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January 22, 2020

Michael Layton, Director
Division of Materials, Safety, Security, State and Tribal Programs
Office of Nuclear Material Safety and Safeguards
Nuclear Regulatory Commission

Dear Michael,

I am writing to inform you of some evidence that your team may be interested in reviewing regarding the nuclear medicine extravasation topic.

On December 31, 2019, BMC Medical Imaging published ahead of print, ***Assessing and reducing PET radiotracer infiltration rates: a single center experience in injection quality monitoring methods and quality improvement***. This article provides additional evidence to disprove the extravasations "are nearly impossible to avoid" assumption that is the basis for the NRC extravasation reporting exemption policy. This high-volume center that performs manual injections reported that 98% of all their injections were performed without extravasating the patient. The paper is attached for your team's review.

I am also attaching a 2017 paper by Jaschke et al. This paper explored equivalent dose to tissue as a result of fluoroscopically guided interventions (FGI). The authors provide information regarding the side effects caused by varying doses of radiation. These doses and the timeframe of the exposure are very similar to the extravasations examples we have provided to NRC. The authors also share the length of time that it takes for the side effects to manifest and point out that most patients do not make the connection that their symptoms were related to a radiation dose received days, weeks, months or years in the past.

Our team will be attending the SNMMI and ACNM Mid-Winter meeting later this week, where we will be presenting the approved poster on the novel dosimetry method, from 12:15-1:15 on Friday, January 24, 2020. Before we depart for the meeting, we wanted to send you three more extravasation cases that possibly exceed the 500 mSv reporting limit. We will be back in the office next week and will be available to answer any questions your team may have.

As mentioned in my previous communication, I will be in town on February 5 and would like to introduce myself or answer any questions your staff may have.

Sincerely,

DocuSigned by:
Ron Lattanze
0C2FCDBE78A7435...

Ron Lattanze
Chief Executive Officer

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Enclosures:
1. BMC Medical Imaging paper
2. Cardiovascular Interventional Radiology paper
3. Three additional dosimetric cases

cc:
Chris Einberg
Lisa Dimmick
Said Daibes
Kellee Jamerson
Donna-Beth Howe

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BMC Medical Imaging

RESEARCH ARTICLE Open Access

Assessing and reducing PET radiotracer infiltration rates: a single center experience in injection quality monitoring methods and quality improvement

Dustin R. Osborne*, Shelley N. Acuff, Michael Fang, Melissa D. Weaver and Yitong Fu

Abstract

Background: Successful injection of radiolabeled compounds is critical for positron emission tomography (PET) imaging. A poor quality injection limits the tracer availability in the body and can impact diagnostic results. In this study, we attempt to quantify our infiltration rates, develop an actionable quality improvement plan to reduce potentially compromised injections, and compare injection scoring to PET/CT imaging results.

Methods: A commercially available system that uses external radiation detectors was used to monitor and score injection quality. This system compares the time activity curves of the bolus relative to a control reading in order to provide a score related to the quality of the injection. These injection scores were used to assess infiltration rates at our facility in order to develop and implement a quality improvement plan for our PET imaging center. Injection scores and PET imaging results were reviewed to determine correlations between image-based assessments of infiltration, such as liver SUVs, and injection scoring, as well as to gather infiltration reporting statistics by physicians.

Results: A total of 1033 injections were monitored at our center. The phase 1 infiltration rate was 2.1%. In decision tree analysis, patients < 132.5lbs were associated with infiltrations. Additional analyses suggested patients ≥ 127.5 lbs. with non-antecubital injections were associated with lower quality injections. Our phase 2 infiltration rate was 1.9%. Comparison of injection score to SUV showed no significant correlation and indicated that only 63% of suspected infiltrations were visible on PET/CT imaging.

Conclusions: Developing a quality improvement plan and monitoring PET injections can lead to reduced infiltration rates. No significant correlation between reference SUVs and injection score provides evidence that determination of infiltration based on PET images alone may be limited. Results also indicate that the number of infiltrated PET injections is under-reported.

Keywords: PET, Positron emission tomography, Infiltration, Injection quality, Quality improvement

Background

Proper administration of a radiotracer dose is essential to positron emission tomography (PET) image quality and quantification [1–5]. Misadministration or infiltration of the dose results in changes to uptake kinetics which may alter the quantitative assessment of PET data. This can impact cancer patient staging, therapy assessment, treatment planning, and can lead to unnecessary invasive procedures and patient radiation exposure [6–9]. Quality control (QC) efforts ensure accuracy of the administered dose for PET quantification; but no routine QC exists to ensure the administered dose completely enters the patient circulation.

The standard quantitative assessment for fluorodeoxyglucose (18F-FDG) PET imaging is the standard up take value (SUV). This value is calculated from the activity concentration measured by the scanner and normalizing by the patient's weight and

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the injected dose (ID). SUV is given by the equation below.

$$SUV_{BW} = \frac{ROI\ Activity\ Concentration}{ID/Weight}$$

If there are errors in the injected dose value (ID), possibly caused by a compromised injection, then this can introduce significant variance into the calculation of SUV and subsequently can lead to inaccurate assessments of quantitative results that are often used for response to therapy assessments [10].

It is also a common practice for radiologists to report the maximum value of the SUV in the left lobe of the liver as a reference region for a given FDG study. The idea behind this methodology is to provide a baseline value for generic FDG uptake in the body to enable better comparison of baseline values to suspected lesion uptake [11, 12]. These values are also sometimes used to make determinations regarding the quality of the scan based on baseline liver values being too low or too high [13], with an exceptionally low value (an SUV of approximately 1) being anecdotally associated with possible infiltration. This is based on a local survey of radiologists that felt like they had noticed an association of uncharacteristically low SUVs in the liver associated with compromised injections.

This study sought to achieve three primary goals. The first was to use new technology to monitor our injection quality and assess our institutional infiltration rates associated with PET/CT radioisotope injections. The second was to use quality improvement techniques to determine potential contributing factors that could be used to reduce our institutional infiltration rates and implement them to determine their true impact on infiltration rates. The third was to assess whether standard baseline PET reporting methods (e.g., SUV max reported in the liver) are able to differentiate between infiltrated and non-infiltrated scans.

Patients and methods

This study was carried out in two primary research phases. The first phase was conducted under a quality improvement project for which the University of Tennessee Graduate School of Medicine Institutional Review Board (UTGSM IRB) determined the project did not meet the definition of research as defined by 45 CFR 46.102(d) and classified the initiative as "quality improvement". In Phase 1 of the quality improvement project, our PET/CT center monitored the injection process of 514 patients with technologists blinded to the injection quality results. Data were analyzed and potential contributing factors were identified using decision tree analysis, with decision trees constructed using 20-fold cross validation with inverse prior weights as the assessment measure (SAS Enterprise Miner, v. 14.1 and v.9.4). A quality improvement plan (QIP) to address these factors was developed and implemented around those targeted factors. In Phase 2 of the QI project, 519 patients were monitored with the technologists unblended and able to immediately see the injection quality results and we re-measured our infiltration rate with adherence to the QIP also assessed. All injections were monitored using an external detector device, called LARA (Lucerno Dynamics, LLC, Cary, North Carolina).

The quality improvement plan focused on two main areas: all patients and patients with lower body weight. For all patients, we implemented the following: (1) use of a blood pressure cuff instead of tourniquets (where possible), (2) contacting patients 24 h prior to their exam to remind them of their appointment and to hydrate well, and (3) questioning patients about water consumption the day of the procedure. For patients less than 135 pounds, technologists applied a warm compress to the injection site for several minutes prior to radiotracer injection.

To monitor the quality of a radiotracer injection, two sensors are placed on the patient using hypoallergenic and atraumatic disposable adhesive pads. One sensor is placed on the injection arm approximately 7 cm proximal to the venous access site. The other sensor is placed on the opposite arm in a mirrored location. Sensors remain in place during the standard resting uptake period prior to imaging (40–60 min post injection). The injection arm sensor records the passage of the bolus and any residual activity at the injection site. The sensor on the opposite arm provides a reference activity level against which the injection sensor is compared. The sensor data, along with procedure-specific information, are analyzed using cloud-based software to generate TACs and QC/QA reports (see Fig. 1 -Lara Device and TAC).

For an ideal injection, the TACs reported by the injection sensor should quickly peak and then rapidly approach the values recorded by the reference sensor as shown in Fig. 2a. For injections which may have been compromised by infiltration or a venous obstruction, the activity at the injection site will remain elevated during part or all of the uptake period as shown in Fig. 2b. TACs with the latter characteristics are indicative that not all of the prescribed radioactivity was delivered as a bolus injection into the patient's circulation. Examples of quality injections and injections with signs of infiltration are shown in Fig. 3.

SUV analysis and correlation to injection scores

Subsequent to the completion of the QI project, we obtained UTGSM IRB approval (#4365) to retrospectively compare PET/CT imaging data to injection quality results. In this companion study, 896 patients whose injections were monitored had their injection quality scores compared to the radiology reports and images from their PET/CT examination. Values for maximum SUV in the

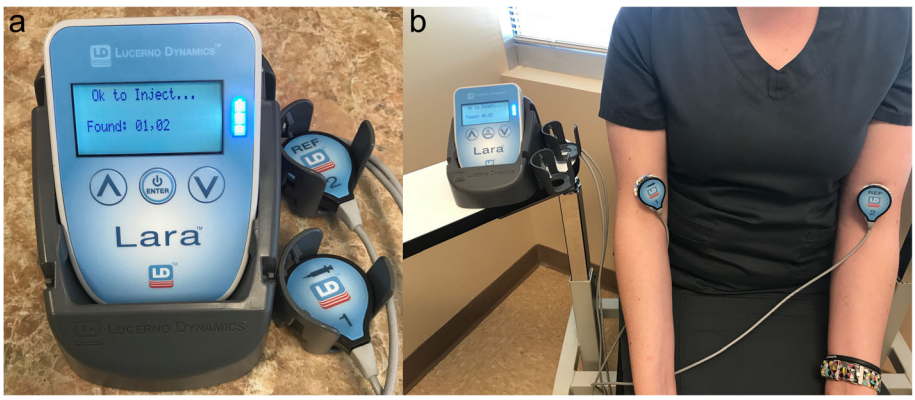

Fig. 1 shows (**a**) The Lara device in its docking station, and (**b**) the Lara device and sensors attached to the patient

reports were compared to injection quality scores from the device to test for correlations between SUV values and injection scores. Scores of greater than 200 were classified by our site as infiltrations with all remaining scores grouped as good injections. Mann-Whitney U tests were used for comparison of group means and Spearman's Rho testing was used to assess non-parametric correlation.

In addition to obtaining SUVs from patient reports, we examined the imaging data for cases considered to be potentially infiltrated (score > 200) to determine the percentage of infiltrations that were visible in the PET field of view (FOV) and specifically called out in the radiology reports. For many infiltrations, the site may not be visible in the scanner because of arm positioning, however, we felt this was an important characteristic to determine what percentage of infiltrations could have been missed by our institution had we not externally monitored for injection quality.

Results

Infiltration quality improvement project

The infiltration rate at our institution from phase 1 was found to be 2.1% (SE .81, 95% CI 1.02, 4.47). In decision tree analysis (Fig. 2), patients < 132.5lbs were associated with a higher number of suspected infiltrations and were shown to be 4× more likely to be infiltrated (4.85 vs. 1.2%). Additional analyses suggested patients ≥ 127.5 lbs. with non-antecubital injections were associated with lower quality injections. Following implementation of our QI plan, the phase 2 infiltration rate was 1.9% (SE .76, 95% CI .87, 4.16) which was a measurable reduction but not statistically significant ($p = 0.785$). The infiltration rate in patients < 132.5 lbs. decreased from 4.8 to 1.4% ($p = 0.23$) and in patients ≥ 127.5lbs with non-antecubital injections increased from 2.7 to 7.5% ($p = 0.20$) as shown in Table 1. Estimates of compliance with QIP measures ranged from 19 to 45%.

SUV analysis and correlation to injection scores

Assessment of the correlation between maximum SUVs in the liver and injection scoring indicated a very weak, non-significant correlation between the injection score and SUV with a Spearman's Rho correlation coefficient of − 0.08 with a p value of 0.17. The average liver SUV for patients considered having infiltrated injection was 3.83 with maximum and minimum values of 6.4 and 2.2, respectively. For patients that were not infiltrated, the average liver SUV was 4.04 with maximum and minimum liver values of 12 and 1.7, respectively. A weak but significant correlation was observed between injection score and patient weight ($\rho = -0.125$, $p = 0.040$) as well as a weak but significant correlation between blood glucose levels and patient weight ($\rho = -0.168$, $p = 0.006$).

Further highlighting the lack of correlation between the injection score and SUVmax values, assessment of the liver SUVmax scores from the twenty worst injections scores and twenty best injection scores indicated that the mean values differed by only 9 % (3.585 ± 0.78 and 3.925 ± 1.12). Two-sample t-tests for means of these two samples were found to not be significant ($p > 0.05$) suggesting that the two means were not significantly different.

Of thirty-eight measured infiltrations during the study period, twenty-four were visible on imaging data while fourteen were not (63% visible on scans). For all scans in which the infiltration was not visible, none were mentioned in the radiology reports. Only in four instances out of twenty-four visible infiltrations were the infiltrations specifically noted in the radiology report. This indicates that during this study, approximately 17% of visible infiltrations were reported, while only 10.5% of the total number of infiltrations were reported by radiologists.

Discussion

No significant correlation was found between SUV maximum measurements in the liver and injection scoring. Contrary to anecdotal and suggested information, there

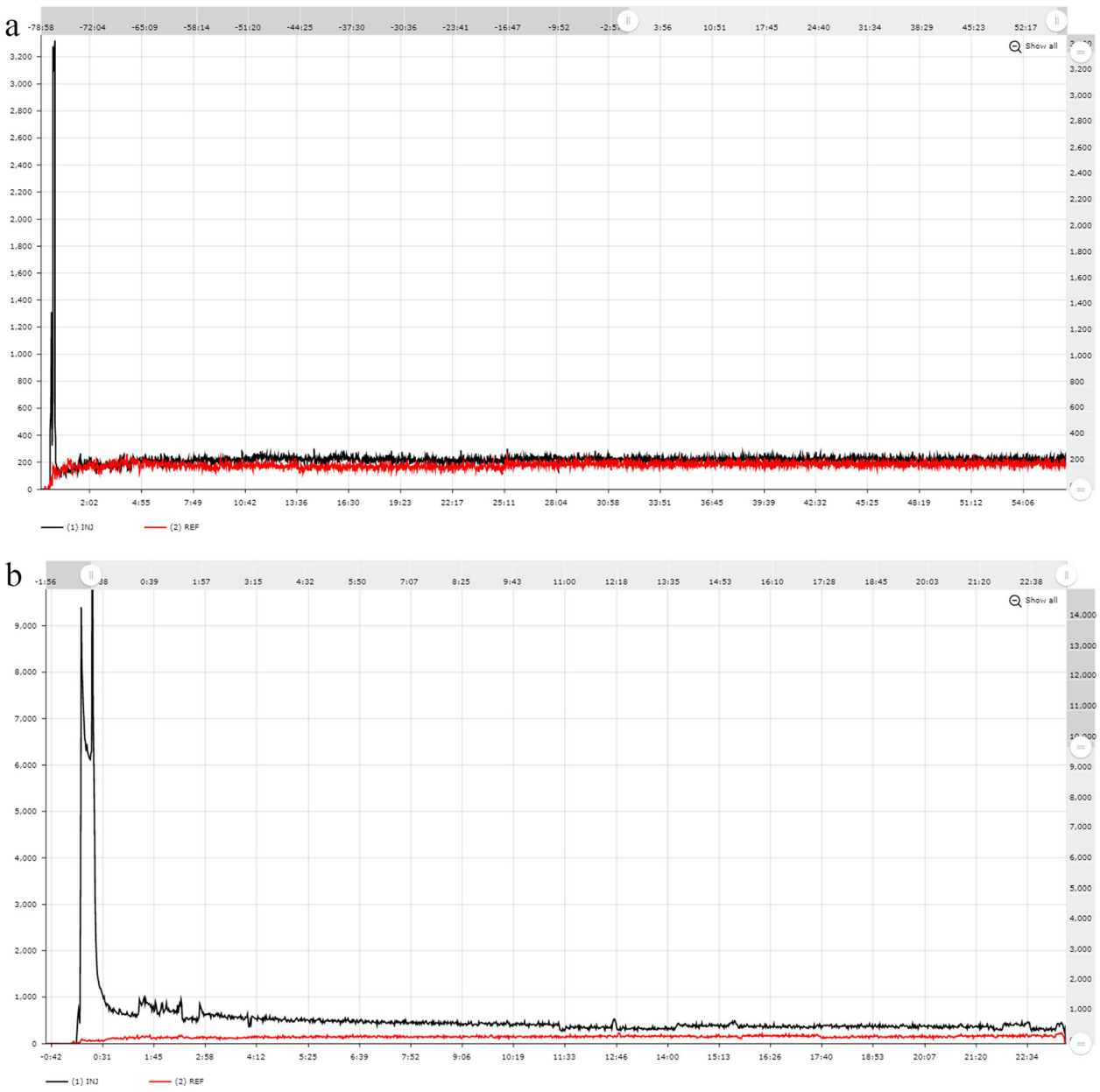

Fig. 2 shows a good quality injection (**a**) as compared to an injection of poor quality (**b**)

appears to be no predictive correlation between the SUV maximum values assessed in the liver as a reference region and whether or not an infiltration occurred in a PET injection. This is true for the average PET scan, however, the authors concede that severe infiltrations may result in potential visual changes to the data that may make it evident that an issue occurred with the injection. Figure 4 shows two examples of compromised injections. These images show different aspects of altered image quality, including increased image noise, non-normal patterns of 18F-Fluorodeoxyglucose (FDG) uptake, and axillary node involvement combined with image quality issues which is a well-known sign of a possibly infiltrated dose [14].

For diagnostic clinical assessments of PET/CT data, the lack of significant correlation between liver SUV measurements and injection quality results demonstrates that the use of liver SUV information cannot be used as a baseline for assessment of the quality of any individual patient injection. Injection quality monitoring is needed to more positively determine the quality of a given injection so that appropriate assumptions about the integrity of the resulting PET/CT scan can be made. This is especially important in longitudinal therapy monitoring where baseline pre-therapy SUV measurements may have

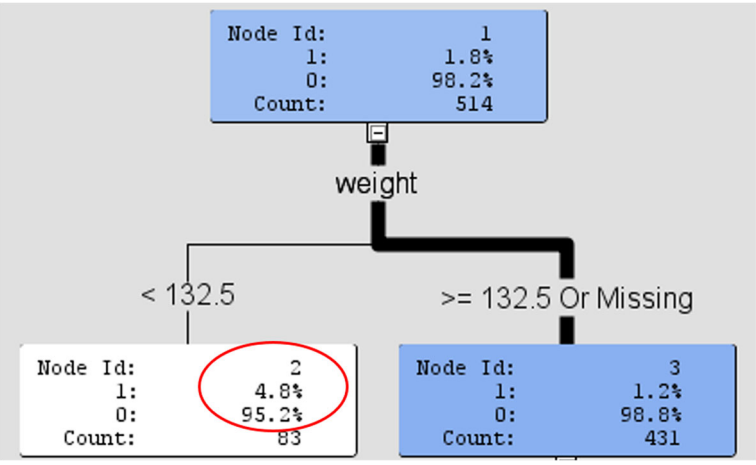

Fig. 3 shows the decision tree analysis results for Phase I injection monitoring

been compromised by poor injection quality and could result in changes to patient management if the compromised SUV comparison to subsequent SUVs factor into the physician determination of appropriate treatment.

Reporting frequency of infiltrations appears to be low. Even in the cases where the infiltration was clearly visible on imaging, only 17% were reported officially on the radiology report. It is our opinion that information about the quality of the injection should be consistently placed into the official radiology report to provide treating physicians with key information regarding potential quality issues related to a metabolic study. Reporting of this information is not a standard practice at many facilities but may improve as access to injection monitoring becomes more readily available and the imaging community becomes more aware of the potential impact unknown infiltrations may have on cancer care.

At our institution, the time activity curve image with the injection score is uploaded to PACS with the PET/CT study images as a secondary capture image. This score is reported on with standardized language, similar to the following text: "The injection quality is good with injection score of -369 (200 or greater suggesting of radiotracer infiltration)". If the injection score were above 200, we would have the language similar to the following: "The injection may be compromised with and injection score of 300 (200 or greater suggesting of radiotracer infiltration)". The goal is not to specifically say an injection is absolutely good or bad, but our goal is to alert referring physicians and radiologists to possible compromises to injection quality that is especially useful if quantitative assessments are being used, or longitudinal patient imaging is being performed.

Limitations exist with this study. Firstly, this is a single center experience and is thus biased by our own processes and patient populations and may not reflect outcomes measured by other centers. Secondly, the retrospective portion of this study only enables us to examine the correlations between existing data as no interventions were used to assess further causal relationships. Further work is needed to validate the complete meaning of the data collected using external sensors for the purposes of injection monitoring and quality control. A recent study has validated that results from external sensors match with information recorded during PET imaging [15], however, this study does not identify how the time activity curves from the external sensors match with the kinetics of the infiltration and redistribution into the body. Although this work remains to be performed, the process of adding better quality improvement through injection monitoring undoubtedly can have an impact on patient care in the outpatient cancer imaging setting.

Previous studies, including a recent multi-center center study of 5541 injection (including some data from our site) that indicated injection monitoring can lead to PET center injection quality improvements and can lead to changes in patient management [1, 7, 16]. At our site, poor injection quality occurred at a lower frequency compared to other sites large multi-center study (2.1% for our site, vs. 6.2% average for other sites), however, we were still able to improve upon our

Table 1 Associations with Infiltrations and Corresponding Phase 1 and Phase 2 Rates

Associations with Infiltrations	Infiltration Rate Phase 1	Infiltration Rate Phase 2	Change in Rate	*p* Value
Patients < 132.5 lbs	4.8% (4/83)	1.4% (1/72)	71% ↓	0.23
Patients ≥ 127 lbs. with non-antecubital injections	2.7% (2/73)	7.5% (5/67)	177% ↑	0.20

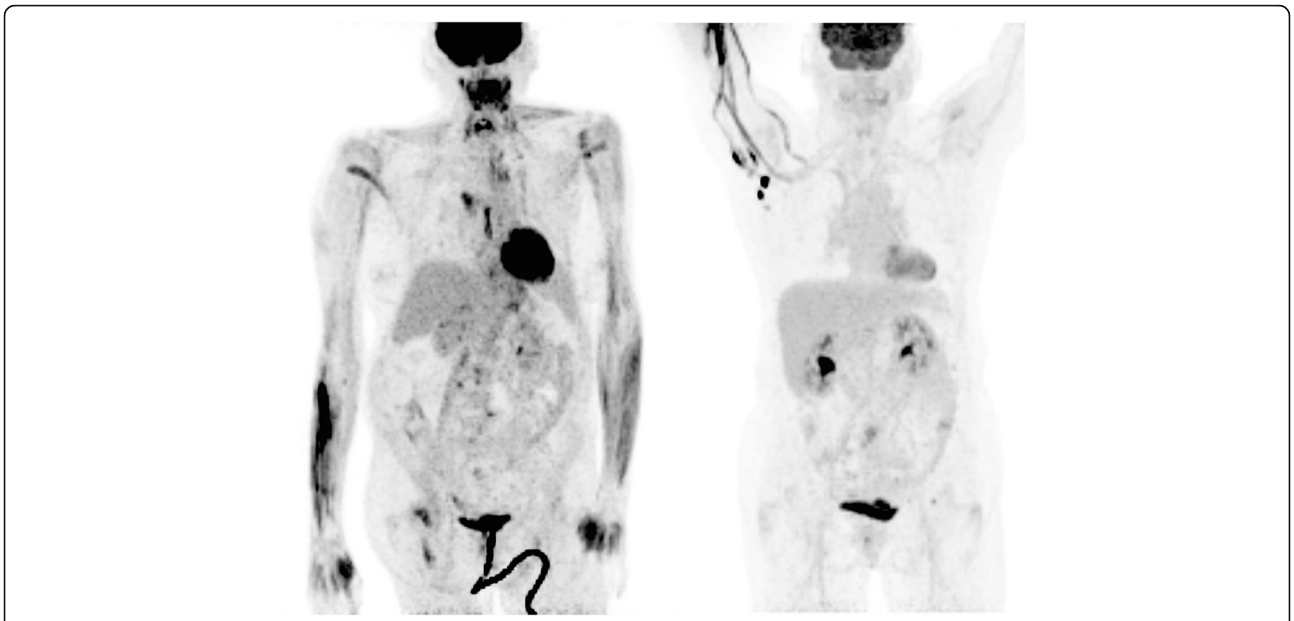

Fig. 4 shows two examples of extravasated doses. The left image shows a visible infiltration with abnormal FDG distributions and high image noise related to reduced counts distributed through the patient. The right image shows the infiltration visible in the arm with high nodal uptake that was later determined to only be related to infiltration of the PET tracer dose

injection quality by implementing an appropriate quality improvement plan. We show in this work that even centers with low suspected infiltration rates can benefit from consistent injection monitoring and quality improvement initiatives.

Novel to this work is our detailed assessment of baseline liver values to injection scoring and information on reporting. Other studies have indicated an 11% reduction of infiltrated liver values and hinted that underreporting of compromised is likely present [1]. In this work we found only a weak, non-significant correlation to SUV max liver values with a difference of approximately 5–9% between good and compromised injections, smaller than previously reported. We also quantitatively assessed reporting of infiltrations showing significant underreporting in radiology reports and the need to improve reporting on injection quality to provide the best possible quality of care.

Conclusions

Previous studies have indicated that infiltration can cause quantitative and visual uncertainty, while this study further illustrates the need for injection quality monitoring by showing that the commonly used reference region of the liver may not be a reliable indicator of the degree of injection infiltration. Injection monitoring, and developing a quality improvement plan can lead to improvements in injection quality for patients. At our center we started with a low infiltration rate of 2.1%, but were able to improve our rates even with those small numbers with a well thought out quality improvement plan based on our specific patient population. For sites with greater infiltration percentages [1], monitoring and development of improvement plans could play a significant role in improving the quality of injections at a given institution.

Abbreviations

18F-FDG: 18F-fluorodeoxyglucose; CT: Computed Tomography; ID: Injected Dose; PET: Positron Emission Tomography; QC: Quality Control; QIP: Quality Improvement Plan; ROI: Region of Interest; SUV: Standard Uptake Value; TAC: Time Activity Curve; UTGSM IRB: University of Tennessee Graduate School of Medicine Institutional Review Board

Acknowledgements

We would like to think our primary PET/CT technologists: Chris Carr and Erica Carroll.

Ethics approval and consent to participate

This study was reviewed and approved by the University of Tennessee Graduate School of Medicine Institutional Review Board and the first part deemed outside the scope of human subjects research while our retrospective analysis was approved by the IRB for this work.
No consent was required for this study according to 45CFR46 and our local IRB determination that the retrospective analysis of our data did not require consent.

Authors' contributions

All authors have read and approved the manuscript. DO was the PI, wrote the manuscript, and performed data analysis. SA wrote the manuscript and worked with management of injection data and patients. MF performed data analysis. MW performed data collation and analysis. YF was our physician and wrote the manuscript.

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Availability of data and materials

All data is available upon request.

Consent for publication
All authors consent for this work and have read and provided feedback on the manuscript.

Competing interests
This work was performed as part of a multi-center quality improvement study with Lucerno Dynamics, LLC. The authors do not have any competing interests other than some equipment for this study was provided as part of the study by Lucerno Dynamics, LLC.

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REVIEW

Radiation-Induced Skin Injuries to Patients: What the Interventional Radiologist Needs to Know

Werner Jaschke[1] · Matthias Schmuth[2] · Annalisa Trianni[3] · Gabriel Bartal[4]

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Abstract For a long time, radiation-induced skin injuries were only encountered in patients undergoing radiation therapy. In diagnostic radiology, radiation exposures of patients causing skin injuries were extremely rare. The introduction of fast multislice CT scanners and fluoroscopically guided interventions (FGI) changed the situation. Both methods carry the risk of excessive high doses to the skin of patients resulting in skin injuries. In the early nineties, several reports of epilation and skin injuries following CT brain perfusion studies were published. During the same time, several papers reported skin injuries following FGI, especially after percutaneous coronary interventions and neuroembolisations. Thus, CT and FGI are of major concern regarding radiation safety since both methods can apply doses to patients exceeding 5 Gy (National Council on Radiation Protection and Measurements threshold for substantial radiation dose level). This paper reviews the problem of skin injuries observed after FGI. Also, some practical advices are given how to effectively avoid skin injuries. In addition, guidelines are discussed how to deal with patients who were exposed to a potentially dangerous radiation skin dose during medically justified interventional procedures.

Keywords Interventional radiology · Radiation · Skin injuries

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Introduction

Radiation injuries were primarily observed in the pioneering days of radiology when the biological effects of radiation were not yet understood and radiation protection was unavailable. The first case of human radiogenic dermatitis of the hand was reported in January 1896 [1]. In 1925, several patients suffering from radiation-induced skin injuries were reported by Groedel [2]. By taking preventive measures, radiation injuries due to medical imaging were completely eliminated within 30 years after the introduction of procedures utilizing X-rays into medicine [1]. Exposures of patients exceeding 100 mSv effective dose were extremely rare in medical imaging until the introduction of multislice CT and fluoroscopically guided interventions (FGI). Thus, CT and FGI are of major concern regarding radiation safety in medical imaging [3–6]. CT and fluoroscopy account for approximately 10% of all imaging procedures, but contribute approximately 80% to the mean collective dose. The number of fluoroscopically guided interventions increased dramatically during the last 30 years and continues to rise [4, 7]. In some countries, numbers doubled every 2–4 years [1, 8, 9]. For example,

percutaneous coronary interventions (PCI) are performed with a frequency of approx. 4500/1 Mill. inhabitants in Germany (http://www.gbe-bund.de/PCI). Furthermore, FGI of the lower extremities is another growing field. The prevalence of peripheral arterial occlusive disease (PAOD) is estimated at 3–10% in the general population; a percentage that is even higher among the population aged 70 and older (15–20%) [10]. The incidence in less developed and developed countries increased within the last 10 years by a rate of 28,7% and 13,1%, respectively [10, 11]. Most of these patients will undergo a percutaneous procedure at some stage of their disease. It is, therefore, not surprising that the number of endovascular procedures is continuously increasing. The first radiation-induced skin injuries associated with PCI were reported in the early nineties [8, 12–14]. Radiation-induced skin injuries and epilation were the most commonly reported side effects following procedures with uncommonly high radiation exposure, mostly resulting from CT perfusion studies of the brain and percutaneous coronary interventions (PCI). In addition, there is an increasing concern about the biological long-term effects of low-level radiation affecting staff and patients [15–18]. Thus, more than a hundred years after the discovery of X-rays, the subject of radiation protection has again emerged as a major concern of the public, medical professionals and health authorities [3].

This paper reviews the most important tissue injuries observed after FGI. The main contribution of this paper is the observation and analysis of skin injuries, as radiation-induced cataractogenesis was just recently covered by a review article in this journal [19]. Moreover, some practical advice is given regarding the effective avoidance of skin injuries.

Radiation-Induced Tissue Injuries

Radiation-induced tissue injuries were previously labeled deterministic effects of radiation. The most important tissue injuries affect the skin and the eye lens. Typically, radiation-induced skin injuries occur after a time delay of days, sometimes weeks following a procedure, in which a threshold of skin exposure has been exceeded (Table 1) [8, 20, 21].

The potential risk of the general patient population for exposure to a radiation dose above a substantial level of 3 Gy skin dose (Table 2) has increased over the years [22].

The reasoning behind this approach is that FGI procedures are more often used, more complex, more frequent and longer lasting. Moreover, the patients are more frequently obese, and obesity is a significant contributing factor to higher exposure. In addition, patients undergoing several interventional procedures in their lifetime are more frequently encountered.

The heavy bias toward elderly patients having X-ray examinations and interventional procedures is shown in Figs. 1 and 2 [23]. Patients at risk for tissue injuries are typically of older age (55–85 years) and suffering from chronic diseases—consequentially requiring multiple imaging and interventional procedures.

Radiation-Induced Skin Injuries

Severe skin injuries from fluoroscopically guided procedures are either still rare, or underreported at present. In 1994, the US Food and Drug Administration (FDA) received approximately 40 separate reports [24]. Radiation-induced ulcers are currently reported in less than 1% of all patients undergoing cardiac FGI [25]. Skin reactions related to radiation exposure can be distinguished as either prompt/acute/subacute (from 24 h up to 2 months) or chronic (more than 2 months up to years) [1, 21, 26]. Prompt radiation-induced skin reactions occur within less than 2 weeks. The most common prompt skin reaction is an erythematous reaction which can occur from a few hours up to 24 h after exposure of more than 2 Gy. This complication is rarely reported in specialist literature, but actually quite commonly observed after long and complex interventional procedures. Acute radiation injury of the skin is characterized by erythema with vesicles, erosion, temporary epilation and pain and itching persisting up to 9 weeks. Chronic radiation injury of the skin (CRIS) presents with an insidious and variable onset of symptoms ranging from erythema, atrophy, epilation, telangiectasia and pruritus, as well as pain due to dermal necrosis and ulceration. CRIS occurs typically months to years after several high-dose radiation exposures or a single very high radiation exposure with a cumulative peak skin dose threshold of 10 Gy. Clinically, the typical patient with CRIS presents with permanent erythema, dermal atrophy and ulceration. An overview of skin lesions, time of onset, development over time and relation to peak skin dose is given in Table 3.

It is important to note that CRIS is not always preceded by an acute skin injury or that a previous minor skin reaction was not detected during initial treatment sessions. A skin lesion may, therefore, not be attributed to a previous radiation exposure. In addition, patients and physicians are often unaware of radiation-induced complications of interventional procedures. Some patients may even be unaware that endovascular procedures are performed under fluoroscopic guidance.

Radiation-induced skin ulcer is the most severe form of radiation-induced dermatitis. The incidence of radiation-induced ulcers is not as rare as previously assumed [25]. Radiation-induced skin ulcer is a consequence of an

Table 1 Radiation-induced lesions of the skin and eye lens with respect to dose and time of onset. Adapted from ICRP publication 85/2000 [8]

Effect	Approximate threshold dose (Gy)	Time of onset
Skin		
Early transient erythema	2	2–24 h
Main erythema reaction	6	~1.5 weeks
Temporary epilation	3	~3 weeks
Permanent epilation	7	~3 weeks
Dry desquamation	14	~4 weeks
Moist desquamation	18	~4 weeks
Secondary ulceration	24	>6 weeks
Late erythema	15	8–10 weeks
Ischemic dermal necrosis	18	>10 weeks
Dermal atrophy (1st phase)	10	>52 weeks
Telangiectasis	10	>52 weeks
Dermal necrosis (delayed)	>12	>52 weeks
Skin cancer	Unknown	>15 years

Table 2 Substantial radiation dose levels which should trigger follow-up of patients in order to detect clinically relevant skin reactions. Adapted from NCRP report Nr 168 (2010)

Peak skin dose	3 Gy
Cumulative air KERMA at RP	5 Gy
Kerma area product	500 Gy cm^2
Fluoroscopy time	60 min[a]

NCRP National Council on Radiation Protection and Measurements, Bethesda, USA

[a] Institutions performing procedures with potentially high dose levels shall measure and record dose metrics, and shall not rely on fluoroscopy time alone

excessively high cumulative skin dose. The correct diagnosis is difficult because the ulcers occur with a considerable time delay of months or even years after exposure, and the causation is not always obvious. Usually, patients do not directly consult the interventionalist, but rather a primary care physician or a dermatologist who may be unaware of previous radiation exposures. Ulcers can be triggered by minor trauma caused by scratching, applying topical agents or hot packing to relieve radiation-induced pruritus or pain.

Obesity, diabetes, nicotine abuse, previous radiation exposure in the same body region, compromised skin integrity, Fitzpatrick skin type I–II (fair skin), diabetes, autoimmune/connective tissue disease(for example scleroderma, lupus erythematosus and mixed connective tissue disease), hyperthyroidism and certain drugs are among many other factors predisposing to an increased radiosensitivity at lower radiation doses [14, 27, 21, 28–30]. The relative contribution of nutritional status or preoperative skin integrity is under debate [31].

Malfunctioning of DNA repair genes (*ataxia* teleangiectasia, xeroderma pigmentosum) and chemotherapy are additional risk factors for radiation-induced skin injuries [28, 29, 32, 33]. Patients suffering from ataxia teleangiectasia carry an autosomal recessive ATM gene. It has been suggested that heterozygous gene carriers (approx. 1% of population) carry a higher risk for radiation-induced skin injuries [21]. Genetic disorders which are connected to higher radiosensivity are listed in Table 4.

A number of drugs increase radiosensitivity. The most important drugs which are known to increase radiosensitivity are listed in Table 5.

Radiation recall refers to inflammation and other reactions developing in previously irradiated areas that are subsequently exposed to a second agent. Radiation recall reactions have been attributed to a wide range of cytotoxic drugs since they were first reported with actinomycin D. These include taxanes, anthracyclines, cytarabine, bleomycin, capecitabine, vinblastine, etoposide, methotrexate, melphalan, dacarbazine, oxaliplatin, hydroxyurea, 5-fluorouracil and IFN. Other noncytotoxic agents such as simvastatin, isoniazid, rifampicin, pyrazinamide and tamoxifen have also been under suspicion. Re-irradiation of a previously irradiated area may also cause a similar response.

Pathophysiology of Radiation-Induced Skin Reactions and Injuries

On histologic examination, morphological findings depend on the phase of radiation injury. The immediate and delayed erythema is accompanied by widening of the rete ridges, edematous swelling of the dermis, dilatation of the dermal vessels, swelling of the endothelia and fibrous

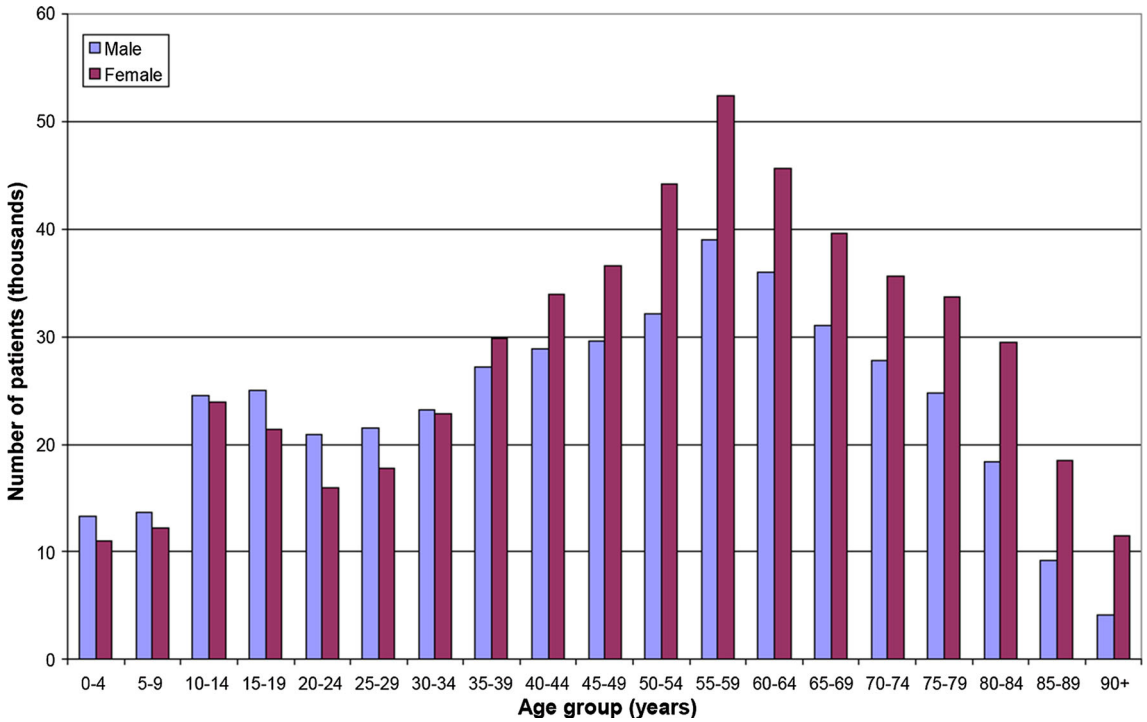

Fig. 1 Number of patients in Denmark having one or more X-ray examinations in 2004 as a function of age and sex (adapted from [18])

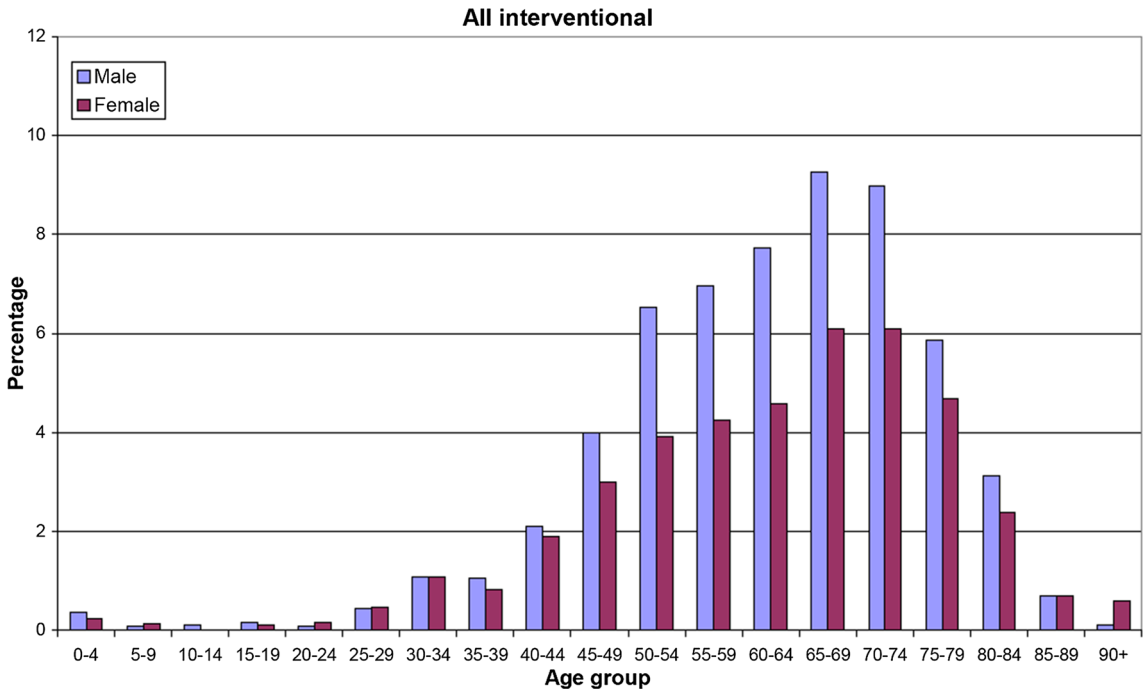

Fig. 2 Age distribution of patients in Denmark undergoing FGI procedures

thickening of the vessel walls, first precipitating erythema and then teleangiectases [36–38]. Intravascular thromboses and erythrocyte extravasation have also been described. Atrophy of the epidermis and adnexal structures (hair follicles, sebaceous glands and sweat glands), and/or degeneration of basal keratinocytes are found at later stages and correlate with hair loss [39]. In addition, dermal collagen fibers appear coarse and increased in number. Hyperpigmentary changes correlate with an increase in dermal melanophages [40].

Table 3 Cutaneous radiation injury: grading, threshold dose and timing

Grade	Skin dose[a]	Prodromal stage	Latent stage	Manifest illness stage	Third wave of erythema[b]	Recovery	Late effects
I	>2 Gy (200 rad)[c]	1–2 days post-exposure or not seen	No injury evident for 2–5 weeks post-exposure[d]	2–5 weeks post-exposure, lasting 20–30 days: redness of skin, slight edema, possible increased pigmentation 6–7 weeks post-exposure, dry desquamation	Not seen	Complete healing expected 28–40 days after dry desquamation (3–6 months post-exposure)	Possible slight skin atrophy Possible skin cancer exposure
II	>15 Gy (1500 rad)	6–24 h post-exposure with immediate sensation of heat lasting 1–2 days	No injury evident for 1–3 weeks post-exposure	1–3 weeks post-exposure; redness of skin, sense of heat, edema, skin may turn brown 5–6 weeks post-exposure, edema of subcutaneous tissues and blisters with moist desquamation possible epithelialization later	10–16 weeks post-exposure, injury of blood, vessels, edema and increasing pain Epilation may subside, but new ulcers and necrotic changes are possible	Healing depends on size of injury and the possibility of more cycles of erythema	Possible skin atrophy or ulcer recurrence Possible telangiectasia (up to 10 years post-exposure) Possible skin cancer decades after exposure

Dose range is given for patients with normal radiosensitivities in the absence of mitigating or aggravating physical or clinical factors. Response to radiation does not apply to the skin of the scalp. Threshold dose and timing are not absolute values, but rather the best appraisal values. Signs and symptoms are expected to appear earlier as skin dose increases

Taken from: Cutaneous radiation injury: factsheet for physicians. CDC Stacks/Center of Disease Control and Prevention, USA; https://stacks.cdc.gov/view/cdc/23969 [26]

[a] Absorbed dose to at least 10 cm^2 of the basal cell layer of the skin

[b] Especially with beta exposure

[c] The Gray (Gy) is a unit of absorbed dose and reflects an amount of energy deposited in a mass of tissue (1 Gy = 100 rad)

[d] Skin of the face, chest and neck will have a shorter latent phase than the skin of the palms of the hands and the skin of the feet

Table 4 Genetic disorders increasing radiosensitivity [21, 34]

Ataxia teleangiectatica
ATM-like disorder
Nijmegen breakage syndrome
Severe combined immune deficiency (SCID)
Ligase IV syndrome
Seckel syndrome
Fanconi anemia
Bloom syndrome
Gorlin syndrome
Familiar polyposis
Gardner syndrome
Hereditary melanoma
Dysplastic nervus syndrome
Xeroderma pigmentosum variant

Table 5 Drugs increasing radiosensitivity [14, 20–22, 34, 35]

Actinomycin D
Doxorubicin
Bleomycin
5-FU
Methotrexat
NNRTI-based antiretroviral therapy in HIV patients
Platinum containing chemotherapeutic drugs
Antiangiogenic drugs
BRAF inhibitors and others

On the molecular level, depending on the absorbed energy, ionizing radiation can break chemical bonds and cause ionization of molecules such as DNA, membrane lipids, proteins and even water [41]. Because ionizing irradiation affects the cell cycle, DNA damage occurs primarily in the proliferating epidermal keratinocytes of the basal cell layer, resulting in various types of cell death (apoptosis, necrosis) [42, 43]. This process is accompanied by the secretion of the second messengers including inflammatory mediators (e.g., cytokines, chemokines and

prostaglandins). In the dermis, these inflammatory mediators cause changes in vessel endothelia, fibroblast proliferation and collagen production. The final result of exposure to ionizing radiation is skin inflammation [44, 45]. In severe cases of radiation exposure, toxins and/or unrestricted inflammation can result in overt destruction of the epidermis [46]. Following restoration of epidermal integrity, long-term effects of skin irradiation comprise increased risk of skin cancers, hyperkeratoses, cutaneous atrophy, hair loss (epilation), telangiectasia, hemangiomas and fibrosis [47–50].

In mild to moderate cases, cytokine release during tissue inflammation indirectly results in impairment of the epidermal permeability barrier [51]. Damage to the permeability barrier facilitates the increased entrance of toxins and antigens, which in turn aggravates inflammation. In addition, ionizing radiation disturbs the antimicrobial properties of the epidermis and predisposes to infections.

In a cohort of patients receiving fractionated radiation therapy for breast cancer at doses ranging between 50–60 Gy, disruption of epidermal permeability barrier function was demonstrated [52]. In these studies, patients received tangential field irradiation to the chest wall by external beam, using photons (8MV) generated by a linear accelerator at single doses of 2 Gy, five times per week. Damage to the epidermis worsened over time, reaching a maximum after a mean of 27 days. In support of the concept that the barrier abnormality could drive inflammation, the onset of increased transepidermal water loss (TEWL), indicative of abnormal permeability barrier function, preceded the appearance of clinical symptoms, and maximal TEWL values preceded the peak of inflammatory skin changes. Moreover, an early increase in TEWL predicted a longer duration of skin symptoms. These studies identify increased TEWL as an early surrogate marker for radiation dermatitis and raise the possibility that preservation of permeability barrier function could decrease radiation-induced cutaneous damage [53]. It is likely that similar mechanisms apply to cutaneous damage observed following very low dose FGI procedures, but this has not formally been shown [54].

Treatment of Radiation-Induced Skin Reactions

A considerable number of compounds have been tested for their ability to mitigate radiation dermatitis [55]. Previous publications demonstrated that topical treatment with corticosteroids improves epidermal barrier function and ameliorates the clinical severity of radiation injury to the skin [56, 57]. The benefits of topical corticosteroids are likely due to their anti-inflammatory effects. Inhibition of the radiation-induced cytokine secretion by glucocorticoids constitutes an important treatment principle for radiation-induced skin inflammation [56]. Yet, despite the short-term benefits, the adverse effect profile of glucocorticoids makes them less than optimal for therapy. Topical corticosteroids inhibit epidermal proliferation and differentiation by down-regulating lipid synthesis and also impair the permeability barrier function of the skin [58, 59].

Therefore, a considerable number of alternate emollients have been tested for their ability to mitigate radiation-induced skin injury [60]. However, the published data lack standardization across treatment protocols, which precludes an assessment of the comparative efficacy of these agents. Consequently, there currently is no entirely evidence-based gold standard for mitigating or treating radiation dermatitis, but topical corticosteroids in the inflammatory phase and emollients for longer term treatment are generally accepted. In the case of skin ulceration, treatment should follow the general principles of wound care, e.g., debridement and moist wound dressings (hydrogel, foam and hydrocolloid). In some cases, excision of the ulcer and skin grafting is necessary [45, 61].

Dose Management Before, During and After the Procedure

The cornerstone of preventing radiation-induced skin injuries is minimizing the radiation dose and monitoring patients who are exposed to a cumulative skin dose above thresholds (Table 2) [4, 62–66]. This goal can only be achieved if the interventionalist is capable of identifying high-dose procedures and is attentive to individual risk factors in patients [62–65]. As mentioned before, a high body mass index (BMI) and previous radiation exposures are among the most important individual risk factors of patients. Thus, the interventionalist should not only focus on the patient's discomfort and pathology, but should also thoroughly evaluate previous radiation exposures. Unless the skin dose from the planned procedure is very low or not affecting the previously irradiated skin area, the interventionalist has to consider an increased risk of skin injury.

During a complex interventional procedure, angiographic equipment can deliver more radiation to the skin than most radiation therapy units deliver in a single treatment session. Monitoring of radiation doses is, therefore, crucial [67]. Online dose monitoring is routinely performed in all patients undergoing FGI at the Department of Radiology in Innsbruck. During the last 2 years (2015–2016), we identified a $K_{ref} > 3$ Gy in 1,6% of all FGI and a $K_{ref} > 5$ Gy in 0,3%. The introduction of real-time dose monitoring decreased the number of high-dose procedures within the first year after introduction. The vast majority of high-dose procedures were neuroembolisations, pelvic and

abdominal embolisations and endovascular abdominal aneurysm repairs (EVAR). A fluoroscopy time exceeding 60 min and a cumulative KERMA at refence point exceeding 5 Gy were quite common during complex endovascular aortic aneurysm repair requiring reconstruction of several aortic and/or iliac side branches. Thus, high-dose procedures are uncommon in routine practice, but do occur in complex endovascular procedures. The interventionalist has, therefore, to be aware of dose monitoring tools which nowadays are an integral part of modern angiographic equipment [5, 63, 65–68]. In state-of-the-art angiographic equipment, the interventionalist gets real-time information on dose in terms of the following parameters: KERMA at reference point (K_{ref}), KERMA area product (KAP) and fluoroscopy time. In addition, the DICOM dose report, which becomes available at the end of the procedure, provides the number of runs, fluoroscopy time, the distribution of dose parameters between fluoroscopy and runs and the cumulative dose in terms of cumulative KERMA at reference point (K_{ref}), cumulative KERMA area product (KAP) and cumulative fluoroscopy time. It is important to note that these displays are granted an uncertainty of ±35% [69]. K_{ref} and KAP are reasonably fit surrogate parameters for the estimation of the skin dose [70, 71]. If K_{ref} exceeds the thresholds level given in Table 1, patients should be counseled and followed as suggested by Balter et al. (Table 6) [21]. As evidenced by the Eurados WG-12 project K_{ref} correlates the best with skin dose in neuroembolisation and PCI, whereas in chemoembolisations KAP was the best skin dose indicator [71].

Regarding dose management, the most efficient way to perform the procedure and to avoid excessive dose to a certain area of skin has to be considered. Thus, careful planning of the procedure and assigning an interventionalist who has sufficient experience and technical skills to handle the case is a first step in dose management [68]. Imaging during the intervention has to be optimized to match the appropriate image quality and the lowest possible dose. Table 7 gives an overview of important imaging parameters which influence patient dose.

Careful planning of the procedure, optimization of imaging parameters and training of staff are essential measures for the avoidance of an excessive dose to patients [8, 68, 72]. Routine evaluation of DICOM dose reports and real-time dosimetry are extremely helpful to optimize radiation protection of patients during interventional procedures. Some vendors even provide skin dose maps which can be of assistance in the identification of areas of skin at high risk [73].

Table 6 General advice to be provided to patients and treating physicians

0–2 Gy	No need to inform patient, because there should be no visible effects
2–5 Gy	Advise patient that erythema may be observed but should fade with time
5–0 Gy	Advise patient to perform self-examination or ask a partner to examine for skin effects (erythema, itching) from about 2 to 10 weeks after the procedure
10–15 Gy	Medical follow-up is appropriate; skin effects may be prolonged, pain and necrosis may occur
>15 Gy	Medical follow-up is essential: radiation-induced wound may progress to ulceration and necrosis

Table 7 Important steps to minimize patient dose and to avoid radiation-induced skin injuries

Keep image receptor as close as possible to the patient
Maximize distance between patient and X-ray tube
Adapt tube settings (tube current, focal spot, filtration, exposure time and tube voltage) to patient size (usually done by automatic exposure control)
Use pulsed fluoroscopy, reduce frame rate and/or dose whenever possible
Use collimation, preferably virtual (off fluoroscopy)
Avoid direct magnification
Avoid angled views (remember that only 3 cm increase in body diameter doubles the skin dose)
Use road map or stored fluoroscopy loops instead of runs
Use last image hold instead of single shot
Avoid unnecessary cone beam CT, long fluoroscopy and multiple runs
Change beam entrance fields in long procedures if possible
Reduce to the minimum overlapping beam entrance fields in sequential FGI

In summary, modern angiographic equipment provides very helpful tools for decreasing and monitoring patient dose and, therefore, avoiding skin injuries.

The interventionalist performing potentially high-dose procedures shall inform patients about the risk of skin injuries. The report of the procedure should comprise dose metrics such as cumulative K_{ref} and cumulative KAP. If multiple procedures are performed on the same region of the body, a summary of all dose metrics shall be included in the final report. If a threshold level has been exceeded, the interventionalist should give a justification and document that the patient was informed about potential skin reactions and the necessity of the procedure. The interventionalist has to make sure that the patient is followed (Table 6) by a physician who is aware of the high radiation dose procedure and familiar with diagnosing radiation-induced skin injuries. Events of radiation doses above critical levels (Table 2) shall be discussed in a Quality Assurance–Peer Review committee including a qualified medical physicist. If possible and necessary, appropriate steps should be taken to avoid future events [74]. In most cases, an excessive patient skin dose can be avoided by simple and clinically feasible changes of practice.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Standard This article does not contain any studies with human participants or animals performed by any of the authors.

Human and Animal Rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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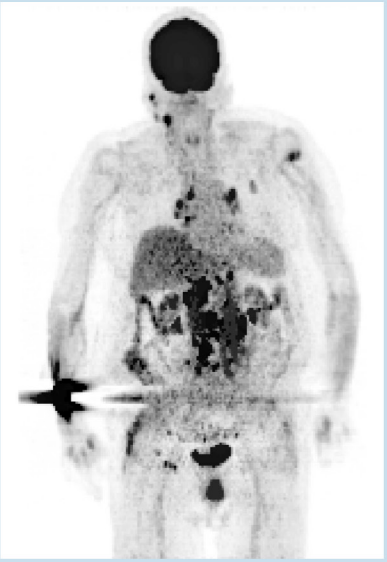
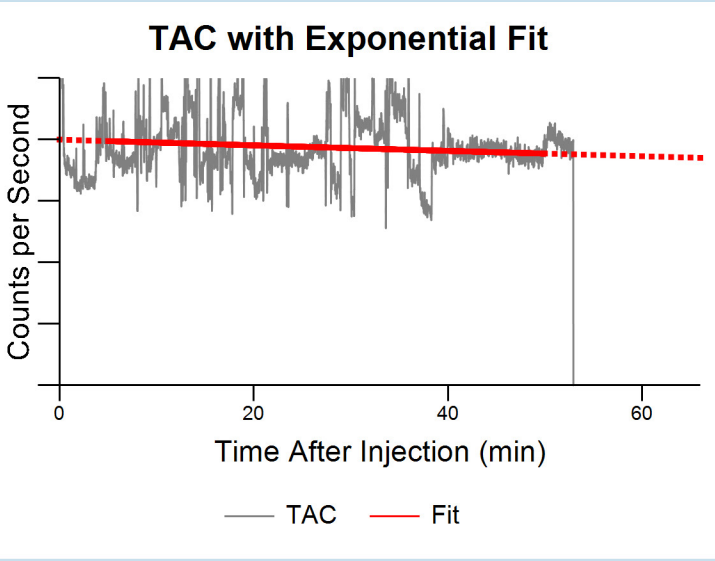
Scan #2169

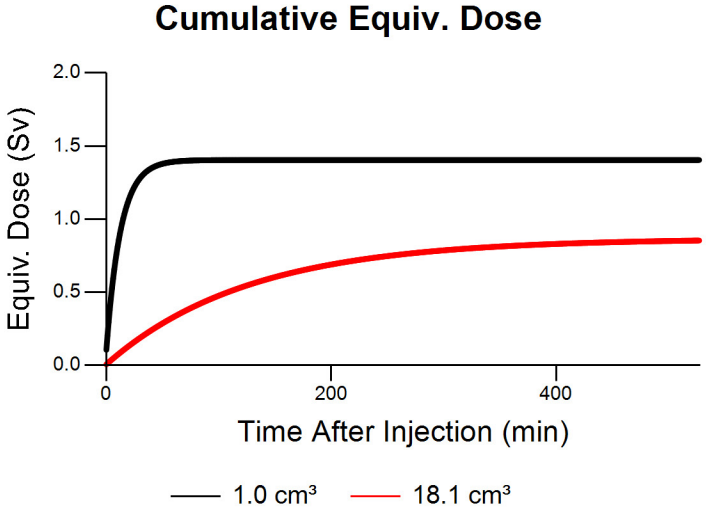
Equivalent Dose: 0.9 to 1.4 Sv



Isotope	F-18
Injection Method	Manual
Injection Location	R Forearm
Injected Activity	16.11 mCi
Radiotracer Volume	1.50 mL
Saline Flush Volume	18.0 mL
Imaging Time	64.9 min
% Extravasation	8 %
Initial Activity	1.32 mCi
Imaging Time Activity	0.81 mCi
Reabsorption Rate	594.3 min
Dose Calculation Volume	1.00 to 18.12 cm^3
Dose Rate	80.5 to 5.2 mSv/mCi-min
Total Equivalent Dose	1.4 to 0.9 Sv



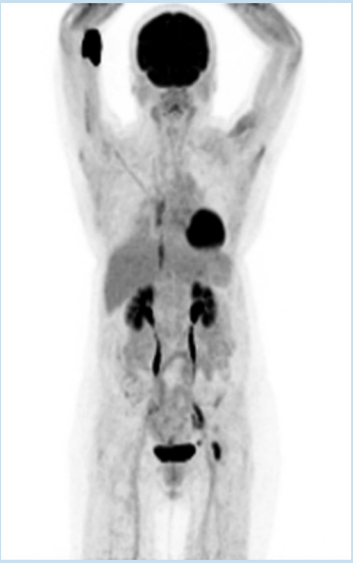
Administration of 18F-FDG consisted of 16.11 mCi injected through an IV in the right forearm followed by 18 mL of saline. Using PET images and TAC data, the extravasation was estimated to be approximately 8% of injected activity. Total equivalent dose to be 1.4 Sv for a tissue volume of 1 cm^3 and 0.87 Sv for a tissue volume of 18.1 cm^3.



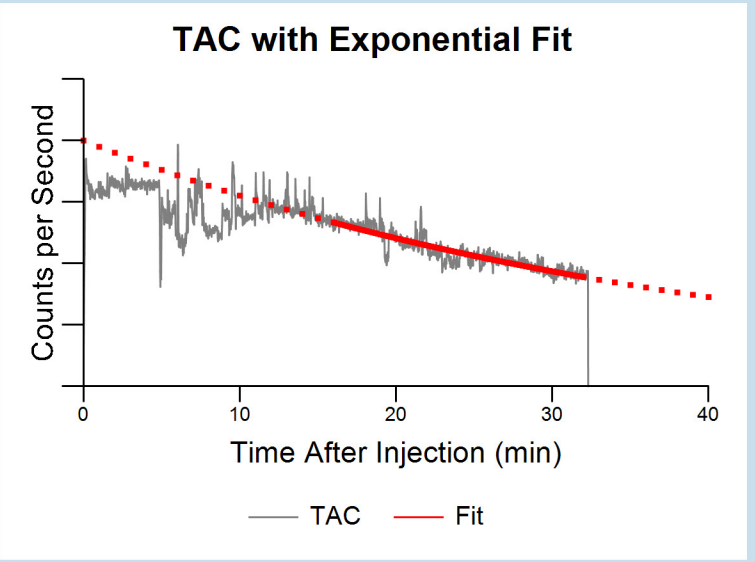
- Dose calculation volume is twice the extravasated radiotracer volume or the total flush volume plus the extravasated radiotracer volume with a minimum volume Of 1 cm^3.
- Initial extravasation amount and reabsorption rate estimates are based on PET measurements and injection site monitoring data from Lara® sensors.
- Volumetric expansion is modeled As a mono-exponential function using initial volumes and PET measurements of volume.
- Dose rates are based on nuclear decay data from ICRP Publication 107 using the IDAC-dose 2.1 software's sphere module.

Scan #8634

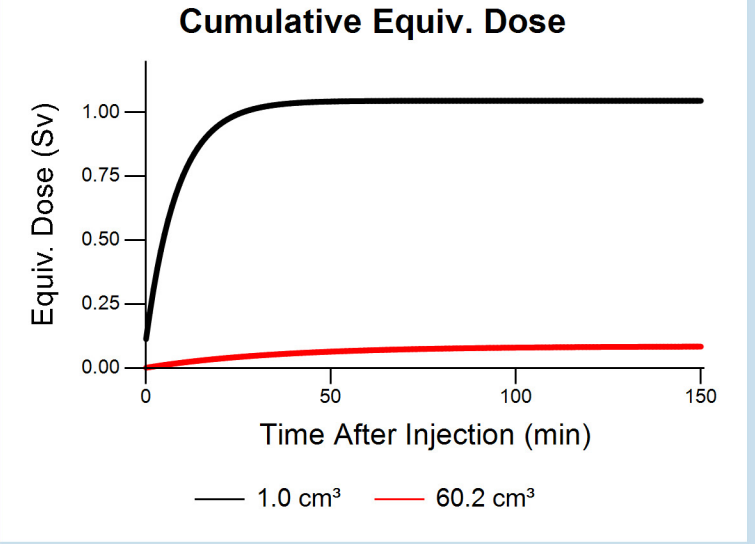
Equivalent Dose: 0.1 to 1.0 Sv



Isotope	F-18
Injection Method	Autoinjector
Injection Location	R Antecubital
Injected Activity	9.98 mCi
Radiotracer Volume	1.50 mL
Saline Flush Volume	60.0 mL
Imaging Time	56.5 min
% Extravasation	14 %
Initial Activity	1.42 mCi
Imaging Time Activity	0.24 mCi
Reabsorption Rate	27.4 min
Dose Calculation Volume	1.00 to 60.21 cm^3
Dose Rate	80.5 to 1.7 mSv/mCi-min
Total Equivalent Dose	1.0 to 0.1 Sv



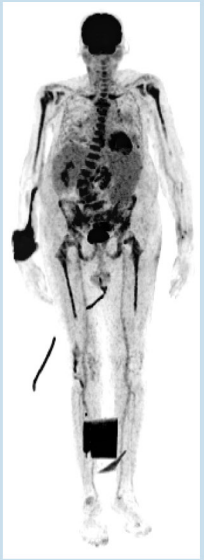
Administration of 18F-FDG consisted of 9.98 mCi injected with an auto-injector through an IV in the right antecubital followed by 60 mL of saline. Using PET images and TAC data, the extravasation was estimated to be approximately 14% of injected activity. Total equivalent dose to be 1.05 Sv for a tissue volume of 1 cm^3 and 0.09 Sv for a tissue volume of 60.2 cm^3.



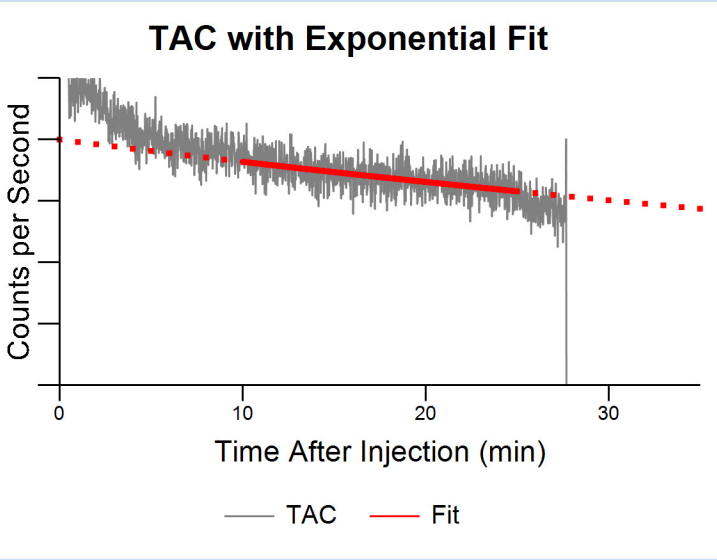
- Dose calculation volume is twice the extravasated radiotracer volume or the total flush volume plus the extravasated radiotracer volume with a minimum volume Of 1 cm^3.
- Initial extravasation amount and reabsorption rate estimates are based on PET measurements and injection site monitoring data from Lara® sensors.
- Volumetric expansion is modeled As a mono-exponential function using initial volumes and PET measurements of volume.
- Dose rates are based on nuclear decay data from ICRP Publication 107 using the IDAC-dose 2.1 software's sphere module.

Scan #9571

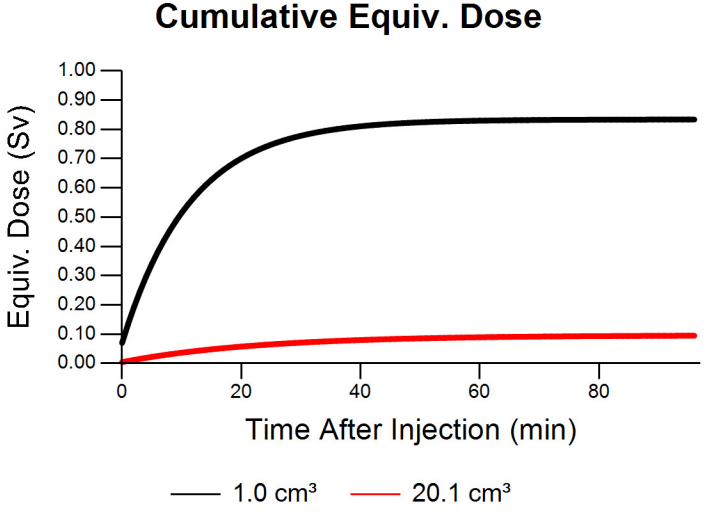
Equivalent Dose: 0.1 to 0.8 Sv



Isotope	F-18
Injection Method	Manual
Injection Location	R Forearm
Injected Activity	9.90 mCi
Radiotracer Volume	1.50 mL
Saline Flush Volume	20.0 mL
Imaging Time	74.0 min
% Extravasation	9 %
Initial Activity	0.87 mCi
Imaging Time Activity	0.27 mCi
Reabsorption Rate	73.4 min
Dose Calculation Volume	1.00 to 20.13 cm^3
Dose Rate	80.5 to 4.7 mSv/mCi-min
Total Equivalent Dose	0.8 to 0.1 Sv



Administration of 18F-FDG consisted of 9.9 mCi injected through an IV in the right forearm followed by 20 mL of saline. Using PET images and TAC data, the extravasation was estimated to be approximately 9% of the injected activity. Total equivalent dose to be 0.83 Sv for a tissue volume of 1 cm^3 and 0.1 Sv for a tissue volume of 20.1 cm^3.



- Dose calculation volume is twice the extravasated radiotracer volume or the total flush volume plus the extravasated radiotracer volume with a minimum volume Of 1 cm^3.
- Initial extravasation amount and reabsorption rate estimates are based on PET measurements and injection site monitoring data from Lara® sensors.
- Volumetric expansion is modeled As a mono-exponential function using initial volumes and PET measurements of volume.
- Dose rates are based on nuclear decay data from ICRP Publication 107 using the IDAC-dose 2.1 software's sphere module.