* angioedema (3), dermatitis exfoliative (3), seizure (2), sudden cardiac death (2), anaphylactic reaction	11
			Other AEs: rash (13), pruritus (12), erythema (9), urticaria (8) dysgeusia (3), nausea (3), vomiting (3), hyperhidrosis (2), local reaction (2), abdominal pain, cardiovascular symptom, chills, diarrhea, discomfort, head tituba-tion, heart rate increased, hypotension, malaise, mental status change, oral pruritus, papule, rash generalized, skin reaction	69
F-18 fluorodihydroxy-phenylalanine (DOPA)	79	1	*IME:* carcinoid crisis	1
Ga-68 DOTA-NOC	78	†	*Other AEs:* none reported	–
			IME: none reported	–
			Other AEs: rash maculopapular	1
Ga-68 DOTA-TATE	46	3	*IME:* none reported	–
			Other AEs: injection site pruritus, oxygen saturation decreased, tachycardia	3
Ga-68 edotreotide (DOTA-TOC)	91,103,114	13	*IME:* none reported	
I-123 iobenguane	53,54,59,65-68,75,77,82,97,116	28	*Other AEs:* adverse event (9), nausea (2), discomfort, dysgeusia, flushing, headache, pain, paresthesia	17
			IME: none reported	–
			Other AEs: injection site pain (8), nausea (3), vomiting (3), dysgeusia (2), dyspnea (2), adverse reaction, blood gases abnormal, blood pressure decreased, discomfort, dizziness, flushing, heart rate increased, hyper-sensitivity, hypertension, hypoesthesia, hypotension, palpitations,	41

Table 5 (*Continued*)

Tumor Detection (ATC Group V09I)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
			persistent depressive disorder, presyncope, procedural nausea, pruritus, pruritus generalized, rash, rash generalized, skin odor abnormal, skin reaction, syncope, urticaria	
I-131 iobenguane diagnostic	70	1	*IME:* erythema multiforme	1
			Other AEs: rash erythematous, rash pruritic	2
In-111 satumomab pendetide	48,53	53	*IME:* angioedema (2), bradycardia, thrombocytopenia	4
			Other AEs: pyrexia (6), pruritus (4), hypersensitivity (3), abdominal pain (2), flank pain (2), human antimouse antibody positive (2), hypertension (2), nausea (2), rash (2), arthralgia, asthenia, chest pain, chills, confusional state, crying, diarrhea, dizziness, headache, hyperhidrosis, hypotension, hypothermia, injection site reaction, nervousness, pain, urticaria, vasodilatation, vomiting	43
Tc-99m arcitumomab	63	1	*IME:* none reported	–
			Other AEs: human antimouse antibody positive, urticaria	2
Tc-99m tilmanocept	84	6	*IME:* none reported	–
			Other AEs: adverse event (5), injection site irritation	6

Other Diagnostic Radiopharmaceuticals (ATC Group V09X)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
Au-198 colloid	28,56,57,125	6	*IME:* none reported	–
			Other AEs: hypersensitivity (5), adverse reaction	6
Hg-308 chlormerodrin	28	3	*IME:* none reported	–
			Other AEs: hypersensitivity (3)	3
I-131 human albumin	28,34,35,47,51,56,58,74,101,104,105	73	*IME:* CSF protein increased (11), CSF white blood cell count increased (8), CSF red blood cell count positive (7), CSF pressure increased (6), CSF test abnormal (3), meningitis aseptic (3), CSF cell count increased (2), CSF glucose increased (2), meningitis (2), CSF glucose decreased, neurogenic bladder, seizure	47
			Other AEs: pyrexia (52), nonspecific reaction (11), meningism (6), nuchal rigidity (6), body temperature increased (4), hypersensitivity (4), confusional state (3), headache (3), musculoskeletal stiffness (3), chills (2), vomiting (2), xanthochromia (2), adverse reaction, agitation, atelectasis,	109

Table 5 (*Continued*)

Other Diagnostic Radiopharmaceuticals (ATC Group V09X)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
			back pain, chest discomfort, hyperreflexia, lethargy, nausea, presyncope, somnolence, toxicity to various agents	
I-131 norcholesterol diagnostic	56,75-77,80-83,90,92, 93,95-97,121	60	*IME:* anaphylactic shock, electrocardiogram ST segment depression, ventricular tachycardia	4
			Other AEs: nausea (16), back pain (14), flushing (14), discomfort (11), hypersensitivity (10), blood pressure increased (8), dyspnea (8), erythema (8), hyperhidrosis (7), palpitations (6), affective disorder (5), blood pressure decreased (5), chest pain (5), dizziness (5), vomiting (5), chest discomfort (4), headache (5), abdominal discomfort (3), cough (3), hypertension (3), pallor (3), rash (3), asthenia (2), feeling abnormal (2), hot flush (2), hypoesthesia (2), malaise (2), pruritus (2), tachycardia (2), abdominal pain, abdominal symptom, abnormal sensation in eye, arthralgia, asthma, cyanosis, emotional distress, eyelid edema, feeling hot, heart rate increased, hyperventilation, hypotension, injection site rash, nasal congestion, neck pain, ocular hyperemia, pain, papule, pulse abnormal, swelling, vertigo positional	186
In-111 colloid	57	1	*IME:* none reported	–
			Other AEs: adverse reaction	1
In-111 platelets	57	1	*IME:* none reported	–
			Other AEs: hypersensitivity	1
In-113m pentetic acid	28	1	*IME:* none reported	–
			Other AEs: hypersensitivity	1
Tc-99m iron hydroxide	28	4	*IME:* none reported	–
			Other AEs: nonspecific reaction (3), toxicity to various agents	4
Tc-99m or In-113m iron precipitate	125	45	*IME:* none reported	–
			Other AEs: adverse reaction (45)	45
Tc-99m plasmin	56	1	*IME:* none reported	–
			Other AEs: hypersensitivity	1
Diagnostic radiopharmaceuticals not specified	57	419	*IME:* none reported	–
			Other AEs: rash (110), vomiting (30), urticaria (24), pruritus (64), skin reaction, adverse reaction	230

AEs, adverse events; IME, important medical event.

*AE reported with 1 patient using both I-123 sodium iodine (capsule) as I-131 sodium iodine diagnostic (capsule) *Cardiovascular System (ATC Group V09G)*.

†Exact number of patients was not given by author.

Technetium (Tc-99m) Oxidronic Acid. For Tc-99m oxidronic acid (oxidronate), we found 200 adverse events in 61 patients. The most reported adverse events were rash, edema, and pruritus. Nine IMEs were reported; 1 patient suffered from respiratory arrest and lost consciousness 2 minutes after injection,[76] 1 lost consciousness 1 minute after injection,[76] 1 suffered from severe respiratory failure,[94] 1 suffered 1 minute after injection from convulsions and lost consciousness,[96] 1 experienced angioedema,[85] and 1 had an anaphylactic shock and lost consciousness.[97]

Renal System (ATC Group V09C)

Technetium (Tc-99m) Mertiatide. For Tc-99m mertiatide, we found 38 adverse events in 23 patients. The most reported adverse events were nausea, dizziness, and rash. No IMEs were reported.

Technetium (Tc-99m) Pentetic Acid. For Tc-99m pentetic acid (pentetate), we found 75 adverse events in 50 patients. The most reported adverse events were presyncope, nausea, rash, and vomiting. Three IMEs were reported. One case described paralysis after intrathecal administration; Tc-99m pentetic acid is not registered for use intrathecally, and the Committee on Radiopharmaceuticals of the European Association of Nuclear Medicine issued a warning after this case that manufacturers do not specify intrathecal use.[129] Another patient experienced respiratory distress 1 hour after injection,[69] and 1 case of seizure was reported.[112]

Technetium (Tc-99m) Succimer. For Tc-99m succimer, we found 35 adverse events in 32 patients. The most reported adverse events were rash, headache, and nausea. No IMEs were reported.

Hepatic and Reticuloendothelial System (ATC Group V09D)

Selenium (Se-75) Tauroselcholic Acid. For Se-75 tauroselcholic acid (SehCAT), we found 18 adverse events in 5 patients. The most reported adverse events were hypersensitivity, pruritus, and rash. No IMEs were reported.

Technetium (Tc-99m) Nanocolloid. For Tc-99m nanocolloid, we found 12 adverse events in 8 patients. The most reported adverse event was urticaria. No IMEs were reported.

Technetium (Tc-99m) Sulfur Colloid. For Tc-99m sulfur colloid, we found 135 adverse events in 110 patients. Besides unspecified adverse events, the most reported adverse events were fever, hypersensitivity, and injection site pain. A study investigating different methods of preparation of Tc-99m sulfur colloid found a frequency of adverse events of 0.1%-0.9%.[118] A study into pain level during Tc-99m sulfur colloid use found that 11 (18.3%) of the 60 patients experienced significant pain.[73] The product's preparation method might cause the injection site pain and is most likely related to the stabilizers used, especially Dextran and Gelatin.[118] Low pH may be another reason, with Johnston showing that bringing the pH of the Tc-99m sulfur colloid solution to the physiological level could reduce pain levels during injection[73]; Canning used anesthetic cream before injection but was unable to demonstrate a reduction in pain.[130]

Six IMEs were reported. One patient suffered from an adverse reaction of the anaphylactoid type to Tc-99m sulfur colloid stabilized with gelatin, diagnosed the next day with acute renal failure; the authors indicated the cause of the acute renal failure is unknown, though the time sequence suggests renal ischemia with resultant acute tubular necrosis.[37] One case of loss of consciousness was reported,[112] and 1 patient experienced an anaphylactic reaction with loss of consciousness.[115]

Respiratory System (ATC Group V09E)

Technetium (Tc-99m) Macrosalb. For Tc-99m macrosalb, we found 84 adverse events in 59 patients. In addition to some unspecified adverse events, the most reported adverse events were hypersensitivity, dyspnea, dizziness, and rash. Fourteen IMEs were reported in 8 patients: 1 case of angioedema,[66] 2 cases of cardiac arrest,[53,112] 1 case in which a patient became unresponsive with bradycardia,[65] 1 case of respiratory arrest,[55] and 3 deaths. The 3 deaths included 2 patients who presented with a history of pulmonary hypertension[41,126] and 1 suffering from an advanced pulmonary vascular disease,[124] all 3 of whom experienced a similar sequence of events (respiratory distress, cyanosis, and hypotension). Similar events are also reported in animal studies when giving a toxic dose of macrosalb particles,[131] and the reported events were likely caused by the size and number of particles.

In a person with a normal pulmonary vascular bed, a usual macrosalb dose of 0.1 mg to 4.0 mg with particle sizes of 10 μm to 50 μm will occlude only 0.1% of the cross-section area of the pulmonary vascular bed.[41,52] However, when a patient is suffering from a disease in which the number of lung capillaries is seriously decreased, blocking a part of the remainder of the capillary bed could lead to respiratory distress. Additionally, particle size is important to consider, as larger particles are likely to occlude larger vessels, and pulmonary vascular diseases such as pulmonary hypertension or other diffuse lung diseases require particular caution. When a pulmonary perfusion scan is needed in patients with pulmonary vascular disease, the number of particles in the dose to be administered should be calculated, quality control for the size of the particles can be performed with light microscopy, and slow injection of the radiopharmaceutical is advised.[41,52,113] Specifications on particle number and size differ by product. In addition to special considerations for patients with pulmonary vascular diseases, additional care is required for children[132] since their pulmonary vascular bed is not fully developed. The number of particles may need to be adjusted depending on the age of the child.

Technetium (Tc-99m) Technegas. For Tc-99m technegas, we found 16 adverse events in 15 patients. The most reported adverse event was a decrease in oxygen saturation, which was reported in a study evaluating oxygen saturation in

patients undergoing lung ventilation scintigraphy using Tc-99m technegas; that study found that 37% of patients experienced a decrease of more than 10% in oxygen saturation.[71] No IMEs were reported.

Thyroid (ATC Group V09F)

Sodium Iodide (I-123). For I-123 sodium iodine, we found 6 adverse events in 5 patients. No IMEs were reported. One patient developed a rash after use of an I-123 sodium iodine capsule, with the report's authors determining the excipients of the capsule or the dyes used in the capsule were most likely the cause of this adverse event.[102]

Technetium (Tc-99m) Pertechnetate. For Tc-99m pertechnetate, we found 26 adverse events in 17 patients. The most reported adverse events were hypersensitivity, rash, and nausea. Two IMEs were reported: 1 patient lost consciousness immediately after injection,[80] and another lost consciousness 5 minutes after injection.[76] Both cases were classified by the author as vasovagal reactions.

Cardiovascular System (ATC Group V09G)

Pyrophosphate (Nonradioactive). For pyrophosphate, we found 9 adverse events in 5 patients. Two IMEs were reported: 1 patient who lost consciousness and another who developed an infection at the site of injection the week after administration, eventually leading to necrosis of this site.[32]

Stannous Agent (Nonradioactive). For stannous agent, we found 3 adverse events in 3 patients. Two IMEs were reported, both anaphylactic reactions not further specified by the author.[7]

Technetium (Tc-99m) Sestamibi. For Tc-99m sestamibi, we found 66 adverse events in 30 patients. The most reported adverse events were vomiting and malaise. Five IMEs were reported: 1 patient suffered from an erythroderma affecting more than 90% of his body,[50] 1 experienced an angioedema,[89] 1 suffered an anaphylactic reaction with a painless macroglossia,[100] 1 presented with an exfoliating itching dermatitis,[107] and 1 was diagnosed with erythema multiforme after Tc-99m sestamibi administration.[123]

Three cases of dysgeusia were reported, with the patients describing the taste as being metallic or bitter. The reasons behind this taste disorder after radiopharmaceutical injection is not well understood. Several possible hypotheses have been proposed: high blood levels for the radiopharmaceutical itself,[67] and one of the excipients of the formulation (eg, the presence of copper ions in some formulations of I-123 iobenguane). The rapid rate of injection may be an additional risk factor. A strange taste can be confusing for the patient, but an explanation can be provided if the nuclear medicine staff are aware of this transient effect.

Technetium (Tc-99m) Tetrofosmin. For Tc-99m tetrofosmin, we found 41 adverse events in 21 patients. The most reported adverse events were rash, nausea, and vomiting. One IME was reported, concerning a patient suffering from an epileptic seizure 24 hours after administration of the radiopharmaceutical; the author specifies the patient also received dipyridamole.[65]

Thallium (Tl-201) Chloride. For Tl-201 chloride, we found 63 adverse events in 25 patients. The most reported adverse events were rash and erythema. Three IMEs were reported: one case of mild anaphylaxis,[55] 1 patient who experienced bradycardia postadministration after exercise on an ergometer,[77] and 1 patient who temporarily lost consciousness 5 minutes after administration of the radiopharmaceutical.[82]

Inflammation and Infection Detection (ATC Group V09H)

Gallium (Ga-67) Citrate. For Ga-67 citrate, we found 82 adverse events in 39 patients. The most reported adverse events were rash, pruritus, and fever. Two IMEs were reported: one patient experienced bradycardia,[76] and another lost consciousness.[81] For Ga-67 citrate, 42 skin disorders were reported. It has been suggested that this high number of adverse events involving the skin is due to the use of a preservative; one report described an adverse event followed by a positive skin test for benzyl alcohol, a preservative used in Ga-67 citrate.[44]

Radiolabeled Leucocytes. For In-111 oxinate-labeled cells, we found 5 adverse events in 3 patients. For Tc-99m exametazime-labeled cells, we found 7 adverse events in 5 patients. No IMEs were reported for radiolabeled leucocytes, which are used to image inflammation and infection processes. Steps involving excipients are required to label blood cells. Anticoagulant agents such as acid-citrate-dextrose are used to prevent the blood from clotting, and sedimentation agents such as methylcellulose, dextran, and hydroxyethyl starch are used to accelerate the sedimentation of blood cells.[133] Although most procedures involve washing the labeled cells, it cannot be excluded that adverse events are related to one of the excipients used.

Technetium (Tc-99m) Sulesomab. For Tc-99m sulesomab, we found 9 adverse events in 3 patients. One IME was reported in 1 patient experiencing pulmonary edema.[54] Tc-99m sulesomab is a radiopharmaceutical based on an antibody, although it is not associated with the development of human antimouse antibodies; Fab fragments of IgG antibody lack the Fc-terminal responsible for the immune reactions.[134]

Tumor Detection (ATC Group V09I)

Fluciclovine (F-18). For F-18 fluciclovine, we found 5 adverse events in 5 patients. In a cohort study with 714 patients, 0.6% reported adverse events.[31] In a small study with 6 patients, 1 patient experienced one adverse event (frequency of 16.5%).[119] No IMEs were reported.

Fludeoxyglucose (F-18). For F-18 fludeoxyglucose, we found 80 adverse events in 17 patients. The most reported adverse

events were rash, pruritus, and erythema. Eleven IMEs were reported: 1 anaphylactic reaction,[86] 3 cases of angioedema, 3 cases of dermatitis exfoliative, 2 cases of seizures, and 2 sudden cardiac deaths.[85] One patient with a history of epilepsy suffered 10 minutes after injection from a convulsive seizure and cardiorespiratory distress, and the other patient had a history of lymphoma and suffered from septic shock 24 hours after injection (October 19, 2018 e-mail from Prof Laroche to N.S.; unreferenced).

Fluorodihydroxyphenylalanine (F-18). For F-18 fluorodihydroxyphenylalanine (DOPA), an adverse event classified as an IME was reported in 1 patient. This IME was a case of a carcinoid crisis, which is the result of a massive release of neurotransmitters such as serotonin and is characterized by flushing, changes in blood pressure, difficulty breathing, and rapid heart rate. Carcinoid crisis can potentially be life threatening, and the authors advise practitioners to be aware of this rare syndrome, slowly inject the tracer, and have appropriate drugs available to treat this condition, such as somatostatin analogs and perhaps ketanserin.[79]

Gallium-68-Labeled Somatostatin Analogs (Ga-68 Edotreotide (DOTA-TOC), Ga-68 DOTA-TATE, Ga-68 DOTA-NOC). For the group of Ga-68-labeled somatostatin analogs, we found 21 adverse events in 16 patients. A study evaluating safety and comparing Ga-68 DOTA-TATE with In-111 pentetreotide imaging (conducted with 97 patients) found 3 adverse events in 3 patients, for a frequency of 3.09%.[46] In a multicenter trial using Ga-68 edotreotide in 20 patients, 4 adverse events possibly related to the radiopharmaceutical were found, for a frequency of 20%.[91] Another study with Ga-68 edotreotide found 9 adverse events in 26 patients (34.6%).[103] No IMEs were reported.

Iobenguane (I-123). For I-123 iobenguane, we found 41 adverse events in 28 patients. The most reported adverse events were injection site pain, nausea, and vomiting. A multicenter clinical trial involving 981 patients reported a 0.407% frequency of adverse events.[68] No IMEs were reported.

Indium (In-111) Satumomab Pendetide. For In-111 satumomab pendetide, we found 47 adverse events in 53 patients. The most reported adverse events were fever, pruritus, and hypersensitivity. Clinical trials involving 1041 patients found an adverse event frequency of 3.79%[38]; a multicenter clinical trial with 116 patients found an adverse event frequency of 6.03%.[48] Four IMEs were found: one study found cases of bradycardia, angioedema, and thrombocytopenia,[38] and one case of angioedema was reported.[48]

In-111 satumomab pendetide contains murine monoclonal antibodies. These antibodies might induce an immune response producing human antimouse antibodies, which may interfere with murine antibody-based immunoassays, could compromise the efficacy of in vitro or in vivo diagnostic or therapeutic murine antibody-based agents, and may increase the risk of adverse reactions (although the frequency and nature of these reactions are unclear). Several factors known to influence a human antimouse antibodies reaction include dose, frequency of dosing, type of immunogenicity of the antibody, and the state of the patient's immune system. When a radiopharmaceutical is only used once, the likelihood of a reaction appears to be low since the immune system needs around 10 days to express IgG and IgM.[63,87,135,136] For some radiopharmaceuticals containing antibodies, the manufacturer provides additional guidelines for use such as to inquire about possible previous exposure to monoclonal antibodies, conduct a human antimouse antibodies test prior to administration, and inform that use could affect future use of murine-based products.[137-139]

Technetium (Tc-99m) Tilmanocept. For Tc-99m tilmanocept, we found 6 adverse events. In a multicenter trial with 85 patients, 36 reported at least 1 adverse event; the authors indicate that 85% of the reported adverse events were unrelated to Tc-99m tilmanocept.[84] No IMEs were reported.

Other Diagnostic Radiopharmaceuticals (ATC Group V09X)

Iodine (I-131) Norcholesterol Diagnostic. For I-131 norcholesterol for diagnostic use, we found 190 adverse events in 60 patients. The most reported adverse events were nausea, back pain, and flushing. Four IMEs were found in 3 patients: one case described an anaphylactic shock 15 minutes after injection,[83] another described a patient with ventricular tachycardia (with the authors believing this patient developed a crisis due to the medical condition),[93] and one describing an atypical anaphylactic reaction.[90]

I-131 norcholesterol is a norepinephrine analog used for adrenal imaging in primary aldosteronism, such as in pheochromocytoma. Adverse events are most frequently reported in Japan, which might be related to this radiopharmaceutical being used there more frequently.[90] The manufacturer states that no pharmacodynamic effects are expected for doses used in diagnostic imaging.[140] However, the reported events suggest involvement of the adrenergic nervous system, as some of the adverse events resemble symptoms also present in pheochromocytoma.[141,142] More research would be needed to clarify if the events are possibly connected to pheochromocytoma.

Discussion

Based on a systematic review of the literature, we selected and analyzed 101 of 20,363 titles and provided an overview of 2447 adverse events associated with the use of diagnostic radiopharmaceuticals. The majority of the reported adverse events with diagnostic radiopharmaceuticals (84.4%) related to 6 system organ classes. Most reported adverse events were in the system organ classes "skin and subcutaneous tissue disorders" and "general disorders and administration site conditions."

Some of the reported adverse events can be described as allergic reactions—for example, skin reactions such as rash

and urticaria, angioedema leading to swelling of face or tongue and breathing difficulty, and even life-threatening anaphylactic shock. Another portion of the adverse events reported with diagnostic radiopharmaceuticals can be described as vasovagal reactions, which include symptoms such as pallor, feeling warm, sweating, a drop in blood pressure, and fainting.

Since most patients typically receive a diagnostic radiopharmaceutical only once, the precise trigger for the allergic reaction is often unknown. Some modern diagnostical radiopharmaceuticals are used in repeated administration for treatment evaluation and follow-up, which might have consequences when the sensibilization risk changes. A limited number of case reports note a positive rechallenge: Spicer reports a case with Tc-99m medronic acid in which a patient developed a pruritic erythematous rash after the first use and erythema multiforme with the second use after 9 months,[120] and Mooser reports a case of an erythematous, pruritic rash after administration of Tc-99m medronic acid, with a rechallenge that Tc-99m was responsible for the rash.[99] Núñez reports a case of rash after the use of I-123 and I-131 sodium iodine capsules, arguing that excipients of the capsules or the dyes used in the capsules were the most likely causes; the patient took an I-123 sodium iodine capsule followed 5 months later with an I-131 sodium iodine capsule and developed an urticarial skin rash similar in appearance on both occasions.[102] Commandeur reports a case of hypersensitivity to Ga-67 chloride, with skin tests demonstrating that the preservative benzyl alcohol caused the reaction.[44]

Our review found the majority of the reported events were minor in severity and often resolved without sequelae. Nevertheless, 165 (6.7%) of the reported adverse events could be classified as IMEs, and 9 deaths were reported: 5 occurring with the use of I-131 or Tc-99m macrosalb for pulmonary scintigraphy in cases of a severe reduction in pulmonary capacity, 2 occurring with F-18 fluorodeoxyglucose, and 2 occurring with the radiopharmaceutical Tc-99m fanolesomab, which is no longer available. We found a median reported frequency of adverse events in diagnostic radiopharmaceuticals of 0.0016%, which is low compared to the 1%-2% reported for therapeutic drugs[143,144] and the 5%-7% reported for drug reactions in hospitalized patients.[145-147] This frequency is also lower than the earlier reported frequency range of 0.7%-3.1% with nonionic iodinated contrast media used in computed tomography (CT).[148,149] For some individual radiopharmaceuticals, we found a frequency ranging from 0.125% to 40.9%, with the higher frequencies including products no longer in use such as I-131 human serum albumin and Tc-99m fanolesomab.

The low reported frequency with some diagnostic radiopharmaceuticals can be explained by a low dose, lack of pharmacologic effect, and low frequency of administration (often only once); another important reason might be that all of the studies reporting on the frequency of adverse events for various radiopharmaceuticals relied on voluntary identification and reporting. The following aspects might also influence the reporting or publication of case reports of adverse events: (1) Some procedures in nuclear medicine departments sometimes use nonradioactive drugs to conduct an examination, such as stress agents in myocardial perfusion imaging or diuretics in renal imaging. Some adverse reactions may result from these nonradioactive drugs and be inadvertently linked to the radiopharmaceutical, and some adverse events might be missed because physicians assume they result from the investigation procedure itself, such as dyspnea during myocardial perfusion imaging; (2) not every institution maintains good records of its adverse events; (3) physicians might not report adverse events considered to be minor; (4) the level of awareness on adverse events might not be consistent across institutions due to different perceptions on the need to report these events; and (5) the nuclear department may not be informed about an adverse event, as the patient left after examination.[15,65]

Our data regarding frequency are in line with findings from a previous literature review by Salvatori, which included 7 studies and found a pooled prevalence rate of 1.9 per 100,000 administrations.[17] Salvatori's review does not include an overview of the most common adverse events and their characteristics. In our review, we use a systematic approach following the PRISMA guidelines, focusing on a transparent and complete reporting. Furthermore, it covers all diagnostic radiopharmaceuticals and the search was not restricted to a specific time period. Although 85.0% of the articles had a moderate or good methodological quality, they consist primarily of uncontrolled clinical observations that might be prone to bias.

The studies in our review were checked for a double presentation of the data, which can occur, for example, when an event is included in a case report and in a spontaneous reporting summary. We determined double reporting occurred in one article,[150] and therefore did not include the paper in this review. However, when an article did not contain a reference to a previously reported case, we were not able to assess double reporting. For 14 articles, the number of events presented could not exact be matched with the number of patients. In these cases, the reported adverse events were counted as one, although the correct number might have been higher; this may have led to some underreporting of adverse events in this review.

Differences in preset definitions and study set-up were found. For example, Silberstein introduced a strict definition of "adverse events"[7] excluding any vasovagal reactions because these are thought to be so common in a clinical setting that it is extremely difficult to determine their relationship with the injected radiopharmaceutical. However, other researchers such as Hesslewood include vasovagal reactions to ensure all events are captured; Hesslewood notes that excluding vasovagal reactions also excludes the possibility of carefully evaluating the event.[67]

It should be noted that the radiopharmaceuticals were divided into several groups, using the ATC classification system. Because a radiopharmaceutical is included in only one group, classification does not specify each indication of that individual radiopharmaceutical. This did not influence our data, but it does require readers to be aware of this classification system when looking for information; for example,

Tc-99m pertechnetate is included in the ATC group "V09F Thyroid" but may also be used to measure the cardiac ejection fraction. Furthermore, this review provides a general overview and therefore does not consider variations in products or procedures that might differ from country to country.

Additionally, some nuclear medicine procedures involve the use of interventional agents to mimic a physiological effect or for preventative use. For example, myocardial perfusion scans often involve the radiopharmaceutical being combined with a pharmacologic stress agent such as adenosine, dipyridamole, or dobutamine, and dynamic renal studies might use furosemide or captopril. For iodinated radiopharmaceuticals, the thyroid might need to be blocked using Lugol's solution or potassium iodine tablets. In addition to these interventional agents, the relatively recent introduction of combined modalities like PET/CT and SPECT/CT sometimes requires the use of contrast media. In the events reported, it may not always have been possible to decide which of the administered agents was responsible for the adverse event.

Future Perspectives

A possible reason for the low frequency of adverse events associated with diagnostic radiopharmaceuticals might be that not all cases are reported or published, and prospective studies describing the experiences of patients with diagnostic radiopharmaceuticals could provide more information.

Several new PET tracers have recently been marketed for use. Our study found 107 adverse events reported with PET tracers (F-18 fludeoxyglucose, F-18 fluciclovine, F-18 fluorodihydroxyphenylalanine (DOPA), and Ga-68-labeled somatostatin analogs). The majority are attributed to F-18 fludeoxyglucose, probably because this agent is mostly used. The number of adverse events we found for PET tracers is far below what has been reported with the conventional gamma tracers. Silberstein also saw this in his 1998 study, finding no adverse events for PET tracers among 81,801 patients.[117] Possible reasons might be that PET tracers are used in even smaller doses (micrograms) than the conventional gamma tracers and are labeled molecules that are normally found in the human body (or are analogs of these). Another reason can be that PET tracers are relatively new. With an increasing number of patients exposed to these new tracers, the number of reported adverse events may increase, providing insight into new adverse events. Reporting of adverse events to the relevant regulatory authorities or marketing authorization holder could detect hitherto unknown adverse events.

Finally, the increasing use of combined modalities like PET/CT and SPECT/CT might further increase the reported frequency of adverse events in nuclear medicine examinations because of the use of contrast media.[151]

Conclusion

This review shows that adverse events can definitely occur with diagnostic radiopharmaceuticals, although the frequency is quite low compared to other types of drugs. The most common adverse events are skin and subcutaneous tissue disorders, and general disorders and administration site conditions. In rare cases, the adverse events can be serious and even life threatening, but most resolve without sequelae. We recommend nuclear medicine departments be prepared to manage these situations. Furthermore, with the introduction of new radiopharmaceuticals and the increasing use of PET/CT, the nuclear medicine community should remain vigilant in terms of new adverse events. Further research should cover the patient's experience with adverse events resulting from diagnostic radiopharmaceuticals.

Acknowledgments

The MedDRA trademark is owned by the International Federation of Pharmaceutical Manufacturers and Associations on behalf of ICH. The authors would like to thank Ms Truus van Ittersum, information specialist and staff advisor at the School of Health Research (SHARE) Institute, University Medical Center Groningen, for assisting with the search strategy.

References

1. Maltby P, Theobald T: Survey of current diagnostic radiopharmaceuticals. In: Theobald T (ed): Sampson's Textbook of Radiopharmacy, ed 4, London: Pharmaceutical Press, 277-301, 2011
2. Chan P, Croasdale J: Survey of current therapeutic radiopharmaceuticals. In: Theobald T (ed): Sampson's Textbook of Radiopharmacy, ed 4, London: Pharmaceutical Press, 303-323, 2011
3. Galbraith W, DePietro AL: Radiopharmaceuticals used in nuclear medicine imaging. In: Smith BT, Weatherman KD (eds): Diagnostic Imaging for Pharmacists, ed 1, Washington DC: American Pharmacists Association, 85-132, 2012
4. World Health Organization: International Drug Monitoring. The Role of National Centres (Technical Report Series No. 498). Geneva: World Health Organisation, 1972
5. World Health Organization. Safety of Medicines: A Guide to Detecting and Reporting Adverse Drug Reactions, Geneva: World Health Organisation, 2002 whqlibdoc.who.int/hq/2002/WHO_EDM_QSM_2002.2.pdf. Accessed November 12, 2018
6. Naranjo CA, Busto U, Sellers EM, et al: A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30:239-245, 1981
7. Silberstein EB, Ryan J: Prevalence of adverse reactions in nuclear medicine: Pharmacopeia committee of the society of nuclear medicine. J Nucl Med 37:185-192, 1996
8. Edwards R, Yixin C: Adverse drug reactions. In: Van Boxtel CJ, Santoso B, Edwards IR (eds): Drug Benefits and Risks: International Textbook of Clinical Pharmacology, ed 2, Amsterdam: IOS Press, 225-245, 2008
9. Abuhanoğlu G, Özer AY: Adverse reactions to radiopharmaceuticals. Fabad J Pharm Sci 37:43-59, 2012
10. Sampson CB: Adverse reactions and drug interactions with radiopharmaceuticals. Drug Saf 8:280-294, 1993
11. Santos-Oliveira R: Undesirable events with radiopharmaceuticals. Tohoku J Exp Med 217:251-257, 2009
12. Santos-Oliveira R, Moriguchi-Jeckel CM, Mills PCPN: Normal or abnormal? Events involving 99m-Technetium. Int J Pharm Sci Rev Res 4:18-24, 2010
13. Santos-Oliveira R, Machado M: Pitfalls with radiopharmaceuticals. Am J Med Sci 342:50-53, 2011
14. Shani J, Atkins HL, Wolf W: Adverse reactions to radiopharmaceuticals. Semin Nucl Med 6:305-328, 1976

15. Pinto SR, Santos LFC, dos Reis SRR, et al: Adverse reactions to radiopharmaceuticals: A survey based on clinical cases using criteria of systematic review. Ther Innov Regul Sci 52:109-113, 2018
16. Ballinger JR: Pitfalls and limitations of SPECT, PET, and therapeutic radiopharmaceuticals. Semin Nucl Med 45:470-478, 2015
17. Salvatori M, Treglia G, Mores N: Further considerations on adverse reactions to radiopharmaceuticals. Eur J Nucl Med Mol Imaging 39:1360-1362, 2012
18. Blaine P, Spicer J, Generali J, et al: Development of a radiopharmaceutical information database. J Nucl Med Technol 27:230-233, 1999
19. Mather SJ: VirRAD: a virtual learning resource for radiopharmacy and nuclear medicine. Nucl Med Rev Cent East Eur 7:77-79, 2004
20. Gomez Perales JL, Martinez AA: A portable database of adverse reactions and drug interactions with radiopharmaceuticals. J Nucl Med Technol 41:212-215, 2013
21. Moher D, Liberati A, Tetzlaff J, et al: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6, 2009 . e1000097
22. Murad MH, Sultan S, Haffar S, et al: Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med 23:60-63, 2018
23. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC Classification and DDD Assignment. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, 2017, 2018
24. MedDRA Browser (2016 version 2.0). https://www.meddra.org/ Accessed April 27 2018
25. European Medicines Agency: Important medical event terms list. London: European Medicines Agency, 2018 https://www.ema.europa.eu/documents/other/important-medical-event-terms-list-version-210-imelist_en.xls Accessed April 27 2018
26. European Medicines Agency: Inclusion/exclusion criteria for the "Important Medical Events" list. London: European Medicines Agency, 2018 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/08/WC500212100.pdf Accessed June 01 2018
27. Alderson PO, Siegel BA: Adverse reactions following 111In DTPA cisternography. J Nucl Med 14:609-611, 1973
28. Atkins HL, Hauser W, Richards P, et al: Adverse reactions to radiopharmaceuticals. J Nucl Med 13:232-233, 1972
29. Atkins HL: Reported adverse reactions to radiopharmaceuticals remain low in 1984. J Nucl Med 27:327, 1986
30. Aziz Jalali MH, Mirzazadeh Javaheri S, Salehian P: Acute generalized exanthematous pustulosis due to thallium. J Eur Acad Dermatol Venereol 18:321-323, 2004
31. Bach-Gansmo T, Nanni C, Nieh P, et al: Staging of biochemically relapsing prostate cancer using the positron emission tomography tracer fluciclovine F18. Int J Radiat Oncol Biol Phys 96:S112, 2016
32. Bagheri H, Galian ME, Bastie D, et al: Enquête prospective sur les effets indésirables des médicaments radiopharmaceutiques. Thérapie 51:550-553, 1996
33. Balan KK, Choudhary AK, Balan A, et al: Severe systemic reaction to (99m)Tc-methylene diphosphonate: A case report. J Nucl Med Technol 31:76-78, 2003
34. Banerji MA, Spencer RP: Febrile response to cerebrospinal fluid flow studies. J Nucl Med 13:655, 1972
35. Barnes B, Fish M: Chemical meningitis as a complication of isotope cisternography. Neurology 22:83-91, 1972
36. Bliek AJ, Bachynski JE: Two severe reactions following a pulmonary scan in a patient with idiopathic pulmonary haemosiderosis. J Nucl Med 12:90-92, 1971
37. Block MB, Thompson JS, Polcyn RE: Anaphylactoid reaction to technetium-99m sulfur colloid stabilized with gelatin: Report of a case. Am J Dig Dis 15:569-571, 1970
38. Bohdiewicz PJ: Indium-111 satumomab pendetide: The first FDA-approved monoclonal antibody for tumor imaging. J Nucl Med Technol 26:155-163, 1998
39. Burton DA, Cashman JN: Allergic reaction to nanocolloid during lymphoscintigraphy for sentinel lymph node biopsy. Br J Anaesth 90:105, 2003
40. Chicken DW, Mansouri R, Ell PJ, et al: Allergy to technetium-labelled nanocolloidal albumin for sentinel node identification. Ann R Coll Surg Engl 89:W12-W13, 2007
41. Child JS, Wolfe JD, Tashkin D, et al: Fatal lung scan in a case of pulmonary hypertension due to obliterative pulmonary vascular disease. Chest 67:308-310, 1975
42. Codreanu I, Dasanu CA, Weinstein GS, et al: Fluorodeoxyglucose-induced allergic reaction: A case report. J Oncol Pharm Pract 19:86-88, 2013
43. Collins MR, James WD, Rodman OG: Adverse cutaneous reaction to technetium Tc 99m methylene diphosphonate. Arch Dermatol 124:180-181, 1988
44. Commandeur C, Richard M, Renzi PM: Severe hypersensitivity reaction to injectable gallium 67 in a worker exposed to silica. Allergy 47:337-339, 1992
45. Cotrina-Monroy A, Perez-Iruela JA, Lopez-López A, et al: Notification of an adverse effect to human albumin 99mTc-nanocolloid. Revista Española de Medicina Nuclear 29:308-309, 2010
46. Deppen SA, Liu E, Blume JD, et al: Safety and efficacy of 68Ga-DOTA-TATE PET/CT for diagnosis, staging, and treatment management of neuroendocrine tumors. J Nucl Med 57:708-714, 2016
47. Detmer DE, Blacker HM: A case of aseptic meningitis secondary to intrathecal injection of I-131 human serum albumin. Neurology 15:642-643, 1965
48. Doerr RJ, Abdel-Nabi H, Krag D, et al: Radiolabeled antibody imaging in the management of colorectal cancer. Results of a multicenter clinical study. Ann Surg 214:118-124, 1991
49. Dos Santos Almeida R, Mamede M, Santos-Oliveira R: Pharmacovigilance of radiopharmaceuticals used for prostate and breast cancer in Brazil. Adverse Drug React Bull 283:1091-1094, 2013
50. Doukaki S, Arico M, Bongiorno MR: Erythroderma related to the administration of 99mTc-sestamibi: The first report. J Nucl Cardiol 17:520-522, 2010
51. Dramov B, Dubou R: Aseptic meningitis following intrathecal radioiodinated serum albumin. Calif Med 115:64-66, 1971
52. Dworkin HJ, Smith JR, Bull FE: A reaction following administration of macroaggregated albumin (MAA) for a lung scan. Am J Roentgenol Radium Ther Nucl Med 98:427-433, 1966
53. EANM Committee on Radiopharmaceuticals: European system for reporting adverse reactions to and defects in radiopharmaceuticals: Annual report 1993. Eur J Nucl Med 21:BP29-BP34, 1994
54. EANM Committee on Radiopharmaceuticals: European system for reporting adverse reactions to and defects in radiopharmaceuticals: Annual report 1994. Eur J Nucl Med 22:BP29-BP33, 1995
55. EANM Committee on Radiopharmaceuticals: European system for reporting adverse reactions to and defects in radiopharmaceuticals: Annual report 1995. Eur J Nucl Med 23:BP27-BP31, 1996
56. The Joint Committee on Radiopharmaceuticals of the European Nuclear Medicine Society and the Society of Nuclear Medicine – Europe: The system for "reporting of adverse reactions and drug defects" (1980-1982): First report. Nuklearmedizin 21:274-277, 1982
57. The Joint Committee on Radiopharmaceuticals of the European Nuclear Medicine Society and the Society of Nuclear Medicine – Europe: European system for reporting of adverse reactions and drug defects: Second report 1982-1983. Nuklearmedizin 23:107-108, 1984
58. The Joint Committee on Radiopharmaceuticals of the European Nuclear Medicine Society and the Society of Nuclear Medicine – Europe: European system for reporting of adverse reactions and drug defects: Third report 1984-1985. Eur J Nucl Med 13:487-490, 1987
59. The Joint Committee on Radiopharmaceuticals of the European Nuclear Medicine Society and the Society of Nuclear Medicine – Europe: European system for reporting of adverse reactions and drug defects: Fourth report 1986. Eur J Nucl Med 13:491-492, 1987
60. FDA: Information for healthcare professionals [Technetium (99m Tc) fanolesomab] marketed as neutrospec (12/2005). FDA ALERT: 1-2, 2005. https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm129299.htm. Accessed November 12, 2018
61. Ford L, Shroff A, Benson W, et al: SNM drug problem reporting system. J Nucl Med 19:116-117, 1978
62. Hart B, Sorenson JF, Eisenberg B, et al: Delayed skin rash following administration of Technetium-99m diphosphonate: A case report. J Nucl Med Technol 17:184-185, 1989

63. Hertel A, Baum RP, Auerbach B, et al: The clinical relevance of human anti-mouse-antibody (HAMA) in immunoscintigraphy. Nuklearmedizin 29:221-227, 1990
64. Hesse B, Vinberg N, Mosbech H: Exanthema after a stress Tc-99m sestamibi study: Continue with a rest sestamibi study? Clin Physiol Funct Imaging 31:246-248, 2011
65. Hesslewood SR: European system for reporting adverse reactions to and defects in radiopharmaceuticals: Annual report 2000. Eur J Nucl Med Mol Imaging 29:BP13-BP19, 2002
66. Hesslewood Stuart SR: European system for reporting adverse reactions to and defects in radiopharmaceuticals: Annual report 2001. Eur J Nucl Med Mol Imaging 30:BP87-BP94, 2003
67. Hesslewood SR, Keeling DH: Frequency of adverse reactions to radiopharmaceuticals in Europe. Eur J Nucl Med 24:1179-1182, 1997
68. Hirosawa K, Tanaka T, Hisada K, et al: Clinical evaluation of 123I-MIBG for assessment of sympathetic nervous system in the heart (multi-center clinical trial) "in Japanese. Kaku Igaku 28:461-476, 1991
69. Hurman DC, Critchley M, Shanahan CV: Adverse reaction to a radionuclide brain-scanning agent. Nucl Med Commun 3:373-376, 1982
70. Ishibashi N, Abe K, Furuhashi S, et al: Adverse allergic reaction to 131I MIBG. Ann Nucl Med 23:697-699, 2009
71. James JM, Lloyd JJ, Leahy BC, et al: The incidence and severity of hypoxia associated with 99Tcm technegas ventilation scintigraphy and 99Tcm MAA perfusion scintigraphy. Br J Radiol 65:403-408, 1992
72. Jayabalan V, White D, Bank M: Adverse reactions (aseptic meningitis) from 111-indium-DTPA cisternographic examinations. Radiology 115:403-405, 1975
73. Johnston MJ, Ntambi JA, Hilliard N, et al: Reducing perceived pain levels during nonbreast lymphoscintigraphy. Clin Nucl Med 40:945-949, 2015
74. Jonas S, Braunstein P: Neurogenic bladder as a complication of isotope cisternography. J Nucl Med 13:763-764, 1972
75. Subcommittee of Safety Issue for the Radiopharmaceuticals Medical and Pharmaceutical Committee Japan Radioisotope Association: The 24th report on survey of the adverse reaction to radiopharmaceuticals (The 27th survey in 2001) "in Japanese. Kaku Igaku 40:39-50, 2003
76. Subcommittee of Safety Issue for the Radiopharmaceuticals Medical and Pharmaceutical Committee Japan Radioisotope Association: The 25th report on survey of the adverse reaction to radiopharmaceuticals (the 28th survey in 2002) "in Japanese. Kaku Igaku 41:33-45, 2004
77. Subcommittee of Safety Issue for the Radiopharmaceuticals Medical and Pharmaceutical Committee Japan Radioisotope Association: The 26th report on survey of the adverse reaction of radiopharmaceuticals (the 29th survey in 2003) "in Japanese". Kaku Igaku 42:33-45, 2005
78. Kennedy-Dixon TG, Gossell-Williams M, Cooper M, et al: Evaluation of radiopharmaceutical adverse reaction reports to the British nuclear medicine society from 2007 to 2016. J Nucl Med 58:2010-2012, 2017
79. Koopmans KP, Brouwers AH, De Hooge MN, et al: Carcinoid crisis after injection of 6-18F-fluorodihydroxyphenylalanine in a patient with metastatic carcinoid. J Nucl Med 46:1240-1243, 2005
80. Kusakabe K, Kasaki K, Kosuda S, et al: The twenty-third report on survey of the adverse reaction to radiopharmaceuticals (The 26th survey in 2000) "in Japanese. Kaku Igaku 39:55-65, 2002
81. Kusakabe K, Okamura T, Kasagi K, et al: The 27th report on survey of the adverse reaction to radiopharmaceuticals (the 30th survey in 2004) "in Japanese. Kaku Igaku 43:23-35, 2006
82. Kusakabe K, Arano Y, Okamura T, et al: The 28th report on survey of the adverse reaction to radiopharmaceuticals (the 31st survey in 2005) "in Japanese. Kaku Igaku 44:29-42, 2007
83. Kusakabe K, Arano Y, Okamura T, et al: The 29th report on survey of the adverse reaction to radiopharmaceuticals (the 32nd survey in 2006) "in Japanese. Kaku Igaku 45:19-35, 2008
84. Lai SY, Civantos F, Agrawal A: Sentinel lymph node biopsy using 99mTc-tilmanocept (Lymphoseek) in patients with oral cavity squamous cell carcinoma: Safety results from phase III clinical trial. Eur J Nucl Med Mol Imaging 43:S40, 2016
85. Laroche ML, Quelven I, Mazere J, et al: Adverse reactions to radiopharmaceuticals in France: Analysis of the national pharmacovigilance database. Ann Pharmacother 49:39-47, 2015
86. Lee Dong Yun DY: An unusual case of anaphylaxis after fluorine-18-labeled fluorodeoxyglucose injection. Nucl Med Mol Imaging 47:201-204, 2013
87. Line BR, Breyer RJ, McElvany KD, et al: Evaluation of human anti-mouse antibody response in normal volunteers following repeated injections of fanolesomab (NeutroSpec), a murine anti-CD15 IgM monoclonal antibody for imaging infection. Nucl Med Commun 25:807-811, 2004
88. Littenberg RL: Anaphylactoid reaction to human albumin microspheres. J Nucl Med 16:236-237, 1975
89. Makaryus JN, Makaryus AN, Azer V, et al: Angioedema after injection of Tc-99m sestamibi tracer during adenosine nuclear stress testing. J Nucl Cardiol 15:e26-e27, 2008
90. Maltby PJ, Smith ML: An adverse reaction to [6-131I]iodomethylnorcholestrol. Nucl Med Commun 23:505-506, 2002
91. Manoharan P, Navalkissoor S, Lamarca A, et al: Safety and tolerability of "Ready-to-Use" (SOMAKIT TOC®) 68Ga-DOTA0-Tyr3-Octreotide (68Ga-DOTATOC) for injection in patients with proven gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs). Neuroendocrinology 105:170, 2017
92. Matsuda H, Arano Y, Okazawa H, et al: The 30th report on survey of the adverse reaction to radiopharmaceuticals (the 33rd survey in 2007) "in Japanese. Kaku Igaku 46:29-41, 2009
93. Matsuda H, Arano Y, Okazawa H, et al: The 33rd report on survey of the adverse reaction to radiopharmaceuticals (the 36th survey in 2010) "in Japanese. Kaku Igaku 49:1-14, 2012
94. Matsuda H, Arano Y, Okazawa H, et al: The 34th report on survey of the adverse reaction to radiopharmaceuticals (the 37th survey in 2011) "in Japanese. Kaku Igaku 50:13-25, 2013
95. Matsuda H, Arano Y, Okazawa H, et al: The 35th report on survey of the adverse reaction to radiopharmaceuticals (the 38th survey in 2012) "in Japanese. Kaku Igaku 51:1-12, 2014
96. Matsuda H, Arano Y, Okazawa H, et al: The 36th report on survey of the adverse reaction to radiopharmaceuticals (The 39th survey in 2013) "in Japanese. Kaku Igaku 52:1-12, 2015
97. Matsuda H, Uehara T, Okazawa H, et al: The 38th report on survey of the adverse reaction to radiopharmaceuticals (The 41st survey in 2015) "in Japanese. Kaku Igaku 54:509-519, 2017
98. Matsuda H, Uehara T, Okazawa H, et al: The 39th report on survey of the adverse reaction to radiopharmaceuticals (The 42nd survey in 2016) "in Japanese. Kaku Igaku 55:51-60, 2018
99. Mooser G, Gall H, Peter RU: Delayed-type allergy to technetium Tc 99m. Contact Derm 39:269-270, 1998
100. Mujtaba B, Adenaike M, Yaganti V, et al: Anaphylactic reaction to Tc-99m sestamibi (cardiolite) during pharmacologic myocardial perfusion imaging. J Nucl Cardiol 14:256-258, 2007
101. Nicol CF: A second case of aseptic meningitis following isotope cisternography using I-131 human serum albumin. Neurology 17:199-200, 1967
102. Núñez R, Sellin RV, Fareau GG, et al: Skin rash after radioactive iodine caught on a cell phone camera. Thyroid 17:277-278, 2007
103. O'Dorisio MS, Abongwa C, Mott S, et al: Safety and accuracy of 68GA-DOTA-TYR3-octreotide PET/CT in children and young adults with solid tumors. Pancreas 47:349, 2018
104. Oldham RK, Staab EV: Aseptic meningitis following the intrathecal injection of radioiodinated serum albumin. Radiology 97:317-321, 1970
105. Oosterhuis HJ, van der Schoot JB: RISA cisternography as a routine procedure in neurological patients. J Neurol Sci 13:209-226, 1971
106. Peller PJ, Khedkar N, Martinez C: Transient renal hypoperfusion during a vasovagal episode. J Nucl Med Technol 22:63-64, 1994
107. Pravettoni V, Piantanida M, Primavesi L: Allergy to technetium: Case report of exfoliating dermatitis after myocardial perfusion imaging. Allergy 64:582-583, 2009
108. Ramos-Gabatin A, Orzel JA, Maloney TR, et al: Severe systemic reaction to diphosphonate bone imaging agents: Skin testing to predict allergic response and a safe alternative agent. J Nucl Med 27:1432-1435, 1986
109. Rhodes BA: Low probability of allergic reaction to albumin microspheres. J Nucl Med 12:649-650, 1971

110. Rhodes BA, Kamanetz GS, Wagner HN Jr: The use of limulus testing to reduce the incidence of adverse reactions to cisternographic agents. Neurology 24:810-812, 1974
111. Rhodes BA: Letter: 111In-DPTA: A safe radiopharmaceutical for cisternography. Radiology 119:749-750, 1976
112. Rhodes BA, Cordova MA: Adverse reactions to radiopharmaceuticals: Incidence in 1978, and associated symptoms. Report of the adverse reactions subcommittee of the Society of Nuclear Medicine. J Nucl Med 21:1107-1110, 1980
113. Roberts HJ: Fatal hemoptysis in pulmonary embolism probably precipitated by pulmonary scanning. Report of a case and suggested precautions. Angiology 21:270-274, 1970
114. Schafer B, Menda Y, O'Dorisio TM, et al: 68Ga-DOTATOC PET/CT effectiveness for diagnosis and staging in neuroendocrine tumors in comparison with octreoscan and high-resolution, contrast-enhanced CT. Pancreas 45:481, 2016
115. Schaub T, Kraus W, Eissner D, et al: Zwischenfall bei der leberszintigraphie mit 99mTc-S-Colloid. Nuc Compact 14:134, 1983
116. Silberstein EB: Prevalence of adverse events to radiopharmaceuticals from 2007 to 2011. J Nucl Med 55:1308-1310, 2014
117. Silberstein EB: Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. J Nucl Med 39:2190-2192, 1998
118. Smith EM, Smoak WM, Gilson AJ: Letter to the editor. J Nucl Med 8:896-898, 1967
119. Sörensen J, Owenius R, Lax M, et al: Regional distribution and kinetics of [18F]fluciclovine (anti-[18F]FACBC), a tracer of amino acid transport, in subjects with primary prostate cancer. Eur J Nucl Med Mol Imaging 40:394-402, 2013
120. Spicer JA, Preston DF, Stephens RL: Adverse allergic reaction to technetium-99m methylene diphosphonate. J Nucl Med 26:373-374, 1985
121. Spyridonidis T, Giannakenas C, Lakiotis V, et al: Adverse reactions following NP-59 administration. Nucl Med Commun 29:749-750, 2008
122. Støckel M, Ennow K, Kristensen K, et al: Anaphylactic reaction to orthoiodohippurate. Eur J Nucl Med 8:89-90, 1983
123. Thomson LE, Allman KC: Erythema multiforme reaction to sestamibi. J Nucl Med 42:534, 2001
124. Vincent WR, Goldberg SJ, Desilets D: Fatality immediately following rapid infusion of macroaggregates of 99mTc albumin (MAA) for lung scan. Radiology 91:1180-1184, 1968
125. Williams ES: Adverse reactions to radio-pharmaceuticals: A preliminary survey in the United Kingdom. Br J Radiol 47:54-59, 1974
126. Williams JO: Death following injection of lung scanning agent in a case of pulmonary hypertension. Br J Radiol 47:61-63, 1974
127. Cordova MA, Hladik W, Rhodes BA: Validation and characterization of adverse reactions to radiopharmaceuticals. Clin Nucl Med 9:P39, 1982
128. Bégaud B, Evreux JC, Jouglard J, et al: Imputabilité des effets inattendus ou toxiques des médicaments. Actualisation de la méthode utilisée en France. Thérapie 40:111-118, 1985
129. Hesslewood SR: Adverse reaction to Tc-99m DTPA. Eur J Nucl Med 20:567, 1993
130. Canning S, Bryson-Campbell M, Suryavanshi R: Effect of topical anesthetic cream on pain during periareolar injection of technetium Tc99m sulfur colloid for sentinel lymph node biopsy in breast cancer: A randomized control trial. J Med Imaging Radiat Sci 49:44-48, 2018
131. Taplin GV, MacDonald NS: Radiochemistry of macroaggregated albumin and newer lung scanning agents. Semin Nucl Med 1:132-152, 1971
132. Heyman S: Toxicity and safety factors associated with lung perfusion studies with radiolabeled particles. J Nucl Med 20:1098-1099, 1979
133. Ellis B: Radiolabelling of blood cells: Theory and practice. In: Theobald T (ed): Sampson's Textbook of Radiopharmacy, ed 4, London: Pharmaceutical Press, 421-445, 2011
134. Gratz S, Reize P, Pfestroff A, et al: Intact versus fragmented 99mTc-monoclonal antibody imaging of infection in patients with septically loosened total knee arthroplasty. J Int Med Res 40:1335-1342, 2012
135. Tate J, Ward G: Interferences in immunoassay. Clin Biochem Rev 25:105-120, 2004
136. Khazaeli MB, Conry RM, LoBuglio AF: Human immune response to monoclonal antibodies. J Immunother Emphasis Tumor Immunol 15:42-52, 1994
137. European Medicines Agency: Scintimun—Summary of product characteristics (SPC). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/001045/WC500075575.pdf. Accessed 27 April 2018
138. European Medicines Agency: Leukoscan—Summary of product characteristics (SPC). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000111/WC500036477.pdf. Accessed 27 April 2018
139. European Medicines Agency: CEAscan—Summary of product characteristics (SPC). https://ec.europa.eu/health/documents/community-register/2002/200202054810/anx_4810_en.pdf. Accessed 27 April 2018
140. CIS bio international: Norchol—Summary of product characteristics (SPC). https://curiumpharma.com/wp-content/uploads/2017/01/S0700nG.pdf. Accessed 27 April 2018
141. Bravo EL, Tagle R: Pheochromocytoma: State-of-the-art and future prospects. Endocr Rev 24:539-553, 2003
142. Kantorovich V, Eisenhofer G, Pacak K: Pheochromocytoma: An endocrine stress mimicking disorder. Ann N Y Acad Sci 1148:462-468, 2008
143. Zhan C, Arispe I, Kelley E, et al: Ambulatory care visits for treating adverse drug effects in the United States, 1995-2001. Jt Comm J Qual Patient Saf 31:372-378, 2005
144. Bourgeois FT, Shannon MW, Valim C, et al: Adverse drug events in the outpatient setting: An 11-year national analysis. Pharmacoepidemiol Drug Saf 19:901-910, 2010
145. Lazarou J, Pomeranz BH, Corey PN: Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. JAMA 279:1200-1205, 1998
146. Pirmohamed M, James S, Meakin S, et al: Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18,820 patients. BMJ 329:15-19, 2004
147. Leendertse AJ, Egberts AC, Stoker LJ, et al: HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med 168:1890-1896, 2008
148. Rose TA Jr., Choi JW: Intravenous imaging contrast media Complications: The basics that every clinician needs to know. Am J Med 128:943-949, 2015
149. Pasternak JJ, Williamson EE: Clinical pharmacology, uses, and adverse reactions of iodinated contrast agents: A primer for the non-radiologist. Mayo Clin Proc 87:390-402, 2012
150. Keeling DH: Adverse reactions to radiopharmaceuticals. In: Abstracts of the Fifth European Symposium on Radiopharmacy and Radiopharmaceuticals Cambridge, U.K.902-931, 1993; Cambridge, UK.
151. Hesse BB: Adverse events in nuclear medicine—Cause for concern? Eur J Nucl Med Mol Imaging 39:782-785, 2012