Abstract. Medical applications of ionising radiation (IR) represent a key component of the diagnosis and treatment of many diseases, guaranteeing efficient health care. The use of IR in medicine, the largest source of general population radiation exposure, is potentially associated with increased risk of cancer and non-cancer diseases, which needs to be evaluated to provide evidence-based input for risk-benefit considerations. Efforts are also needed to improve the safety and efficacy of medical applications through optimisation. The EC Euratom programme enhances research in medical radiation protection. The four complementary multidisciplinary projects presented here contribute to (1) improving knowledge on exposure and effects of diagnostic and therapeutic applications and (2) transferring results into clinical practice. The common aim is to optimise use for individual patients, enhance education and training, ensuring adherence to ethical standards, particularly related to technologies based on artificial intelligence. MEDIRAD, SINFONIA and HARMONIC focus on improving exposure estimation and studying the detrimental effects of diagnostic and therapeutic medical exposures in patients and staff using different endpoints. EURAMED rocc-n-roll brings together the results of the projects and the recommendations generated by them to build, in collaboration with the EU Radiation Protection research platforms, a strategic research agenda and a roadmap for research priorities.

1 Introduction

Medical applications of ionizing radiation (IR) play a crucial role in the efficient health care, diagnosis and treatment of many diseases. There are, however, also risks associated with the medical application of ionizing radiation, including an increased risk of cancer and non-cancer diseases. As medical IR applications constitute the largest human-made source of radiation exposure to the European population [1], it is particularly important to optimize their use and the doses they entail. In addition, there is a historical radiation protection (RP) culture in Europe, well-illustrated by the Euratom directives, the Basic Safety Standards [2] being the most recent one.

In recent years, with the growing awareness of risks from such applications, EURATOM has funded four large-scale projects (MEDIRAD, HARMONIC, SINFONIA and EURAMED rocc-n-roll) which all contribute, in a complementary fashion, to improve estimates of the detrimental effects of medical applications, and to provide evidence-based input and new approaches to optimise their use, the resulting doses, to reduce associated risks to patients and medical professionals and ultimately to provide evidence for further updating of the current BSS. These projects were chosen because they contribute to optimising medical applications of IR and improving our understanding of radiation effects. Based on these contributions, they aim at generating evidence-based recommendations to the main stakeholders (including funders, RP authorities, medical societies and researchers as well as clinicians),
fostering collaboration between the radiation protection and medical scientific communities. They are particularly pertinent to the issue of RP in medicine since they cover the most important sources of diagnostic and therapeutic medical radiation to patients and workers, as well as one of the most sensitive patient groups for radiation protection: children (see Tab. 1).

The current paper provides a cross-cutting description of the four projects and their achievements to date, stressing commonalities and highlighting the challenges encountered, research needs and the need for a future overarching strategy in medical RP research.

2 Ongoing European research in RP

The four projects together (Tab. 1) target all applications of radiation in medicine:

- Cancer treatment: HARMONIC (paediatric cancer patients), MEDIRAD (thyroid cancer patients and cardiovascular changes after radiotherapy (RT) for breast cancer) and SINFONIA (patients and workers);
- Cardiology: HARMONIC (paediatric cardiology) and MEDIRAD (patient and workers in fluoroscopy-guided procedures); and
- Diagnostic exposures: MEDIRAD (Computed Tomography (CT) scanning) and SINFONIA (Diagnosis of brain tumour and lymphoma).

SINFONIA also considers the impact on humans and biota from the release of radiopharmaceuticals by hospitals.

All of these aspects are considered in the strategic research agenda (SRA) to be developed in EURAMED rocc-n-roll.

The goal of all the projects is to contribute to better safety and efficacy for medical applications of IR. This implies the need for transferring the research results into clinical practice and daily medical use. To allow this, education and training is a fundamental prerequisite, which is addressed by all four projects. Successful transfer to clinical practice will not only result in better healthcare and improvement in RP for individual patients and medical professionals throughout Europe but also allow the development of potential socio-economic benefits for the European Union as a whole.

The success of all four projects relies on a well-integrated interdisciplinary approach, essential not only to ensure the quality of the research results but also, very importantly, for their translation to the efficient and safe use of IR in clinical practice, supported by professional/regulatory guidance and recommendations. A further shared component of these projects and all research in medical RP is the importance of ethical considerations throughout the implementation of the projects, as well as in the medical uses of IR.

2.1 Optimisation for medical radiation safety

A major focus of all selected research projects is research to improve the assessment of organ doses from medical procedures, the registration of these doses in real-time in the clinic, and to use them for the estimation of the adverse effects of exposure and quantification of risks (Tab. 1).

Real-time assessment of appropriate dose quantities is essential for the adequate protection of patients. Indeed, though dose estimates are provided routinely for diagnostic procedures using external photon radiation and for RT, they are measurable quantities that characterise the external radiation field, useful to assist in managing the patient dose, but not appropriate for evaluating the potential health effects of the exposure. For this, estimates of absorbed dose to organs and tissues of interest are more relevant but not currently available routinely. Thus, the projects focus on research, to estimate relevant dosimetric quantities in real-time in the clinic for different types of procedures and to establish dose biobanks in which they can be registered for research on potential health effects but also for evaluation of the cumulative doses received by patients to improve their radiological protection. In imaging applications, optimisation has always been based on guaranteeing a sufficient image quality, for which determination methods are developed.

Managing and potentially reducing staff doses is of utmost importance and is addressed in MEDIRAD and SINFONIA, in particular during nuclear medicine and fluoroscopically-guided procedures, where dose optimisation together with appropriate use of protective equipment contribute to workers safety.

The overarching objective of the projects is to identify where optimisation of doses and uses is needed to minimise health risks while maintaining the benefits to the patients. MEDIRAD has now delivered its evidence-based recommendations. The detailed recommendations can be found on the project website (www.medirad-project.eu) and are summarized below with a focus on optimisation:

- Reco 1 – Consolidation of patient data repositories across Europe, in particular:
  - Develop an interconnected and sustainable system of image and dose repositories at the European level.
- Reco 2 – Optimisation of radiation-based protocols for medical diagnostics or therapy, specifically:
  - Develop robust tools for optimisation of CT scanning and multimodality imaging.
  - Develop dosimetry-based protocols for molecular RT across Europe.
  - Actively promote good practices aimed at reducing cardiovascular risks after breast RT.
  - Deploy an EU-wide strategy to better predict and reduce secondary cardiovascular risks in breast cancer patients treated with RT.
  - Accelerate the generalised use in clinical practice of modelled total delivered doses to individual patients within Europe.
<table>
<thead>
<tr>
<th>MEDIRAD</th>
<th>HARMONIC</th>
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<th>EURAMED rocc-n-roll</th>
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<tbody>
<tr>
<td><strong>Objectives</strong></td>
<td>Enhance the scientific basis and clinical practice of radiation protection in medicine.</td>
<td>Investigate the relationship between early-life exposure to ionizing radiation and development of cancer and non-cancer effects.</td>
<td>Appraisal of detrimental effects of medical exposure for treatment of lymphoma or brain tumours.</td>
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<td><strong>Optimisation</strong></td>
<td>Improve organ dose estimation and registration to optimise doses for CT scans and nuclear medicine (NM) applications.</td>
<td>Improve estimation of patient-specific organ doses, and non-targeted organs in radiotherapy (RT).</td>
<td>Develop novel personalised dosimetry methods and tools to estimate the radiation burden to brain tumours and lymphoma patients undergoing radiological, NM and RT procedures.</td>
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<tr>
<td><strong>Risk</strong></td>
<td>Evaluate and understand the effects of low-dose medical exposures, focusing on the two major endpoints of public health relevance:</td>
<td>Investigate the late health effects of low, moderate and high radiation doses from modern RT using protons or photons with focus on cancer and non-cancer effects (endocrine, neuro and cardiovascular, QoL).</td>
<td>Development of a risk appraisal tool that will consider, (a) the best radiation-induced cancer risk models, (b) accurate patient organ dose data based on personalised dosimetry methods developed within the project, (c) age-at-exposure and sex-related differences in radiation risk, (d) radiation quality, and (e) SINFONIA results related to variations in radiation susceptibility between individuals.</td>
</tr>
<tr>
<td><strong>Interdisciplinarity</strong></td>
<td>Clinicians (pediatric oncologists, radiation oncologists, cardiologists), epidemiologists, biologists, medical physicists, and sociologists; patients and regulators in stakeholder groups.</td>
<td>Clinicians (pediatric oncologists, radiation oncologists, cardiologists), epidemiologists, biologists, medical physicists, and sociologists.</td>
<td>Clinical dosimetry, medical physics, NM, radiology, radiation oncology, radiation biology, computing and artificial intelligence.</td>
</tr>
<tr>
<td><strong>Translation into practice</strong></td>
<td>Set of science-based consensus policy recommendations for the effective protection of patients and staff were prepared, discussed with stakeholders and issued – Deliverables 6.5–6.8.</td>
<td>Provide guidelines on optimization techniques to guide treatments.</td>
<td>Science-based recommendations on radiological protection for the development of new applications of radiation in medical care, per category and per procedure.</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>The importance of education and training is highlighted in various elements of the science-based MEDIRAD Recommendations targeted at policymakers and the scientific/medical communities.</td>
<td>Training of pre- and post-doctoral students within the partners institutions.</td>
<td>Dedicated work package on education and training with implementation of various specific courses on radiation biology, AI applications etc.</td>
</tr>
</tbody>
</table>
• Reco 3 – Further optimisation of radiation protection for patients and medical workers:
  ○ Optimise systems for quantitative imaging irrespective of imaging system manufacturer or model.
  ○ Encourage harmonisation of practices through active engagement of health professionals, researchers, health authorities and patients.
  ○ Optimise the use of protective equipment to improve radiation protection of medical workers in interventional settings.

• Reco 4 – Future research on medical radiation protection in Europe, specifically:
  ○ Investigate new and optimise existing medical imaging procedures to improve benefit/risk ratios and personalised approaches.

In this respect, EURAMED rocc-n-roll is currently working on identifying research gaps to set up a new strategic research agenda (SRA) and a framework for the transfer of research results into clinical practice.

2.2 Radiation-induced risk

The potential health impact of the application of IR is important to appraise at the moment of choosing the particular modality for diagnostic and therapeutic purposes, particularly in sensitive populations such as children, and when introducing new IR applications and optimising existing ones.

Work in the research projects (Tab. 1) includes evaluating and understanding the effects of medical exposures:

(1) in children, from CT scanning (the largest diagnostic contribution to medical radiation dose) (MEDIRAD), from X-ray guided procedures for the diagnosis and treatment of cardiac defects, and cancer treatment, in particular from modern RT techniques using protons and photons (HARMONIC). As IR exposure in childhood is known to infer a greater risk of some cancer [3] and possibly non-cancer effects than exposure later in life, and as children have a longer life expectancy, it is particularly important to adequately understand the effects of these exposures and quantify them in order to minimise the long-term effects of IR on health and wellbeing of the patients;

(2) in adults, in particular, cardiovascular effects of external beam radiotherapy for breast cancer (the most prevalent cancer type in women in Europe); and feasibility of studying effects of molecular radiotherapy for thyroid cancer (less frequent, but for which little research has been conducted either in terms of actual doses delivered to the target and surrounding tissues or in terms of long-term sequelae of the exposure). As both breast and thyroid cancer have a good prognosis, there are large numbers of long-term survivors at risk of adverse effects from the treatment in Europe, hence understanding and minimising the long-term consequences of the treatment is of utmost importance;

(3) as well as on factors (genetic or environmental) which may confer increased sensitivity to radiation-induced cancer and non-cancer effects.

In addition to the work on specific populations and outcomes, SINFONIA aims to develop a novel radiation risk appraisal tool, including estimation of uncertainties, to support research not only on patients with suspected or diagnosed brain tumours and lymphomas undergoing radiological, nuclear medicine and radiation therapy procedures for diagnosis, staging, treatment response and follow-up but also on staff, comforters, the public and the environment.

Finally, MEDIRAD has issued a number of recommendations for future research on health effects:

• Recommendation 4 – Future research on medical radiation protection in Europe, specifically:
  ○ Conduct further research into the adverse effects of ionising radiation on healthy tissue;
  ○ Develop biologically-based models to evaluate radiation-induced disease risk;
  ○ Conduct large-scale clinical epidemiological follow-ups of patients to assess the late health effects of radiation in particular high-risk populations.

2.3 Interdisciplinarity of the projects

As shown in Table 1, the four projects rely on an integrative approach for RP research, strengthening the multidisciplinary collaboration between researchers, the medical community, and relevant stakeholders including patients. The multidisciplinary consortia in all four projects bring expert knowledge in a wide range of medical and scientific disciplines including, but not restricted to, radiologists, oncologists, cardiologists, paediatricians, medical physicists, radiographers, epidemiologists, biologists, computing and artificial intelligence experts and social scientists including those dealing with ethics. Such multidisciplinary cooperation necessarily involves ethical and data protection issues to conduct research in a responsible manner.
collaboration will enhance the interaction between the relevant communities to integrate clinical, biological and epidemiological investigations and promote the identification of biological mechanisms strengthening the understanding of health effects. Collaboration between medical physicists and IT specialists will contribute to determining relevant image quality parameters and develop optimization tools while dose reconstruction, an essential aspect of radiation epidemiology, results from a strong collaboration between (medical) physicists, radiologists, epidemiologists and statisticians.

The European RP research community relies on existing RP research platforms including MELODI, EURAMED and EURADOS which have developed and regularly update their SRAs to prioritise research topics for the European research community. All four projects carefully consider these priorities and are strengthening privileged relationships and integration within and between the platforms. EURAMED rocc-n-roll will develop, in collaboration with these and other platforms, an SRA for medical applications of IR and the corresponding radiation protection integrating the SRA of EURAMED as well as a corresponding roadmap. The development of such a coordinated and systematic European approach to research and innovation in medical applications of IR aims to improve patient care and quality of life of EU citizens, support growth and jobs in the EU and improve the EU’s position on the global market.

2.4 Translation of research results into clinical practice

A commonly expected impact of the four research projects is the translation of the research results into improved practical measures for the effective protection of people in the medical sectors, leading to a more robust system of protection of patients, workers and the general public. Scientific evidence is to be comprehensively translated into procedure and practice guidelines as well as into policy recommendations, beyond the classical exploitation of scientific publications. MEDIRAD recommends the implementation of guidelines to help European countries (and the scientific community) implement European regulatory requirements on ethics (including compliance with the GDPR Directive) to strengthen the multinational epidemiological framework. Collectively we contribute to producing science-based recommendations for the protection of patients and staff and guidelines on optimization techniques to guide diagnosis and treatments. As an example, two follow-up projects aiming to bring investigated methods into clinical practice have recently been launched: EU-JUST-CT on the justification of CT examinations within Europe and iViolin on implementing image quality assessment in oncological imaging. Where relevant, tailored material for patients and the public is or will be generated in the framework of the projects (see Fig. 1). We are building the infrastructures for harmonized patient data collection from different disciplines and treatments to account for the mechanisms leading to health detriment and to enable improved diagnosis and treatment. Ultimately, our contribution to understanding the health effects of ionizing radiation in all aspects of medical use intends to promote improved medical protocols, personalization of treatment, applied research and development of safer diagnostic and treatment modalities.

Finally, the main common objective is to impact patients throughout Europe with increased benefits from a better, high-quality and safe healthcare system toward equal access to medical applications using IR for diagnosis and treatment throughout Europe which could serve as a model for a more international approach.

2.5 Education and training

Education and training of the new generation of scientists and healthcare professionals devoted to RP in Europe are embedded in each of the four projects with the involvement of pre-and post-doctoral students in most participating institutions. In addition, SINFONIA and EURAMED rocc-n-roll have dedicated WPs devoted to analysing the current offer of academic and professional study programmes in the field of RP research and medical applications (including radiology, nuclear medicine, radiation oncology, medical physics, and other health care disciplines as well as epidemiology, biology, modelling, artificial intelligence (AI) and machine learning methods and applications in medicine). Based on these analyses, proposals for training programmes will be made to ensure high-level future research but also more harmonised patient care throughout Europe.

2.6 Ethical issues

Research involving patients, in particular children, and patient data sets and images raises a number of ethical issues which are systematically foreseen and addressed in the research protocols in MEDIRAD, HARMONIC and SINFONIA (GDPR compliant protocols that need to be approved by all appropriate ethics committees before any data collection or analysis can start). Informed decision of patients is a central aspect of today’s diagnostic and especially therapeutic approaches, which definitely holds for the medical use of ionizing radiation, and is an important pre-condition for any radiation protection research project. Research for optimisation of the use of IR for individual patient care also raises ethical issues in particular when harmful effects are expected. The use of AI in medical applications, and its associated ethical concerns, is an important aspect of current and future projects. AI will help to develop diagnostic and treatment approaches that are better tailored to the specific characteristics of the patient to improve therapeutic outcomes and minimise short and long-term adverse effects of radiation. AI will therefore be applied to clinical data (patient history, treatment and follow-up) to provide individualized recommendations for treatment. As such, AI brings ethical challenges associated with, for example, the potential for bias and gender issues and access to sensitive personal information as well as questions of software-based treatment decisions.
Fig. 1. MEDIReAD recommendations.
In EURAMED rocc-n-roll all ethical aspects of research and medical use of ionising radiation are systematically reviewed in a number of different tasks dedicated to the patient perspective, data protection issues, data-banks, and evaluation of the societal impact of the applications, and, in particular with a dedicated evaluation of the ethical aspects of AI-based approaches.

3 Discussion

3.1 Why research in medical RP is needed

To maximise the potential benefits and minimise the potential adverse effects of IR exposure, the growing use of medical applications of ionising radiation requires more research than ever in the field of radiation protection. The following examples give an overarching vision of what is still needed.

Patient A has a tumour in the left breast and must undergo RT, the standard treatment. RT has demonstrated that it can shrink the tumour and lengthen the life expectancy of the patient. Despite the best precautions, however, RT induces damage to the neighbouring organs and in particular the cardiovascular system, resulting in a significant risk of coronary disease and cardiac failure. Research needed in this context would address the development of new technologies and methods to maximise RT effects but minimise damage to healthy tissue. Also, the development of new tools for the detection and prediction of complications are potential consequences of a better understanding of the biological mechanisms of IR effects, and ethical issues must be examined for a proper benefit-risk balance of RT.

Patient B has cancer that requires regular follow-up of the tumour response during chemotherapy. Today this is done with recurrent CT examinations, although the total cumulative dose could easily exceed 100 mSv, a level beyond which stochastic complications are supposed to occur. In this context, the number of examinations should not matter because the benefit of a precise tumour response outweighs the hypothetical risk of IR. Since this is under debate [4], a better understanding of low-dose effects on human tissue must be developed. Biological approaches combined with epidemiological studies are still needed as well as personalised dosimetric methods in a wide context beyond oncology. In addition, the development of dose-reduction systems remains as crucial as other optimisation techniques for developing appropriate metrics and interoperability with the IT environment.

These two examples connect the four projects discussed here and will need to be addressed in the future to improve the benefits of IR applications to patients as well as the radiation protection of staff for such procedures.

3.2 Issues/challenges

Developing interdisciplinary approaches, especially between the radiation protection community and the health community as well as the digitisation community is critical, especially when referring to the rapid developments and new possibilities. In this context, the need of developing European-wide interconnected dose data repositories has to be stressed and would need a specific effort, in parallel to developing sustainable infrastructures for long-term clinical epidemiological follow-up of patients.

The transfer of research results into industrial products as well as into clinics in a harmonized way is a key element for future EC projects and needs a new framework which should be considered in future calls. Ensuring dissemination and uptake of MEDIRAD recommendations as well as from all projects and the EURAMED rocc-n-roll SRA by policymakers and scientific/medical communities and scientific exploitation will remain challenging and should be encouraged and supported as such.

3.3 Impacts

Our four projects impact radiological protection in the medical community by developing improved dosimetry and optimization tools which aim at providing, in the real-time, more accurate and personalised assessment of doses and lead to a more precise estimation of the dose-risk relationship for the benefit of the patients, staff and the general population.

The RP and medical communities are joining forces to understand the relationship between exposure to ionising radiation from diagnostic or therapeutic procedures and the development of cancer and non-cancer effects in specific populations integrating the identification of biomarkers of sensitivity to identify patients with a potential higher risk of short, medium or long-term radiation-induced effects.

The results of our research are to be translated into new/updated guidelines to assist clinicians, practitioners and medical physicists in properly balancing the risks and benefits of ionising radiation procedures and developing dose optimisation strategies for the protection of the patients and reduction of late toxicities. Guidelines for the protection of comforters, carers and medical staff are also developed. Our main objective is to promote high-quality healthcare minimizing side effects to reduce the overall burden of diseases.

3.4 Recommendations

The research in the current projects outlines the need for an overarching strategy for prioritising and implementing medical radiation protection research in Europe, to optimise diagnostic and treatment procedures and benefit European patients. Following up on the MEDIRAD recommendations, EURAMED rocc-n-roll aims to provide this strategy and to prioritise research needs to improve medical applications of IR, ensure the best medical practice and protection of patients. It will help to integrate the different approaches and will emphasize the importance of the patient-centred view, promoting
better and harmonized patient care throughout Europe while allowing socio-economic benefits including industrial welfare.

4 Conclusion

Medical use of IR is currently the largest human-made source of exposure to ionising radiation in the population in Europe and use and applications are growing. It contributes greatly and effectively to health care in terms of diagnosis and treatment of patients. The four European projects described have in common to rely on interdisciplinary consortia with partners from different regions to integrate regional differences, establishing close collaboration between the different disciplines to achieve reliable and meaningful results. Their achievements have the potential to be transferred into clinical practice and daily medical use as they include the generation of easily applicable tools as well as corresponding education and training recommendations. Overall, research on medical applications of ionizing radiation and the corresponding radiation protection has been proven to have a great potential for better and more safe healthcare for individual patients within Europe. Further research, in particular into new applications, will be important to continue in order to improve medical care and the quality of life of patients. Special consideration should be given to data protection, especially considering the potential benefits of safely used AI applications in radiation-based medicine.

Conflict of interests

The authors declare that they have no competing interests to report.

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Data availability statement

Within MEDIRAD, a matrix of historical doses associated with diagnostic radiological procedures has been generated and could be found at https://radiation.isglobal.org/medirad/2022/10/21/36/. Within EURAMED rocc-n-roll various surveys for example regarding the translational challenge and the current situation on education and training had been performed. The main results are published elsewhere, dedicated data can be made available on request. Within the SINFONIA project, radiation doses and other data associated with radiological procedures are currently being generated. Data associated with the HARMONIC project cannot be disclosed due to legal and ethical reasons. However, dosimetric tools and software will be made available.

Author contribution statement

Isabelle Thierry-Chef and Elisabeth Cardis took the leading role in proposing the strategy and overall organisation of the manuscript. They wrote the main text which has received very valuable inputs and comments from John Damilakis, Guy Frijia, Monika Hierath, and Christoph Hoeschen.

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