MEDIRAD

RECOMMENDATION 4

FUTURE RESEARCH ON MEDICAL RADIATION PROTECTION IN EUROPE

PROJECT TITLE

Implications of Medical Low Dose Radiation Exposure

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About MEDIRAD Recommendations

MEDIRAD is a research project funded by EURATOM under Horizon 2020 Programme (2016-2022). Bringing together radiation research and clinical research teams from several European countries, it aimed to enhance the scientific basis and clinical practice of radiation protection in the medical field, in particular by better understanding and evaluating the health effects of ionising radiation exposure from diagnostic and therapeutic applications. MEDIRAD was designed to have direct implications for the radiological safety of European patients undergoing medical imaging and therapy procedures involving ionising radiation, and of exposed medical professionals. For this purpose, one of the goals of MEDIRAD was to establish science-based consensus policy recommendations for enhancing the effective protection of patients and medical professionals, as well as for identifying further research priorities.

The scientific basis for the following recommendation stems from the research developed in the course of the MEDIRAD project. In order to achieve a sufficient degree of consensus, MEDIRAD engaged in a substantial dialogue with relevant stakeholders in Europe and internationally. The MEDIRAD Stakeholder Forum, which underpinned this dialogue, included representatives from 86 organisations, who were invited to express their views on issues to be considered as priority, and to comment on the draft formulation of MEDIRAD recommendations.

MEDIRAD Recommendations are made publicly available under the sole authority of the MEDIRAD Consortium.

Competent international organisations, public authorities at European and national level, and organisations such as European research platforms and professional or patient are invited to consider these recommendations and engage or support actions towards their implementation as they see fit, taking the opportunity of initiatives such as the SAMIRA (Strategic Agenda for Medical Ionising Radiation Applications) European Action plan.

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Introduction

Medical procedures are the largest source of exposure to man-made radiation in Europe. This medical use of radiation has greatly improved diagnosis and treatment, and is therefore justified by a net benefit to the patient. According to European legislation, radiation doses received by individual patients must be optimised in order to maximise the benefit/risk ratio to that patient. The past two decades have seen the competitive development of innovative medical technologies using ionising radiation which offer new diagnostic and therapeutic opportunities and require anticipation of potential risks. This is especially true for the diagnosis and treatment of cancer patients.

The ultimate goal is to optimise the use of ionising radiation for the diagnosis and treatment for each patient through an individualised approach based on generalised use of the most advanced risk-informed exposure protocols across Europe. However, significant differences in medical radiation exposure can be observed between different European countries, for similar protocols. Therefore, it is of great importance for the radiation protection community to conduct research, development, and innovation to further optimise and standardise the medical application of ionising radiation, and to disseminate best practice protocols throughout Europe, especially with respect to protecting patients from the adverse health effects of ionising radiation.

The MEDIRAD project has addressed specific areas of importance identified from clinical needs, with the aim of optimising radiation protection of patients and medical staff. While MEDIRAD Recommendations 1, 2, and 3 include further research needs specific to the technical fields covered by these recommendations, Recommendation 4 focuses on five key research issues which policymakers and relevant research communities are invited to consider.

The overarching perspective of the MEDIRAD project is to demonstrate the added value of close cooperation between medical and radiation sciences in addressing complex research questions. This set of key research issues does not seek to establish a new strategic research agenda, but rather highlight the strategic significance of addressing these five key research issues with adequate resources, and through the close cooperation of medical and radiation research communities.

1. Promoting optimisation in radiation therapy: deciphering the biological mechanisms of healthy tissue response, sensitivity, and adverse effects:

The growing number of cancer survivors in Europe, over half of whom are treated with radiation therapy, emphasises the priority to prevent or mitigate radiation-adverse treatment effects, which can have a significant impact on treatment outcome and on the patient's health and quality of life (QoL) [1]. Radiation effects in normal, healthy, tissue surrounding the tumour depends on many parameters, including the tissue type, dose/volume of the irradiation, functional status of organs at risk, age, smoking habits, comorbidities (diabetes, collagen vascular disease), and the patient's genotype [2]. Current understanding of the biological mechanisms underlying radiation adverse effects (cancer, fibrosis, non-cancer disease such as cardiovascular disease), combined with advanced methodological frameworks such as the adverse outcome pathway (AOP) approach, will facilitate research to identify and validate sets of molecular (genetic and epigenetic) biomarkers [3] of healthy tissue response, sensitivity, and adverse effects and of patient radiation susceptibility. These potential biomarkers could then be used to personalise treatments and support patient follow-up including treatment of adverse effects on healthy tissue when necessary.

2. Facilitating innovation in artificial intelligence (AI) for personalised diagnostic and therapeutic protocols:

Historically, diagnostic and therapeutic applications of ionising radiation have relied on consensual clinical protocols with standardised clinical dose and dose/volume recommendations. MEDIRAD stakeholders identified the development of more personalised diagnostic and therapeutic protocols as a need with significant impact on clinical practices. Given the large amounts of multisource patient data produced during routine clinical activities, AI and machine learning will play a major role in the use of big data for improving diagnostic and therapeutic applications of ionising radiation by helping to translate multisource data into clinical decision aids [4]. AI will help to develop diagnostic and treatment approaches that are better tailored to the specific characteristics of the patient and to improve therapeutic outcomes and minimise short and long-term adverse effects of radiation.

3. Modelling of radiation induced disease processes:

While the role of ionising radiation exposure in inducing DNA mutations is undisputed, research in the last decades has uncovered a multitude of other biological effects that contribute to the induction of cancer or other pathologies such as cardiovascular disease [5,6]. Key biological events in response to radiation exposure have been identified at different biological levels: from genes, RNA or proteins, to cells, tissues and organs, and they are interrelated. The challenge for future research is to develop models which correctly aggregate these biological effects to provide clinicians with advanced predictive tools.

The adverse outcome pathways (AOP) approach was designed by the OECD [7,8] to understand the complex health effects of toxic chemical compounds. European radiation and clinical research groups would benefit from the AOP investigation methodology by providing a common framework for scientific and clinical data integration. It would also open the way to future models that could take into account the effects of combined oncological treatments associating chemotherapy with radiation therapy.

4. Implementing EU-wide epidemiological studies to enhance quality and safety of medical radiation applications:

The use of ionising radiation in medicine represents a tremendous benefit for the diagnosis and treatment of diseases. While the benefits to the patient largely outweigh the risks, assessing the long-term adverse effects of radiation exposure is particularly important in cohorts of patients who may live for decades after exposure, particularly children [9]. Large scale clinical epidemiology studies, that follow exposed patients for decades, are essential to identify and quantify the late health effects of medical low, moderate, and high radiation doses and provide the basis for the implementation of high standards for quality and safety of medical radiation applications [10-12]. The success of such studies relies on careful patient follow-up and collection of detailed patient demographic, clinical, and dosimetric data, images and biological samples (through linkage with clinical, radiological, and therapeutic records) [3].

5. Optimising radiation-based medical imaging procedures for improved benefit/risk ratios and individualised procedures:

The use of ionising radiation in medicine may present some risk especially in situations that require repeated imaging for diagnostic, planning, or staging purposes and that result in non-negligible exposures, at least in certain body regions. Thus, there is a constant need for optimisation towards improved benefit/risk ratios and individualised procedures. Such optimisation will include the use of new methods and technologies, for better and more reliable diagnosis, the use of new evaluation techniques, such as those based on AI applications as described above, as well as the optimisation of existing procedures in terms of improved benefit/risk ratios on a population basis and for each individual patient. To achieve the latter, it is necessary to investigate the patient exposure in a more accurate and meaningful basis and correlate this information to the required image quality, which needs to be analysed and evaluated for each imaging procedure of each patient.

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Promoting optimisation of radiation therapy: deciphering biological mechanism of healthy tissue response, sensitivity and adverse effects.

Overall recommendation

Conduct further research into adverse effects of ionising radiation on healthy tissues in order to contribute to the optimisation of radiation therapies.

» Specific recommendations:

1. Encourage research on healthy tissue radio-sensitivity and related biomarkers, based on adverse outcome pathways (AOPs) approaches.
2. Facilitate clinical transfer of predictive radio-sensitivity assays and related biomarkers for personalised treatment decisions.
3. Encourage research on early detection of radiation adverse outcomes and personalised patient follow-up.
4. Promote further clinical studies and optimise predictive assays of tissue response to ionising radiation.

1.1. Justification

Cancer is a major health concern in the European Union, with about 2.8 million new cases and 1.7 million deaths per year. It is indisputable that radiation oncology is a treatment strategy which plays a major role in the management of cancer patients. However, given the impact of acute and late normal tissue complications of radiotherapy on the patient's quality of life (QoL), efforts should be made to increase the efficacy of radiotherapy while decreasing side effects on healthy tissue.

Numerous normal tissue complication probability (NTCP) models have been developed. It is known that 5 to 10% of the patients will develop late adverse effects resulting from their radio-oncological treatment. The severity of radiation toxicity is the result of several biological parameters, including cell composition, cell renewal, and cell differentiation capacity, tissue organisation, as well as cellular radio-sensitivity [13,14]. The pathophysiology of exposed organs depends on many parameters, such as age, functional status of organs at risk, smoking habits, comorbidities (diabetes, collagen vascular disease) or patient genotype, and influence human response to ionising radiation [2]. Multiple genetic pathways such as DNA damage repair, oxidative stress, inflammation, and fibrogenesis contribute to the initiation and progression of adverse tissue reactions following radiation oncology treatment [15].

In addition, epigenetic factors may also play a crucial role in temporal and spatial control of gene activity. However, normal tissue responses to radiation remains to be fully explored and reliable biological markers are still not available to predict the onset and severity of radiotherapy side effects. The challenge today is to reduce a patient's adverse effects resulting from low, moderate, and high doses of exposure during medical interventions including radiotherapy as well as combined therapy, nuclear medicine, interventional radiology, and radiology. The ultimate aim is to promote early detection of cancer and non-cancer secondary effects. This early detection, especially in children, will help achieve better cancer post-treatment management and reduce the treatment constraints, improving thus patient's QoL [16,17].

1.2. Implementation

Four specific recommendations are presented hereinafter. Capturing the dose distribution in patients is a key first step for investigating healthy tissue response (occurrence and severity). However, a single patient can be subject to different radiation exposures during the diagnosis and the treatment of his/her tumour. For example, patients undergoing radiotherapy often receive radiation doses outside the target volume from a combination of diagnostic imaging, radiological treatment planning imaging, nuclear medicine treatment planning imaging (for example from a PET/CT study for radiotherapy treatment planning purposes), treatment verification imaging, as well as peripheral doses to the treated volume from the radiotherapy (external beam therapy or radionuclide therapy) treatment.

In that respect, dosimetrically combining different radiation exposures in an accurate way is a challenging task, and requires adapted methodology. Implementing and analysing patient dose repositories is a further technical challenge.

1.2.1. Encourage research on normal tissue radio-sensitivity and related biomarkers based on adverse outcome pathways (AOPs) approaches.

There is a crucial need to measure individual tissue response and predict individual risk of adverse effects after diagnostic and therapy procedures, as well as to identify subjects at greater risk of radiation-induced disease. To this end, the adverse outcome pathway (AOP) framework, which has not been fully explored in radiation research, would help guide relevant research on subsequent risk assessment in cancer and non-cancer diseases related to radiation exposure. AOP were experimentally implemented within MEDIRAD to model a path to cardiac toxicity as an adverse outcome, and to help identify relevant molecular and imaging biomarkers.

These, if validated, would be used in daily clinical practice for screening breast cancer patients, identifying those at risk of cardiovascular toxicity, and designing personalised follow-up after the completion of their cancer treatment. Large scale studies should be encouraged to identify the robustness of relevant biomarkers that can be translated to the clinic to detect early effects or identify patients for which personalised follow-up/screening and/or treatment approaches are required. In addition, radiation research has also been conducted for identifying relevant biomarkers of susceptibility to radiation-induced cancer, which could identify patients for whom alternative diagnostic and treatment approaches are needed.

Large scale epidemiological studies of patients need to integrate radiation-responsive genes, single nucleotide polymorphism (SNP) discovery through genome-wide association studies (GWAS), epigenetics, and next-generation sequencing, to obtain a holistic view of adverse effects of radiation oncology treatment and identify AOP for individual adverse effects and key related biomarkers.

» Target audience: medical professional organisations, scientific communities.

1.2.2. Facilitate clinical transfer of predictive radio-sensitivity assays for personalised treatment decisions.

There is a growing tendency to move towards 4P Medicine (Predictive, Preventive, Personalised, Participatory), with a specific focus in MEDIRAD project on predictive and personalised medicine. Over the last decades, a large number of tests for evaluating radio-sensitivity have been investigated, of which only SNP assays and the radiation-induced lymphocyte apoptosis assay (RILA) [18] have shown replicated performance in the development phase. Several genes involved in tissue response to radiation were identified because homozygous mutations resulted in unusually severe reactions to radiation-oncology treatment (angiotensinogen, ataxia telangiectasia-mutated, etc.) [19,20].

Development of predictive radio-sensitivity assays and molecular biomarkers should focus on their use in daily clinical decision making (treatment, follow-up, interventions). In this sense, developing methodologies that can be implemented into clinical practice should be addressed. This research will require large clinical studies to identify normal tissue-specific and significant molecular modifications as a valid signature for radiation sensitivity or healthy tissue response [21]. Advanced bioinformatics and mathematical modelling are crucially needed to combine multiomics data for identifying robust and reliable predictive signatures that allow clinicians to identify patients most at risk.

» Target audience: medical professional organisations, medical practitioners, scientific communities.

1.2.3. Encourage research on early detection of radiation adverse outcomes and personalised patient follow-up.

Early detection of secondary and long term cancer and non-cancer diseases in cancer survivor patients would improve cancer management, patient long term QoL, and provide cost-effective therapeutic interventions to reduce the side effects of radiation oncology. MEDIRAD research reinforces that secondary complications after radiotherapy can be substantial. For example, cardiovascular toxicity can develop after radiotherapy of thoracic cancer (breast cancer or lung cancer), and repetitive low doses from CT-scanning can lead to leukaemia and brain tumours. Costs associated with adverse outcomes following radiation oncology are often hard to quantify, because they represent a small part of a complex disease management protocol. Personalised risk-adapted approaches should decrease the rate of late toxicities by providing more effective treatments and lower long-term costs of cancer survivorship, thereby improving the patient's QoL.

The use of predictive assays (including molecular and imaging biomarkers) described above will help to anticipate clinical outcomes. Careful long-term clinical follow-up studies should focus on patient groups at particularly high risk of radiation-induced adverse effects (cancer and cardiovascular toxicity) due to their age, genetic predisposition, and comorbidities. Strategies to mitigate side effects should be also encouraged in combination with early screenings.

» Target audience: policy makers, European research communities (Euratom & Horizon Europe Health), scientific communities, patient associations, health authorities.

1.2.4. Promote further clinical studies and optimise predictive assays of tissue response to ionising radiation.

Research has been performed in MEDIRAD to identify predictive assays for cardiac tissue response to ionising radiation. A predictive signature of cardiotoxicity was proposed as a specific combination of molecular markers (MEDIRAD cardio signature). However, both the prevalence and severity of adverse effects vary from patient to patient, as can be expected from the ethnic, geographic, gender, and age diversity of the general European population.

Inevitably, the conditions under which a biomarker is applied will differ in some ways from those under which it was developed.

Thus, predictive assays, including multiple biomarkers, need to be tested and validated [3] in diverse cohorts of patient and medical settings to ensure their clinical robustness. Moreover, optimising methods to test predictive assays in easily accessible body fluids such as urine and saliva would facilitate their clinical implementation in daily practices, in a cost-effective way, to monitor patient for both risks and benefits of radiation-based diagnosis and treatment protocols. All this requires large scale clinical studies with adapted procedures for easy access to clinical data, biobanks, and patient samples (body fluids and tissue samples). This will be essential for validating and optimising assays that can be translated to the clinic to detect early effects, or identify patients for which personalised follow-up/screening and/or treatment approaches are needed.

» Target audience: policy and clinical decision makers, European research communities (Euratom & Horizon Europe Health), scientific communities.

1.3. MEDIRAD scientific achievements supporting these recommendations

- MEDIRAD identifies potential biological indicators of dose (H2AX in blood PBMC) to assess the impact of low dose radiation exposure from 131I-NaI radioiodine ablation of thyroid cancer in nuclear medicine.

- MEDIRAD brings the proof of concept for early detection of innovative circulating biomarkers (microparticles and specific microRNA) for radiation-induced cardiotoxicity in preclinical studies.

- MEDIRAD brings the proof of concept for early detection of innovative circulating biomarkers (microparticles, specific microRNA, and specific DNA methylation) of radiation-induced cardiovascular toxicity from breast cancer radiotherapy in clinical studies.

- MEDIRAD identifies the potential miRNA candidates as biomarker of radiation sensitivity of paediatric CT patients.

2

Facilitating innovation in artificial intelligence (AI) for personalised diagnostic and therapeutic protocols.

Overall recommendation

Promote EU-wide research strategy to use AI for optimising radiation protection in radiation oncology.

» **Specific recommendations:**

1. Promote a "dosiomic" approach based on optimised patient-specific 3D distribution of radiotherapy dose.
2. Promote development of "radiomics" supporting personalised medicine.

2.1. Justification

The last two decades have seen the development of innovative medical technologies using ionising radiation and offering new diagnostic and treatment opportunities. Optimisation of radiation protection for patients highlight the need for prospective research on these new or optimised procedures for medical imaging, nuclear medicine, as well as radiation therapy.
A special focus should be made on (diagnostic and therapy) quality assessment, dose assessment, new promising approaches for imaging, and/or therapeutic applications (new radiopharmaceuticals, emerging technologies, and techniques in radiation therapy and imaging, hypo-fractionation therapy, flash or micro-beam therapies, new geometries or detectors for imaging, etc.).

Within the MEDIRAD project, different strategies were tested with the objective of re-enforcing image, dosimetry, and biology-based risk assessment for new diagnostic and therapeutic applications of ionising radiation. Substantial progress was made in the development of (i) a 3D spatial features for dose distribution (OpenDose3D) in nuclear medicine, (ii) a semi-automatic evaluation of physics-based image quality for chest CT, (iii) a model of patient dosimetry at the voxel scale, and (iv) an automatic segmentation tool to delineate heart sub-structure. This work illustrates the potential benefits, and the complexity of, implementing computational analysis of patient dosimetry (dosiomics) and patient imaging (radiomics).

These developments are based on qualitative and quantitative performance analyses with high throughput extraction of numeric radiologic, dosimetric, and biological data to obtain predictive or prognostic information, thereby increasing diagnostic and treatment efficacy and limiting as much as possible adverse effects of ionising radiation. Artificial intelligence (AI) technology can be used to support these development.

2.2. Implementation

2.2.1. Promote dosiomic approaches based on optimised patient-specific volumetric distributions of dose imparted.

Dosiomics was initially introduced as a novel texture analysis procedure to harvest dose features that encode the spatial, temporal, and statistical distribution of radiotherapy dose [22]. In this regard, MEDIRAD's results highlight the importance of developing computational methods for volumetric distribution calculations based on patient-specific characteristics for all medical procedures using ionising radiation (including for example: CT, interventional, nuclear medicine, and radiotherapy procedures) taking into account different dose indicators for different types of procedures to get comparable, and meaningful, information on normal and pathological tissue doses between individuals.

Moreover, MEDIRAD results provide a proof of concept for developing optimal dose measurement protocols in nuclear medicine for the accurate estimation of normal tissue absorbed doses (mean organ doses and 3D distributions) using validated quantitative imaging and dose/volume calculation methods. Refinement, validation, and implementation of new bio-kinetic models are needed for dosimetry in molecular radiotherapy using for example physiologically-based pharmacokinetic (PBPK) models for the individual assessment of bio-kinetics.

Finally, dosiomics are increasingly used in clinical studies aimed at improving the prediction of clinical outcomes (including tumour control probability (TCP) and normal tissue complication probability (NTCP) models) in radiation oncology.

The use of dosiomics in clinical practice could represent a powerful tool to better handle the three-dimensional (3D) dose spatial, temporal and statistical information if compared with conventional tools, such as dose-volume histograms [23].

Automatic delineation algorithms have demonstrated their efficacy compared to previous methodologies (e.g. atlas, thresholding, etc.). AI (Deep Learning) could play a role in the prediction of the delivered dose according to the patient's anatomy, with the advantage of a short calculation time compared to treatment planning systems (TPS).

» Target audience: medical professional organisations, medical physicists, radiation oncologists, medical practitioners, scientific communities, European research communities (Euratom & Horizon Europe Health).

2.2.2. Promote development of radiomics supporting personalised medicine.

AI is leading to a significant evolution of automatic diagnosis systems supporting researchers and clinicians. Radiomics provides high-performance qualitative and quantitative analysis, consisting of high-throughput extraction of digital medical imaging data of the tumour and the surrounding organ at risk, to obtain predictive and/or prognostic information (treatment efficacy and toxicity) of individual patients undergoing radiotherapy treatment [24,25]. MEDIRAD contributed to highlighting the importance of developing computational methods for the diagnosis and prognosis of image and functionality-based assessments of cardiac toxicity.

Radiomics need to be further implemented to develop optimisation approaches, for target and non-target tissue, on an individual patient basis. Investigation on 1) variations in tumour heterogeneity and surrounding healthy tissue response during radiotherapy treatment and 2) definition of the minimal spatial and temporal variations that could have an impact on dose distribution to the target volume and the organs at risk should be encouraged, as they will contribute to the optimisation of personalised clinical protocols.

Such approaches would need to focus on specific applications / diseases before being transferred to the clinical environment in daily practices, with the aim of facilitating, and not superseding, clinical interpretation of patient's data.

» Target audience: medical professional organisations, medical practitioners, European research communities (Euratom & Horizon Europe Health), scientific communities.

2.3. MEDIRAD scientific achievements supporting these recommendations

- MEDIRAD has developed and validated a prediction model to assess the risk of acute coronary events (ACE) in the first 10 years after radiotherapy in individual breast cancer patients based on 3D cardiac dose distribution and need for further dosiomic approach.

- MEDIRAD brings the proof of concept for developing optimal dose measurement protocols in nuclear medicine for the accurate estimation of normal tissue absorbed doses (mean organ doses and 3D distributions) using validated quantitative imaging and dose/volume calculation methods.

- MEDIRAD refines, validates, and implements a new bio-kinetic models are needed for dosimetry in molecular radiotherapy using for example physiologically-based pharmacokinetic (PBPK) models for the individual assessment of bio-kinetics.

- MEDIRAD identifies potential specific image markers from echocardiography, cardiac CT, cardiac MRI, and circulating molecular biomarkers for early detection of cardiac changes arising within the first 2 years after breast cancer radiotherapy.

- MEDIRAD identifies the potential miRNA candidates as biomarker of radiation sensitivity of paediatric CT patients.

3

Modelling of radiation-induced disease processes.

Overall recommendation

Develop biologically based models that integrate biological processes of radiation toxicity and relate them to radiation-induced disease risk.

» **Specific recommendations:**

1. Conduct further research on radiation effects on existing cardiovascular disease.
2. Support integrative analyses taking into account effects at several levels of biological organisation.
3. Support efforts to develop radiation-related adverse outcome pathway (AOP) approaches.

3.1. Justification

Standard radiation epidemiological models can be usefully complemented by the development and use of so-called "mechanistic" or "biologically-based" models aiming to relate disease risk to underlying disease processes [26] as epidemiological studies alone are insufficiently powered to directly determine risks at low doses. Biologically based models therefore allow improving risk assessments by taking into account known or postulated low dose mechanisms in the process of extrapolating risk from high to low doses [27].

Understanding underlying processes may, in addition, help identify subgroups of patients with increased risk, based on interactions with other risk factors, or pre-existing conditions. Over the last years, knowledge of disease aetiology has greatly improved, and more realistic and predictive models have been developed [28]. The OECD has promoted the concept and development of adverse outcome pathways (AOPs) to facilitate the inference of causality and the transfer of results from different chemicals or other stressors [29,30].

AOPs are a framework to provide a science-based but simple scheme of successive biological processes that link the perturbation of a specific biological target to a disease or other adverse outcome. At present, AOPs are used only to provide rationale for the existence of risk but not for assessment of its magnitude. Although first attempts have been made, the concept has not yet widely been adopted in radiation research and radiation protection. The development of an AOP related to radiation-induced cardiovascular diseases has been initiated in a recent workshop [31].

Biologically based models can relate the accumulated knowledge of AOPs to radiation-induced cancer risk. State-of-the art normal tissue complication probability (NTCP) models in radiation oncology describe probability and severity of normal tissue complications as a function of dose distribution in the heart volume and its surrounding cardiovascular structures.

Biologically based models provide interfaces for stressors acting on different levels of biological organisation from gene to tissue. In future applications, models could be informed by cardiovascular disease-related stressor-agnostic AOPs to investigate the toxicity coming from combined (radio-chemo-immuno) therapy [32].

3.2. Implementation

3.2.1. Conduct further research into radiation effects on existing cardiovascular disease.

Radiation can injure different heart structures including the pericardium, the myocardium, the heart valves, coronary arteries, or the heart's electrical system, depending on the dose distribution to specific heart sub-structures. Related cardiac radiation pathologies include pericarditis, premature coronary artery disease, atherosclerosis, myocarditis, or congestive heart failure [33]. A detailed risk analysis revealed atherosclerosis as the most important underlying disease for acute cardiovascular events following radiotherapy for breast cancer patients [34].

Hence, modelling risk of acute cardiovascular effects related to atherosclerosis has been one of the focuses of the MEDIRAD work programme. This involves not only studying the effects of ionising radiation on the early phase of cardiovascular disease, but conducting experiments and developing biologically based models of the effect of radiation at later stages, on already established disease. Radiopathologists and mathematicians should be encouraged to work together in order to develop new models of risk for other radiation induced cardiac diseases (congestive heart failure and pericarditis, among others).

» Target audience: medical professional organisations, medical practitioners, European research communities (Euratom & Horizon Europe Health), scientific communities.

3.2.2. Support integrative analyses taking into account effects at several levels of biological organisation.

To fully exploit data obtained from several biological levels, an integrative analysis is necessary. It can help to better understand and quantify the relations between different levels and higher confidence can be achieved through a more comprehensive picture of disease processes. Network analysis can cope with the large amount of data obtained from modern omics technology. Therefore, the integration of information at several levels by network analysis should be considered and supported in the research of disease pathways.

» Target audience: policy makers, research community.

3.2.3. Support efforts to develop radiation-related AOP approaches.

A major motivation for developing the concept of AOPs was facilitating regulatory decision-making by aggregating knowledge in an accessible format. These pathways are a practical tool to assess the evidence and identify knowledge gaps, highly relevant for researchers as well as funding agencies, as this approach facilitates the integration of results from complementary research projects. Thus, development of radiation-related AOPs should be encouraged.

Particular effort should be made to reduce barriers between disciplines and provide more support to mathematics, statistics or informatics in medical research project for disease modelling, thus favouring a quantitative risk estimate and not only a rationale for risk existence. Biologically based models help assessing the contribution of different pathways to risk.

» Target audience: policy makers, regulatory authorities, European research communities (Euratom & Horizon Europe Health), research community.

3.3. MEDIRAD scientific achievements supporting these recommendations

- MEDIRAD has developed a biologically based risk model suggesting radiation effect complicated lesions (plaques).
- MEDIRAD has developed a biologically based risk model suggesting that heart sparing techniques in radiation therapy is needed also for older patient.
- MEDIRAD has developed a network analysis that links biomarkers on different levels of biological organisation (molecular and cardiac tissue).
- MEDIRAD has developed a biologically based model informed by network analysis allowing quantitative risk assessment of cardiotoxicity within the AOP concept.

4

Implementing EU-wide epidemiological studies to enhance quality and safety of medical radiation applications.

Overall recommendation

Conduct large scale clinical epidemiological follow-up of patients to understand and quantify late health effects of radiation and provide evidence for setting high quality and safety standards for medical radiation applications.

» **Specific recommendations:**

1. Foster interactions between clinicians, radiobiologists, physicists, and epidemiologists to provide a clinical epidemiological framework for patient follow-up.
2. Provide funding through concerted provisions in Horizon Europe (Health) and Euratom (Radiation Protection) research programmes.
3. Conduct patient follow-up after medical ionising radiation exposure by means of well-designed clinical epidemiological studies, focusing on most at risk populations.
4. Promote reliance on, and maintenance of, appropriate patient registries and secure mechanisms for linking data across registries for patient follow-up and dose optimisation, respecting patient privacy.
5. Consider patient-specific dose modifiers in derivation of dose estimates as appropriate to different settings.
6. Increase capability for radiation dose tracking and managing programmes to provide relevant and standardised dose estimates.
7. Validate biomarkers of radiation exposure, effects and sensitivity to better identify patients at higher risk of radiation-induced health effects.
8. Use results of clinical epidemiological studies to optimise treatment and imaging protocols and patient follow-up.
9. Harmonise data protection guidelines at the European level to facilitate EU-wide epidemiological studies in medical radiation protection.

4.1. Justification

Historically, the optimisation of radiation-based diagnostic and therapeutic protocols has been pursued through the analysis of the benefit/risks balance for the patients, informed, for diagnostic radiation, by existing low dose risk estimates from epidemiological studies of higher dose populations (e.g. the atomic bomb survivors) and, for radiotherapy, by the clinical follow-up of patients for up to 5 years after the end of the treatment, a medical consensus period during which the success of the therapy, and the occurrence of adverse effects of radiation exposure could be appropriately assessed.

To this day, numerous clinical trials are being conducted to support the ongoing optimisation of new technologies or new therapeutic protocols in radiation oncology. Typical clinical outputs of such trials include the occurrence and the severity (CTCAe grading) of the adverse effects correlated to dose/volume (dose-volume histograms), and imaging data that allow evaluation of normal tissue complication probability (NTCP). These trials do not, however, allow the evaluation of longer-term effects (on cancer and non-cancer endpoints, including QoL) in the growing number of cancer survivors in Europe. Therefore, careful long-term clinical epidemiological follow-up of these patients is needed.

Moreover, outside of clinical trials, observations based on patient follow-up are often difficult to interpret because subjects included may not be representative of the relevant patient population and/or because key information on other risk factors or effect modifiers is not available.
The current recommendation therefore focuses on promoting the general use of a "clinical epidemiology" framework for patient follow-up whereby all appropriate disciplines collaborate (clinicians, biologists, dosimetrists, and epidemiologists). This includes:

- Ensuring the EU patient registries include all the necessary information for the patient follow-up and for dose optimisation in a standardised fashion.
- Ensuring the EU patient registries can be linked.
- Tracking and managing radiation exposure and dose information.
- Taking into account patient-specific characteristics to derive doses;
- Validating, developing and implementing relevant biomarkers (example.g. imaging biomarkers in the follow-up of CVD in breast cancer patients) of exposure, susceptibility and early effect in the clinical epidemiological follow-up.

Such a framework will be useful to ensure follow-up data can be used to draw appropriate conclusions regarding radiation effects, and improve treatment and diagnostic protocols. The collaboration between epidemiologists and clinicians is an added value.

Clinical epidemiological investigations (i.e. the clinical follow-up of patients exposed to medical sources of radiation using epidemiological methods) require the follow-up of large exposed populations for decades to i) identify and quantify the late effects of medical low, moderate and high radiation doses on the health and wellbeing of patients; ii) provide the evidence base for

the development and implementation of high standards for quality and safety of medical radiation applications; and iii) provide a mechanism for continuous surveillance of the effects of the medical radiation exposure. The success of optimising patient follow-up is determined by efficient patient monitoring and quality of demographic and clinical data repositories linked with appropriate dose data and imaging repositories.

In the years to come, there are strategic opportunities in continuing to leverage on cohorts of patients treated with radiotherapy (including both novel and traditional modalities), patients at higher risk of radiation-induced health effects (for example cohorts of ataxia telangiectasia heterozygotes), and cohorts with relevant "higher-dose" diagnostic exposures (including in nuclear medicine), bringing together data related to (i) patient dose information (including patient dose-volume histograms), (ii) relevant outcomes (including toxicity and clinical indicators), and, where relevant (iii) information on factors that may affect sensitivity (genetic and epigenetic factors, other exposures, other patient characteristics).

Long-term patient follow-up should be ensured to adequately assess the short, medium and long-term effects of the exposures. This clinical epidemiological framework approach requires strong cooperation between clinicians and radiation protection research communities, including epidemiologists, biologist, physicists, and dosimetrists in developing adequate follow-up protocols and identifying important clinical questions to be studied. It will also require high quality achievements in patient monitoring methodologies, and in the quality of patient demographic and clinical repositories, linked with dose data, molecular bio-indicators information, and imaging repositories through innovative AI applications which allow the processing of vast number of data sets.

4.2. Implementation

4.2.1. Foster interactions between clinicians, radiobiologists, physicists, and epidemiologists.

Such interactions, generating a close collaboration between oncologists and other clinicians, researchers and medical professionals from relevant disciplines including epidemiology, medical physics, radiobiology, and radiation protection, would enable the development of a standard clinical epidemiological framework for the follow-up of patients exposed to radiation in medicine, the identification of clinical research priorities and the design, operational planning and implementation of future Europe-wide clinical epidemiology studies.

» Target audience: European research communities (Euratom & Horizon Europe Health), medical professional organisations, scientific communities.

4.2.2. Provide funding through concerted provisions in Horizon Europe (Health) and Euratom (radiation protection) research programs.

The conjunction of programme objectives from the Horizon Health and Euratom research communities in Europe would offer unique opportunities to facilitate the development of large scale trans-European clinical epidemiological studies in medical radiation protection, scientifically and clinically design to be fundable.

» Target audience: European research communities (Euratom & Horizon Europe Health).

4.2.3. Conduct patient follow-up after medical ionising radiation exposure by means of well-designed clinical epidemiological studies, focusing on most at risk populations.

Apart from the use of a more standardised clinical epidemiological framework of long-term patient follow-up, which would help ensure that patient cohorts are "portable" over time through successive research consortia, specific studies should be set-up to answer most pressing clinical and radiation protection needs. These studies should help assess the risk of late health effects of radiation exposure on patient health and well-being, and provide the evidence base for optimising patient care protocols.

A single large-scale epidemiological study cannot answer all questions. Hence specific Europe-wide large-scale studies should be conducted in different priority populations. Of particular importance at present are:

- Cancer patients undergoing radiation oncology, in particular paediatric patients and patients receiving new radiotherapy modalities [35,36].
- Cancer patients undergoing nuclear medicine procedures for diagnostic and treatment purposes [37].
- Patients at particularly high risk – in particular paediatric populations and patients with specific genetic profiles (none exclusively BRCA1/2 mutation carriers, AT heterozygotes) which may confer a higher risk of radiation-induced health effects and may warrant alternative treatment/diagnostic strategies.
- Patients treated through interventional radiology [38,39].
- Large populations undergoing recurrent CT scanning and other radiological imaging and screening procedures [40- 42].

As AI innovative developments are expected to make a major contribution to the future optimisation of the patient follow-up, consideration should be given to embed AI applications in the design of future European clinical-epidemiology studies, facilitating the exploitation of large repositories related to patient dose/image/biology data sets.

» Target audience: medical professional organisations, European research communities (Euratom & Horizon Europe Health), scientific communities.

4.2.4. Maintain appropriate Europe-wide patient registries and secure mechanisms for linking data across registries while respecting patient privacy.

Clinical epidemiological studies need to rely on well-designed and complete data registries. Interoperability between registries is essential in order to link all needed data on patient condition, treatment, outcomes, doses, and risk factors. However, for protecting patient privacy, it is essential that all registries be secure and that linking them is only feasible under the strictest security and privacy conditions and following the GDPR.

» Target audience: health authorities, medical professional organisations, scientific communities.

4.2.5. Consider patient-specific dose modifiers in derivation of dose estimates as appropriate to different settings.

This recommendation covers both diagnostic and therapeutic procedures. Absorbed dose to a specific organ, tissue or relevant volume varies from patient to patient, in particular in nuclear medicine, but also for external irradiation, depending, for example, on anthropomorphic parameters of the patient, something which is often not taken into account, particularly in diagnostic procedures.

» Target audience: medical professional organisations, scientific communities.

4.2.6. Increase capability for radiation dose tracking and managing programmes.

This will allow provision of relevant and standardised dose estimates for input both to clinical decision and epidemiological studies. Patients may receive radiation doses in many settings and up to now it is extremely difficult to collect all information in a comprehensive and standardised fashion.

» Target audience: medical professional organisations, scientific communities.

4.2.7. Validate biomarkers of radiation exposure, effects, sensitivity and susceptibility to better identify patients at higher risk of radiation-induced health effects.

Use of appropriate, sensitive, specific, and validated biomarkers of healthy tissue radiation response, radiation sensitivity and radiation susceptibility would greatly enhance the power of clinical epidemiology to assess health effects of radiation exposure and to identifying, in the clinic, subjects at higher risk of radiation induced health effects, and subjects with markers of early effect (for example imaging biomarkers for cardiovascular effects) for whom screening and/or alternative treatments or procedures may be adapted.

For this, collection, processing, and storage of appropriate biological samples is needed for the study of biomarkers (those currently available, as well as markers which may be developed in the future), together with patient's informed consent to the use of the samples for this purpose.

» Target audience: medical professional organisations, scientific communities.

4.2.8. Use results of clinical epidemiological studies to optimise treatment and imaging protocols and patient follow-up.

Rapid communication of results of clinical epidemiological studies is needed to ensure optimisation of protection and follow-up. This includes, for example, the follow-up of imaging biomarkers in women treated with radiotherapy for breast cancer, in order to screen for possible toxicity of radiation on the cardiovascular system, as observed in MEDIRAD.

» Target audience: health authorities, medical professional organisations, scientific communities.

4.2.9. Harmonise data protection guidelines at the European level to facilitate EU-wide epidemiological studies in medical radiation protection (see RECO 1).

Application of data protection and security recommendations, including the implementation of the GDPR, vary between member states and within, making it difficult to conduct large scale multinational clinical epidemiological studies in medical radiation protection. Guidance and harmonisation of practices are needed (see Recommendation 1) in order to ensure the feasibility of conducting informative clinical epidemiological studies of patients exposed to radiation, while ensuring privacy and security of their personal information.

Such studies are important as they provide a surveillance tool for monitoring the health effects of medical radiation exposure (including new treatment modalities) with implications for clinical management of patients and for dose optimisation.

Bringing together the Horizon-Europe Health and Euratom research communities would offer unique opportunities for the development of large scale trans-European clinical studies in medical radiation protection. The convergence of these two communities is key for preparing future clinical epidemiology studies. These studies should be planned and conducted as a close collaboration between clinicians, scientists, and medical professionals from relevant disciplines, including epidemiologists, medical physicists, radiobiologists, and radiation protection experts.

» Target audience: health authorities, medical professional organisations, scientific communities.

4.3. MEDIRAD scientific achievements supporting these recommendations

- MEDIRAD has implemented a retrospective cohort study (BRACE study): our two preliminary conclusions underpin (i) the heart is an important organ-at-risk in breast cancer radiotherapy and should be spared as much as possible (ALARA-principle) and (ii) multivariable NTCP-models provide information on the excess risk of acute coronary events on an individual patient basis, and can be used to decide if more advanced radiation technologies are indicated.

- MEDIRAD has implemented a multicentric prospective cohort study (EARLY HEART): our first results showed a dose-response relationship between subclinical left ventricular dysfunction (defined by a decrease in left ventricular global longitudinal strain 6 months after radiotherapy) and whole heart and left ventricular doses.

- MEDIRAD has set up of the nested case-control study of cancer risk in the cohort of CT patients involved collaboration between oncologists, radiologists, epidemiologists, dosimetrists, and radiobiologists. Update of EPI-CT cohorts of paediatric CT patients.

- MEDIRAD has implemented a nested case-control study of brain and haematological malignancies

- MEDIRAD has developed a biologically based model informed by network analysis allowing quantitative risk assessment of cardiotoxicity within the AOP concept.

5

Optimising radiation based medical imaging procedures in terms of improved benefit/risk ratios and individualised procedures.

Overall recommendation

Investigate new and optimise existing medical imaging procedures to improve benefit/risk ratios and personalised approaches.

» **Specific recommendations:**

1. Establish research on individualised benefit/risk ratio determination for diagnostic applications of ionising radiation.
2. Facilitate the broader implementation of detailed exposure characterisation for imaging procedures.
3. Conduct research determining indication dependent appropriate image quality.
4. Promote implementation of combined exposure and appropriate image quality determination for optimising benefit/risk ratios in existing and new diagnostic.

5.1. Justification

Today, the majority of patients arriving to a European hospital undergo one or more imaging procedures for diagnosis, treatment, or staging. Many of these procedures are based on the use of ionising radiation. Thus, for the average European population, medical imaging based on ionising radiation is one of the largest contributors (in some countries the largest) to the average

exposure of the population. Various procedures like CT, some interventional procedures, as well as some nuclear medical imaging procedures, represent potentially relevant exposures, particularly when they are repeatedly performed within the disease management process. Taking into account potential differences in the patient's response to radiation, the type of exposure, and the technology used, it is of great importance to define the patient-specific benefit/risk ratios for such procedures and optimise them in various scenarios.

These may include new technologies for individualised diagnostic approaches, optimisation schemes based on correlated analysis of suitable exposure parameters as well as image quality determination adapted for specific medical indication. Finally, it is relevant to transfer the optimisation into clinical practice, which requires a lot of research on how to implement the developed optimisation tools as well as to define appropriate image quality for the relevant indications.

When preparing the MEDIRAD project, the importance of optimising imaging procedures in terms of characterising and potentially improving benefit/risk ratios was already clear. Therefore, methods for exposure determination in various imaging procedures like chest CT, nuclear medical imaging, and some interventional imaging procedures had been developed, together with methods of subjective and objective image quality determination in chest CT. The example of chest CT, showed the importance of indication-based optimisation, especially with respect to image quality aspects, as well as the potential for correlated optimisation of image quality and patient specific exposure. It also proved that, by developing semi-automated tools, its implementation into clinical daily routine is feasible. However, this was only developed for unenhanced chest CT.

5.2. Justification

Based on the above four specific recommendations are presented. First of all, it is relevant to define how benefit/risk ratios can be determined for an individual patient. An individual patient can be subject to different radiation exposures depending on the patient specific status, individual sensitivity, and technology used. A combination of diagnostic imaging, radiological treatment planning imaging, nuclear medicine treatment planning imaging (for example from a PET/CT study for radiotherapy treatment planning purposes), treatment verification imaging, and imaging in staging purposes will determine the total exposure of the patient.

The second recommendation is thus to develop methods for patient-specific exposure characterisation at the organ level, shown for some examples in MEDIRAD for all relevant imaging procedures. This must be accompanied by research on indication dependent appropriate image quality and the corresponding methods to determine related characteristics. Finally, translating these results into optimisation schemes in daily clinical routine is a challenge that needs to be addressed.

5.2.1. Establish research on individualised benefit/risk ratio determination for diagnostic applications of ionising radiation.

As stated in the first overall recommendation, the adverse outcome pathway (AOP) framework has not been fully explored in the radiation field to guide relevant research on risk assessment of subsequent cancer and non-cancer diseases related to medical radiation exposure. However, once factors influencing the sensitivity and susceptibility of patients undergoing radiation exposure for diagnostic purposes are identified, this information has to be implemented for determining individualised benefit/risk ratios. In addition, it is necessary to understand how to deal with unknown potential risk factors.

MEDIRAD had identified potential influencing factors and has also determined exposure characteristics for individual patients undergoing chest CT imaging. Results clearly show that there various factors influence exposure at the organ level, including difference in local hospital practice, technological differences in the various hospitals, and patient parameters. In addition, using the example of unenhanced chest CT imaging, MEDIRAD showed that appropriate image quality is indication dependent. Therefore, it needs to be discussed how potential risk factors of individual patients, patient parameters, technology of imaging equipment, differences in local hospital practice as well as necessary diagnostic image quality and or potential diagnostic substitute procedures can be incorporated into benefit/risk ratio determination on an individual patient basis and if and for which procedures this would be necessary.

» Target audience: medical professional organisations, scientific communities for radiation protection, social sciences and humanities, radiobiology, patient associations.

5.2.2. Facilitate the broader implementation of detailed exposure characterisation for imaging procedures.

Patient dose from medical imaging exposure requires a paradigm shift from current practice. Currently, patient dose and associated risk estimation relies heavily on the use of effective dose. Effective dose represents a metric of equivalent radiation detriment compared to a uniform body irradiation based on organ weighting factors using a reference population. As such, it is not suitable for individual patient dose and risk estimation from non-uniformly irradiating techniques that can have markedly different dose distributions in different patients and human tissues. Other quantities such as computed tomography dose index (CTDI) provide a metric for quality control and technique comparison, rather than patient dose, and should not be used either as dose estimates for individual patients.

MEDIRAD has tested a methodology to estimate 3D patient dose distributions from CT examinations and extract organ doses based on patient-specific, equipment-specific and protocol-specific models. In addition, AI algorithms can be readily applied to support further research in patient-specific dosimetry estimations.

Potential areas and applications that will benefit from such development are: i) the estimation of rapid, "on-the-fly", personalised 3D dose distribution for every patient undergoing a CT or cone beam computed tomography (CBCT) scan, ii) estimation of dose in partially exposed organs, e.g., the liver during a chest CT examination, and iii) estimation of dose in patients with truncated field of view (FOV). Further work is needed on uncertainties that arise at various stages of the organ dose estimation procedure. Research in these fields will allow the development of real-time personalised dosimetry and its application in everyday clinical routine. As shown in MEDIRAD, dose evaluation is critical for various types of imaging procedures such as CT imaging, some interventional procedures, as well as nuclear medical imaging procedures, due to current regional and technological differences.

» Target audience: medical professional organisations, medical physicists, medical practitioners, scientific communities.

5.2.3. Conduct research determining indication dependent appropriate image quality.

Optimisation of currently available imaging procedures or evaluation of new imaging technologies in terms of benefit/risk ratios can only be performed in a meaningful way if an appropriate image quality for a given indication is guaranteed, and the influence of parameter changes on the image quality can be determined. Thus, it is necessary for relevant imaging procedures to find a consensus regarding clinically relevant image features and the required image quality on such features in terms of contrast, detail representation, sharpness, noise, and artefacts for a secure diagnosis. Within MEDIRAD, such consensus was achieved for unenhanced chest CT in the context of lung nodule detection, lung fibrosis, and mycobacterial infections. Obviously, there are many more clinical imaging indications, including unenhanced and enhanced CT imaging procedures, interventional imaging procedures, nuclear medical imaging procedures, and hybrids of these, which are relevant in terms of radiation protection research. The consensus on relevant image content and corresponding subjective quality parameters needs to be elaborated in future research projects on an international or at least European level. It is also a necessary prerequisite for the benefit/risk evaluation.

MEDIRAD also developed methods to determine objective image quality parameters directly in patient images and correlate the results of such parameters to the subjective image quality, through a large Europea-wide reader study. This approach provided important insight into the relevant image quality characteristics when determined in patient images for unenhanced chest CT examinations. This approach now needs to be further developed for all relevant clinical indications and imaging procedures, as stated above.

Similarly, the semi-automated tools developed by MEDIRAD for the objective image quality evaluation need to be further developed into fully automated tools suitable for online quality control and optimisation in the clinics, without adding to the workload of the clinical community. Suitable ways of presenting the results need to be further elaborated. AI based approaches for establishing automated image quality descriptors might be feasible and should also be investigated.

» Target audience: medical professional organisations, radiologists and nuclear medicine specialists, medical physicists, medical practitioners, scientific communities.

5.2.4. Promote implementation of combined exposure and appropriate image quality determination for optimising benefit/risk ratios in existing and new diagnostic tools.

Using unenhanced chest CT as an example, MEDIRAD has shown that it is feasible to evaluate individual patient exposure and corresponding image quality descriptors for the same examination and thereby provide a tool for optimisation of such imaging procedures. This was only feasible by integrating research approaches of radiologists, medical physicists, and radiographers. Optimisation in daily clinical routine will only happen if the approach is understood and easy to implement. The effect of changing parameters has to be clearly shown and the potential for individual patient-specific optimisation has to be presented.

MEDIRAD has shown that semi-automated approaches are feasible but must be further developed to fully automated tools that provide easy-to-understand results, if they are to be used broadly throughout Europe. Such tools need to use different characteristics, e.g. for image quality determination, but allow the same classification of images as well as the same indications for optimisation potential. Such aspects have to be taught to the medical practitioners through education and training programmes. Finally, ways need to be developed to implement such tools into legislation without increasing daily workload for practitioners, guaranteeing their use for optimised radiation protection on an individual patient basis. One option could be to develop the methodology of diagnostic reference levels into an advanced tool that performs all necessary documentation in a software-driven manner.

» Target audience: policy and clinical decision makers, scientific communities, medical practitioners.

5.3. MEDIRAD scientific achievements supporting these recommendations

- MEDIRAD had identified potential influencing factors and has also determined exposure characteristics for individual patients undergoing chest CT imaging.
- MEDIRAD has tested a methodology to estimate 3D patient dose distributions from CT examinations and extract organ doses based on patient-specific, equipment-specific and protocol-specific models.
- MEDIRAD also developed methods to determine objective image quality parameters directly in patient images and correlate the results of such para meters to the subjective image quality, through a large Europea-wide reader study.
- MEDIRAD has shown that it is feasible to evaluate individual patient exposure and corresponding image quality descriptors for the same examination and thereby provide a tool for optimisation of such imaging procedures.
- MEDIRAD has shown that semi-automated approaches are feasible.

4

Annex 1
Supporting evidence resulting from MEDIRAD research.

1. Recommendation 4.1 Promoting optimisation in radiation therapy: Deciphering biological mechanism of healthy tissue response, sensitivity and adverse effects

MEDIRAD clinical development of biological indicators of dose (blood PBMC) in nuclear medicine to assess the impact of low dose radiation exposure from 131I-NaI radioiodine ablation of thyroid cancer.

The time- and absorbed dose-dependent induction and repair of DNA double-strand breaks (DSBs) in peripheral blood mononuclear cells (PBMCs) after internal irradiation with radioiodine was investigated on 32 patients. Significant RIF reduction was observed after 50 mGy internal irradiation with I-131, after 4 hr and 24 hr. DNA damage was observed as nearly completely repaired after 24 hr. Repair rate is comparable to studies with external irradiation with gamma or X-rays. Sequential blood sampling was performed on 18 patients before and after administration of I-131 and whole body scans. Dose rate measurements were simultaneously provided. Continuous irradiation with decreasing but non-negligible dose rate in the patients leads to altered repair kinetics in vivo as there is, most likely, still DSB induction competing with repair.

MEDIRAD clinical identification of standard and innovative circulating biomarkers of radiation-induced cardiovascular toxicity from breast cancer radiotherapy.

The main objective is to define a biomarker profile for cardiac damage induced after breast cancer radiotherapy. It is expected that identification of relevant biomarkers from preclinical animal studies, validated in humans, if validated will lead to refined models of the risk of cardiac and vascular toxicity after low to moderate dose radiation exposure.

Gold standard/routine circulating biomarkers of myocardial injury (C protein, pro-BNP, high sensitive cardiac troponin I and T) were measured in serum/plasma of animal models and human patients before and after exposure to low dose radiation. New circulating biomarker candidates, such as microRNAs and extracellular vesicles (microparticles (MPs) and exosomes) were also measured and correlated/compared with the classical biomarkers of above and with the preclinical and clinical imaging data allowing quantify the myocardial injury severity.

Our preclinical studies have provided evidence of molecular changes in the plasma and whole blood of irradiated rats. Some of these changes appear to be dependent upon the dose and time point after radiation exposure. Importantly and linked to the above, preliminary statistical analyses have showed promising correlations between the biomarkers identified and cardiac function.

The clinical validation of standard and innovative blood biomarkers of radiation-induced cardiovascular toxicity is ongoing based on the multi-centric prospective cohort of breast cancer patients treated with radiotherapy at five centres (Netherlands, Germany, France, Portugal, and Spain). MEDIRAD EARLY HEART study included 200 patients. Currently statistical analyses are being performed to identify blood biomarkers of radiation-induced cardiovascular toxicity. Data of preclinical and clinical studies will be combined.

2. Recommendation 4.2 Facilitating innovation in artificial intelligence (AI) for personalised diagnostic and therapeutic protocols

Promote dosiomic approach based on optimised patient-specific 3D distribution of internal radiotherapy dose.

Within the scope of MEDIRAD, novel methodologies were developed to estimate personalised organ dose from chest CT examinations and hybrid examinations. Methodologies were based on personalised Monte Carlo (MC) simulations. Moreover, an image quality module was developed to be used in combination with the dosimetry tool for chest CT as well as for verifying that the images acquired provide a sufficient image quality for the diagnostic purpose. Towards clinical implementation, real time personalised dosimetric map generation is imperative.

The advent of sophisticated AI algorithms that will produce 3D dosimetric maps for each patient and provide dose information in segmented organs and other anatomical regions will greatly reduce the time required to estimate and assess individual patient dose and radiogenic risk (practically on-the-fly generation). Replacing the need of MC simulations with AI-based patient-specific 3D dose generation, renders the technique suitable for high patient-throughput, whereas suitable AI training schemes can mitigate current limitations in dose estimation for partially exposed organs and truncated FOV.

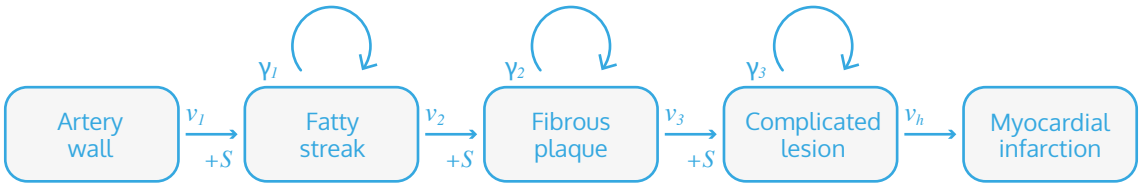
Promote development of radiomics supporting personalised medicine.

Within MEDIRAD, the EARLY HEART study showed that specific image markers from echocardiography, cardiac CT, cardiac MRI and circulating molecular biomarkers have the potential to early detect cardiac changes arising within the first 2 years after breast cancer radiotherapy. These biomarkers may help to identify, at the early stage, patients who may develop a cardiovascular effect due to breast cancer radiotherapy. If validated, these combined image and molecular biomarkers, radiomic approach, would be of great value to optimise patient follow-up.
A study protocol combining EARLY HEART and BRACE studies would take advantage of both enhanced knowledge for early cardiac changes and long term evolution of these early changes to develop preventive measures.

3. Recommendation 4.3 Modelling of radiation induced disease processes

Atherosclerosis is characterised by the progressive accumulation of lipids and fibrous elements in the walls of large arteries. Lipid deposition starts at preferred sites and results in atherosclerotic lesions. With time, the area involved with lesions increases and lesion appearance progresses. In the model, lesions are classified into three categories: fatty streaks, fibrous plaques, and complicated lesions. Main variables in the model are the percentages Fk of the coronary artery intimal surface area involved with these lesions.

The total percentage of the intimal surface area involved with any type of atherosclerotic lesions is denoted by F_1. The percentage involved with raised lesions, defined as fibrous plaques or more advanced lesions, is called F_2. Finally, F_3 relates to the most advanced, complicated lesions. Correspondingly, F_0 refers to the total, healthy or affected, intimal area of the artery wall. Risk was modelled to be proportional to the area involved with complicated lesions F_3. A schematic model representation is presented in the below Figure for the endpoint of myocardial infarction:



The percentages Fk are supposed to increase by two processes: formation of new lesions and growth of existing ones. As long as the lesion area is small, exponential growth is assumed with a growth rate γk, which is assumed to be normally distributed in the population. On the other hand, initiation of new lesions is assumed to be associated with the permeability or adhesiveness of individual endothelial cells and thus modelled stochastically. The probability of formation of a new lesion of stage k is assumed to be proportional to Fk-1[1,2].

[1] Simonetto C et al. Simulating the dynamics of atherosclerosis to the incidence of myocardial infarction, applied to the KORA population. Accepted by Statistics in Medicine. Circulated within MEDIRAD on 11.10.2019.

[2] Simonetto C et al. From atherosclerosis to myocardial infarction - a process - oriented model investigating the role of risk factors. Submitted. Circulated within MEDIRAD on 21.12.2020.

Within MEDIRAD project, a mathematical model on atherosclerosis and subsequent cardiovascular disease was developed within a new, versatile modelling approach. Based on individual information, several potential histories of disease development are simulated. This allows taking time-dependent cofactors, such as radiation exposure, into account.

Next, this process oriented model of atherosclerosis and subsequent ACEs was applied to a contemporary breast cancer cohort of 810 patient part of the BRACE cohort with measurements of coronary artery calcification. Patients with prior ischemic heart disease were excluded. For each disease stage in the model, association of model parameters with mean heart dose was tested.

The model reproduced the prevalence and associated risk of coronary calcifications (during a mean follow up of 9.1 years, 25 ACEs occurred). Mean heart dose significantly improved the fit only when implemented as affecting a late stage of atherosclerosis on already existing, complicated lesions (achieving $p = 0.007$). Therefore, an increase of ACEs few years after RT requires advanced atherosclerosis at the time of RT. At an earlier stage, calcified and non-calcified coronary plaques evolution from baseline before RT to 2 years after BC RT is under analysis in the EARLY-HEART study. According to the results, we will see whether EARLY-HEART study support these findings.

Partly based on these results, the calcified coronary plaques of the whole BRACE cohort (N=5825) are currently being delineated with a semi-automated segmentation method. The mechanistic model can be applied again to this larger cohort to validate the finding that ACEs few years after radiotherapy require advanced coronary plaques at time of RT. Furthermore, it will be studied whether volume of the calcified coronary plaques and/or dose distribution parameters of the calcified coronary plaques can further improve the prediction model for acute coronary events.

4. Recommendation 4.4 Implementing EU-wide epidemiological studies to enhance quality and safety of medical radiation applications

Foster interactions between clinicians, radiobiologists, physicists and epidemiologists to provide a clinical epidemiological framework for patient follow-up.

Within the MEDIRAD project, the BRACE study, a retrospective cohort study, consisted in the inclusion of more than 3000 breast cancer patients treated with radiotherapy between 2009 and 2013 with a mean follow-up of 9 years after radiotherapy; the EARLY HEART study, a multicentric prospective cohort study, consisted in the inclusion of 250 breast cancer patients treated with radiotherapy between 2017 and 2019 with a prospective follow-up of 2 years after radiotherapy.

The setting of these both cohorts involved collaboration between radiation oncologists, cardiologists, radiologists, radiobiologists, dosimetrists and epidemiologists.

These two clinical studies are still running, and our two preliminary conclusions underpin (i) the heart is an important organ-at-risk in breast cancer radiotherapy and should be spared as much as possible (ALARA-principle) and (ii) multivariable NTCP-models provide information on the excess risk of acute coronary events on an individual patient basis and can be used to decide if more advanced radiation technologies are indicated.

Moreover, within the MEDIRAD project, the setting up of the nested case-control study of cancer risk in the cohort of CT patients involved collaboration between oncologists, radiologists, epidemiologists, dosimetrists and radiobiologists.

Conduct patient follow-up after medical ionising radiation exposure by means of well-designed clinical epidemiological studies, focusing on most at risk populations.

MEDIRAD project focused on women who were irradiated for breast cancer, a procedure which results in substantial doses to the heart and vessels and hence this is a population at particular risk for radiation induced cardiovascular diseases. In the BRACE study, which aimed to model the risk of acute coronary event arising from few to 10 years after breast cancer radiotherapy, the results showed a dose-response relationship with whole heart doses and left ventricle doses.

In EARLY-HEART study, which aimed to identify cardiac changes arising within the 24 months after radiotherapy, the first results showed a dose-response relationship between subclinical left ventricular dysfunction (defined by a decrease in left ventricular global longitudinal strain 6 month after radiotherapy) and whole heart and left ventricular doses. These results remained to be confirmed with 24 month follow-up echocardiography data, and additional data based on cardiac CT and cardiac MRI still need to be analysed.

MEDIRAD project focused on populations of paediatric CT patients, chosen because exposure in childhood and adolescence tends to result in a higher risk of radiation induced cancer than exposure late in life. CT-scanning was chosen as one of the most common "higher-dose" diagnostic procedures. Results of the dose estimation in the study, showed that paediatric patients can receive doses of the order of 20-50 mSv to the brain from head CTs and varying between 2 and 20 mGy to the red bone marrow depending on anatomical region examined (head, chest or abdomen), age and time period of exposure.

Results of preliminary analyses of the nested case-control study in Sweden, based on a small number of cases suggest a dose-related increased risk of haematological malignancies which will need to be verified in the larger study. Results of the full cohort analysis are expected shortly.

Promote reliance on, and maintenance of, appropriate patient registries and secure mechanisms for linking data across registries for patient follow-up and dose optimisation, respecting patient privacy .

The cohort study in MEDIRAD was based on identification of patients and procedures from RIS and DICOM of specific hospitals and linkage with national/regional mortality and cancer registries. Difficulties were encountered in linking information from different hospitals (as patients could have received CTs in more than one) and, in some instances, with vital status and cancer registries because of the use of different patient identifiers in the different registries, particularly in early years.

The adequacy of the study could be much improved in the future through the use of common identifiers, the ability to link data from different registries within the same hospital (this was found to be difficult, particularly retrospectively) and across hospitals and should be much improved with careful digitalisation of patient registries and the setting up of adequate infrastructures to link them in a way that respects patient privacy.

Consider patient-specific dose modifiers in derivation of dose estimates as appropriate to different settings.

Within the MEDIRAD project, for all patients from BRACE and EARLY HEART study, individual patient 3-dimensional dose distributions were evaluated for the whole heart and cardiac substructures (including left ventricle) using previously published multi-atlas based auto-segmentation of the heart and these substructures in planning CT scans. For such methods based on multi-atlas, accuracy can be enhanced by taking into account patient specificities, such as breathing technique (free breathing or deep inspiration breath hold).

Within the MEDIRAD project conducted estimation of organ doses from CT scanning and other radiological procedures for patients in the cohort and the nested case-control studies. Doses varied substantially depending on the age at exposure (and assumed weight), with doses estimated for six different groups: New-born (0 to 3 months) with corresponding weight category (3-6 kg); 1 year (4 to 30 months) with corresponding weight category (7-13 kg); 5 years (31 to 90 months) with corresponding weight category (14-22 kg); 10 years (91 to 150 months) with corresponding weight category (23-42 kg); 15 years (151 to 210 months) with corresponding weight category (43-55 kg); adult (>210 months) with corresponding weight category (56+ kg).

Height and weight are additional important determinants of doses to specific organs but were not available for the subjects in the study. It will be important to obtain such information in the future, at least within case-control studies, in order to reduce uncertainties in dose estimates.

Increase capability for radiation dose tracking and managing programmes to provide relevant and standardised dose estimates.

The nested case-control study in Sweden conducted in MEDIRAD identified missing procedures for a number of subjects, even within a single hospital, which could have non-negligible impact on patient dose estimates. Comparison of RIS and PACS data in one of the hospitals in Spain, also identified inconsistencies in recording of procedures, and inconsistencies with the data available (in recent years) in the centralised image databases at the level of Catalonia.

In order to provide relevant and standardised dose estimates, these observations illustrate the need for improved radiation dose tracking and managing programmes, including all necessary technical parameters for dose calculation, in order to provide relevant and standardised dose estimates for clinical epidemiological studies.

Develop and validate biomarkers of diagnostic radiation exposure to better identify patient at risk of adverse effects.

MEDIRAD aims at identifying potential tissue markers of radiation sensitivity and radiation-induced cancer risk, based on a molecular epidemiological case-control study of haematological malignancies and brain tumours after paediatric CT scanning. Differentially expressed miRNA biomarkers were identified in glioblastoma tissue samples and in glioblastoma cell primary culture exposed to dose levels corresponding to CT scan exam. Analysis of the raw sequencing data identified six miRNAs found to be significantly altered (False Discovery Rate< 0.05) in glioblastoma tissue relative to normal brain tissue which were miR96-5p, miR1246, miR549a-3p, miR183-5p, miR183-3p, and miR182-5p. Our data was compared through meta-analysis with open source glioblastoma databases to select epigenetic non-coding RNA biomarkers potentially capable of predicting brain cancer initiation and progression.

These results, if confirmed with a bigger sample size, could suggest that patients with different radio-sensitivities would respond differently at low doses than after intermediate or high doses. For RS individuals, irradiation at intermediate or high doses should not be extrapolated to what happens at low doses. The implication of this possible effect on radio-induced cancer after low doses should be further elucidated.

Use results of clinical epidemiological studies to optimise treatment and imaging protocols and patients follow-up.

Within MEDIRAD, EARLY HEART study showed that specific image markers from echocardiography, cardiac CT, cardiac MRI, and circulating molecular biomarkers have the potential to early detect cardiac changes arising within the first 2 years after breast cancer radiotherapy. These biomarkers may help to identify, at the early stage, patients who may develop a cardiovascular effect due to breast cancer radiotherapy.

If validated, these combined image and molecular biomarkers would be of great value to optimise patient follow-up. A study protocol combining EARLY HEART and BRACE studies would take advantage of both enhanced knowledge for early cardiac changes and long term evolution of these early changes to develop preventive measures.

Harmonise data protection guidelines at the European level to facilitate EU-wide epidemiological studies in medical RP.

MEDIRAD experienced major delays due to the differences in implementation and interpretation of the GDPR, which varied across countries and even institutions within the same country. This effectively paralysed for several years the conduct of the cohort and case-control studies in Catalonia, despite these studies being recognised by the Director General of Public Health of the Department of Health as a public health priority and surveillance of the impact of diagnostic procedures in the patient population.

5. Recommendation 4.4 Optimising radiation based medical imaging procedures in terms of improved benefit/risk ratios and individualised procedures

MEDIRAD aims at facilitating the broader implementation of detailed exposure characterisation for imaging procedures such as computed tomography, hybrid imaging procedures and fluoroscopically guided procedures. Personalised 3D dose distributions for adult (203 patients) and paediatric (93 patients) populations undergoing diagnostic chest CT scans were generated using Monte Carlo (MC) computations. Individual clinical indications, such as pulmonary fibrosis, metastatic disease and other lung infections in adult population were considered. Patient-specific organ-doses were extracted and final results using regression analysis demonstrated that average organ doses and associated risks differentiate based on many parameters such as age, gender, clinical indication, body size, and exposure parameters.

The outcome of the study suggested that optimal patient management has to adhere to CT protocol dosimetric optimisation based on the aforementioned patient characteristics. This requirement for optimisation prompts further research on i) fast, automated, generation of three dimensional dosimetric maps for each patient undergoing a CT examination, and ii) fast and automatic extraction of organ-doses that can be readily used as indication of individual patient risk from a specific medical imaging procedure that uses ionising radiation. The European Union Basic Safety Standards states that the interventional radiology X-ray systems must be equipped with a device informing the practitioner of relevant parameters for assessing patient dose. MEDIRAD presented and validated a patient dose monitoring tool for fluoroscopically guided procedures based on a freely available MC code of photon transport (MC GPU) in a voxelised geometry. This tool provides the dose values at specific organs and positions as well as the dose distribution and the position of maximum dose. This dosimetric information is useful at multiple levels. Improvements in relevant technologies and guidelines around the appropriate use of these systems are required and should be anticipated soon.

Annex 2

Supporting evidence resulting from the stakeholder consultation process.

MEDIRAD stakeholder forum outcomes.

At the onset of the MEDIRAD project a stakeholder forum (SF) was established as a means of engaging in meaningful dialogue with a multidisciplinary group of representatives from the field of medical ionising radiation and associated protection research. The SF was consulted via a comprehensive questionnaire which aimed at ranking various broad-ranging approaches for optimisation of exposure to ionising radiation of patients and medical professionals and prioritise technical topics for inclusion in the current MEDIRAD recommendations.

Of the 86 SF members, there were 85 respondents to the questionnaire offering an interdisciplinary perspective from 69 nationals within Europe and 16 international representatives.

MEDIRAD stakeholder forum expectations.

Table 1
EUROPEAN STAKEHOLDERS' EXPECTATIONS: HIGH PRIORITY TECHNICAL TOPICS

Rank	Topics
1	Optimising image quality / dose during CT scans, including multimodality imaging procedures (e.g. SPECT-CT and PET-CT-scans).
2	Improved protocols aimed at reducing exposure whilst preserving or improving diagnostic quality/ therapeutic benefits (e.g. better accounting of potential secondary or late effects of healthy tissue exposure).
3	Optimising patient follow-up care after radiation therapy and collecting valuable epidemiological data through a better linkage of medical professionals from relevant disciplines.
4	Increasing education and training of medical professionals on radiation protection optimisation.

Table 2
EUROPEAN STAKEHOLDERS' EXPECTATIONS: INTERMEDIATE PRIORITY TECHNICAL TOPICS

Rank	Topics
5	Promoting individualised patient care in nuclear medicine. Procedure for evaluating patient-specific doses deliver to volumes and organs through activity uptake.
6	Improvement of target definition by better delineation of the target volume, better margins definition and better definition of the heterogeneity and of the biological volumes of the tumour at the voxel scale.
7	Modelling of patient dosimetry at the voxel scale. It is necessary to move from planned dose maps to delivered dose maps. (Treatment planning improvement, doses delivered during diagnostic and positioning imaging procedures, modelling simulations, clinical Decision Support System, Data standardisation and machine learning data base...).
8	Predicting quickly and accurately the response of tumours and normal tissues to ionising radiation using new multimodal and functional imaging and/or new biological and molecular surrogates. The development and validation of novel biomarkers will be required in order to develop treatment personalisation approaches.
9	Development of European registries of patient dose/imaging with recommended appropriate quantities (effective dose, organ dose) for radiological examinations.
10	Developing and validating operational biomarkers predictive of patient exposure – side or late adverse effects - following repeated radiological examinations, or radiotherapy protocols.
11	Optimising medical staff protection during interventional radiological procedures by ensuring proper availability and use of shielding equipment, while at the same time considering their actual effectiveness and efficacy.

Table 3
EUROPEAN STAKEHOLDERS' EXPECTATIONS: LOW PRIORITY TECHNICAL TOPICS

Rank	Topics
12	Technology development.
13	Future radiation protection research for radiation-oncology: Normal tissue response.
14	Development of European patient registries of dose/image/clinical diagnosis and patient follow-up, for the purpose of clinical procedure standardisation and radiation protection optimisation (European radio-vigilance).
15	Future radiation protection research for radiation-oncology: Combined treatment.
16	Modelling of patient dosimetry on an individual basis by highlighting the range of absorbed doses delivered from fixed administrations of activity, in order to evaluate the range of possible secondary effects, including long-term risks of secondary malignancies.
17	Future radiation protection research for radiation-oncology: Medical countermeasure.

Table 4
EUROPEAN STAKEHOLDERS' EXPECTATIONS: LOW INTEREST TECHNICAL TOPICS

Rank	Topics
18	Facilitating the development of large-scale multinational epidemiological studies by proposing guidelines to help European countries to implement at the national level European regulatory requirements on ethics (including compliance with GDPR directive).
19	Development of personalised protocols that factor in individual patient radiation sensitivity (e.g. via biomarkers of radiation sensitivity).
20	Exploring of the potential of patient-specific radiobiology tests to assess individual radio-sensitivity, in order to personalise treatment protocols.
21	Protocols to set up optimised imaging systems for quantitative imaging of I-131 irrespective of camera make or model.
22	Outlining a plan for a large-scale and multi-site epidemiological study to evaluate the effects of low absorbed doses of radiation as a result of nuclear medicine imaging procedures in a population with an expected normal life expectancy.
23	Consideration of individual bio-kinetics in patients with residual thyroid tissue or adjuvant disease, rather than reliance on models and values established for a healthy population.
24	Reinforcing regulations (e.g. by extending the scope of Diagnostic Reference Levels (DRLs) at the European level), and regulatory oversight (e.g. radiation protection experts, inspections).
25	Web/smartphone application for adverse effects.

For more information on the stakeholder consultation process and outcomes, see: M. Benderitter, E. Herrera Reyes, M.A. Benadjaoud, F. Vanhavere, N. Impens, U. Mayerhofer-Sebera, M. Hierath, J.R. Jourdain, G. Frija and J. Repussard. MEDIRAD formulation of science-based recommendations for medical radiation protection: a stakeholder forum survey. Radioprotection. 2021. 56(4), 275–285. doi: 10.1051/radiopro/2021030.

Annex 3

Stakeholder involvement in the development and implementation of Recommendations.

MEDIRAD Recommendations were elaborated on the basis of scientific findings from the research developed during the project, in consultation with stakeholder organisations which were invited to take part in the MEDIRAD Stakeholder Forum. This consultation process included an enquiry, based on on-line questionnaires aiming to identify priority concerns among stakeholder organisations, in the field of MEDIRAD scientific investigations, and a review of draft recommendations which were presented on-line to Forum members, and discussed at two workshops organised by MEDIRAD.

The list of MEDIRAD Stakeholder Forum members is provided hereafter. The publication of this list does not imply that the contents of MEDIRAD Recommendations are formally endorsed by these organisations. MEDIRAD Stakeholder organisations are invited to contribute to the dissemination and implementation of Recommendations or parts thereof, as they see fit within the limits of their missions and attributions.

MEDIRAD Stakeholder Forum Members, in alphabetical order:

· Associação Portuguesa dos Técnicos de Radiologia, Radioterapia e Medicina Nuclear
· Associazione Italiana di Radioprotezione Medica
· Associazione Italiana di Radioterapia Oncologica
· Associazione Italiana Medicina Nucleare
· Belgian SocieTy for Radiotherapy & Oncology
· Belgian Society of Radiology
· Biobank of Eastern Finland and University of Eastern Finland
· Bulgarian Society of Biomedical Physics and Engineering
· Bundesamt für Strahlenschutz (Federal Office for Radiation Protection)
· Cardiovascular and Interventional Radiological Society of Europe
· Commissariat à l'Energie Atomique et aux Energies Renouvelables
· Croatian Society of Radiology
· Czech Association of Medical Physicists
· Danish Health Authority, Radiation Protection
· Danish Society for Medical Physics
· Deutsche Gesellschaft für Biologische Strahlenforschung
· EFRS Educational Wing
· ESR EuroSafe Imaging
· ESR Patient Advisory Group
· European Network for Training and Education of Medical Physics Experts
· European Nuclear Education Network Association
· European Nuclear Education Network Association +project
· European Organisation for Research and Treatment of Cancer
· European Society for Vascular Surgery

· European Society of Medical Imaging Informatics
· European Society of Paediatric Radiology
· Federal Agency of Nuclear Control
· Federazione nazionale Ordini dei Tecnici di radiologia e delle professioni sanitarie tecniche, della riabilitazione e della prevenzione
· Finnish Advisory Committee for clinical audit
· Food and Drug Organization
· German Commission on Radiological Protection
· German Roentgen Society
· Greek Atomic Energy Commission
· Heads of the European Radiological Protection Competent Authorities
· Hellenic Society of Gastroenterology
· Hungarian Society for Medical Physics
· Institut National du Cancer
· International Agency for Research on Cancer, Section of Environment and Radiation
· International Atomic Energy Agency - Radiation Protection of Patients Unit
· International Commission on Radiological Protection
· International Organization for Medical Physics
· International Radiation Protection Association
· International Society of Radiographers and Radiological Technologists
· International Society of Radiology
· Irish Institute of Radiography and Radiation Therapy
· Irridium Network
· Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro the National Institute for Insurance against Accidents at Work
· Italian Association for radiation Protection
· Italian Association of Medical Physics
· Kuopio University Hospital, Cancer Centre
· Lithuanian Association of Medical Physics and Engineering
· National Professional Association of Italian Qualified Experts
· Nordic Association of clinical Physics
· Nordic Working Group on Medical Applications
· Österreichische Röntgengesellschaft (Austrian Soicety of Radiation Protection)
· Plataforma Nacional de I+D en Protección Radiológica
· Quality Assurance Group in Radiotherapy
· Radiation Protection Association of Serbia and Montenegro
· Radiation Protection Officers working group on the West Coast of Norway
· Radiotherapy Translational and Preclinical Research network
· Romanian College of Medical Physicists
· Sociedad Española de Oncologia Radioterapica
· Società Italiana di Cardiologia
· Società Italiana di Cardiologia pediatrica e di cardiopatie congenite
· Società Italiana per la Radiologia Medica
· Societatea Română de Medicină Nucleară și Imagistică
· Société Française de Physique Médicale
· Société Française de Radiologie
· Société Française de Radiothérapie Onocologie
· Society and College of Radiographers
· St. James's University Hospital
· Superior Health Council
· Swedish Society for Medical Physics
· Swedish Society of Medicine
· Swiss Society of Radiobiology and Medical Physics
· University Hospital Leuven
· University of Arkansas
· University of California
· University of Eastern Finland
· University of Ghent
· University of Malta
· WHO network of Patients for Patient Safety

Annex 4

The MEDIRAD Project

Implications of Medical Low Dose Radiation Exposure.

A European multi-disciplinary project to enhance the scientific bases and practice of radiation protection in the medical field.

Coordinator	**European Institute for Biomedical Imaging Research (EIBIR), AT** **Coordinator contact: Monika Hierath, mhierath@eibir.org**
Scientific Coordination	**Prof. Elisabeth Cardis** **Barcelona Institute for Global Health (ISGlobal), ES**
Clinical Coordination	**Prof. Guy Frija** **Paris Descartes University, FR**
Duration	**1 June 2017 – 28 February 2022 (57 months)**
Total max EU Funding	**€9,995,145.75**
Website	**www.medirad-project.eu**

Ambition

MEDIRAD is a multi-disciplinary, cross-cutting project that aims to enhance the scientific bases and clinical practice of radiation protection in the medical field. MEDIRAD addresses the need to better understand and evaluate the health effects of low-dose ionising radiation exposure from diagnostic and therapeutic imaging and from off-target effects in radiotherapy. The MEDIRAD key research objectives are summarised in three pillars:

- **Pillar 1:** Development of innovative tools to increase the efficiency of future radiation protection research activities and support good clinical practice.
- **Pillar 2:** Improvement of the understanding of low-dose ionising radiation risks associated with major medical radiation procedures.
- **Pillar 3:** Development of recommendations based on research results and establishment of information exchange infrastructure to facilitate consensus.

Work plan

The MEDIRAD Project consisted of six interdependent and complimentary work packages (WP).

- **WP1:** Project management and dissemination: Scientific and clinical coordination, ethics management, knowledge management and exploitation, internal and external communication.
- **WP2:** Dose evaluation and optimisation in medical imaging: Optimisation of chest CT, interventional procedures and multimodality imaging, and development of imaging and radiation dose biobank.
- **WP3:** Impact of low-dose radiation exposure: Standardisation, biokinetic modelling and treatment planning, dosimetry, biomarkers of absorbed doses, protocol for epidemiological study.
- **WP4:** Breast radiotherapy and secondary cardiovascular risks: Epidemiological study on cardiovascular changes after radiotherapy, measuring markers of exposure and risk modelling.
- **WP5:** Possible health impact of paediatric scanning: Epidemiological study of paediatric CTs and cancer, including (epi)genetic biomarkers of possible sensitivity, dosimetry and statistical analyses.
- **WP6:** Bringing together medical & nuclear scientific communities: Formulation of science-based policy recommendations, consultation of stakeholders, organisation of dissemination seminars.

Impact

MEDIRAD will achieve significant progress in the interaction between the radiation protection and medical scientific communities at EU level, leading to cross-fertilisation of research efforts and the provision of more consolidated and robust science-based policy recommendations to decision makers in the respective sectors.

MEDIRAD will allow a better evaluation of the risks from radiation and better quantification of the necessary precautionary measures, leading to a more robust system of protection of patients, workers and the general public, whilst not unduly penalising activities through unnecessary and costly measures.

MEDIRAD will endeavor to positively modify the public perception of risks associated with ionising radiation thanks to the results of such combined nuclear and medical research.

MEDIRAD's long-term impacts are additional and improved practical measures for the effective protection of people in the medical and nuclear sectors.

Consortium

The multi-disciplinary consortium combines the expertise of 34 partners from 14 European countries. It includes major universities and research institutes as well as clinical partners.

· European Institute for Biomedical Imaging Research, AT
· Belgian Nuclear Research Centre, BE
· Ghent University, BE
· University of Geneva, CH
· Otto von Guericke University Magdeburg, DE
· University Medical Center of the Johannes Gutenberg University Mainz, DE
· Helmholtz Zentrum München German Research Center for Environmental Health, DE
· University Hospital of Würzburg, DE
· Philipps University of Marburg, DE
· University Hospital rechts der Isar of the Technical University Munich, DE
· Brandenburg Medical School, DE
· Barcelona Institute for Global Health, ES
· Polytechnic University of Catalonia, ES
· Autonomous University of Barcelona, ES
· Catalan Institute of Oncology, ES
· Paris Descartes University, FR
· Institute for Radiological Protection and Nuclear Safety, FR
· B-COM, FR
· French National Institute of Health and Medical Research FR
· Claudius Regaud Institute FR
· University of Crete GR
· University College Dublin, National University of Ireland, IE
· Sapienza University of Rome, IT
· Italian National Institute of Health, IT
· University Medical Center Groningen, NL
· VU University Medical Center, NL
· Netherlands Cancer Institute, NL
· Nofer Institute of Occupational Medicine, PL
· Polytechnic Institute of Coimbra, PT
· Cardiovascular Centre of the University of Lisbon, PT
· Region Västra Götaland, SE
· The Royal Marsden National Health Service Trust, UK
· University of Newcastle upon Tyne ,UK
· Imperial College London, UK

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