MEDIRAD

RECOMMENDATION 2

OPTIMISATION OF IONISING RADIATION-BASED MEDICAL PROTOCOLS FOR DIAGNOSTICS OR THERAPY

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 radiological 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 exposure to low doses of ionising radiation resulting 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 evidence-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. More information on MEDIRAD is available in Annex 3.

Competent international organisations, public authorities at European and national level, and organisations such as European research platforms and professional or patient associations, 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

MEDIRAD has conducted research on five key elements for further optimisation of radiation-based medical protocols for diagnostics or therapy. The related results have led to the elaboration of novel practical recommendations in the following fields.

1. Optimisation of image quality and dose in CT scanning, including CT in multimodality imaging and paediatric CT scanning

Computed Tomography (CT) is the largest contributor to the European population's collective exposure from medical uses of ionising radiation, and poses a potential health risk to patients [1, 2]. It is thus critical to employ the principle of optimisation in radiological protection to ensure doses are as low as reasonably achievable (ACLARA), unproductive exposure is avoided, and the benefit to risk ratio is maximised for all CT examinations [3]. This is of particular importance for the paediatric population as a result of their higher radiosensitivity and prolonged life expectancy [3]. While dose reduction inherently reduces the risk of potential harmful radiation effects, the extent to which doses can be reduced is constrained by image quality, which in turn is dependent on clinical needs [3-5]. Therefore, to effectively optimise exposure to ionising radiation from CT examinations and multimodality imaging, optimisation strategies should be based upon patient and organ dosimetry, image quality, patient characteristics, and clinical indications. The development of robust optimisation tools that account for each of these contributing factors, along with further advancements in personalised medicine, are therefore needed.

2. Patient-specific dosimetry in molecular radiotherapy (nuclear medicine therapy)

Patient-specific dosimetry to assess the radiation absorbed doses in target volumes and organs at risk is important to understand and improve the safety and efficacy of both existing and new radiopharmaceuticals. The planning and confirmation of absorbed doses is required under Council Directive 2013/59/Euratom [6] for molecular radiotherapy (MRT) as well as for external beam radiotherapy (EBRT). The evaluation of patient dosimetry on an individual basis can help to highlight the range of absorbed doses delivered from empirically-based fixed administrations of activity and the consequent range of likely outcomes, including long-term risks of secondary malignancies.

Multi-centre studies are required to develop personalised treatments with radiotherapeutics due to the limited numbers of patients treated at single centres. Individualised biokinetics should be considered rather than models and values established for a healthy population, and biomarkers of radiosensitivity can inform further levels of personalisation. While the clinical studies performed within MEDIRAD focused on radioiodine therapy for thyroid cancer, the methodologies developed for harmonised data collection and analysis are widely applicable to existing, and novel, radiotherapeutics as MRT experiences rapid expansion.

3. Breast radiotherapy and secondary cardiovascular risks: establishing risk models for clinical support and improving individual risk assessment with the help of specific biomarkers

Breast cancer (BC) is among the most commonly diagnosed cancers in women. Around 21% of BC cases occur in women younger than 50-64 years of age and 35% occur in those aged 50-64. Radiotherapy plays a pivotal role in the treatment of breast cancer BC patients, but may induce cardiac damage and subsequent major cardiac events like acute coronary events, which may occur relatively early or up to decades after completion of radiation treatment. As overall survival of BC patients has significantly improved, the prevalence of BC survivors at risk of developing cardiac toxicity is increasing. This is relevant at the individual level, as cardiac toxicity has a major impact on quality of life and leads to increased morbidity and mortality, but also at the societal level, as it leads to secondary health costs and may interfere with daily functioning and subsequent labour participation.
Therefore, identification of BC patients at high risk for cardiac toxicity is crucial for developing effective strategies for individualised primary and/or secondary prevention of cardiac toxicity.

4. Breast cancer radiotherapy: practical aspects on heart sparing

The radiation dose to the heart is an important risk factor for radiation-induced cardiac toxicity and it has been generally acknowledged that there is no threshold dose below which no toxicity will occur. Therefore, cardiac dose should be kept as low as reasonably achievable (ALARA) to prevent radiation-induced cardiac events.

There are several options to lower the dose to the heart, e.g. by means of reducing the radiation target volume (e.g. partial breast irradiation) and/or using more advanced radiation techniques (e.g. breath hold techniques and proton therapy). However, not all patients are suitable candidates for reducing the target volume. In addition, applying more advanced radiation techniques generally requires more resources, is more expensive, and may be more burdensome to patients.

Although there is an increasing awareness among radiation oncologists that sparing the heart is essential to broaden the therapeutic ratio in BC patients, the currently available options are not always applied in routine clinical practice.

5. Modelling of patient dosimetry at the voxel scale

Patient dosimetry is an essential part of ensuring quality and safety both in radiotherapy and diagnostic imaging. In radiotherapy, the determination of the radiation doses has to be improved, especially in nuclear medicine therapy. In external radiotherapy, knowledge about radiation dose, especially outside the planning target volume, also has to be improved. It is therefore necessary to move from planned dose distribution to delivered dose distribution in order to improve the quality of care, including person-centred care, and the radiological protection of the patient. In diagnostic imaging, where the radiation dose is not planned for individual patients, better knowledge about the radiation dose to organs is needed to improve optimisation in general and for individualisation of imaging processes.

Today, to a great extent, only radiation dose indices are used to document patient doses. This lack of information hinders real optimisation and can also conceal radiation-related risks to specific organs also in the field of diagnostic imaging.

Recent advances in computer science will facilitate progress in this field, since the specific constitution of the patient, as well as technical parameters specifying the exposure, are now available and usable for dose estimation. Internal dosimetry can also include information from molecular imaging to advance the knowledge about patient-specific biokinetic data. The MEDIRAD project has made several contributions to this end.

The following science-based policy recommendations have been produced in an effort to advocate and facilitate the further development of tools and techniques to optimise both image quality and patient exposures to ionising radiation. They are addressed to different stakeholders in an effort to disseminate and implement the project's key findings and learnings.

1

Optimisation of image quality and dose in CT scanning, including CT in multimodality imaging and paediatric CT scanning.

Overall recommendation

Develop and implement robust tools for optimisation of CT scanning and multimodality imaging that account for whole-body and organ-specific dosimetry, image quality, and radiogenic risk.

» Specific recommendations:

1. Accompany all exposure documentation and reporting by suitable measurable indicators of image quality.
2. Evaluate organ doses prospectively and retrospectively in patient sub-cohorts to assess individual risks and better inform patient management.
3. Pay special attention to keep doses to radiosensitive organs to a minimum while maintaining appropriate image quality, especially in paediatric populations undergoing recurrent CT exams.
4. Encourage further research into methods to accurately estimate individual patient organ doses.
5. Support the transfer of image quality assessment tools developed in MEDIRAD to other clinical indications, both for chest CT and other CT protocols.
6. Support further research and development towards an integrated dosimetry and image quality approach that incorporates equipment-specific, patient-specific, and protocol-specific assessments of exposure.
7. Establish indication-specific diagnostic reference levels (DRLs) for organ dose values that are accompanied by image quality reference levels (IQRLs).
8. Encourage standardisation of CT radiation exposure in nuclear medicine to improve optimisation of multimodality imaging.

1.1. Justification

CT scanning is being increasingly used for diagnosis based on imaging and contributes considerably to radiation exposure among the population. Therefore, optimisation in terms of benefit-to-risk ratio is of extreme importance, particularly for paediatric applications. On the basis of experience acquired through the MEDIRAD project (see Annex 1), this recommendation aims to overcome current barriers to achieving effective and efficient optimisation in CT scanning and multimodality imaging by translating the MEDIRAD research findings into daily clinical routine procedures. Additionally, it encourages the extension of MEDIRAD's overarching methodological approach beyond CT scanning and multimodality imaging, in order to develop an integrated optimisation system for diagnostic radiology, interventional radiology and nuclear medicine imaging.

1.2. Implementation

1. Accompany all exposure documentation and reporting by suitable, measurables, indicators of image quality.

Optimisation of the benefit-to-risk ratio for imaging procedures can only be achieved if the exposure is reduced in a way that guarantees appropriate image quality, maintaining diagnostic accuracy for the pathology/clinical indication of interest. Therefore, in all future optimisation studies, both the exposure, preferably as organ doses, and the image quality derived from the corresponding patient images (e.g. by way of the MEDIRAD project's semi-automatic evaluation of physics-based image quality parameters [5]) have to be determined.

If broadly established, fast and objective image quality and dose evaluations could greatly benefit the diagnostic use of ionising radiation and facilitate easy approaches to quality assurance. It is important that this approach is easy to implement and does not increase the workload of the clinicians. A most promising approach would be to integrate such tools in the vendors' software, and appropriate steps should be taken in this direction.

» Target audience: practitioners, policy makers, regulatory authorities, medical professional organisations, research community.

2. Evaluate organ doses prospectively and retrospectively in patient sub-cohorts to assess individual risks and better inform patient management.

Patient organ doses from thoracic CT may rise to tens of mGys and even exceed established thresholds for tissue effects after repeated CT acquisitions. These doses, and the potential resulting risk of radiation induced malignancies or other health effects, should not be ignored. Practitioners (including radiologists, cardiologists, oncologists, radiographers), in collaboration with the research community, should make a concerted effort to record organ doses and follow

various sub-cohorts of patients over time (i.e. years to decades) as a means of monitoring primary exposure and evaluating individual risk. MEDIRAD has developed methods to estimate patient organ dose for chest CT examinations and determine image quality, integrating state-of-the-art objective and subjective image analysis [5,7]. It is recommended that practitioners / investigators implement these methods alongside established risk calculations as robust optimisation tools in thoracic CT scanning. Additionally, the MEDIRAD method of organ dose estimation can be employed retrospectively as a means of informing current patient management. It also offers a tool to expedite epidemiological research related to dose effects and radiation induced risk for the selected thorax protocols.

» Target audience: practitioners, research community, regulatory authorities, patient associations.

3. Pay special attention to keep doses to radiosensitive organs to a minimum while maintaining appropriate image quality, especially in paediatric populations undergoing recurrent CT exams.

The risk of stochastic radiation effects in the paediatric population has been shown to be at least twofold higher than in adult patients. Additionally, severely ill (in particular neurologic and haematologic) paediatric patients may undergo multiple CT studies of the head and thorax in a short period of time. A significant percentage of active bone marrow is present in the cranium, ribs, and vertebrae of young children, and effective dose estimation does not adequately describe dose variations in superficially located organs.

Therefore, novel methodologies must be employed to better estimate and further optimise CT examinations within the paediatric population as a means of keeping organ-doses as low as reasonably achievable while still maintaining appropriate image quality. The MEDIRAD project provides new evidence to inform dose reduction strategies that focus on tube current modulation and tube voltage selection techniques [8,9]. Practitioners, medical professional organisations, and the research community are encouraged to incorporate and further develop these findings into robust and practicable organ-dose reduction methods that can be widely implemented within the clinical setting.

» Target audience: practitioners, medical professional organisations, research community, regulatory authorities, patient associations.

4. Encourage further research into methods to accurately estimate individual patient organ doses.

Further research efforts should be employed to estimate doses to partially irradiated organs such as the thyroid and liver. This is particularly important for patients undergoing multiple CT scans, given the heightened risk associated with cumulative organ-doses. Over-ranging can represent a significant portion of the overall exam dose, particularly for short scan lengths. A patient-specific method for the estimation of organ doses based on Monte Carlo calculations will be useful for CT optimisation and as input for epidemiological research and modelling of radiation induced risks.

It is expected that this could have an important impact on reducing doses to partially irradiated organs. Medical professional organisations and the research community are encouraged to direct future research efforts on using the capabilities of modern CT scanners employing beam overscanning, organ-based tube current modulation, as well as on indication-specific scan protocols in order to optimise the scan length, beam collimation, pitch, and effective mAs.

» Target audience: practitioners, research community, regulatory authorities, research community, patient associations.

5. Support the transfer of image quality assessment tools developed in MEDIRAD to other clinical indications, both for chest CT and other CT protocols.

Within the scope of the MEDIRAD project, an approach for semi-automatic evaluation of physics-based image quality parameters [5], which is correlated with subjective image quality evaluations, has been developed for three clinical indications for Chest CT: mycobacterial infections and pulmonary tuberculosis; interstitial pathology (suspicion of pulmonary fibrosis); and pulmonary metastases and nodules.

Given the positive MEDIRAD findings, practitioners and the medical research community are encouraged to translate the current evaluation technique to other relevant clinical indications (e.g. aortic disease), as well as CT protocols beyond the thoracic region (e.g. head and neck, abdominal/pelvic). When prioritising allocation of research efforts, clinical needs and feasibility of clinical implementation for the specified indication must be taken into account to ensure maximum impact of research outputs.

» Target audience: practitioners, research community, regulatory authorities, research community, patient associations.

6. Support further research and development towards an integrated dosimetry and image quality approach that incorporates equipment-specific, patient-specific, and protocol-specific assessments of exposure.

To best optimise CT scanning it is important to consider the diagnostic quality of the image based on clinical needs, the radiation dose to the patient, which should be as low as reasonably achievable, and the examination exposure techniques based on relevant protocols. To this end, CT dosimetry should be patient-specific, equipment-specific, and protocol-specific. There are currently no systems that offer a fully integrated approach; however, the MEDIRAD project's methodology and associated tool for determining image quality and patient organ dose offers a valuable path forward (see Annex 1 for detailed information).

On this basis, further research and development should be encouraged to realise a robust and fully integrated system for CT dosimetry and diagnostic image quality that allows for traceability of all generated data and is applicable to CT imaging of any region of the body.

» Target audience: practitioners, regulatory authorities, medical professional organizations, research community, industry.

7. Establish indication-specific diagnostic reference levels (DRLs) for organ dose values that are accompanied by image quality reference levels (IQRLs).

The current approach to establishing diagnostic reference levels (DRLs), as outlined in ICRP Publication 135 [10] and mandated under Council Directive 2013/59/EURATOM [6], is an effective method for optimising medical exposure to ionising radiation; however, CT exposure could be further optimised through the incorporation of indication-based organ dose values and accompanying image quality reference levels (IQRLs). Policy makers and the radiation protection research community are encouraged to further explore the establishment of organ dose values with accompanying IQRLs as a more nuanced approach to DRL-based optimisation. This novel approach should have regard for clinical needs, prioritising the most prominent examinations with notably high doses of radiation for maximum impact.

Clearly, there are many steps to be taken in terms of development to allow fully automated evaluations to be stored in databases relevant for DRL applications. In addition, it is necessary to educate and train the medical professionals as well as regulators regarding organ dose-based DRLs and IQRLs. These new approaches, while slightly more complex than the existing DRLS, allow for more efficient optimisation. The system for evaluations of organ dose values and image quality parameters must be fully automated to avoid new barriers for adopting the DRL concept. It is important to foster the DRL concept in general and provide support to the different countries within the EU need in adopting this concept.

» Target audience: policy makers, regulatory authorities, research community.

8. Encourage standardisation of CT radiation exposure in nuclear medicine to improve optimisation of multimodality imaging.

The establishment of European DRLs for specific applications of CT in multimodality imaging has proven extremely difficult, notably because numerous CT dose indicators are currently in use across Europe [11]. A standardised approach to calculating and reporting CT radiation exposure is required to significantly improve optimisation of multimodality imaging and allow a better standardisation of CT applications in nuclear medicine. A holistic optimisation approach should be taken, accounting for both the CT and nuclear medicine components.

DRL quantities of CTDIvol and DLP should be used for CT radiation exposure, while effective dose or even organ doses are recommended as a means of comparing the effects of CT and nuclear medicine procedures. The effective doses and organ doses can be used as a potential benchmark quantity for combined irradiation in hybrid imaging. Again, standardisation of protocols for CT applications in hybrid imaging is essential. Suitable databases are also required to compare procedures from various hospitals throughout Europe and optimise these procedures in a harmonised way.

» Target audience: policy makers, regulatory authorities, medical professional organisations, research community.

1.3. MEDIRAD scientific achievements supporting recommendations

- Dose evaluation tools, in tandem with correlated objective and subjective image quality evaluations of chest CT examinations, have been integrated into a freeware, open access, modular software expert system, which can be used to determine patient-specific exposure descriptors as well as patient-specific image quality parameters and thus identify the optimal Chest CT protocol.

- MEDIRAD has studied how to improve the direct estimation of cancer risk following low doses of ionising radiation from CT scanning in childhood and adolescence and has investigated factors, such as genetic and epigenetic variants, which may modify this risk. More information is found in Annex 1.

2

Patient-specific dosimetry in molecular radiotherapy (nuclear medicine therapy).

Overall recommendation

Develop and implement dosimetry-based protocols for molecular radiotherapy across Europe.

» Specific recommendations:

1. Develop a roadmap for dosimetry-based treatment planning and verification of the radiation doses delivered to target volumes and organs at risk for treatments with radiotherapeutics.
2. Provide adequate resources, including medical physics support to perform patient dosimetry, to centres providing radionuclide therapy.
3. Support development of observational and interventional multi-centre, multi-national clinical studies.
4. Harmonise the implementation of Council Directive 2013/59/Euratom with respect to patient dosimetry within Europe.
5. Record radiation doses and treatment details in dose data repositories..

2.1. Justification

The radiation doses delivered to patients undergoing molecular radiotherapy (MRT) can be calculated from quantitative imaging of the biodistribution of uptake of a radiotherapeutic, a capability unique to nuclear medicine. Patient-specific dosimetry may be used to personalise treatment planning and to verify the radiation doses delivered, as mandated by Council Directive 2013/59/EURATOM [6].

The need to improve clinical and cost effectiveness of existing and new radioactive drugs, and to evaluate the risks entailed by their use, are of increasing importance as the field undergoes rapid expansion. Multi-centre clinical studies are necessary to overcome the limited number of patients treated in individual centres. Within MEDIRAD, the radiation doses delivered to patients undergoing radioiodine treatment for low and intermediate risk thyroid cancer were calculated in four centres, in three countries, through a multidisciplinary approach involving medical physics, nuclear medicine, and radiation oncology.

Site visits were performed to prepare imaging systems for quantitative imaging and dosimetry was performed centrally in two centres. The studies demonstrated the feasibility of acquiring, processing, and collating dosimetry data. In addition, pharmacokinetic modelling was performed and a protocol for a prospective epidemiological study was developed to assess the risks of low dose radiation. A further study of radiosensitivity biomarkers is reported separately.

2.2. Implementation

1. Develop a roadmap for dosimetry-based treatment planning and verification of the radiation doses delivered to target volumes and organs at risk for treatments with radiotherapeutics.

Currently, the majority of MRT procedures are performed using empirically-based fixed activity administrations of radioisotopes. This leads to a wide range of absorbed doses delivered both to tumours and to organs at risk, as also shown by results from MEDIRAD. While quantitative imaging and dosimetry is feasible for therapy procedures, possibly aided by 'companion diagnostics', dosimetry is not routinely performed [12, 13].

However, patient-specific dosimetry is mandated and recommended by Council Directive 2013/59/Euratom [6], ICRP Publication 140 [17] and position statements from medical professional organisations [19-21], and has been incorporated into national legislation.
A coordinated European approach should be developed in consultation with all relevant stakeholders, including nuclear medicine and radiation oncology, to enable dosimetry-based treatment planning and verification of the radiation doses delivered, with initial focus on therapeutic procedures of greatest clinical and cost impact.

» Target audience: policy makers, regulatory authorities, medical professional organisations, research community.

2. Provide adequate resources, including medical physics support to perform patient dosimetry, to centres providing radionuclide therapy.

Many centres currently do not have sufficient medical physics support or the necessary resources to prepare scintillation cameras and ancillary equipment for quantitative imaging or to perform routine calculation of absorbed doses in MRT.

Existing training schemes should guarantee a constant supply of suitably qualified medical physicists with a comparable level of training, to enable local data processing supported by external validation and quality control. MEDIRAD has demonstrated that dosimetry verification of radioiodine therapy is feasible but that an infrastructure is necessary to acquire, process and analyse the data and to report the results. The healthcare costs of setting up the necessary infrastructure should be supported alongside the cost implications of new radiotherapeutics.

» Target audience: policy makers, regulatory authorities, medical professional organisations, research community.

3. Support development of observational and interventional multi-centre, multi-national clinical studies.

Currently, clinical trials of novel radiotherapeutics incorporate a limited degree of dosimetry, with little or no consideration of dosimetry-based treatment planning. It is therefore of particular importance that patient-specific dosimetry is fully integrated into early and late phase clinical trials, and that results are made available to clinical users. This will require close collaboration between industry, professional societies and academic research.

MEDIRAD has shown the practical feasibility of multi-centre clinical studies incorporating patient dosimetry, although there is a need to conduct these as single multi-national studies under the umbrella of international organisations such as the EORTC, rather than as separate studies as was done in this project. Protocols developed within MEDIRAD for site set-up measurements and for dosimetry calculations should be further refined in collaboration with national and international societies. To support under-resourced centres, MEDIRAD performed site visits for the preparation of imaging systems and centralised dosimetry calculations in 'dosimetry hubs', an approach that should be further explored (see Annex 1 for details).

In addition, interventional trials are required to investigate the clinical and cost effectiveness of personalised dosimetry-based treatments with radiotherapeutics. To facilitate multi-national trials, regulatory authorities should ensure that the process of ethical approval is standardised across Europe.

» Target audience: policy makers, regulatory authorities, medical professional organisations, research community.

4. Harmonise the implementation of Council Directive 2013/59/Euratom with respect to patient dosimetry within Europe.

Throughout the MEDIRAD project and from the answers to the Stakeholder questionnaire, it became evident that the implementation and interpretation of Council Directive 2013/59/Euratom [6] varies widely between countries and centres in Europe with respect to patient dosimetry. Sharing the expertise gathered in the context of the MEDIRAD project could contribute to regulatory development and help harmonise the implementation of these regulations across Europe.

» Target audience: policy makers, regulatory authorities, medical professional organisations.

5. Record radiation doses and treatment details in dose data repositories.

The studies conducted within MEDIRAD demonstrated that although data may be acquired and processed with different methodologies in different centres, similar results may be obtained. Radiation dosimetry may be further harmonised with the incorporation of uncertainty analysis, allowing a flexible approach to the acquisition of data and to dosimetry calculations. An imaging and dose data repository, the IRDBB, was developed within MEDIRAD to store image data, radiation absorbed doses, and ancillary information including electronic case report forms (see Annex 1). A similar database should be developed and maintained to collate patient-specific details, information relating to the treatments, and outcome data including quality of life.

Nuclear medicine and MRT procedures provide a suitable framework to assess the effects of low-dose radiation, due to the large number of patients treated each year throughout Europe and the ability to accurately calculate organ level absorbed dose and effective absorbed doses. Funding and resources should be made available to support a prospective epidemiological study which would inform the continuing debate concerning the validity of the linear-no-threshold method. In addition, a European database would offer the potential for application of AI and machine-learning techniques to interrogate the wealth of data that may be collected.

» Target audience: practitioners, policy makers, regulatory authorities.

2.3. MEDIRAD scientific achievements supporting recommendations

- Developed standard-operating-procedures for set up of centres for quantitative imaging of radioiodine.
- Set up of the first European network for quantitative imaging of radioiodine.
- Successful set up and running of a multi-national multi-centre study involving dosimetry in MRT.
- Development of an imaging and dose data repository for transfer of MRT imaging and dosimetry data.
- Identified a lack of medical physics support in smaller centres which are currently not set up to perform dosimetry in MRT.
- Identified differences in the implementation of Council Directive 2013/59/Euratom between centres and countries of the MEDIRAD consortium.

3

Breast cancer radiotherapy and secondary cardiovascular risks: Establishing risk models and identifying relevant biomarkers for improving clinical support and individual risk assessment.

Overall recommendation

Deploy a EU-wide strategy to better predict and reduce secondary cardiovascular risks in breast cancer patients treated with radiotherapy.

» Specific recommendations:

1. Use multivariable normal-tissue complication probability (NTCP)-models for cardiac toxicity in all breast cancer patients to identify those at risk of major radiation-induced cardiac events.
2. Continuously improve multivariable NTCP-models for cardiac toxicity on the basis of new data.
3. Set up a European prospective data registration programme.
4. Use cardiac imaging and circulating biomarkers for follow-up of early cardiovascular changes following breast cancer radiotherapy.
5. Conduct long-term longitudinal studies combining imaging and circulating biomarkers to develop successful preventive measures for radiation-induced cardiac toxicity.

3.1. Justification

Within the MEDIRAD project, two studies were conducted to identify patients at risk for radiation-induced cardiac toxicity and who may benefit from preventive measures.

Firstly, an international multi-center study (MEDIRAD-BRACE) was conducted to develop prediction models for cardiac toxicity based on pre-treatment variables and 3-dimensional distributions. The so-called normal-tissue complication probability (NTCP) models are used to predict the risk for individual patients of developing complications after radiation-based therapy, based on patient, disease, and treatment characteristics, including the dose distributions given to the healthy tissue surrounding the tumor. Besides informing patients about their expected risks of radiation-induced complications, NTCP models are clinically used to guide treatment decisions by looking at the difference in predicted risk of complications between treatment plans. The models developed in the BRACE study enable identifying breast cancer (BC) patients at risk of developing radiation-induced cardiac toxicity. To this purpose, a centralised and integrated clinical data and radiation dose repository was established from four European cancer centres, containing integrated data of over 6,000 breast cancer patients.

Secondly, an international multi-centre prospective cohort study (MEDIRAD EARLY-HEART) was conducted to discover early biomarkers of cardiac events after completion of radiation treatment, using blood and imaging biomarkers. The results from this study provide essential information for developing strategies for secondary preventive measures that can be tested in future projects.

The following science-based policy recommendations have been established in an effort to advocate and facilitate the establishment of a prospective data registration programme and a repository of clinical, dose and imaging data for BC patients undergoing radiotherapy at a European level, to enable continuous adaptation of prediction models as radiation technologies improve.

3.2. Implementation

1. Use multivariable normal-tissue complication probability (NTCP)-models for cardiac toxicity in all breast cancer patients to identify those at risk of major radiation-induced cardiac events.

Multivariable NTCP-models should be used by clinicians in all BC patients to identify those at risk of radiation-induced major cardiac events, including pre-existing risk factors at baseline, other treatment modalities, and cardiac radiation dose parameters.
BC patients with pre-existing risk factors for major cardiac events have an increased absolute excess risk to develop radiation-induced cardiac events already within the first five years after radiotherapy. Consequently, elderly BC patients are also at increased risk of radiation induced-coronary events.

A recent study with 910 BC patients who are also part of the BRACE cohort showed that radiation dose to pre-existing calcified atherosclerotic plaques in the left anterior descending coronary artery (LAD) is strongly associated with the development of acute coronary events [22]. Based on this BRACE subcohort, a preliminary mechanistic model of radiation-induced cardiovascular risk was developed that will be validated in the complete BRACE cohort. The results imply that, in patients with pre-existing advanced plaques, acute coronary events can already emerge within few years after radiotherapy.

With the availability of the NTCP-model, which is based on the mean heart dose, left ventricle V5, and pre-existing cardiovascular risk factors, it is possible to predict the risk of acute coronary events 10 years after radiotherapy for each individual BC patient, so that preventive measures can be taken or information on risk of cardiac complications can be provided accordingly. It is therefore recommended to apply NTCP-models for cardiac toxicity in all BC patients regardless of treatment site, boost, and/or inclusion of internal mammary chain or not.

» Target audience: regulatory authorities, medical professional organisations, research community.

2. Continuously improve multivariable NTCP-models for cardiac toxicity.

NTCP-models for cardiac toxicity should be continuously improved, as more data become available, for example when longer follow-up is available, cohorts become larger, or new radiotherapy or systemic treatments are introduced. Typically, these late side effects of irradiation increase with time of follow up. Larger (prospective) cohorts with longer follow up will enable to predict very long-term risks and to develop NTCP-models for subgroups of BC patients, e.g. younger and elderly BC patients, and BC patients with or without atherosclerotic plaques in the coronary arteries. Furthermore, radiomic features (other than the coronary artery calcium score) of the planning CT scans could be included.

Recently, it was confirmed that hypofractionated breast radiotherapy (26 Gy in five fractions over 1 week) is not inferior to the standard of 40 Gy in 15 fractions over 3 weeks for local tumour control [23]. This schedule may soon be the standard schedule for a large group of BC patients from European countries. It is therefore important to check whether NTCP-models for cardiac toxicity need to be updated when radiotherapy schedules based on fewer, larger fractions and lower total dose become standard treatment. Moreover, because of national/regional differences in patient population and treatment protocols, NTCP-models for cardiac toxicity may have to be finetuned as well.

» Target audience: research community.

3. Set up a European prospective data registration programme.

To enable improvement/updating of NTCP-models for cardiac toxicity, it is recommended to collect pre-treatment tumour and patient characteristics (including cardiovascular risk factors), treatment data, tumour status, dose distribution parameters, and cardiac events systematically

in each BC patient as part of lifetime routine follow up, preferably using a uniform and standardised prospective data registration programme. The European Particle Therapy Network (EPTN) has already developed the Proton International Research INSPIRE (www.protonsinspire.eu) infrastructure for standardised prospective data registration and this may also be used to collect high quality data for BC patients treated with photon therapy. Electronic Patient Reported Outcome Measures (PROMs) can be part of a centre's infrastructure to efficiently collect patient data at standardised time intervals.

» Target audience: regulatory authorities, medical professional organisations, research community.

4. Use cardiac imaging and circulating biomarkers for follow-up of early cardiovascular changes following breast cancer radiotherapy.

There is a need for precise knowledge on the relationship between radiation dose to specific cardiac structures and early subclinical cardiac changes that could eventually lead to cardiac complications.

The MEDIRAD EARLY HEART study has attempted to identify new cardiac imaging (based on echocardiography, cardiac CT, and cardiac MRI) and circulating biomarkers of radiation-induced cardiovascular changes arising within the first two years of BC radiotherapy [24]. Knowledge developed within EARLY-HEART can provide additional leads to improve early detection and prediction of cardiac events and should provide further insight on pathophysiological mechanisms. Results from this study complement those from the BRACE study.

» Target audience: medical professional organisations, research community.

5. Conduct long-term longitudinal studies combining imaging and circulating biomarkers to develop successful preventive measures for radiation-induced cardiac toxicity.

Imaging of cardiac damage and identification of circulating biomarkers is essential to unravel pathophysiological mechanisms of radiation-induced cardiac toxicity. Understanding the pathophysiology is essential for developing optimised radiation dose distributions aimed at reducing cardiac damage and subsequent cardiac events (primary prevention). Furthermore, targets may be identified for secondary preventive measures. Moreover, imaging and circulating biomarkers of subclinical cardiac damage may help to identify BC patients at high risk of future cardiac events and guide individualised cardiac screening programmes.

It is likely that different pathophysiological mechanisms play a role in radiation-induced cardiac toxicity at different time periods after radiotherapy, partly dependent on age of the patient and the presence of pre-existing cardiovascular risk factors. In this regard, follow up for two years after radiotherapy is still too short for unravelling the pathophysiological mechanisms based on imaging and circulating biomarkers of subclinical cardiac damage. Adding timepoints at 5, 10 and 25 years after radiotherapy to assess circulating and imaging biomarkers (echocardiography, cardiac MRI, and cardiac CT) will provide information on mechanisms that may come into

play later. Typically, these late side effects of irradiation increase with time of follow up, and correlation with earlier biomarkers could help to preventively treat patients at risk.

» Target audience: research community.

3.3. MEDIRAD scientific achievements supporting recommendations

- Multivariable NTCP-models to predict the risk for individual BC patients of developing acute coronary events were developed in BRACE study based on cardiac dose parameters and pre-existing cardiac risk factors.
- Our results show that these multivariable NTCP-models for cardiac toxicity need to be regularly updated with new data available and as radiotherapy techniques evolve.
- EARLY HEART study showed that specific markers from echocardiography, cardiac CT, cardiac MRI and circulating biomarkers have the potential to detect early cardiac changes arising within the first two years after BC radiotherapy.
- A study protocol combining EARLY HEART and BRACE studies would allow to detect early cardiac changes, follow their long-term evolution, and develop preventive measures accordingly.

4

Breast cancer radiotherapy and secondary cardiovascular risks: practical aspects on heart sparing.

Overall recommendation

Actively promote good practices aimed at reducing secondary cardiovascular risks after breast radiotherapy.

» Specific recommendations:

1. Utilise automatic segmentation tools to delineate the heart and its substructures.
2. Treat all left-sided breast cancer patients and right-sided breast cancer patients receiving radiotherapy of the internal mammary chain with deep inspiration breath-hold radiotherapy.
3. Consider proton therapy in cases of a clinically relevant estimated excess risk of acute coronary events, especially in younger patients.

4.1. Justification

Within the MEDIRAD project, an international multi-centre study (MEDIRAD-BRACE) was conducted to develop prediction models for cardiac toxicity based on pre-treatment variables and 3-dimensional distributions. The models developed in this study enable identifying breast cancer (BC) patients at risk of developing radiation-induced cardiac toxicity. To this purpose, a centralised and integrated clinical data and radiation dose repository was established from four European cancer centres, containing integrated data of over 6,000 BC patients.

The prediction models developed within the MEDIRAD-BRACE study contain dose parameters that are most predictive for the development of cardiac toxicity. This information is essential for the radiation oncology community to guide radiation dose optimisation in BC patients aimed at curing the cancer and preventing radiation-induced cardiac toxicity. The following science-based policy recommendations specifically address primary preventive strategies that radiation oncologists can implement.

4.2. Implementation

1. Utilise automatic segmentation tools to delineate the heart and its substructures.

It is advised to use an automatic segmentation tool to delineate the heart and substructures to prevent inter observer variation and hence generate more consistent cardiac dose volume histogram parameters (MHD and LV-V5) to calculate the individual absolute excess risk of acute coronary events. Furthermore, an automatic segmentations tool has the advantage of saving time.

» Target audience: medical professional organisations, research community, manufacturers.

2. Treat all left-sided breats cancer patients and right-sided breast cancer patients receiving radiotherapy of the internal mammary chain with deep inspiration breath-hold radiotherapy .

All left-sided BC patients should preferably be treated with deep inspiration breath-hold (DIBH). To spare treatment time, and spare patients the burden of DIBH when DIBH does not help in reducing cardiac dose, both a free breathing (FB) and DIBH planning CT scan can be made for treatment preparation. Right-sided BC patients receiving radiotherapy of the internal mammary chain can also benefit from DIBH radiotherapy as well as from a FB and DIBH planning CT scan for treatment preparation.

» Target audience: medical professional organisations.

3. Consider proton therapy in cases of a clinically relevant estimated excess risk of acute coronary events, especially in younger patients.

More advanced radiation techniques (such as protons) may be reserved for BC patients with a high absolute excess risk of radiation-induced acute coronary events based on advanced photon techniques (IMRT/VMAT). BC patients can be selected for protons based on a model-based planning comparison [25]. There should be a significant (predefined) reduction in absolute excess risk of acute coronary events as calculated with the NTCP-model (i.e. ≥2%) between the more advanced photon treatment plan and the proton plan to be eligible for treatment with the more advanced radiation technique.

When the absolute excess risk of acute coronary events is less than 2% with photons, no planning comparison has to be performed.
This way of selecting BC patients for proton therapy saves resources and will help to reduce the prevalence of radiation-induced cardiac toxicity.

» Target audience: medical professional organisations, research community.

4.3. MEDIRAD scientific achievements supporting recommendations

- The MEDIRAD BRACE study showed that the risk of acute coronary events afte BC radiotherapy increases with increasing dose to the heart. This excess risk can be determined by using the multivariable MEDIRAD-BRACE NTCP-model, which contains a number of dose volume parameters next to some baseline risk factor for acute coronary events.

- Using this NTCP-model, the risk reductions that can be obtained with more advanced radiation techniques can be calculated on an individual patient basis.

5

Modelling of patient dosimetry.

Overall recommendation

Accelerate the generalised use of modelled total delivered doses to individual patients in clinical practice within Europe.

» **Specific recommendations:**

1. Perform advanced assessment of the delivered dose in radiotherapy applications to improve and optimise treatment protocols for a personalised medicine approach.
2. Estimate patient-specific organ doses in diagnostic imaging applications, to allow better optimisation schemes.
3. Improve dosimetry of the total delivered dose outside the planning target volume in radiotherapy.
4. Determine and document patient organ doses in CT, interventional radiology and hybrid imaging.
5. Create databases using common nomenclature at the national and international level to facilitate personalised radiation therapy and diagnostic imaging.
6. Provide education and training on patient-specific dosimetry and the use of new technologies.
7. Better coordinate ongoing and new research initiatives in the field at the EU-level.
8. Promote research on quality and safety issues related to artificial intelligence in the field.

5.1. Justification

Artificial Intelligence (AI) will play a major role in the continuous effort to improve patient dosimetry, especially by providing solutions for fast and accurate dosimetric calculations, independently of the planned dose computed by the equipment. MEDIRAD research has shown that these solutions are close at hand. However, there are several challenges to overcome in order to

transfer research results to clinical everyday practise, ranging from the need for large transnational high-quality databases required for AI tools, machine learning, and deep learning, to the need for better coordination of the European research effort, and to improved education and training of clinical teams in this field.

5.2. Implementation

1. Perform advanced assessment of the delivered dose in radiotherapy applications to improve and optimise treatment protocols for a personalised medicine approach.

For personalised medicine, and patient-specific optimisation, it is necessary to assess the delivered dose to critical organs in radiation therapy, as this is the relevant dose to determine potential adverse acute and late effects. However, the currently documented planned radiation dose may differ significantly from that actually delivered. In nuclear medicine therapy, the current situation is even worse, since the estimation of the radiation dose to critical organs specific to each patient is still a challenge for many treatments.

MEDIRAD research has shown that accurate biokinetic modelling, and better molecular imaging data can be used to address this challenge. The knowledge obtained can be used to improve treatment protocols and optimise treatment for the individual patient in the context of a personalised medicine approach.

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

2. Estimate patient-specific organ doses in diagnostic imaging applications, to allow better optimisation schemes.

Regarding the application of ionising radiation in diagnostics, MEDIRAD research has shown that organ dose values can be determined accurately by means of Monte Carlo methods and that those are related to image quality. Thus, it is feasible and important to determine and document patient-specific organ doses to verify the efficient use of the infrastructure. This would also be a cornerstone to allow better optimisation schemes for each individual patient. Today, patient indices are often used to document patient dose. This does not allow optimisations on an individual patient basis.

As for nuclear medicine examinations, generic models are still being used, with their inherent substantial uncertainties. The speed at which radiation dose in connection to the patient examination can nowadays be calculated, allows an easy implementation of individualised nearly real-time optimisation of diagnostic procedures for every single patient.

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

3. Improve dosimetry of the total delivered dose outside the planning target volume in radiotherapy.

Improved dosimetry of delivered dose includes the need to derive and document radiation dose outside the planning target volume, since this is related to health effects such as cardiovascular effects. Radiation therapy protocols include a substantial amount of imaging to guide the treatments to optimise the irradiated volume. This imaging-related exposure increases the radiation to organs outside the planned target volume, which might contribute significantly to long-term radiation effects such as cardiovascular disease or secondary malignancies.

The importance of optimising these ancillary imaging protocols through a better documentation of related patient dose needs to be highlighted through education and training of radiation oncologists and other contributing health professionals.

» Target audience: medical professional organisations, medical practitioners.

4. Determine and document patient organ doses in CT, interventional radiology and hybrid imaging.

The radiation doses in CT, interventional radiology, and hybrid imaging approaches need to be determined and documented at the individual patient level. This is required by the EU BSS and will improve the data used for optimisation studies, as well as for epidemiological studies, in the future. Patient dosimetry at the patient level is today a major uncertainty in such studies. As stated above, this should be determined and documented as organ doses.

» Target audience: medical professional organisations, medical practitioners.

5. Create databases using common nomenclature at the national and international level to facilitate personalised radiation therapy and diagnostic imaging.

In order to perform a more personalised radiation therapy and diagnostic imaging, databases that can be read and used by other researchers must be created at the national and international level in a way that the standards of GDPR are met, so as to justify patients' trust in the legitimacy of use of their personal data. However, the generation of these databases might be seriously hampered by the variability of the national implementations of these GDPR regulations.

These issues are described under MEDIRAD Recommendation No. 1. Radiation dose data from hospitals are an important data input that need to be of high quality and reliability to contribute to optimisation or quality assurance. These data sets should consist of patient specifications as well as organ dose values or parameters from which such organ dose values can be derived as well as a systematic description of the medical procedure.

» Target audience: competent Authorities, medical radiation protection experts.

6. Provide education and training on patient-specific dosimetry and the use of new technologies.

Education and training courses on patient-specific dosimetry need to be established. The new approaches have to be understood and implemented in the clinics. The strengths and weaknesses of different approaches including their uncertainties have to be broadly understood. This is essential for the use and future use of the data. The new technologies provide the opportunity of a broad use of such personalised dosimetry, but these approaches are not always implemented and used in the hospitals. Education is needed, as well as hands-on training regarding theses aspects.

» Target audience: competent Authorities, medical radiation protection experts.

7. Better coordinate ongoing and new research initiatives in the field, at the EU-level.

Research in this field is ongoing in various areas. Different research initiatives are sometimes undertaken independently of each other. Ensuring the coordination of these initiatives will be greatly beneficial, especially in terms of quality assurance. A significant research effort is already underway in the area of patient-specific dosimetry for medical applications, but it needs to be better coordinated at the EU-level in order to provide maximised applicable results.

» Target audience: policy makers, scientific communities.

8. Promote research on quality and safety issues related to artificial intelligence in the field.

MEDIRAD has shown that individual patient dose assessment is feasible. The same holds for image quality assessment. For optimisation of therapeutic and diagnostic procedures at an individual patient level, this evolution in clinical practice should be as fast as possible. To allow that, AI-based methods for individual patient dosimetry and image quality assessment should be developed with a European perspective. This could be a first major step for the more general approach to use AI to optimise quality and safety issues in the medical use of radiation. Research in this field should therefore be strongly encouraged.

» Target audience: policy makers, scientific communities.

5.3. MEDIRAD scientific achievements supporting recommendations

- MEDIRAD research provided valuable insights regarding potential acute and late effects of healthy tissue exposure as well as dosimetric. evaluation in chest CT and PET/CT investigations.

- Using dedicated, varying sized, phantoms and patient models derived in a patient cohort, personalised dosimetry has been performed for CT exams based on Monte Carlo simulations and correlated to results from AI-based dosimetric evaluations. The AI approach showed very good results, even on a voxel scale approach, and can thus be used for medical treatment planning options and personalised dosimetry. A corresponding dose evaluation software tool for web-based use has been developed.

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6

Annex 1
Supporting evidence from MEDIRAD research.

1. Optimisation of image quality and dose in CT scanning, including CT in multimodality imaging and paediatric CT scanning

Novel Optimisation Methods in Chest CT.

A primary objective of the MEDIRAD project has been to optimise chest CT examinations through the development of a novel tool that, for the first time, can determine the optimal chest CT protocol through a fully integrated system that relates clinical indication, required image quality and lowest achievable patient radiation dose. To date, a dedicated method for evaluating organ doses for chest CT examinations has been developed. The scanner- and patient-specific Monte Carlo (MC) method has been shown to accurately estimate absorbed doses to irradiated organs during thoracic CT examination and is applicable to both paediatric and adult populations [7]. Objective image quality assessment methods to be used in real patient images and validated on the same image data sets have also been developed that are based on the characterisation and analysis of noise power spectrum (NPS) and modulation transfer function (MTF) [4], with regard for automatic tube current modulation (ATCM), automatic tube voltage selection (ATVS), and organ-based tube current modulation (OTCM) [8,9].

Additionally, image quality criteria based on clinically relevant structures have been identified by way of a Delphi consensus process and a subjective image quality assessment study using these structures is currently ongoing. The aforementioned methods that have been developed, combined with the final results of the subjective image quality assessment, will be integrated into a freeware modular software expert system [CT Image Quality and Radiation Dose (CT-IQU-RAD)] that will provide a) image quality information, b) accurate estimation of patient organ doses and c) estimation of radiogenic risk associated with chest CT examinations performed for several clinical indications.

Dose Evaluation and Optimisation in Multimodality Imaging.

The field of multimodality or hybrid imaging has seen rapid growth in the past decade, offering an effective means by which to diagnose and monitor disease at both the functional and molecular levels. However, CT protocols related to multimodality imaging are not often optimised leaving much room for improvement with regards to radiological protection within hybrid imaging. To gather information on the current use of multimodality imaging in nuclear medicine, and to provide a baseline for the availability and use of DRL values for CT examinations of this nature, a literature review was conducted and subsequently followed by an EU-wide survey [11].

From this work, it was determined that:

- Published national DRL values for CT acquisitions in nuclear medicine are scarce.
- CT scanning is most commonly used for attenuation correction and localisation rather than for diagnostic purposes.
- Substantial variation exists across different hospitals with regard to CT protocols and SPECT/CT and PET/CT systems.
- Currently there is a lack of paediatric specific CT protocols in nuclear medicine; and
- Increased education and training in CT technology and dosimetry is required, which could be achieved by addressing this topic in CME sessions of radiological and nuclear medicine conferences.

With the specific aim of establishing European DRLs for CT applications in multimodality imaging, an EU-wide patient dose survey was conducted in alignment with the recommendations established in ICRP Publication 135. Establishment of DRLs proved extremely difficult due to the challenges presented by subdivided datasets and the large variation in CT dose indicators and exposure levels. Despite these issues an initial set of DRL values have been proposed for localisation CT in half-body 18FDG PET, 99mTc-bone SPECT, and parathyroid SPECT as well as the first European DRL and achievable dose levels for attenuation correction CT in cardiac SPECT has been established.
Full reports on the current use of multi-modality systems in nuclear medicine and European DRLs for specific applications of CT in multi-modality systems can be accessed via the MEDIRAD website.

Radiogenic Risk.

Additionally, within the scope of Work Package 5, MEDIRAD is working to improve the direct estimation of cancer risk following low doses of ionising radiation from CT scanning in childhood and adolescence. By way of a cohort and nested case-control study, the role of factors which may modify cancer risk such as age, as well as genetic and epigenetic variants are being investigated. This work is ongoing and results will be integrated with the optimisation tools previously developed once available.

2. Patient specific dosimetry in molecular radiotherapy (nuclear medicine therapy)

The overall objectives of this sub-study within MEDIRAD were 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 would enable patient-specific treatment planning that will minimise the risk to the patient while ensuring a successful outcome.
The protocol for a future large-scale epidemiological study of the effect of low absorbed doses from the irradiation of normal organs by internal radionuclide sources was developed as part of MEDIRAD. This could potentially allow individualised risk/benefit treatment planning for these procedures. As a preparatory step for future clinical trials and studies, recommendations and protocols have been developed for the calculation of absorbed doses from internal [^{131}I]NaI sources.
To achieve these objectives, the following aims were identified:

- 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 for 100 patients to establish the range of absorbed doses delivered to thyroid remnants and to normal organs from fixed levels of administered activity.
- To enable collation of absorbed does and outcome data a database was developed. The range of absorbed doses delivered to potential organs-at-risk were 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 the therapeutic ratio can be optimised.

Within the scope of the MEDIRAD a multi-national multi-centre clinical study was set-up including quantitative imaging of radioiodine [131I]NaI and radiation absorbed dose calculations. Standardised site set-up protocols and imaging protocols were developed to allow the collation of quantitative imaging and absorbed dose calculations from four centres across Europe. This was a proof-of-concept study to highlight that multi-national multi-centre studies including a dosimetry component are feasible in molecular radiotherapy (MRT) and to show the wide-range of radiation absorbed doses delivered from administrations with standard activities.

The developed protocols and methodologies can be used for future studies to allow for quantitative imaging of high-activity radioiodine and for radiation absorbed dose calculations. Protocols were published by Taprogge et al [14]. The results have been published as publicly available documents on the MEDIRAD webpage as part of deliverables D3.1, D3.2, D3.3, D3.6, D3.8. Detailed guidelines and recommendations for quantitative [131I]NaI imaging and dosimetry are provided in D3.8.

Set-up of a European imaging network for quantitative [^{131}I]NaI.

A network of centres for standardised quantitative imaging of radioiodine was set-up comprising of four centres in three countries (UKW, UMR, IUCT-O and RMH). Further details of the developed protocols as part of MEDIRAD can be found in the publicly available deliverable 3.8 "Guidelines and recommendations for quantitative [131I]NaI imaging and dosimetry".

Multi-centre multi-national dosimetry study.

Ethics approval was granted to all investigating clinical centres of MEDIRAD by the respective ethics committees for an observational clinical study and recruitment of 100 patients across four centres was performed. MEDIRAD has set up the first multi-centre clinical study to measure absorbed doses to healthy organs for patients treated with radioiodine for thyroid cancer.

Participating research sites were required to have obtained ethical and management approval prior to opening for recruitment. As radiation protection regulations and laws differ between countries, the ethics approval process had to be performed in three countries. Delays in the ethics approval process and required changes in the protocol in one of the countries resulted in an overall delay of at least 1 year before recruitment could be started in each country. Furthermore, differences in the interpretation of the respective legislation and guidance resulted in the original protocol being denied ethics approval in one country, while it was accepted in other countries. A total of 100 patients were recruited with up to 5 SPECT/(CT) scans to perform dosimetry.

Dosimetry calculations.

SPECT images were quantified and corrected for dead time. WB, CT and SPECT DICOM images were anonymised and uploaded to a database, while retaining all header data describing the SPECT(/CT) system. These were required to apply the correct calibration factors. Throughout the process it was found that dosimetry calculations were only possible if the required DICOM header information was preserved; this required changes to the pseudo-anonymisation process and to the developed dosismetric bio-bank (IRDBB).

Dosimetry was performed for volumes-of-interest (VOIs) or on a voxel-by-voxel basis. For VOI-based dosimetry, the outlining techniques were well defined and were based on anatomical imaging in conjunction with visible uptake on the SPECT images. Dosimetry results from single time and multiple time point scans showed a range of maximum absorbed doses to the thyroid remnants from 0 to 150 Gy. Whole-body, lung and bone absorbed doses were < 0.1 Gy for all patients. Results from the study suggest a broad range of absorbed doses to the thyroid remnant.

Biokinetic modelling.

Bio-kinetic models published by the International Commission on Radiological Protection (ICRP) are based on measurements involving healthy, so-called reference, humans and animals [15,16]. These models are often not appropriate to estimate radiation doses for a specific patient cohort in nuclear medicine imaging or molecular radiotherapy [17]. Development of a patient-population specific pharmacokinetic model using actual patient data is important to compare the bio-kinetic properties to the established ICRP models and to potentially allow for patient-tailored treatment planning.

Feasibility of the modelling was assessed using retrospective data of 23 patients from a previous dosimetry study [18] for whom biokinetic data were available for thyroid remnant, blood, protein-bound-iodine and whole body. The modified ICRP-128 model (see Figure 1) was able to accurately reproduce the activity retention of the retrospective data. The modified model had slower transfer rate constants from blood to thyroid (0.12 day-1) compared to ICRP-128 (7.26 day-1). Thyroid to blood transfer in both models was found to be comparable (30 day-1 and 36 day-1). The model was subsequently further adapted using data acquired as part of the MEDIRAD multi-centre multi-national prospective studies.
The ICRP 128 bio-kinetic model was updated and a set of rate constants determined to accurately describe bio-kinetics of a thyroid cancer patient population. The developed model can be used for radiation protection assessments for this patient cohort. Furthermore, the model can potentially be used for personalised treatment planning to assess radiation doses to dose-limiting normal organs. For details see MEDIRAD deliverable D 3.7.

3. Breast radiotherapy and secondary cardiovascular risks: establishing risk models for clinical support, individual risk assessment

WP4 “Breast radiotherapy and secondary cardiovascular risks: establishing risk models for clinical support” of MEDIRAD project aimed to integrate clinical epidemiology, radiobiology, and modelling approaches to gain more insight into the mechanisms leading to radiation-induced cardiotoxicity in breast cancer (BC) patients and to develop and validate classical Normal Tissue Complication Probability (NTCP) and mechanistic models to relate doses to the heart to a variety of biological, subclinical and clinical endpoints.

WP4 aims to contribute to more accurate risk estimations for early and late radiation-induced cardiovascular biological and clinical events and thus provide potential targets for primary and secondary prevention.

Recommandations were based on two studies developed in MEDIRAD:

• MEDIRAD-BRACE aims to determine the relationship between 3D dose distributions in cardiac substructures and the risk of acute coronary events (ACE) and other cardiac complications in BC patients in order to develop an externally validated multivariable Normal Tissue Complication Probability (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. This is a retrospective study in in two parts: part one for model development (test cohort) and part two for external model validation (validation cohort). The test cohort is composed of 5,000 breast cancer patients treated at UMCG between 2006 and 2011.

The validation cohort is composed of 2,000 patients treated at the other 3 participating centres in the same period (IRSN, NKI, TUM-MED). The cohorts consist of female breast cancer patients treated with primary surgery, either by mastectomy or breast conserving surgery, and postoperative radiotherapy in the period 2005- 2010 and who were aged 40-75 years at time of RT start.

• MEDIRAD EARLY-HEART study aims to identify and validate new cardiac imaging and circulating biomarkers of radiation-induced cardiovascular changes arising within first 2 years of breast cancer radiotherapy and to develop risk models integrating these biomarkers combined with precise dose metrics of cardiac structures based on three-dimensional dosimetry. The EARLY HEART study is a multicenter, prospective cohort study in which 250 women treated for breast cancer and followed for 2 years after radiotherapy were included. Women treated with radiotherapy without chemotherapy for a unilateral breast cancer and aged 40-75 years met the inclusion criteria.

Baseline and follow-up data include cardiac measurements based on two-dimensional speckle-tracking echocardiography, computed tomography coronary angiography, cardiac magnetic resonance imaging, and a wide panel of circulating biomarkers of cardiac injury. The absorbed dose was evaluated globally for the heart and different substructures.

4. Breast cancer radiotherapy: Practical aspects on heart sparing

The MEDIRAD BRACE study showed that the risk of acute coronary events after breast cancer radiotherapy increases with increasing dose to the heart. This excess risk can be determined by using the multivariable MEDIRAD-BRACE NTCP-model, which contains a number of dose volume parameters next to some baseline risk factor for acute coronary events. Using this NTCP-model, the risk reductions that can be obtained with more advanced radiation techniques can be calculated on an individual patient basis.

5. Modelling of patient dosimetry at the voxel scale

To evaluate and understand the effects of medical exposures, focusing on two major endpoints with public health relevance: cardiovascular effects of low to moderate doses of radiation from either Chest CT or PET/CT investigations or in radiation therapy in breast cancer treatment including an understanding of mechanisms. The final expected objectives are better accounting of potential acute and late effects of healthy tissue exposure as well as dosimetric. evaluation in chest CT and PET/CT investigations.

Based on dedicated specific different sized phantoms and patient models derived in a patient cohort personalised dosimetry had been performed for CT exams based on Monte Carlo simulations and correlated to results from AI-based dosimetric evaluations. The AI approach showed very good results even on a voxel scale approach and can thus be used for medical treatment planning options and personalised dosimetry. A corresponding dose evaluation software tool for web-based use has been developed.

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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