Editorial

It is a great pleasure to introduce this second special issue dedicated to MEDIRAD, a very ambitious project on the medical use of radiation. After an open preparation process, the coordinators have managed the feat of assembling a multidisciplinary team that includes experts in radiation protection, radiology, radiotherapy, epidemiology, biology, biomedical imaging, and dosimetry. Very promising results are expected. Undoubtedly, there are close links between MEDIRAD and CONCERT that will contribute to improving the development of a joint roadmap for radiation protection.

Dr Laure Sabatier, CEA

The floor to...

I have high expectations that MEDIRAD will:

- Increase our knowledge of the health effects of both diagnostic and therapeutic radiation exposure, including the study of individual susceptibility biomarkers.
- Improve the recording and estimation of doses from various procedures, paving the way for future real-time monitoring and dosimetric databases for both clinical practice and epidemiology.
- Help develop evidence-based policies for medical radiation protection.
- It is the first time that such an ambitious project is to be conducted!

Due to the complexity and strong multi-disciplinary character of the MEDIRAD project, the administrative management is separated from the scientific (E. Cardis) and clinical coordination (G. Frija). The European Institute for Biomedical Imaging Research (EIBIR, Austria) acts as coordinator of the project, in charge of overall project management, as well as communication and dissemination activities. EIBIR has a vast and long-standing experience in managing European projects, including numerous research projects and coordination actions under FP6, FP7, and Horizon 2020. In addition, the five medical societies involved in the project’s Stakeholder Board are shareholders of EIBIR.

In the MEDIRAD project, we are responsible for contractual and financial management, quality assurance, and risk management, as well as the overall monitoring of compliance with the project plan. Moreover, we are the contact point for the European Commission and provide day-to-day support to all project partners to facilitate efficient internal communication. We are particularly excited about this project as the medical and nuclear sectors join forces for the first time to work together towards the radiation protection of patients and staff.

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MEDIRAD: Implications of medical low dose radiation exposure

MEDIRAD (Implications of Medical Low Dose Radiation Exposure) is a multidisciplinary, cross-cutting project funded under the Euratom research and training programme of Horizon 2020. The four-year MEDIRAD project kicked off in June 2017 and is led by the European Institute for Biomedical Imaging Research (EIBIR). The consortium brings together a wide range of expertise, with 33 partners from 14 European countries, and involves research groups that focus on radiology, nuclear medicine, radiotherapy, dosimetry, epidemiology, biology, bioinformatics, modelling, radiation protection, and public health.

The expected impact of the MEDIRAD project is multifaceted. MEDIRAD will achieve significant progress in the interaction between the radiation protection and medical scientific communities at the 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 relevant sectors. The project will also allow better evaluation of the risks from radiation and better quantification of the necessary precautionary measures, leading to a stronger system of protection for patients, workers, and the general public.

MEDIRAD will endeavour to positively modify public perception of risks associated with ionising radiation, thanks to the results of such combined nuclear and medical research. MEDIRAD’s long-term impact will lead to new and improved practical measures for the effective protection of people in the medical and nuclear sectors.

MEDIRAD has received funding from the Euratom research and training programme 2014-2018 under grant agreement No 755523.
The aim of Work Package 2 (WP2) is to develop novel methodologies to reduce the radiation dose received by patients and staff and potential radiation-related risks of cancer and non-cancer outcomes from chest imaging, while maintaining or improving the diagnostic information from existing and emerging techniques. Work will focus on CT, fluoroscopically-guided interventional procedures, and hybrid systems.

Parameters for quantifying image quality are generally measured using standardised phantoms. However, the optimisation of clinical protocols and the prediction of diagnostic performance using phantoms containing standard test objects may be inadequate. Methods are needed to estimate organ and tissue doses based on patient models or detailed voxelised phantoms based on various body statures or models of real patients, representing as many human body anatomies and sizes as possible, and taking into account all parameters that influence patient dose. WP2 will develop a novel tool for the optimisation of patient dose and image information for chest CT, based on the assessment of image quality and detailed spatial three-dimensional (3D) organ and tissue dose distributions from chest-CT examinations.

A state-of-the-art method has been described for dose monitoring for interventional cardiology procedures, based on the accelerated Monte Carlo (MC) code, MC-GPU. The programme has only been tested on several simple, ideal, simulated cardiac procedures, but has not been benchmarked against standard simulation codes, nor tested in the clinical environment. WP2 will provide detailed spatial 3D dose distributions from fluoroscopically-guided ablative procedures for dose optimisation, as well as the optimisation of a novel dose-monitoring system for interventional cardiology procedures and testing of the effectiveness of newly developed tools for brain and eye lens protection of staff who perform fluoroscopically-guided procedures.

There is a strong need for standardisation and optimisation of CT protocols for multi-modality imaging. The establishment and use of Dose Reference Levels (DRLs) in hybrid imaging are required and have been recommended by international organisations. WP2 will perform a European study on the current use of multi-modality systems as a basis for establishing European DRLs for specific applications of CT in PET/CT and SPECT/CT, develop a method for estimating patient organ doses and risks from chest PET/CT and SPECT/CT, and optimise protocols for multi-modality imaging.

A European image and dose repository for benchmarking and research is also needed. In addition, coding is not harmonised in Europe and beyond. WP2 will develop and operate an integrated imaging and dose biobank to address the needs of MEDITRAD researchers (WP2-5); develop a common catalogue for names of procedures, clinical symptoms, anatomical locations, and findings; and develop structured reporting templates.
The overall objectives of MEDIRAD WP3 are to develop and implement the tools necessary to establish, for the first time in a multicentre setting, the range of absorbed doses delivered to healthy organs in patients undergoing thyroid ablation and the threshold absorbed dose required for thyroid ablation. This will enable patient-specific treatment planning that will minimise the risk to the patient while ensuring a successful outcome.

We will facilitate the development of a large-scale epidemiological study of the effect of low absorbed doses from the irradiation of normal organs by internal radionuclide sources. This will allow individualised risk/benefit treatment planning for these procedures and lead to recommendations and protocols for the calculation of absorbed doses to normal organs from internal $^{131}$I sources, thus facilitating accurate risk analysis in a large population.

To achieve these objectives, we have identified the following aims:

- Gamma camera characterisation for high activity quantitative imaging to enable standardised collation of quantitative image data and absorbed dose calculations obtained at different centres.
- Dosimetry and kinetic modelling will be performed for 100 patients at four sites, to establish the range of absorbed doses delivered to thyroid remnants and to normal organs from fixed levels of administered activity.
- Biomarker studies will be performed to assess individualised radiosensitivities from a subset of patients.
- A database will be developed, in collaboration with WP2, to collect dosimetry and outcome. Within this study the absorbed doses required for successful ablation will be established, and the range of absorbed doses delivered to potential organs-at-risk determined to enable the evaluation of short- and mid-term risk.
- These data will be used to develop personalised risk/benefit dosimetry-based treatment-planning protocols as recommendations for best practice, whereby absorbed doses delivered to organs-at-risk will be minimised while ensuring a successful response.

The methods and tools developed will provide the means to prepare and plan a large-scale study that will evaluate long-term risk from absorbed doses delivered to normal organs and will be translatable to all radionuclides used for diagnostic and therapeutic procedures.

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**MedIRAD WP3**

**Impact of low dose radiation exposure from $^{131}$I radioiodine ablation of thyroid cancer**

An absorbed dose map overlaid onto a corresponding transaxial slice of the CT scan (Flux et al. 2010).

**Photo:** RMH/ICR

SPECT/CT gamma camera for the acquisition of quantitative imaging data.

**Photo:** RMH/ICR

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Breast radiotherapy and secondary cardiovascular risks: Establishing risk models for clinical support

The main objectives of MEDIRAD WP4 are to assess early and mid-term cardiovascular effects after breast radiotherapy (RT) and to develop a time-dependent risk model for these injuries. In addition, prediction models for major cardiac events in the long term will be developed and externally validated to quantify the risk, based on biological and imaging biomarkers for clinically apparent major cardiac events. These prediction models can be used to estimate the impact of various preventive strategies and provide essential information for decision making on the most effective and cost-effective measures.

Tasks of MEDIRAD WP4

The six specific aims of WP4 are to:

- Identify and validate most important cardiac imaging and circulating biomarkers of radiation-induced cardiovascular changes arising in the first two years after breast RT.
- Develop individual risk models (Normal Tissue Complication Probability (NTCP) models) integrating these biomarkers combined with dose metrics of cardiac structures based on 3D-dosimetry.
- Determine the relationship between 3D dose distributions in cardiac substructures and the risk of Acute Coronary Events (ACE) and other cardiac complications in breast cancer patients to develop an externally validated multivariable NTCP model to assess the risk of ACE in individual patients, based on cardiac dose metrics in the first 10 years after breast-cancer RT.
- Investigate the biological mechanisms of heart damage, as a function of dose in rodents, for radiation qualities used in radiology and radiotherapy.
- Define a biomarker profile for cardiac damage induced by low to moderate dose exposure. Identification of relevant biomarkers from preclinical animal studies, validated in humans, will lead to refined models of the risk of cardiac and vascular toxicity after low- to moderate-dose radiation exposure.
- Describe cardiovascular risk by a mathematical model of disease development based on the findings from the above described aims.

WP4 integrates clinical epidemiology, radiobiology, and various modelling approaches to obtain more insight into mechanisms that lead to radiation-induced cardiovascular effects in breast-cancer patients and to develop and validate classical Normal Tissue Complication Probability and mechanistic models to associate low-dose delivery to the heart with a variety of biological, subclinical, and clinical endpoints. The results will contribute to more accurate risk estimations for radiation-induced cardiovascular biological and clinical events and provide potential targets for prevention.

Example of 3D (left) and 2D (right) planning of irradiation plan for breast cancer, showing dose on the heart.

Validation and modification of a prediction model for acute cardiac events in patients with breast cancer treated with radiotherapy based on three-dimensional dose distributions to cardiac substructures. van den Bogaard V. A., Ta B. D., van der Schaaf A. et al. (2017), J Clin Oncol., 35 (11), 1171–1178

Possible health impact of paediatric scanning- A molecular epidemiology study

WP5 is devoted to improving our understanding of the potential association between cancer risk and low doses of ionising radiation from CT scans in childhood and adolescence, and to studying the role of factors, including age and genetic/epigenetic variants, which may modify this risk. It builds upon a subset of national studies from the European EPI-CT cohort (http://epi-ct.iarc.fr) of over 1.1 million patients (Bosch de Basea et al. 2015) and comprises two main studies:

1) A follow-up study, with an update of the cancer incidence, vital status, and CT scanning data of the largest national cohorts in EPI-CT (from France, the Netherlands, Spain, and the UK). The main objective of the follow-up study is to improve the statistical power for direct estimation of cancer risk compared to the original EPI-CT study and to assess recent changes in CT practices in paediatric radiology. This study is purely record based, with no patient contact.

2) A molecular epidemiological case-control study of haematological malignancies and brain tumours nested within the French and Spanish EPI-CT cohorts. This will allow the collection of individual data on other sources of radiation exposure, syndromes, and diseases that could potentially confound any association observed in EPI-CT and the collection of biological samples to study potential markers of radiation sensitivity (exome sequencing and methylation profiling) on a subset of the nested case-control study (Hall et al. 2017).

Activities in the follow-up study, after obtaining ethics approval, will involve updating the CT history of patients already included in the CT cohorts in the participating countries. We will update the follow-up for mortality and cancer incidence, as well as the incidence of rare diseases and genetic syndromes through record linkage with appropriate population and hospital registries, where available. This will provide five additional years of follow-up, increasing the total number of cancers by approximately 7,500, approximately 60% more than those included in the original cohorts, and approximately 25% more leukaemia and brain cancer cases. This will improve the statistical power of the risk analyses.

In the case-control study, two controls matched for age, sex, and region of residence will be selected per case and a third, matched for radiation dose, to maximise the statistical power to detect genetic/epigenetic-environment interactions. All participants will be contacted, informed about the study, and asked to answer an online questionnaire and give permission for the study investigators to contact their physicians and access medical and radiological records and provide two saliva samples. Exome sequencing and methylation profiling will be performed to identify genetic and epigenetic variants, such as microRNA and IncRNA.

Organ dose estimation following CT exposures will be updated in both studies and in the case-control study, organ doses due to other types of examinations will be estimated.
The central objectives of MEDIRAD WP6 are to formulate science-based policy recommendations for the effective protection of patients, medical workers, and the general public to decision-makers and practitioners; to organise a web-based consultation of a wide range of stakeholders; and to disseminate the MEDIRAD results to broader communities interested in radiation protection.

The four specific aims of WP6 are to:

- Develop and promote a consensus on standardised procedures, based on the results of WP2, to advocate and facilitate the development of Europe-wide data repositories of patient exposure to ionising radiation (dosimetric information, imaging records) for the purpose of optimising medical protocols and facilitating further research on low-dose effects.

- Develop and promote consensus recommendations on the optimised medical use of ionising radiation, based on the findings of MEDIRAD WP2, WP3, WP4, and WP5, and disseminate relevant information among clinicians, radiologists, radiographers, nuclear medicine physicists, and medical physicists.

- Develop and promote consensus recommendations towards enhancing the robustness of the European radiation protection system, based on the findings of the MEDIRAD WP’s and the lessons learned from a web consultation of a wide range of stakeholders, in the context of the implementation of Council Directive 2013/59/Euratom (the revised European BSS Directive).

- Disseminate relevant information about MEDIRAD results to the concerned scientific communities, both in the medical and nuclear sectors, to further bring them together, as well as to competent authorities, and contribute to the continuous elaboration and updating of Strategic Research Agendas (SRAs) and associated roadmaps relevant to radiation protection research in Europe.

MEDIRAD WP6 will set up a Stakeholder Board (SHB), as well as a Stakeholder Forum (SHF), to facilitate the stakeholder consultation.

The SHB will consist of a group of experts, bringing together one representative from each of the following organisations: MELODI (Multidisciplinary European Low Dose Initiative), EURADOS (European Radiation Dosimetry Group), EURAMED (European Alliance for Medical Radiation Protection Research, ESR (European Society of Radiology), ESTRO (European Society for Radiotherapy & Oncology), EANM (European Association of Nuclear Medicine), EFRS (European Federation of Radiographer Societies), EFOMP (European Federation of Organizations for Medical Physics), EPF (European Patients’ Forum), and WHO (World Health Organization).

The Stakeholder Forum will consist of a maximum of 150 stakeholder representatives who will be invited to answer the web-consultation that SCK•CEN will implement with the objective of consulting stakeholders on the content of recommendations that will be developed within MEDIRAD WP6.