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RECOMMENDATIONS ON DIAGNOSTIC RADIOLOGY, NUCLEAR MEDICINE AND RADIATION THERAPY

RADIATION RISK APPRAISAL FOR DETRIMENTAL EFFECTS FROM MEDICAL EXPOSURE DURING MANAGEMENT OF PATIENTS WITH LYMPHOMA OR BRAIN TUMOUR (SINFONIA)

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Radiation risk appraisal for detrimental effects from medical exposure during management of patients with lymphoma or brain tumour (SINFONIA)

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These recommendations are based on the research work carried out by the SINFONIA consortium partners throughout the project.

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TABLE OF CONTENTS

LIST OF TABLES

ABBREVIATIONS

AI	Artificial intelligence
ALARA	As low as reasonably achievable
BEIR	Committee on the Biological Effects of Ionizing Radiation
CBCT	Cone-beam computed tomography
CT	Computed tomography
DICOM	Digital Imaging and Communications in Medicine
DL	Deep learning
DNA	Deoxyribonucleic acid
DRL	Diagnostic reference level
EC	European Commission
ICRP	International Commission on Radiological Protection
LET	Linear energy transfer
LNT	Linear no-threshold
MC	Monte Carlo (simulation)
MIRD	Medical internal radiation dose
ML	Machine learning
NM	Nuclear medicine
PBMC	Peripheral blood mononuclear cell
PET	Positron emission tomography
RT	Radiation therapy
SMN	Second malignant neoplasm
SPECT	Single photon emission computed tomography
TAT	Targeted alpha therapy
TLD	Thermoluminescence dosimetry
TPS	Treatment planning system
WWTP	Wastewater treatment plants

1. INTRODUCTION

Ionising radiation can damage cellular structures and the deoxyribonucleic acid (DNA) of patients, leading to an increased risk of cancer. Repeated or high-dose radiation exposure during medical imaging procedures can also cause radiation-induced skin injuries. These injuries might appear as skin redness or hair loss, particularly in areas directly exposed to radiation. Similarly, patients undergoing radiotherapy might suffer from early and late effects from the inadvertent irradiation of normal tissues during the therapeutic procedures. Radiation exposure can also increase the risk of cataracts. Healthcare personnel performing X ray-guided interventional procedures and patients undergoing repeated head scans are particularly at risk. Pregnant patients are advised to avoid unnecessary exposure to ionising radiation. Exposure during pregnancy can lead to conceptus health effects, including increased risk of cancer later in life, growth retardation, and congenital malformations, especially if the conceptus dose is higher than 100 mGy. Other studies suggest a link between radiation exposure and increased risk of cardiovascular disease (Little et al. 2023). This risk is associated with radiation-induced damage to heart muscles and blood vessels, potentially leading to long-term health issues such as heart disease, especially with high cumulative doses. Furthermore, ionising radiation can cause direct damage to the DNA in reproductive cells, which can lead to passing hereditary mutations on to future generations. While the risk is generally very low, it is a potential concern for patients undergoing repeated or high-dose diagnostic and interventional procedures.

Advancements in imaging technology and dosimetry have led to the development of systems that require lower doses of radiation, thereby reducing exposure without compromising image quality. SINFONIA has developed advanced artificial intelligence (AI)-powered technologies for personalised dosimetry in medical imaging, namely a web-based tool for the estimation of organ doses from various X ray modalities (iDose, http://idose.med.uoc.gr/) and advanced methodologies for dosimetry in computed tomography (CT) imaging and theranostics. As a result, novel methods for dose reduction and patient-specific dose estimation in CT and radiopharmaceutical therapies are now suitable for implementation in clinical settings. Research work has also been carried out on measuring, calculating, and simulating the doses from secondary radiation and imaging in patients receiving proton and photon therapy as well as estimating neutron doses to staff and comforters. A modular radiogenic risk assessment tool has been developed to estimate the risk associated with medical radiation imaging and radiation therapy (RT).

Despite these measures, several challenges persist in the area of medical use of ionising radiation. One major challenge is the variation in practices and access to advanced low-dose technologies across different healthcare settings. Additionally, the cumulative effect of radiation exposure is a concern, especially for patients undergoing multiple scans or those with chronic conditions requiring frequent imaging. There is also an ongoing challenge in educating both patients and healthcare providers about the risks of radiation and the importance of adhering to guidelines. Misunderstandings and lack of awareness can lead to either unnecessary medical imaging or undue anxiety about necessary diagnostic procedures.

The SINFONIA project aimed to tackle some of these challenges by developing new frameworks for personalised dosimetry and risk appraisal in diagnostic radiology, nuclear medicine (NM) and RT investigating possible individual factors influencing the susceptibility to second malignant neoplasms. and conducting research to support radiation risk appraisal for staff, comforters, the public and the environment. Last, but not least, SINFONIA aimed to provide multidisciplinary education and training for healthcare professionals and researchers working in these areas.

This present report provides recommendations on diagnostic radiology, NM and RT derived from SINFONIA's research. They are directed towards professionals working with ionising radiation or having to determine doses and assess risks from the medical use of ionising radiation. The main recommendations are prominently featured in boxes throughout the subsequent sections of this document.

Looking towards the future, ongoing research and development are poised to further mitigate the risks associated with medical imaging. AI and machine learning (ML) are emerging as transformative tools in radiology. These technologies have the potential to optimise the process of image capture, reduce the need for repeated scans, and potentially lower the doses required by enhancing image processing and interpretation.

2. DOSE DETERMINATIONS FROM DIAGNOSTIC RADIOLOGY IMAGING PROCEDURES

Highlights

- Scanner-specific and patient-specific Monte Carlo simulations combined with patient computational models from CT scans are recommended as the gold standard for personalised medical dosimetry.
- Artificial intelligence models are recommended as suitable tools to quickly generate personalised dose distributions and patient organ doses, thus reducing reliance on complex Monte Carlo simulations in medical imaging dosimetry.
- We recommend repeated validation and continuous quality assurance of artificial intelligence algorithms used in dose prediction to ensure accuracy, reliability, and safety across different patient groups and imaging scenarios.

2.1 CURRENT PRACTICE

Medical radiation plays a pivotal role in modern healthcare by aiding in the diagnosis and treatment of a wide range of conditions from cancer to cardiovascular diseases. However, the increased utilisation of medical imaging and RT has raised concerns about the potential health risks associated with excessive radiation exposure (Bosch de Basea Gomez et al. 2023, Frush et al. 2024). In response, current medical practices are focused on optimising the delicate balance between the benefits of accurate diagnosis and treatment and the potential risks of radiation-induced harm.

Numerous techniques have been developed for the assessment of patient radiation doses resulting from X ray imaging. Measuring organ doses can be accomplished through the utilisation of dosimeters like thermoluminescence dosimetry (TLD) crystals, as well as physical anthropomorphic phantoms that emulate average-sized individuals (Damilakis et al. 2001). However, a significant drawback of this approach is its failure to account for variations in anatomy, body dimensions, and organ properties across different patients. Additionally, employing TLD dosimetry or similar methods involves substantial labour, time, and financial expenses (Damilakis et al. 2021).

The current gold-standard technique in medical X ray imaging dosimetry for individual patients combines Monte Carlo (MC) simulations with computational models derived from CT images of each patient (Myronakis et al. 2009, Damilakis et al. 2010a). These simulations offer patient-tailored precise three-dimensional (3D) distributions of radiation dose. Data related to CT scanner specifications and examination protocols are required to conduct these simulations. A non-exhaustive example of required data is the beam spectrum, filtration composition and thickness, geometry parameters, and variations in tube current throughout the scan.

Results from MC-personalized dose simulations for X ray imaging procedures have demonstrated variation in dose distributions and organ dose based on patient age, size, tissue composition, and biological sex. Subsequently, individualised dose maps and organ dose reports for every patient undergoing X ray imaging can substantially facilitate procedure optimisation towards dose reduction (Damilakis et al. 2010b).

Nevertheless, the adoption of MC-assisted dosimetry remains limited in clinical practice mainly due to the time commitment and high-end dedicated computing resources demanded by the simulation process. The development of AI models trained to promptly generate personalised 3D dose distributions or organ and tissue dose following an X ray examination, without relying on MC simulations, has the potential to revolutionise the current utilisation of medical imaging dosimetry (Juszczyk et al. 2021, Salimi et al. 2023, Myronakis et al. 2023, Tzanis et al. 2024, Berris et al. 2024).

2.2 RECOMMENDATIONS AND CHALLENGES

Balancing effective medical imaging and radiation safety requires a comprehensive and collaborative approach involving various stakeholders, including radiologists, medical physicists, technologists, and clinicians. Central to this approach is the application of the ALARA principle (as low as reasonably achievable), which advocates for minimising radiation doses to the lowest level possible while still achieving the desired diagnostic or therapeutic outcome. However, challenges arise due to the diversity of medical equipment, imaging protocols, and the need for continuous education to ensure healthcare providers remain up to date with the latest techniques and guidelines.

Healthcare institutions may sustain a large patient workload for X ray imaging examinations. In busy environments, MC simulation of every procedure for every individual patient can be impractical in most clinical settings. Replacement of MC simulations with AI-assisted rapid estimation of patient organ doses can mitigate high patient workloads and simulation time bottlenecks and can become part of the workflow in daily clinical practice. Additionally, appropriate AI training methods can alleviate current limitations in dose estimation for partially exposed organs.

Effective collaboration between medical physicists, radiologists, and AI experts is paramount. Developing AI models for patient dose prediction is a multidisciplinary effort to leverage the expertise of all relevant healthcare professionals. Seamless integration of AI algorithms into clinical workflows requires clear communication, training, and education of the medical staff to ensure accurate interpretation and appropriate action based on AI-generated dose predictions.

It is essential to choose AI models that offer transparency and interpretability in their predictions. Medical physicists and radiologists should select AI algorithms that provide insights into how predictions are made, allowing for better understanding and acceptance by healthcare professionals. Transparent AI models not only enhance trust but also facilitate meaningful adjustments to imaging protocols and patient care strategies based on AI-generated dose predictions.

As medical physicists and radiologists embrace AI algorithms for patient dose prediction, an unwavering commitment to rigorous validation and continuous quality assurance becomes paramount. The role of medical physicists and radiologists in this context extends beyond traditional practices. They bear the responsibility of ensuring that AI algorithms used for patient dose prediction are not only accurate but also reliable and safe. Just as medical equipment undergoes routine calibration and maintenance, AI algorithms must undergo periodic assessments and updates to uphold their accuracy and clinical relevance. Meticulous validation protocols must be established to thoroughly assess the algorithms' performance across diverse patient populations, imaging modalities, and clinical scenarios. This validation process should encompass a comprehensive evaluation of sensitivity, specificity, precision, and robustness to outliers.

2.2.1 Patient perspective

From the perspective of patients, the prospect of medical radiation exposure can be distressing. The intricacies of radiation's benefits and potential risks are often not fully understood by patients, leading to concerns about potential long-term consequences. To address these anxieties, clear communication becomes imperative. By effectively conveying information about the intended advantages of radiation-based procedures, as well as transparently outlining the potential hazards, healthcare providers empower patients to make informed decisions about their medical care. This proactive approach not only bridges the knowledge gap, but also cultivates a sense of trust between patients and medical professionals, ultimately fostering a more holistic and reassuring healthcare experience.

2.2.2 Potential of artificial intelligence for dose determinations

Artificial intelligence algorithms can process and analyse an extremely large number of patient-specific data, imaging parameters, and historical dose information. Tailored recommendations for personalised imaging protocols that minimise radiation exposure without sacrificing diagnostic value can be realistically pursued. Such AI-driven approaches not only enhance patient safety but also contribute to the efficient allocation of healthcare resources.

2.3 FUTURE DIRECTIONS

The future trajectory of medical radiation exposure is shaped by ongoing technological advancements. Potential directions include:

- AI-driven dose optimisation: Further refinement of AI algorithms could enable the precise prediction of patient-specific radiation doses. This advancement would facilitate the customisation of radiation exposure based on individual patient characteristics, thereby minimising unwarranted variability.
- AI-driven rapid dose prediction: Implementation of AI algorithms can provide organ-dose predictions within seconds. The pre-trained underlying AI models can be seamlessly integrated as part of the imaging procedure without hindering the established daily workflow of the clinic.
- Quantitative imaging: As quantitative imaging techniques continue to develop, healthcare professionals can obtain more accurate assessments of disease progression and treatment responses. This enhanced accuracy contributes to better-informed medical decisions and a reduction in the need for repeated imaging procedures.
- Radiation monitoring and reporting: The implementation of comprehensive radiation dose monitoring systems allows for real-time tracking of patient exposure. This proactive approach enables healthcare providers to intervene promptly if doses exceed established safety limits.
- Individual sensitivity to radiation exposure: Sensitivity to both tissue damage and cancer induced by radiation depends on genetic and environmental factors. However, the precise interaction of the factors and the magnitude of their impact on individual radiation response are not well understood. More research is necessary for the efficient inclusion of individual radiosensitivity in patient protection.
- Patient education: Strengthening patient education efforts is paramount for fostering a nuanced understanding of medical radiation's benefits, potential risks, and associated safety measures. Empowered patients are better equipped to actively participate in decisions about their medical care.
- Regulatory frameworks: The continual refinement of regulatory guidelines and standards is essential to adapt to emerging technological breakthroughs and ensure consistent and safe practices across diverse healthcare facilities.
- Ethical concerns: Ethical concerns encompassing decision transparency and accountability further accentuate the intricacies. Addressing challenges through collaborative efforts between healthcare professionals, AI experts, and regulators will be pivotal in harnessing AI's full potential for accurate and optimised radiation dose determinations, ultimately advancing patient care and outcomes.

Implementation of reasonable recommendations driven by robust research findings and the growing impact of AI evolution can help resolve current challenges in medical exposure optimisation. Collaboration among vendors, healthcare providers, technology experts, and patients to embrace such recommendations will eventually lead to smoother healthcare workflows, enhanced diagnostic and therapeutic outcomes, and, foremost, improved patient safety.

3.
DOSE DETERMINATIONS FROM NUCLEAR MEDICINE IMAGING PROCEDURES

Highlights

- It is recommended to use ring dosimeters to assess the maximum extremity dose of workers handling radiopharmaceuticals in nuclear medicine and to use a correction factor greater than four, which depends on the isotope, to estimate the maximum extremity doses. These dosimeters should be sensitive to beta radiation.
- If possible, the use of automatic dose dispensers is recommended in nuclear medicine with minimal operator intervention. Where this is not possible, the use of leaded aprons and syringe shielding is recommended. The use of V-form vials allows for reduced handling of the vials to achieve dose utilisation.
- As doses are very much procedure-dependent, it is recommended that whenever a new technique is started, an attempt should be made to optimise the procedures. For this purpose, the use of direct reading dosimeters providing the instantaneous dose rate is desirable. The maximum number of patients to be treated per worker should be calculated, either with their own measurements or based on the literature, and the annual limits or 3/10 of the annual limit for the occupational exposure should be avoided.

3.1 CURRENT PRACTICE

Nuclear medicine is based on the introduction of unsealed radioactive sources, either by intravenous injection, inhalation or swallowing of a pill or liquid, in order to obtain functional images for diagnostic purposes or target malignant cells for therapeutic purposes. This mode of administration implies that, unlike other medical procedures using ionising radiation such as radiology or RT, radiation exposure is not limited to the patient alone but also extends to the personnel involved in the procedure and any other person who remains near or in contact with the patient until the radioactive material has decayed. Therefore, exposure in NM procedures requires special attention in terms of radiation protection (RP), and it can be medical, occupational, public and environmental, as defined by the International Commission on Radiological Protection (ICRP) in 1991. The first refers to the radiation to which a patient is exposed as a result of undergoing diagnostic or therapeutic procedures and is therefore expected to benefit from such exposure. The second refers to NM personnel exposed as a result of handling radiopharmaceuticals or unsealed sources, and the third to the rest of the public and the environment.

In the last decades, the role of NM has become evident in the clinical diagnosis and treatment of multiple pathologies, including cancer. The number of approved radiopharmaceuticals and novel techniques in NM has experienced a remarkable increase, as reflected by a remarkable boost in the number of therapeutic procedures, which, according to the latest report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) in 2020/2021, has risen from 880,000 in the 2008 report to 1.4 million, an increase of 63%. Contrary to the benefits for patients, this trend inevitably implies an increase in the number of patients, members of the public and nuclear workers exposed to ionising radiation. A methodological and personalised assessment of the doses absorbed by patients, workers and the environment has therefore become of the utmost importance.

Historically, dosimetry in external beam RT has been extensively studied, as well as the optimisation of radiation doses in order to maximise tumour absorbed doses while sparing healthy tissues. In contrast, the assessment and quantification of absorbed doses in NM has not been as much of a concern, and due to the intrinsic nature of NM images, noisy and with poorer resolution, it is more challenging (Stabin et al. 2019). However, with the introduction of theranostics as a combination of imaging and therapeutic capabilities in a single technique, personalised dosimetry and treatment planning in NM has become more accessible. Currently, radiation doses in NM are delivered according to a standard planification based on fixed activity values or patient-related parameters such as their body weight or surface area, an approach commonly known as “one dose fits all.” In contrast, personalised dosimetry will allow not only a more precise optimisation of the doses absorbed by the patient and organs, with better control of

tumour and non-tumour uptake, but also the verification of the radiopharmaceutical distribution, thus improving the therapeutic outcome and our knowledge of the dose–response relationship. There are several techniques to evaluate absorbed doses in NM. However, most of these methods are based on analytical models, such as the medical internal radiation dose (MIRD) standard (ICRU 2002, ICRP 2015, MIRD 2022), and therefore do not take into account possible heterogeneities within an organ caused by differences in radioactivity uptakes. MC simulations are considered the gold standard for personalised dosimetry, but they are time consuming and require high computational power. On the other hand, AI has proven to be a fast, accurate, and reliable tool for assessing absorbed doses at the voxel level, providing a clear overview of the radiopharmaceutical distribution and thus improving personalised dosimetry (Arabi et al. 2021, Brosch-Lenz et al. 2023). Therefore, research into new AI-based methods of determining absorbed doses should be encouraged in order to standardise personalised dosimetry, as they will show superior performance in terms of time-results.

Finally, NM departments are associated with the highest occupational doses, especially in the case of the extremities due to the handling of particle-emitting sources at short distances to the hands, which may even exceed recommended dose limits if RP standards are low. Moreover, the exponential growth of therapeutic and theranostic agents makes it necessary to strengthen RP and dosimetry measures in NM, as the energies and activities involved with these radiopharmaceuticals are considerably higher than with diagnostic ones (Al-Ibraheem et al. 2024). In addition, the rapid incorporation of these components in hospitals may hamper the correct adoption of procedures and correct practices, so its introduction may imply challenges such as lack of trained personnel or standardisation. These issues may have a negative impact on staff doses, so proper monitoring and dose evaluation of staff doses during these new practices should be carried out to ensure safety standards. On the other hand, although considerable progress has been made in understanding the diffusion of radionuclides through the food web following the Chernobyl and Fukushima nuclear incidents, there is limited information on the processes of transfer to humans and biota from radiopharmaceuticals, which is necessary to assess their radiological impact. Therefore, studies are needed to determine the risks to the population and environment associated with waste management and handling of new radiopharmaceuticals.

3.2 RECOMMENDATIONS AND CHALLENGES

3.2.1 Patient perspective

Radiation is popularly regarded as dangerous, and knowledge about it is generally low. This unawareness can lead to fear and even rejection in a patient who is about to undergo a diagnostic or therapeutic procedure with ionising radiation, which can aggravate the patient's clinical experience. This perception can be even more acute in NM, as the prospect of having to swallow, inhale or be injected with radioactive material can be disturbing. Moreover, in contrast to external RT, the fact that the patient becomes radioactive and therefore has to isolate from relatives or close people for some time can be detrimental to his or her psychological state, which can be critical in cases of ongoing illness.

To reduce the anxiety and discomfort associated with undergoing radiopharmaceutical testing, it is important that the patient is well-informed from the outset. The patient should always be aware of the exact details of the procedure, the purpose of the procedure, and the possible consequences, with the emphasis always on dose optimisation and ensuring the treatment's benefit outweighs the risk. In the case of a diagnostic test or outpatient treatment where the patient will remain in the hospital for a few hours, they should know who should not be approached after discharge from the hospital through appropriate guidelines provided by staff. In the case of an inpatient therapeutic examination, they should know exactly why they are staying in the hospital and why the staff uses radiation protection measures such as lead aprons or clamps, as it may happen that a patient feels concerned about all the protective measures taken by the staff which they are not. Patients should also be informed of the reasons why certain family members may or may not be present in their hospital room. Regarding internal dosimetry, it is important that the patient knows how much radiation they have received if they so wish, which is another positive aspect of personalised dosimetry.

3.2.2 Potential of artificial intelligence for dose determinations

Artificial intelligence is a computational process mimicking human behaviours, whereas machine learning (ML) is the use of an algorithm to implements this task without explicit programming. Different ML algorithms have been developed during the last decades that require different steps, including feature extraction, feature selection, and classifier/regression/time-to-event. Deep learning (DL) performs different ML algorithm steps in one package by feeding the input and desired target to the DL algorithm. DL algorithms can effectively learn from complex high-dimensional datasets such as medical data to overcome limitations and improve performance on different tasks. In NM, AI-based solutions have been proposed to address various challenges,

from image acquisition to tasks that depend on human cognition. Moreover, given the superior performance of ML–DL techniques over conventional methods, a paradigm shift is anticipated in different nuclear medical imaging tasks.

The NM framework consists of several steps, including data acquisition, image pre-processing, quality control and assurance, data management, detection and characterisation, and quantitative image analysis. Currently, these steps are performed using conventional algorithms and human observers. We recommend the integration of AI in NM to enhance the performance of these steps. AI can enable fast acquisition, dose reduction, and protocol optimisation for data acquisition.

Tomographic imaging modalities, including positron emission tomography (PET) and single photon emission computed tomography (SPECT), require reducing acquisition time to improve patient comfort, enhance scanner throughput, and minimise sources of image artifacts such as motion. Achieving these goals is particularly challenging for vulnerable patient populations such as the elderly and children. Furthermore, in imaging modalities using ionising radiation (CT, PET, and SPECT), reducing the radiation dose is highly appreciated to decrease the potential of ionising radiation hazards, especially in paediatrics and patients requiring multiple or longitudinal scans. However, reducing the acquisition time and radiation dose in tomographic imaging can result in increased Poisson noise, leading to compromises in image quality, confidence, lesion detectability, and extracted quantitative metrics. Various hardware and software solutions have been proposed to mitigate this issue to decrease patient acquisition time and radiation exposure. In recent years, AI-based algorithms have emerged as a promising approach to address time and dose limitations in the image acquisition process.

In addition, DL algorithms have been suggested for image-to-image conversion, aiming to generate contrast-enhanced MR sequences from non-contrast images. This approach can potentially minimise the dosage of contrast-enhancing agents administered to patients. Furthermore, AI-based algorithms have enabled the reduction of acquisition time and ionising radiation dose in CT imaging through techniques, such as sparse view reconstruction in the projection space and generating contrast-enhanced images from non-contrast CT scans. In addition, DL-based algorithms have been proposed to reduce ionising radiation dose in CT imaging for various organs and applications.

Hardware development in SPECT imaging, such as new electronics and detector technologies (solid-state detectors) or designs of SPECT, i.e., multi-pinhole SPECT, are able to decrease the acquisition time and injected radiopharmaceutical activities to patients. DL-based algorithms have also been suggested to reduce the number of acquired projections or time per projection to decrease acquisition time. Furthermore, these algorithms are utilised to decrease the injected activity in SPECT imaging. In PET imaging, faster electronics, new detector technologies (i.e., high energy and time resolution to distinguish scatter and random photons from true coincidences and high coincidence time resolution of time-of-flight (TOF)) or gantry design (i.e., total body PET) could decrease acquisition time and injected activity. On top of that, faster acquisition and dose-reduction approaches became feasible using AI-based algorithms.

Deep-learning-assisted radiation dose calculation in NM proved to be feasible and numerous publications in the literature highlighted the advantages of this technique compared to conventional approaches based on the MIRD formalism. The results are promising and mature. Large-scale validation studies using multi-institutional datasets are still required prior to the adoption of these techniques in the clinical setting.

3.2.3 Staff, comforters, and general public perspective

Staff working in the field of NM are subjected to high quantities of ionising radiation, especially on the skin of the hands during the preparation and injection of radiopharmaceuticals, potentially exceeding legal dose limits for the skin. With the growing trend of NM therapy applications, these doses are going to increase even further, together with the number of exposed personnel. New radiopharmaceuticals that are introduced in clinics for theragnostic applications need to be evaluated as well in terms of the possible increasing risk for the personnel. The radiation dose of NM staff is monitored by personal dosimeters, specifically ring dosimeters for estimating doses to the skin of the hands. Unfortunately, ring dosimeters tend to underreport the maximum dose received, as the dose distribution over the hands can be very heterogeneous with local maxima. From this point of view, the development and implementation of an innovative methodology to apply digital approaches in combination with flexible computational models is recommended to take into consideration the dynamic context of exposure scenarios for NM staff. MC simulations are commonly used in radiation protection scenarios, and the method is well validated by the scientific community. However, as the radioactive sources (i.e., syringes or vials) are continuously moved in working practice, an unrealistic number of simulations need to be performed to accurately assess the cumulated absorbed dose distribution over the worker's hand. Accurate representation of digital twins can boost the accuracy of MC simulations for personal dosimetry in NM, but it is a challenging task, as the hands and sources are constantly moving. New ongoing developments are needed where the 3D movement of hands and radioactive sources are tracked, acquired with depth cameras and using a combination of computer vision and AI techniques. The real-time nature of the tracking allows the creation of 3D geometries for MC simulations while the NM operations are being performed and will effectively reduce the time necessary to get a dose estimation. This can even be further improved by combining or even fully replacing MC simulations with dose-predicting AI methods. It is important

that this computational online dosimetry tool is developed with portability in mind and that the setup can be placed inside a laminar airflow cabinet.

The growing use of NM procedures and diversity of new radiopharmaceuticals also stimulate the need for a more comprehensive re-evaluation of the radiological risk for caregivers and the general public coming into proximity of NM patients. Risk assessment studies for both diagnostic and therapeutic procedures are based on dose rate measurement in a single position at a specified distance from the patient and carried out at several time points after administration to estimate the whole-body retention. To assess the exposure level, these dose rate measurements are then combined with specific exposure scenarios, describing how long individuals are in close contact with the patient over time. Based on this, recommendations are drafted for the NM patient. As such, these external doses are estimated by making a series of simplifications for modelling both the radiation emitted by the patient and the dose absorbed by the caregiver or a person from the general public. Although these approximations reduce the complexity of dose assessments, they also affect their accuracy. Since the patient is a physically large radiation source with varying activity distribution over time, reducing that source to a dose rate in a single point is prone to lead to large errors in dose estimations, especially at short distances from that patient. These limitations can also be addressed by making use of recent advancements in computational dosimetry such as the use of realistic and flexibly computational human models to represent realistic close-contact scenarios between an NM patient and a caregiver or family member such as children. Such a more advanced computational framework can help in creating a tool for the calculation of effective dose rates per injected activity for a large variety of close-contact configurations for a range of radiopharmaceuticals. Hospitals or regulatory bodies can use such a database to evaluate the exposure to comforters or the general public for specific scenarios as part of risk assessment studies. Together with the choice of appropriate dose constraints, this would facilitate the setting of release criteria and patient restrictions. Moreover, besides determining the effective dose rates, also organ-specific dose rates per injected activity such as gonad dose rates, eye lens dose rates or foetus dose rates can be calculated separately. The framework can be further improved if more extensive biokinetic data will become available from NM patient populations.

3.2.4 Environmental perspective

For the environment, the highest priority is to produce improved models for dose assessment of radionuclide releases from hospitals to the environment via wastewater treatment plants (WWTPs), not only for members of the public but also for wildlife. The reason to include wildlife is that the ICRP has established that, in addition to humans, the environment should similarly be protected from the deleterious effects of radiation (ICRP 2008).

The goal to protect the environment is motivated by a significant evolution of thought based on both moral and scientific grounds.

In this project, we have made a significant advance towards a practical demonstration of an approach for the environmental impact assessment of radiopharmaceuticals released from medical facilities considering simultaneously both human and non-human biota. We generated radionuclide dispersion simulation results and selected a specific scenario (radionuclide discharges in Belgium's Molse Nete River during the year 2018), to symbolise typical environmental conditions likely to be found at the source and downstream from a hospital. This covered the radionuclides ^{18}F, ^{123}I, ^{131}I, ^{153}Sm, ^{99}mTc and ^{201}Tl, the only ones for which environmental monitoring data were available. The dose rates calculated in the example Molse Nete scenario appear very low, indicating low risk for the radionuclides and scenarios concerned. Nevertheless, it is not possible to state "case closed," and it is necessary to continue to perform such assessments, since they are still infrequent (because the primary focus is on exposure to patients), and there is a wider range of radionuclides to investigate (e.g., ^{89}Zr, ^{90}Y, ^{99}Mo, ^{131}mXe, ^{133}Xe, ^{177}Lu, ^{177}mLu, ^{223}Ra, ^{226}Ra, ^{225}Ac and ^{227}Th). Moreover, occasional accidental discharges in European facilities where higher concentrations are involved are not unheard of, and exposures to medical radionuclides may increase with new targeted therapies in the future. Along the way, there is a need to improve and standardise modelling methods to be able to explicitly demonstrate that people and the environment are adequately protected.

In line with the above, we have made the following specific recommendations so that the screening approach used here can be improved. Firstly, we believe that significant radiopharmaceutical industries and hospitals should conduct and publish annually their environmental radioactivity monitoring, just as the nuclear industry does. There is a knowledge gap here, and significantly we had to resort to monitoring data on radionuclides at the outlet of WWTPs obtained by the Belgian regulatory body, the Federal Agency for Nuclear Control, to make our assessment because environmental release data from hospitals could generally not be found.

Secondly, we recommend extending the assessment approach to other radionuclides, which necessitates biokinetic research to establish the transfer parameters of the relevant radionuclides in their relevant physicochemical chemical form (speciation) for biota. In the present study this occasionally had to be deduced based on a chemical analogue methodology and other proven extrapolation methods.

Thirdly, better knowledge of the modus operandi of WWTPs will help better define the assessment scenario. We had to make certain reasonably conservative assumptions and simplifications to cover for a certain lack of generalizable WWTP process information. In order to reduce conservatism and minimise model

conceptual uncertainties, there is a need for actual knowledge of the retention/separation efficiencies of the different waste streams (water and sludge), as well as a need to represent the basic working pattern (occupancy fractions) at WWTP plants in terms of worker hours per year spent between plant operation and plant maintenance. Other improvement aspects include establishing the transit times of the different effluents to calculate accurately the relevant radionuclide decay factors and also the realistic shielding conditions for external beta and gamma exposure, which is especially important for 201Tl, which appears to dominate external exposure to workers.

Finally, there should be a move towards a unified European approach for dose assessment from medical radionuclides, preferably by further developing the modelling methodology that we have developed in the present project. With this, we also recommend that the environmental impact assessment approach should be part of the development process of radionuclide treatments.

3.3 FUTURE DIRECTIONS

The environmental perspective is linked to the fact that there are novel sources of radioactivity involved in radionuclide and radiopharmaceutical manufacturing, medical use and waste disposal, and so radiopharmaceuticals in WWTPs and watercourses are on the increase. Radiological impact assessments are being conducted for some of these sources even though data are lacking, which likely leads to overly conservative assessments. Although from our case study, the resulting predicted doses to WWTP workers, the public and the environment are very low, there is a need to explicitly prove this for a wider variety of radionuclides and assessment cases. There are significant assessment uncertainties that only a few radionuclides had in-situ monitoring data and parameter values to represent the relevant accumulation and dispersion pathways, signalling the need for further investigations and for a standardised fit-for-purpose assessment approach for the EU member states. Therefore, from our perspective, and in line with the European Radioecology Alliance recommendations provided to the EURAMED rocc-n-roll project (Vives i Batlle et al. 2022), we indicate the general research needs to (a) identify the behaviour of relevant radionuclides and exposure pathways, (b) improve datasets and assessment methods to identify the relevant data gaps and (c) provide advice to operators and regulators, leading to a pan-European fit-for-purpose assessment approach, for all of which the present project has been the initial necessary (but not sufficient) step.

For medical applications, current radiopharmaceutical therapy regimens are in a transition phase from a one-size-fits-all concept to a personalised approach by increasing the radiation dose to the target while minimising the absorbed dose to healthy tissues. Therefore, establishing a practical framework for patient-specific dosimetric data estimation can be used in the optimisation of medical procedures involving radiation to ensure the minimum radiation dose necessary while improving the efficacy of the medical task at hand. A better understanding of radiobiology in molecular radionuclide therapy is strongly needed. Radiobiology has been a key factor in establishing optimal treatment regimens for external beam RT. Nowadays, there is some evidence that the extrapolation of radiobiology of external beam RT to molecular radionuclide therapy is not straightforward, because of dose-rate effects and more importantly owing to the different molecular and cellular signalling pathways. Therefore, there is a need for the establishment of specific radiobiological models in targeted radionuclide therapy.

4. DOSE DETERMINATIONS FROM RADIATION THERAPY PROCEDURES

Highlights

- Modern radiation therapy procedures are imaging intensive, reflecting their complexity. While image guidance is required to ensure the correct positioning of the patient in relation to the treatment beams, it is recommended to record the dose contribution from imaging procedures, especially when they exceed 2% of the prescription dose.
- It is recommended to include into treatment planning systems' accurate algorithms for calculating out-of-field doses from both photon and proton radiation therapy, in the latter case also considering the dose contribution from neutrons, to reduce reliance on multiple systems for assessing doses to organs far from the target volume that may contribute to the overall risk of the patient.
- Analytical algorithms and artificial intelligence tools are recommended as alternative tools to quickly calculate imaging doses from positioning and verification of treatment to complement dose assessment in radiation therapy.

4.1 CURRENT PRACTICE

Radiation therapy is an effective treatment form for cancer that eradicates localised disease by damaging the DNA of tumour cells. However, normal tissues around the tumours are inadvertently irradiated in the process and can suffer from side effects. Treatment optimisation is therefore required to maximise the dose to the tumour while minimising the irradiation of normal tissues, and thus to increase the therapeutic window. Several treatment techniques are available for this purpose, the majority involving external beam irradiation with photons and increasingly with protons and other particles. However, their requirements in geometrical accuracy are very high, which leads to the frequent use of advanced image guidance to ensure the correct positioning of the patient in relation to the treatment beams.

The irradiation of normal tissues in RT is a concern due to the risk of side effects that may affect the quality of life of the patients. The main concern has historically been the non-stochastic effects in tissues in and in the proximity of the target irradiated directly by the treatment fields. The effects depend on the irradiated tissue and age at exposure and include various early and late toxicities (Wang and Tepper 2021). The doses absorbed by the affected tissues are typically calculated with dedicated algorithms available in treatment planning systems (TPSs) that have a high in-field and near-field accuracy (Howell et al. 2010). These are the dosimetric bases for evaluating the risk for non-stochastic effects in normal tissues and increasingly for the determination of the risk of inducing second cancers in normal tissues either from correlations with epidemiological studies (de Gonzalez et al. 2013) or through calculations (Dasu and Toma-Dasu 2017). Nevertheless, the contribution of other sources of radiation has been considered in line with the implementation of more advanced treatment methods such as intensity-modulated RT, volumetric-modulated arc therapy or even particle therapy. The focus has been on the contribution of secondary radiation generated by interactions of the primary radiation, but also additional doses from various imaging modalities employed during the treatment of the patients.

Consequently, an increasing number of studies have been published on the determination of out-of-field doses that may be used for risk estimations from RT. One of the first reviews on the topic was published by Xu et al. (2008), who analysed studies on out-of-field dose determinations for photon and proton therapy. This was followed by an American Association of Medical Physicists (AAPM)-sanctioned code of practice on the measurement and calculation of out-of-field doses (Kry et al. 2017) as well as more recent overviews (Hägl and Schneider 2020, Mazonakis and Damilakis 2021). In addition, the contribution of doses from the increasing use of imaging modalities has also been explored (Palm et al 2010, Hyer et al 2010, Gudowska et al 2014, Ardenfors et al 2014). These overviews and the original studies to which they refer outline good methods to determine the doses, but some of these may be unpractical for routine clinical applications. This is

the case of MC simulations, which are very demanding from the point of view of computational resources they need as well as rather slow in delivering results with high enough accuracy. Other methods employing direct dose determination from detector measurements are labour intensive and may not be applicable for individual dose determinations in patients. Alternative analytical methods have been the development, but these are largely applicable to the treatment approaches in use at their development, which limits their transferability to newer treatment methods. Indeed, recent years have seen widespread adoption of volumetric treatment methods with photons and pencil beam scanning with protons, for which little dosimetric data exists.

Furthermore, cross-comparisons between doses from modern treatment methods are lacking.

In this context, the SINFONIA project aimed to fill the identified knowledge gap and to investigate the magnitude of secondary doses and the associated risks from treatment methods employed in the management of brain tumours and Hodgkin lymphomas (Romero-Exposito et al. 2024a). These are examples of diseases affecting younger patients who have a long life expectancy if their primary disease is cured.

4.2 RECOMMENDATIONS AND CHALLENGES

4.2.1 Patient perspective

Given the negative perception of radiation in the general public, the prospect of RT can be distressing for many patients. It is therefore important that the situation is mitigated through information to the patient on the procedures to be performed and the optimisations involved as well as the doses and associated risks. It is also quite important to point out that in many cases the risks of abstaining from RT can outweigh the risks of inducing a second cancer.

4.2.2 Imaging doses for patients

Imaging has a central role in RT, covering a multitude of steps of the treatment process. The use of imaging for diagnostic and disease staging as well as for treatment follow-up has been covered by the corresponding sections on DR and NM. In addition, modern radiation treatment techniques increasingly employ images for treatment planning and simulation, treatment verification and position verification. Indeed, image guidance has become a critical component for achieving accurate and precise radiation delivery in RT and especially in particle therapy, thus increasing the therapeutic window for many patients.

The SINFONIA project has mapped the current use of imaging in the RT process as well as the associated doses from these imaging modalities. Thus, CT is an established imaging modality for 3D target volume and organ at risk delineation as well as for accurate dose calculation through the underlying representation and 3D simulation of mass or electron density values of the patient tissues. While having a central role in both photon and proton treatments, CT simulation is seldom repeated in photon treatment. In contrast, CT scans are repeatedly acquired in proton therapy to ensure that the patient's anatomy and positioning variations do not interfere with the dose distribution accepted following plan optimisation.

The development of clinical protocols should consider the doses the patients receive during imaging techniques for simulation and pre-treatment verification (positioning and anatomical changes), especially when they exceed a certain threshold level defined in relation to the prescription dose. Collecting dosimetric imaging data, as done in SINFONIA, is an essential first step on this path. Thus, it has been found out that cancer patients show large variations in the number of CT scans acquired during their treatment, depending on the treatment modality and technique. These exhibit large variations in protocols and purposes, such as single energy and dual-energy scans, scans for planning in free breathing or deep inspiration breath hold, as well as standard dose or low dose protocols for verification CTs. The methods available for dose determination from CT doses are identical to those employed in DR employing scan parameters obtained from the DICOM files. Dedicated software applications, allowing organ dose assessment are available, e.g., Virtual Dose (Ding et al 2015), while AI tools offer the potential for increased accuracy in individual organ dose determinations.

Individual dose calculations have shown that in-field and near-field organs have the largest radiation burden from repeated CTs. In addition, the inclusion of normal tissues among the in-field and near-field organs largely depends on target extension. Nevertheless, the in-field and near-field organs can receive total doses in the interval 10–200 mGy from CT scans associated with proton therapy, which typically represents less than 1% of the prescription dose. The corresponding doses from CT scans in photon therapy are typically 3–10 times lower.

Imaging practices for daily target localisation represent the other major contributor to the radiation burden for imaging during the RT process. A broad array of imaging techniques could be employed for this purpose to allow 2D/2D, 2D/3D and even 3D/3D image registrations and calculations of correction vectors for patient positioning. 2D/2D and 2D/3D approaches are the least dose intensive, as they employ orthogonal planar imaging of the treated

volumes. The dose contributions could be determined through the use of organ dose conversion factors and are in the order of 0.1–0.5 mSv per image to in-field and near-field organs, similar to those from planar images in diagnostic radiology. 3D/3D imaging for position verification has seen increased use (Hvid et al. 2018) due to the widespread availability of gantry-mounted cone-beam computed tomography (CBCT) imaging for both photon and proton treatments. This dosimetrically more intensive imaging modality results in organ doses 10 to 100 times higher than planar imaging (Palm et al. 2010, Ardenfors et al. 2018). The use of the various imaging modalities varies however greatly between proton centres (Bolsi et al. 2018), with some having a 2D/3D-based workflow, while others employ more the 3D/3D approaches for the same type of treatments. In addition, the frequency of imaging depends on many factors, including the mobility of the treated area, the use of patient immobilisation devices and their performance or the need for verification imaging.

Analyses carried out in SINFONIA have shown the wide variability that can be encountered in a number of planar images acquired during the treatment of Hodgkin lymphoma or for brain treatments. The cumulative dose from these images however does not exceed 0.4% of the prescription dose for in-field and near-field organs. It therefore appears that these imaging doses represent a low contribution to the total radiation burden of brain cancer and Hodgkin lymphoma patients, typically in the range of clinically acceptable dose variations. These dose contributions are therefore not expected to influence risk estimations from RT. Indeed, earlier studies have shown that imaging doses have a mild modulating effect on risk predictions (Ardenfors et al. 2014), much lower than uncertainties associated with risk coefficients. The routine employment of CBCT could however represent a source of higher radiation burden for in-field organs.

Nevertheless, good radiation hygiene is recommended both for photon and proton treatments. While in-treatment imaging's critical role for the success of the treatment is the main justification for its use, protocol optimisation is recommended for all imaging modalities, with priority given to the use of low-dose modalities or protocols. Given the large variation of imaging approaches and frequencies employed, an individual accounting of all the imaging sessions is recommended. In addition, inter-centre cooperation on imaging protocols and practices is warranted. The European Particle Therapy Network (EPTN) works towards this purpose by enhancing harmonisation through sharing practice parameters and guidelines based on expert opinions and formal consensus between the European centres (Bolsi et al. 2018), such that these activities are expected to benefit photon treatments as well.

4.2.3 Secondary doses for patients

Determination of the dose delivered to the treatment target and in-field organs is rather accurately carried out by the algorithms of the TPS. However, below approximately 5% of the prescription dose, the calculation accuracy of the TPS algorithms decreases (Howell et al. 2010), and organ doses are due to secondary particles produced by the interaction of the treatment beam with the elements of the delivery system and the patient. In the case of photon RT, the secondary particles are scattered photons and neutrons produced through nuclear interactions (the latter when energies above approximately 10 MV are used for treatment). In the case of particle therapy, nuclear interactions could lead to the generation of photons, neutrons and even nuclear fragments that can deposit doses far from the interaction site or the treatment target. Dose determination for out-of-field organs is, however, challenging due to the limited availability of calculation methods on the one hand and the unavailability of whole-body CT scans for out-of-field organ identification on the other hand.

Within SINFONIA, novel methods to individualise out-of-field dose determinations from photon and proton treatments have been implemented. For photon treatments, a two-step framework for dose determination has been developed. Thus, the first step concerns the image registration of the planning CT with the ICRP110 computational phantom for the generation of a synthetic patient-specific whole-body CT using a dedicated software, IS2aR (Muñoz et al. 2022). In the second step, the synthetic CT is used together with dedicated Periphocal software (Sánchez-Nieto et al. 2022) for the evaluation of peripheral photon doses from the number of monitor units, the prescription dose and the mean field size of the treatment plan. No additional doses were considered, as the photon treatments employed low energy photons for which neutron production is negligible. This is the most comprehensive approach for out-of-field dose determination in photon therapy. The approach for treatments with proton beam scanning has several similarities. Thus, the first step was the generation of a synthetic patient-specific whole-body CT from the planning CT by using the dedicated software, IS2aR. Neutron doses were subsequently estimated at voxel level with MC simulations of the individual treatment plans or using a newly developed three-Gaussian analytical model (Romero-Exposito et al 2024b).

The results indicate that scattered doses from photon treatments to out-of-field organs may be significant, and therefore accounting for these doses is warranted. Thus, scattered doses up to 3 or 4 Gy could be found for distant organs from treatments employing typical fractionations for which the TPS predicted less than 1 Gy. For scanned beam proton treatments to the brain, neutron doses on the level of 1.5–2 mSv/Gy to target were found for near-field organs, decreasing to 2–100 µSv/Gy for more distant organs. It is important to notice that lower levels of neutron doses have been determined from proton treatments rather than corresponding scattered doses from photon treatment. These findings indicate the general benefit of modern proton delivery techniques and the low absolute contribution of neutrons, in contrast to historically used passive scattering techniques (Romero-Expósito et al. 2022). In addition, analytical models could be used as an alternative to resource-demanding MC approaches, the dosimetric accuracy provided being better than 20–30% for distant organs and thus

comparable to the dosimetric accuracy available for imaging doses of comparable magnitude.

4.2.4 Staff, comforters, and general public perspective

Doses to staff, comforters and the general public in conventional RT departments are well known, as are the regulations put in practice around these facilities. The resulting doses are low and indeed, in many such departments, personnel categorisation has been removed, as staff doses were consistently below the lower threshold for occupational exposure. Furthermore, strict regulations govern the shielding of treatment bunkers and prohibit the presence of caregivers in treatment rooms. Therefore, conventional RT activities lead to very low doses to the staff, caregivers and the general public.

Nevertheless, neutron doses have traditionally represented a concern within proton therapy facilities. Within SINFONIA, a survey was conducted on the current doses and practices in European proton therapy centres. The results of the survey showed that no elevated staff doses were recorded in particle therapy centres with modern radiation delivery techniques, even when accounting for neutron doses. A possible overprotection of the pregnant staff has been suggested as several countries prohibit pregnant personnel from working with ionising radiation irrespective of the doses. This is, however, governed by the corresponding national legislation of the concerned centres.

Dedicated neutron dose measurements have shown that the total neutron exposure of a person staying at a position perpendicular to the beam axis at a distance greater than 2 m from the isocentre remains well below the dose limit of 1 mSv per year for the general public (Mares et al. 2022). Nevertheless, current radiation protection protocols prohibit the occupancy of the treatment room during beam delivery. In addition, immobilisation requirements imply the use of general anaesthesia for very young patients which further removes the need for caregivers present in the room during proton treatments.

Similarly, external shielding of photon and proton facilities is governed by strict protocols designed for the protection of the general public. In addition, the creation and release of radioactive isotopes from proton therapy facilities is negligible, further strengthening the situation.

It can therefore be concluded that normal RT practices do not imply important risks for the staff, caregivers or the general public. Nevertheless, one has to consider the impact of accidental irradiations which can be mitigated through good working practices.

4.2.5 Environmental perspective

The creation and release of radioactive isotopes from RT facilities in general and proton therapy facilities in particular is negligible, and therefore radiation protection perspectives for the environment are less of an issue.

More general environmental perspectives related to energy production and consumption for RT procedures have however been outside the scope of the SINFONIA project. These could however be included in an overarching socioeconomic benefit analysis of RT as a medical procedure. Recommendations and implications could be derived from a broader perspective, also depending on reimbursement characteristics in various healthcare systems.

4.3 FUTURE DIRECTIONS

Dose determinations according to the SINFONIA approaches have posed some challenges which will have to be addressed in future studies. Thus, the analytical model developed for predicting out-of-field doses from proton treatments will have to be validated on a larger population of patients with various field numbers and sizes. More importantly, it will have to be validated on a group of patients different from those from which it has been derived. AI developments in imaging dose determination may also improve the evaluation of doses from imaging procedures during RT, which will improve the determination of total doses and consequently the total risk associated with RT, especially in young patients with a high life expectancy. Last, but not least, variations of the relative biological effectiveness of protons in near-field organs, a direction that has received increased attention in proton therapy in recent years, should also be taken into account.

Adding the doses corresponding to the different imaging modalities associated with both the treatment and the diagnosis, the follow-up of cancer is also a major challenge in RT. This requires the use of segmentation and automated image registration, and the establishment of a model that allows the doses to be summed for each organ, to correctly assess the associated risk.
Assessing the potential for positioning and verification of treatment or simulation of other techniques that do not include the use of radiation (ultrasound, magnetic resonance imaging, optical surface guidance), may reduce patient doses and in some cases even improve the quality of the delivered treatment. From this perspective, it is important to generate guidelines that recommend the best imaging technique to be used in each case to ensure that the prescribed dose is delivered to the patient and maximise the chances that the patient will live for many years after the treatment.

5. PRODUCTION OF RADIONUCLIDES

Highlights

- It is recommended that all actors in the supply chain of radionuclides for medical applications should be aware of the importance and specific characteristics of radioisotopes to allow a smooth delivery of these life-saving products.
- It is recommended to establish new standards for the safe handling of new radionuclides and their novel applications, in particular in clinical trials, based on the well-functioning practices of established radionuclides.
- It is recommended to give additional consideration to the dosimetry and safety aspects of alpha-emitters, as these radionuclides are challenging from the perspective of radioactivity and dose assessment because of their complex decay schemes.

5.1 CURRENT PRACTICE

Practically all radionuclides for medical use are artificially produced using man-made devices, i.e. nuclear reactors and accelerators of charged particles. ^{131}I was used to diagnose and treat multiple thyroid disorders as early as the 1940s (Hertz 2019). Radioiodines are perhaps the first and a classic example of theranostic agents because ^{123}I can be used as a SPECT agent and Auger electron emitter therapy agent, ^{124}I is a PET radionuclide, ^{125}I also has therapeutic properties, and ^{131}I is widely used for both SPECT imaging and β-particle emitter therapy. The first use of beta-radiation emitter radiometal ^{89}Sr in the treatment of metastatic bone cancer was reported in 1942 (Pecher 1942). Since then, several radionuclides have been administered to patients in the form of medicinal products named radiopharmaceuticals, and NM is the medical speciality utilising them in various diagnoses and treatments (Cutler et al. 2013, Mikolajczak et al. 2019).

The potential usefulness of radionuclides for medical applications is determined by their nature (Cieszykowska et al. 2023). In diagnostic applications, the emitted radiation is expected to leave the human body. It is then detected and converted into an image that demonstrates the localisation of radioactivity in the diagnosed organism. Diagnostic radionuclides are characterised by gamma or positron emission, with a high enough energy to penetrate the body and to be detected externally by a camera and with no accompanying emission of particle (α or β^-) radiation. Gamma-emitting radionuclides such as ^{99}mTc are used for diagnostic imaging by SPECT. Radioisotopes that emit positrons are useful for imaging using PET. ^{68}Ga is an example of a positron emitter that has played an important role in the development of novel PET tracers over the past two decades. ^{166}Ho, ^{177}Lu, ^{186}Re, ^{188}Re, and ^{153}Sm are some of the most frequently used neutron-activated radionuclides well-established in clinical practice and undergoing clinical research for theranostic applications.

In therapy, the emitted corpuscular radiation (α, β^- or Auger electrons) is absorbed in the targeted tissue thus leading to its damage while sparing the adjacent tissues and organs. The action of radiation into the matter can be modulated by the linear energy transfer (LET) – the amount of energy that an ionising particle transfers to the tissue per unit distance (keV/µm). Since the emitting particles vary in penetrating range and LET, the choice of radionuclide will depend on several factors, such as the type and size of the targeted disease, the density of the target, and its heterogeneity. Alpha emitters characterised by high LET values deliver very high energy in a very small volume and are therefore particularly useful in the case of micro-metastases and blood-borne cancer cells (Eychenne et al. 2021).

At present, β^- emitters play a dominant role in targeted therapy due to their well-known production methods and thus great availability (Quaim 2019). The value of LET for β^- emitters is lower than for β emitters. Its penetration range in soft tissue is between a few micrometres to a few centimetres, proportionally to the energy of the particle. Thus, low to medium-energy β^- particle-emitting radionuclides e.g., ^{177}Lu, are considered more effective for treating small tumours, while high energy β^- particle-emitting radionuclides, e.g., ^{90}Y are more appropriate for the treatment of larger tumours (de Jong 2005). Some β-emitting radionuclides

also decay with γ-radiation, which allows the ability to visualise the radiopharmaceutical distribution within the patient's body using SPECT (e.g., ^{177}Lu). Physical characteristics of radiometals for molecular imaging and therapy, production methods, and medical application are presented in Table 1.

5.2 RECOMMENDATIONS AND CHALLENGES

The requirements for the safe production of radionuclides for medical applications, whether in nuclear reactors, accelerators of charged particles, or obtained from the radionuclide generators, are regulated by Directive 2013/59/Euratom (available online at https://eur-lex.europa.eu/eli/dir/2013/59/oj), which details basic safety standards for protection against the dangers arising from exposure to ionising radiation. On top of that, when the radionuclide is incorporated into the radiopharmaceutical with the aim to be administered to the patient for either diagnostic or therapeutic use, its production should also comply with the pharmaceutical regulations according to Directive 2001/83/EC (available online at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32001L0083:EN:HTML). Meeting both these regulatory requirements creates a challenge in everyday practices in radionuclide production and radiopharmaceutical preparation, in particularly in healthcare establishments (Lange et al. 2015). Although there are well-functioning practices, the new radionuclides and their novel applications, in particular in clinical trials, generate a continuous need for establishing standards for their safe handling.

Other challenges are related to the physical characteristics of the radionuclide. The emitters of Auger electrons are difficult to measure because of their very short range in matter. Several β-emitting radionuclides also decay with γ-radiation. This associated γ-radiation could be advantageous if the energy and intensity are within the diagnostic range, as it provides the ability to visualise the distribution of the radiopharmaceutical within the patient's body using gamma scintigraphy methods. However, this γ-radiation creates a burden for workers and caregivers and needs to be considered in the general dose assessment. Among positron emitters, ^{89}Zr with a long half-life of 78.4 h is advantageous in radiopharmaceuticals based on antibodies. On the other hand, it emits a high abundance of 909 keV γ-radiation (Sarcan et al. 2021).

Commonly used positron emitters such as ^{18}F and ^{68}Ga are well suited for diagnostic imaging but due to the relatively short half-lives cannot be used for the dosimetry assessment in patients. The need for appropriate dosimetry calculation in the diagnostic application stimulated the development of positron emitters with longer half-lives such as ^{44}Sc, also in combination with its matched pair ^{47}Sc (Huclier-Markai et al. 2018). Other matched pairs of interest are ^{64}Cu and ^{67}Cu or the terbium isotopes ^{149}Tb, ^{152}Tb, ^{155}Tb and ^{161}Tb, even possibly combining SPECT, PET, beta and alpha therapy. Most of these emerging radionuclides require special production techniques such as high energies and highly specialised infrastructure. Among all existing radionuclides, only a few are of interest for therapeutic applications and more specifically for targeted alpha therapy (TAT). From this selection, ^{225}Ac, ^{211}At, ^{212}Bi, ^{213}Bi, ^{212}Pb, ^{223}Ra and ^{227}Th are considered the most suitable. Alpha emitters, despite the very promising outcomes of therapies, are challenging from the perspective of radioactivity and dose assessment because of their complex decay schemes. In particular, ^{225}Ac with a 9.9 d half-life gains interest. Its disintegration follows a six-step decay chain to reach stable nuclei of ^{209}Bi, which generates multiple alpha particles that contribute to increasing the potential cytotoxicity in comparison with other α emitters. Besides, with the γ emission of some of its daughter nuclides such as ^{221}Fr or ^{213}Bi, it provides the possibility for tracing after injection. Nevertheless, it must be mentioned that these radiations make reaction monitoring difficult, and the secular equilibrium has to be reached before one can measure a reliable radiochemical yield (at least 6 h) (Eychenne et al. 2021). Another example, ^{149}Tb, decays to several radio lanthanides by emission of low-energy α (3.97 MeV, 17%), electron capture (76%), and β^+-particle emission (730 keV, 7%), making it interesting for TAT and a possible follow-up by PET. It must be mentioned that the potential radiotoxicity of the daughter isotopes (long half-life) generated is still to be determined.

5.3 FUTURE DIRECTIONS

In the scenarios concerning the future of radionuclides in theranostic applications, PET remains an important diagnostic tool in molecular imaging and a mainstay of research, preclinical, and translational imaging applications. Particularly the interest is in ^{68}Ga, not only because of its availability from generators or cyclotrons but also because of the growing availability of other positron emitters (Notni and Wester, 2018). RT will continue to rely on radiometals. There is still growing interest in beta-radiation emitters for therapy and ^{177}Lu became a strategic radionuclide due to its relatively wide access to the irradiation sites because of the high neutron capture cross sections and the choice of production methods (Dash et al. 2015). The potential of scandium radionuclides, although demonstrated in several successful preclinical and clinical studies, has yet to be translated into practical application. The situation may change in the future with the progress in optimised production techniques and new ligand development. Copper radionuclides are very attractive because of their chemical and physical properties (Mou et al. 2022).

There is more evidence of the therapeutic efficacy of alpha emitters. Not only ^{223}Ra is of interest but also ^{212}Pb, ^{213}Bi, ^{225}Ac and Tb (^{161}Tb, ^{149}Tb) radionuclides, although these are less available. One should also mention new developments in scanners for SPECT and PET, hybrid technologies, whole-body PET, etc., which will create demand for novel radioisotopes for medical use. In addition, the role of AI in support of NM and radiology is growing, making nuclear techniques very attractive (Jha et al. 2021). It is worth emphasising that medical radioisotopes play a vital role in diagnosing cancer, cardiac conditions and other diseases, and are increasingly used for cancer treatments (See the recent European Council conclusions on the security of supply of radioisotopes for medical use – EC 2024).

TABLE 1: Physical characteristics of radiometals for molecular imaging and therapy, production methods and medical application

Radionuclide	T1/2	E [keV] particle/photons per 100 decay	Production method	Medical application
^{43}Sc	3.9 h	β^+ 1199 (70.9), 826 (17.2); γ 511 (176.2), 372 (22.5)	^{40}Ca(α,p)^{43}Sc ^{42}Ca(d,n)^{43}Sc ^{46}Ti(p,α)^{43}Sc ^{43}Ca(p,n)^{43}Sc	PET
^{44}Sc	3.97 h	β^+ 1474 (94.3); γ 511 (188), 1157 (99.8)	^{44}Ti → ^{44}Sc generator ^{nat}Ca(p,n)^{44}Sc	PET
^{47}Sc	3.35 d	β^- 441 (68.5), 601 (31.5); γ 159 (68.1)	^{47}Ti(n,p)^{47}Sc ^{46}Ca(n,γ)^{47}Ca → ^{47}Sc	Therapy
^{52}Mn	5.59 d	β^+ 575 (29.4); γ 511 (58.8), 744 (90.0), 935 (94.5), 1434(100)	^{52}Cr(p,n)^{52}Mn	PET
^{55}Co	17.5 h	β^+ 2535 (46), 2059 (25.6); γ 477 (26.9), 511 (151.8), 931 (100), 1408 (22.5)	58Ni(p,α)55Co	PET
^{61}Cu	3.4 h	β^+ 1215 (61.4); γ 282.9 (12.2), 511 (123.8), 656 (10.8)	^{61}Ni(p,n)^{61}Cu	PET
^{64}Cu	12.7 h	β^+ 653 (17.5); β^- 579 (38.5); γ 511 (35.0)	^{64}Ni(p,n)^{64}Cu ^{68}Zn(p,α)^{64}Cu	PET
^{67}Cu	2.7 d	β^- 562 (20), 468 (22), 377 (57); γ 93 (16.1), 185 (48.7)	^{67}Zn(n,p)^{67}Cu ^{64}Ni(α,p)^{67}Cu ^{70}Zn(p,α)^{67}Cu ^{68}Zn(γ,p)^{67}Cu	Therapy

Radionuclide	T1/2	E [keV] particle/photons per 100 decay	Production method	Medical application
^{68}Ga	67.8 m	β^+ 1899 (87.7); γ 511 (177.8), 1077 (3.2)	^{68}Ge → ^{68}Ga generator ^{68}Zn(p,n)^{68}Ga	PET
^{86}Y	14.7 h	β^+ 1545 (5.6), 1221 (11.9); γ 511 (63.8),1076 (82.5), 1153 (30.5), 1921 (20.8)	^{86}Sr(p,n)^{86}Y ^{67}Zn(p,n)^{86}Y	PET
^{90}Y	2.7 d	β^- 2280 (100%);	^{235}U(n,f)^{90}Sr → ^{90}Y ^{89}Y(n,γ)^{90}Y	Therapy
^{89}Zr	78.4 h	β^+, 902 (22.8); γ 511 (45.4), 909 (99)	^{89}Y(p,n)^{89}Zr	PET
^{99}Mo	2.75 d	β^- 436 (16.4), 1214 (82.2) γ 739.5 (12.3),	^{235}U(n,f)^{99}Mo ^{98}Mo(n,γ)^{99}Mo	
^{99m}Tc	6.01 h	γ 140.5 (88.5)	^{99}Mo → ^{99}mTc generator	SPECT
^{111}In	2.8 d	γ 17.3 (90.6), 245.4 (94.1)	^{111}Cd(p,n)^{111}In ^{112}Cd(p,2n)^{111}In	SPECT, Therapy Auger
^{117m}Sn	13.6 d	γ 156 (86.4)	^{nat}In(α,xn)^{117m}Sn ^{nat}Cd(α,xn)^{117m}Sn	Therapy Auger
^{132}La	4.8 h	β^+ 3203 (14), 2636 (11); γ 464.5 (76), 511 (84.2),	^{nat}Ba(p,xn)$^{132/135}$La	PET
^{135}La	19.5 h	γ 480.5 (1.5),	^{nat}Ba(p,xn)$^{132/135}$La	Therapy Auger
^{153}Sm	1.93 d	β^- 641 (31.3), 694 (49.4); γ 103 (29.2)	^{152}Sm(n,γ)^{153}Sm	Therapy
^{149}Tb	4.12 h	α 3967 (16.7); β^+ 1409 (4.6); γ 165 (31.6), 352 (35.3), 389 (22.0), 511 (9.2), 652 (19.5), 853 (18.6) [^{149}Gd, ^{149}Em, ^{149}Sm, ^{145}Nd][a]	^{181}Ta(p,spallation)^{149}Tb	Therapy
^{152}Tb	17.5 h	β^+ 2968 (8.0), 2624 (5.9); γ 344 (63.5), 511 (40.6)	^{181}Ta(p, spallation)^{152}Tb	PET
^{155}Tb	5.32 d	γ 87 (32.0), 105 (25.1)	^{155}Gd(p,n)^{155}Tb ^{nat}Gd(p,xn)^{155}Tb ^{nat}Gd(d,xn)^{155}Tb ^{155}Dy decay	SPECT
^{161}Tb	6.89 d	β^- 460 (25.7), 522 (65.0); γ 26 (23.2), 49 (17.0), 75 (10.2)	^{160}Gd(n,γ)^{161}Gd → ^{161}Tb	Therapy
^{166}Ho	26.8 h	β^- 1773 (49.9), 1855 (48.8); γ 81 (6.6)	^{nat}Dy(n,γ)^{166}Dy → ^{166}Ho ^{165}Ho(n,γ)^{166}Ho	Therapy
^{169}Er	9.4d	β^- 343 (45), 351 (55);	^{168}Er(n,γ)^{169}Er	Therapy
^{177}Lu	6.65 d	β^- 177 (11.6), 498 (79.3); γ 113 (6.2), 208 (10.4)	^{176}Lu(n,γ)^{177}Lu ^{176}Yb(n,γ)177Yb → ^{177}Lu	Therapy

Radionuclide	T1/2	E [keV] particle/photons per 100 decay	Production method	Medical application
^{186}Re	3.72d	β^- 932 (21.5), 1069 (70.9); γ 137 (9.4)	^{185}Re(n,γ)^{186}Re ^{186}W(p,n)^{186}Re ^{186}W(d,2n)^{186}Re	Therapy
^{188}Re	17.0 h	β^- 965 (25.6), 2120 (71.1); γ 155 (15.2)	^{187}Re(n,γ)^{188}Re ^{187}W(n,γ)^{188}W → ^{188}Re generator	Therapy
^{212}Pb	10.6 h	β^- 590 (11.9), 335 (83.1); γ 238.6 (43.6) [^{212}Bi, ^{212}Po, ^{208}Tl][a]	^{228}Th decay	Therapy
^{213}Bi	45.6 m	α 5869 (1.9); β^- 983 (30.8), 1423 (66.2); γ 440.4 (26.1) [^{213}Po, ^{209}Tl, ^{209}Pb][a]	^{209}Bi(α,2n)^{213}Bi ^{225}Ac → ^{213}Bi generator	Therapy
^{223}Ra	11.4 d	α 5607 (25.8), 5716 (49.6), 5747 (10.0); γ 154 (5.8), 269 (14.2) [^{219}Rn, ^{215}Po, ^{215}At, ^{211}Pb, ^{211}Bi, ^{211}Po, ^{207}Tl][a]	^{235}U(n,f)^{223}Ra ^{226}Ra(n,γ)^{227}Ra → ^{223}Ra ^{227}Ac → ^{223}Ra	Therapy
^{225}Ac	10.0 d	α 5793 (18.9), 5830 (52.4); γ 99 (1.1) [^{221}Fr, ^{221}Ra, ^{217}At, ^{217}Rn, ^{213}Bi, ^{213}Po, ^{209}Tl, ^{209}Pb][a]	^{226}Ra(p,2n)^{225}Ac ^{233}U → ^{229}Th → ^{225}Ac ^{232}Th(p,spallation)^{225}Ac	Therapy
^{227}Th	18.7 d	α 6038 (24.2), 5978 (23.5), 5757 (20.4); γ 236 (12.9), 256 (7) [^{223}Ra, ^{219}Rn, ^{215}Po, ^{211}Pb, ^{211}Bi, ^{211}Po, ^{207}Tl][a]	^{227}Ac decay	Therapy

[a] – Decay chain of main radionuclide

6. HEALTH HAZARDS OF MEDICAL RADIATION EXPOSURE

Highlights

- Risk assessment in cancer patients and patients suspected of cancer could be performed with the same risk parameters, as peripheral blood mononuclear cells of second malignant neoplasms patients do not demonstrate an enhanced in vitro radiation sensitivity compared to patients with primary cancers.
- Although the inter-donor variability is weakly higher than the intra-donor variability in terms of in vitro radiation-induced responses of peripheral blood mononuclear cells, this is more of an effect of the potential of the assays to reflect intrinsic radiosensitivity than an indication of varying levels of intrinsic radiosensitivity.

Exposure of healthy cells and tissues to ionising radiation causes damage to the subcellular structures that in turn may lead to side effects. The type and severity of the side effects depend on several factors, including the part of the body being irradiated, the radiation dose it receives, the radiosensitivity of the irradiated tissues to radiation, the use of modifiers of response and others. In addition, the effects may manifest at different time intervals following the irradiation. Thus, one distinguishes between acute effects appearing during or a relatively short time after irradiation, and the late effects appearing several months or years after irradiation. Another distinction is made between the non-stochastic effects whose severity increases with the radiation dose and stochastic effects that have the same severity, but whose likelihood increases with the radiation dose. Functional failure of irradiated organs and tissues usually falls in the former category, while the induction of cancers and hereditary effects are included in the latter.

Non-stochastic effects have thresholds for their appearance. This is relevant mainly for therapeutic irradiation, but also a few dose-intensive diagnostic procedures. In contrast, stochastic effects are relevant for all types of medical irradiations since they do not have a threshold for appearance and their severity is independent of the radiation dose.

Although the radiation dose to normal tissue is the major determinant of side effects of RT, patient-related factors may modulate the risk of both tissue effects and cancer. The factors can be divided into non-modifiable and modifiable ones. The former include age, sex and genetic predisposition. The latter include behavioural components. Concerning age and tissue effects, children are generally more sensitive than adults. The relationship between age, exposure and cancer strongly depends on the type of cancer.

A high sensitivity is seen for leukaemia, brain, skin and thyroid cancer (UNSCEAR 2013). The sensitivity to breast cancer peaks around the age of puberty, with an inversed correlation between the sensitivity and age at menarche (Brenner et al. 2018). For all other cancers, no clear relationship exists between age at exposure and sensitivity. For tissue effects, no clear difference exists between males and females, while females show a higher sensitivity than males for radiation-induced solid cancer (Grant et al. 2017). A genetic predisposition to radiation-induced cancer exists among a few hereditary conditions such as ataxia telangiectasia or Nijmegen breakage syndrome (Pollard and Gatti 2009). Patients suffering from these diseases lack genes that are essential for the proper repair of DNA damage (Guleria and Chandna 2016).

However, these monogenic syndromes are rare, affect only a small proportion of the general population (Rothblum-Oviatt et al. 2016) and the affected people can be readily identified by their phenotype. The much more common heterozygote carriers of the gene defects exhibit normal radiosensitivity (Bremer et al. 2003). A large number of studies have been carried out to identify biomarkers that allow the identification of people developing RT-induced tissue toxicities, but the results were disappointing (Rajaraman et al. 2018, Applegate et al. 2020). Concerning cancer predisposition, studies suggest an increased in vitro response of normal cells to radiation among cancer patients (Scott et al. 1996, Kryscio et al. 2001) but the response is characterised by low specificity and sensitivity making it unsuitable for individual patients. Also, negative results exist (Tawn et al 2005).

Patient behaviour can modify the risk of both RT-induced tissue toxicities and cancer. A known factor that reduces the risk of toxicities in the mouth cavity such as mucositis and radioosteonecrosis is mouth hygiene (Wang and Tepper 2021). It can be expected that good body hygiene will also reduce the toxicities of the skin. Other risk factors include obesity (Dandapani et al. 2015), smoking and alcohol abuse (Peppone et al. 2011, Pratson et al. 2021). For radiation-induced cancer, smoking is the only documented behavioural factor that potentiates the risk of lung cancer both in combination with radon (Darby et al. 2005) and gamma radiation (Cahoon et al. 2017). It is, however, generally assumed that radiation interacts with other carcinogens in a multiplicative manner. Apart from smoking, strong carcinogens include obesity, sunlight and infectious agents (Golemis et al. 2018). It can be expected that a reduction in exposure to these carcinogens will also reduce the risk of radiogenic cancer.

Apart from modifiable risk factors, it is not known if and to what extent patients who are treated by RT for primary cancers differ with respect to the intrinsic (i.e., genetically determined) risk of developing cancers induced by RT, referred to as second malignant neoplasms (SMN).

Within SINFONIA, we have collected peripheral blood samples from patients treated with RT for primary cancers (brain, lymphoma and breast) and from patients who developed SMN. Blood was collected before RT and at one or two time points after RT. Peripheral blood mononuclear cells (PBMC) were isolated and analysed for RT-induced levels of stable chromosomal aberrations (translocations), micronuclei (representing unstable chromosomal aberrations) and gamma H2AX foci (representing DNA repair). PBMC analysed for micronuclei and gamma H2AX foci were also irradiated under in vitro conditions to measure intrinsic radiosensitivity. In vivo and in vitro responses of PBMC to radiation are known to show a high level of intraindividual variability (Vral et al. 2004), but it is not known if the interindividual variability is higher than the intraindividual variability. An affirmative result would suggest the existence of differences in the intrinsic radiosensitivity of PBMC. Multiple blood collections per patient allowed to compare the levels of inter-, and intraindividual variability of patients with primary cancers treated by RT. The results from analysing blood samples from 200 patients with primary cancers and 100 patients with SMN demonstrate that SMN patients do not show an enhanced in vitro radiation sensitivity that could be used as a biomarker of SMN susceptibility. The inter-donor variability in the levels of in vitro radiation-induced micronuclei and repair kinetics of gamma H2AX foci is weakly higher than intra-donor variability reflecting the potential of the assays to reflect intrinsic radiosensitivity. However, in view of the response variability, multiple analyses of a single patient are needed to determine the level of intrinsic radiosensitivity. Moreover, we observed a correlation between the level of chromosomal damage (translocations and micronuclei) and both the tumour dose and volume of tissue receiving >2 Gy, indicating that these endpoints can detect differences in characteristics of RT.

7.
RISK APPRAISAL

Highlights

- To have an accurate risk assessment from medical procedures involving ionising radiation, it is recommended to include all dose contributors during the course of the medical investigation and treatment.
- To maintain risks from medical procedures to a low level, it is recommended to continuously optimise medical procedures while maintaining their diagnostic and therapeutic value.

7.1 CURRENT PRACTICE

Current practices in radiogenic risk appraisal primarily rely on risk coefficients developed by authoritative bodies such as the Biological Effects of Ionizing Radiation (BEIR) Committee and the ICRP. The BEIR VII report provides risk estimates for cancer incidence and mortality due to low-dose ionising radiation exposure (BEIR 2006). It adopts a linear no-threshold (LNT) model, which assumes that any amount of radiation exposure carries a risk of causing cancer and that this risk increases linearly with the dose. The ICRP also provides guidelines and coefficients for estimating the risk from exposure to ionising radiation, with an emphasis on both cancer and hereditary effects (ICRP 2007).

Risk estimation tools, such as those based on BEIR VII and ICRP coefficients, are used to calculate the expected increase in the incidence of cancer following radiation exposure. These tools consider factors such as age and gender. Such calculations are crucial for making informed decisions about the medical necessity of imaging procedures, especially in cases involving repeated exposures or sensitive populations like pregnant patients and children.

7.2 RECOMMENDATIONS AND CHALLENGES

Major challenges in radiogenic risk appraisal include the lack of information about the inherent uncertainty in risk estimates as well as the lack of relevant computational tools. The uncertainties stem from several sources, including variability in individual sensitivity to radiation, differences in life expectancy, and statistical limitations of epidemiological studies used to derive risk coefficients. The LNT model itself is a subject of debate, as it extrapolates cancer risks from higher to lower doses, potentially overestimating risks at very low doses. SINFONIA analysed uncertainties in risk estimates. Moreover, a modular radiogenic risk assessment tool has been developed to estimate the risk associated with medical radiation imaging and RT. In this respect, the determination of the total dose to affected organs from RT procedures and associated imaging as developed in the SINFONIA project provides a significant improvement for risk determination.

7.3 FUTURE DIRECTIONS

Future directions in radiogenic risk appraisal include refining risk models to better account for individual susceptibilities and low-dose exposure effects. Research into genetic markers and other biomarkers of radiation sensitivity could lead to more personalised risk assessments. Advancements in imaging technology that reduce radiation doses and improve image quality will also play a critical role in managing radiogenic risks. Finally, there is a pressing need to improve the estimation of uncertainties in risk appraisal. Developing models that provide not just point estimates but also confidence intervals around these estimates can enhance the decision-making process by clearly communicating the range of potential outcomes to clinicians and patients alike.

8. EDUCATION AND TRAINING ON DOSE AND RISK ASSESSMENT

Highlights

- It is recommended that professionals employing ionising radiation for medical procedures have regular education on the most relevant approaches for dose determination and risk estimation, as well as on communication of risks to the patients and the general public.
- It is recommended that educational efforts should also be made towards the patients and the general public on the benefits and risks of medical radiation to enable their informed participation in healthcare decisions or to remove unnecessary anxiety.

8.1 CURRENT PRACTICE

Current educational practices for dose and risk assessment are integrated into the curricula of various medical disciplines, including diagnostic radiology, NM, interventional radiology, radiation therapy and medical physics (EC 2014, EC 2015). Training typically covers the fundamental physics of radiation, radiation biology, and radiation safety principles (ICRP 2009). A significant focus is placed on the practical aspects of dose measurement, dose optimisation techniques, and the interpretation of dose values in a clinical context (IAEA 2013).

Medical professionals are also educated on regulatory requirements and guidelines set by bodies such as the ICRP and national regulatory agencies. This includes training on dose limits, patient consent processes, and the maintenance of dose records.

8.2 RECOMMENDATIONS AND CHALLENGES

Recommendations for enhancing education and training in dose and risk assessment emphasise the need for continuous professional development and certification. Given the rapid evolution of imaging technologies and techniques, ongoing training is crucial. This ensures that healthcare providers remain current with the latest dose reduction strategies and risk assessment methodologies. SINFONIA has organised sustainable, high-level multi-disciplinary training in the field of patient and staff radiation dosimetry, radiobiology/radiation sensitivity, radiation risk evaluation and radiation protection applicable to medical imaging and radiation oncology. Moreover, SINFONIA has created an interactive and multidisciplinary MOOC (Massive Open Online Course) on dosimetry, radiobiology and radiation protection.

One of the primary challenges in education and training is ensuring uniformity and consistency across different institutions and geographic regions. There can be significant variation in how training programmes are implemented, which can affect the competence of professionals in performing risk assessments and managing patient doses effectively. Another challenge is the integration of advanced risk communication skills in training programmes. Healthcare providers must not only understand the risks associated with radiation exposure but also effectively communicate these risks to patients to help them make informed decisions. Additionally, there is often a gap between the knowledge gained through formal education and its practical application in clinical environments. Bridging this gap requires not only theoretical knowledge but also practical skills in dose management and patient safety protocols, which can be difficult to standardise across diverse clinical settings.

8.3 FUTURE DIRECTIONS

Looking forward, there is a push towards more integrated and interactive educational tools such as virtual reality and augmented reality to enhance understanding and retention of complex concepts related to dose and risk assessment. These technologies offer immersive learning experiences that can simulate real-world scenarios and allow for practice without the risk of exposing patients to radiation. There is also a growing emphasis on interdisciplinary training programmes that involve not just radiologists but also referring physicians, medical physicists, and other professionals. This approach fosters a more comprehensive understanding of dose optimisation and risk management across different specialities, promoting a culture of safety in the use of medical imaging. Moreover, as personalised medicine continues to evolve, there is an increasing need for training programmes to include education on personalised dose management and risk assessment based on individual patient characteristics. SINFONIA's efforts to organise a course on personalised dosimetry and quantitative radiation risk assessment are important steps in this direction.

9. SUSTAINABILITY PERSPECTIVES

Sustainability in the maintenance and updating of SINFONIA's data and tools is crucial for extending the impact and utility of scientific findings well beyond the initial funding period. By continuously updating and maintaining these resources, researchers and practitioners can build upon prior work without the need to start from scratch.

The SINFONIA project has established a central repository for data and resources developed throughout its duration. This repository is essential for the project's long-term sustainability, as it ensures that the accumulated knowledge and tools are preserved and can be further enriched by subsequent research initiatives. The repository's design facilitates easy access and user-friendly interfaces, making it an invaluable resource for researchers involved in radiogenic risk assessment and related fields.
To further solidify the future of the SINFONIA results, there are ongoing discussions with the EUCAIM EC project to explore avenues for collaboration. Collaboration with EUCAIM could lead to several beneficial outcomes. First, it would ensure the continuity and expansion of SINFONIA's mission by embedding its data and tools within a larger network of scientific resources, thereby increasing its accessibility and impact. Second, it would provide a framework for updating and expanding the repository's contents with new data and insights from subsequent studies. Finally, this integration would foster a more collaborative environment in which researchers can contribute to and benefit from a collective pool of knowledge, enhancing the quality and efficacy of radiogenic risk research.

An important element in SINFONIA's strategy for sustained impact is the maintenance of its web-based tools. Post-project, the iDose tool developed by the University of Crete research group will be hosted on the University's servers, which ensures that this valuable tool remains accessible to researchers and health professionals globally. Hosting iDose at the University of Crete not only secures a stable and reliable digital environment but also benefits from the university's commitment to academic excellence and technological advancement.

Additionally, the context-aware training module will remain available for interested researchers and health professionals to further evaluate the applicability of this technology in the fields of radiation protection and radiation dose management.

10. CONCLUSIONS

The SINFONIA project has made great strides in dose determination and risk estimation for patients suspected or treated for cancer. Thus, AI tools have been developed for individual dose determinations from imaging procedures in DR and NM. Significant advances have also been made concerning low dose determinations from RT applications, including imaging procedures and the summation of the dose contributions. These developments have brought better understanding of the magnitude of doses and risks as well as the potential of novel approaches for individualisation of dose and risk determinations. Important learnings have been made with respect to the need for education of the professionals employing ionising radiation in procedures on dose determination and risk estimation as well as communication of risks to the patients and the general public. The work carried out within the project has also highlighted the need for interaction within the EU on diagnostic and therapy procedures that could be recommended to patients in an optimised and individualised manner.

The results have also suggested an important distinction in the necessary approaches for various categories of patients. Thus, for patients suspected of a serious diagnosis of cancer, good radiation protection practices are essential to ensure that doses from diagnostic imaging are kept as low as reasonably achievable while maintaining the quality of the diagnostic images and that individual imaging protocols and dose determinations are needed to minimise the risk from these procedures. However, for patients with a confirmed diagnosis, it is important to prioritise the delivery of the therapeutic dose to the target to ensure the long-term survival of the patient. Individual dose and risk assessments will have a secondary purpose to ensure that the risks from the treatment procedures are kept at a reasonably low level.

The production and administration of radionuclides have additional risks for the workers, general public and environment. However, suitable education on radionuclides, techniques and procedures of the professionals working in these fields can effectively minimise these risks. These measures will ensure the skilled labour force within the EU required for the safe use of ionising radiation for medical applications.

The SINFONIA project has therefore contributed to increasing European knowledge and competence on the safe use of advanced, optimised and individualised diagnostic and therapy procedures for the benefit of European citizens.

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