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Health effects of ionising radiation in paediatrics undergoing either cardiac fluoroscopy or modern radiotherapy (The HARMONIC project)

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Abstract. The use of ionising radiation (IR) for medical diagnosis and treatment procedures has had a major impact on the survival of paediatric patients. Although the benefits of these techniques lead to efficient health care, evaluation of potential associated long-term health effects is required. HARMONIC aims to better understand the increased risk of cancer and non-cancer effects after exposure to medical IR in children with cancer treated with modern external beam radiotherapy (EBRT) – radiation energy in MeV range – and in children with cardiac defects diagnosed and treated with cardiac fluoroscopy procedures (CFP) – radiation energy in keV range. The project investigates, among survivors of paediatric cancer, potential endocrine dysfunction, cardiovascular and neurovascular damage, health-related quality of life and second (and subsequent) primary cancer (SPC). The cardiac component builds a pooled cohort of approximately 90 000 paediatric patients who underwent CFP during childhood and adolescence to investigate cancer risk following exposure to IR and explore the potential effects of conditions predisposing to cancer. HARMONIC develops software tools to allow dose reconstruction in both EBRT and CFP to enable epidemiological investigations and future optimisation of treatments. With the creation of a biobank of blood and saliva samples, HARMONIC aims to provide a mechanistic understanding of radiation-induced adverse health effects and identify potential biomarkers that can predict these effects.

1 Introduction

Advances in imaging procedures and radiotherapy have resulted in major improvements regarding the long-term survival of paediatric patients. The risks of late effects of radiation exposure in populations with long life expectancy remain important to investigate. Until recently, most of our understanding of the effects of radiation exposure on children was based on large epidemiological studies where children were included as part of the groups under study (i.e. A-bomb survivors) [1–3]. These studies have recently been supplemented by large cohort studies investigating cancer effects of exposure to ionising radiation (IR) in childhood and adolescence in computed tomography (CT) scanning [4–12], showing an increased risk of leukaemia, lymphoma, and brain tumours. Moreover, since the 1970s, large-scale follow-up studies among childhood cancer survivors include individuals treated with high-dose radiotherapy, typically based on 2D and early 3D conformal radiotherapy techniques and other anti-cancer treatment modalities, who are followed for a variety of health outcomes [13,14]. The HARMONIC project aims at complementing existing studies by addressing the long-term health effects of low-to-high dose IR exposures focusing on two contemporary, distinct and complementary populations of paediatric patients exposed to a wide range of doses from photons with energy ranging from keV to tens of MeV, protons, and secondary neutrons as a consequence of their treatment:

- *cancer patients treated with modern EBRT using photon and proton beams.* High doses of IR (of several tens of Gy) are delivered to a target volume to induce malignant cell death. Despite overall good survival rates, childhood and adolescent cancer survivors are at high risk of developing severe late morbidities, due to cancer itself or to the treatment, during the years or decades following a primary cancer diagnosis. Iatrogenic effects of radiotherapy may occur in body regions exposed to low-to-high doses (from out-of-field to edge-of-field).
- *patients with congenital and acquired heart defects undergoing cardiac fluoroscopy procedures*[1] *(CFP).* Heart defects are the most common congenital anomalies among live-born children with about 8 out of every 1000 children born in Europe and about 25% of these babies generally requiring surgery or other procedures in the first years of life [15]. IR is used to guide interventions for both the diagnosis and treatment of congenital and acquired heart defects. A substantial number of children are therefore exposed to low-to-moderate doses of photon radiation (from a few to hundreds of mGy in the X-ray beam).

In radiation oncology, technology evolved substantially since 2000 when recruitment in existing European childhood cancer survivors' studies ended [16], generating a gap in knowledge on the potential effects of modern radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT) or proton beam therapy (PBT). In both IMRT and PBT, the objective is to improve conformity of the high/intermediate dose region closer to the tumour compared with 3D conformal radiotherapy [17–19] and estimating the doses received by organs outside the field remains a challenge.

[1] "Cardiac Fluoroscopy Procedures" encompasses a range of X-ray guided procedures used to diagnose, monitor and treat a variety of heart conditions, including cardiac catheterizations, electrophysiology studies and pacemaker insertions.

In cardiology, the use of CFP has increased rapidly over the past decades, particularly due to the development of new devices that have expanded its potential applications in paediatrics. These procedures use X-rays to guide catheters inserted into a peripheral vein or artery, allowing both diagnostic imaging and increasingly complex therapeutic (interventional) procedures to correct various heart defects. They, therefore, allow relatively non-invasive and complication-free treatment of many congenital and acquired heart diseases. CFP often involves prolonged exposure to X-ray delivering doses primarily to the chest region, with a relatively small volume being exposed. They generate highly uneven dose distribution within large organs and show large variations in a dose per exposure [20].

Multidisciplinary in nature, HARMONIC aims to strengthen the epidemiological basis on possible health effects of early exposure to IR by forming the basis of a European registry of paediatric cancer patients treated with modern EBRT and by setting up the largest cohort of paediatric cardiac patients exposed to IR. Its objective is to improve our knowledge of the detrimental biological and health side-effects related to medical exposure to IR in childhood and adolescence with a view to optimising therapeutic, interventional and diagnostic protocols.

The current manuscript briefly introduces the study protocols, the status of activities (as of November 2022) and the analyses expected within the framework of the project, which started on June 1, 2019, and will be conducted until November 30, 2024, as part of the Euratom Research and Training Programme 2014–2018 Grant Agreement No. 847707.

2 Material and methods

The HARMONIC project is organised around four scientific work packages (WP) to build the structure and instruments for the medical and scientific communities to be able to evaluate the potentially detrimental effects of contemporary medical exposure to IR in children, with the potential for advanced patient-specific dose reconstructions and biological investigations (see Fig. 1).

An initial phase of the project was devoted to setting up the legal and ethical framework for the implementation of activities in 8 countries, including both retrospective and prospective inclusion and setting up a biobank. Information letters and informed consent forms were designed in each specific language for parents/guardians of paediatric patients and for assent to consent to participate. After ethics approvals are obtained, demographic, clinical, radiological, biological, dosimetric and social data are collected for ongoing and future long-term follow-up.

2.1 Radiotherapy

HARMONIC (WP2) is establishing the first European registry of paediatric cancer patients treated with modern radiotherapy techniques, in the context of rapid technological developments. It is supported by several medical organizations: the EPTN[2], PTCOG[3], PROS[4] and SIOP[5]. Liaising with these organisations facilitates direct communication with health care providers with the objective to engage with them in further development of the project and analyses of the data to provide insights into late health effects, as well as associated patient/parent-reported outcomes (HRQoL, fatigue, education). The registry includes patients treated with external beam radiotherapy (EBRT) from 2000 onwards (providing that treatment data are available in DICOM[6] format) at age <22 years. Data on exposures, outcomes and potential confounding factors are collected retrospectively based on medical records, or prospectively when direct contact with the study participants is required for additional exams and questionnaires. Passive, long-term follow-up is performed by linkage with external, national/regional morbidity and mortality registries as well as health care databases (in countries where it is feasible). To complement follow-up data collected at the treatment centre, passive follow-up is essential to allow for a (very) long period of follow-up (i.e. decades) which is necessary to investigate late outcomes such as SPC, cardio and neurovascular diseases. It also allows for minimizing biased assessment of outcomes, i.e. to compensate for potential differential follow-up strategies and methods at the treatment centres depending on health status, treatment-related factors and outcomes (and also possibly on socioeconomic and other potential patient-specific factors).

Enrolment which successfully started in 2021, aims at including about 2500 patients to estimate the impact of radiation factors (i.e. total dose, dose fractionation, volume, beam quality, including proton and neutron doses from proton therapy and high energy (>8−10 MV) photon radiotherapy) on late effects. The study participants can contribute to one or several of the tasks described below, depending on the irradiated field and the patient/parent's agreement to undergo additional exams and questionnaires.

2.1.1 Quantification of risks of endocrine dysfunctions related to radiation doses

In order to identify affected children with endocrinopathies, clinical outcomes (anthropometric criteria and pubertal development) and blood hormone levels will be evaluated. In addition, the dose and volume of radiation for pituitary, hypothalamic and thyroid structures will be quantified in study participants treated for cranial or head and neck tumours.

2.1.2 Quantification of risks of cardiovascular diseases related to radiation doses

In study participants who received chest or craniospinal irradiation, we will investigate cardiovascular effects in our

[2] European Particle Therapy Network, a task force of European SocieTy for Radiotherapy and Oncology (ESTRO).
[3] Particle Therapy Co-Operative Group.
[4] Paediatric Radiation Oncology Society.
[5] International Society of Paediatric Oncology.
[6] Digital Imaging and Communication in Medicine.

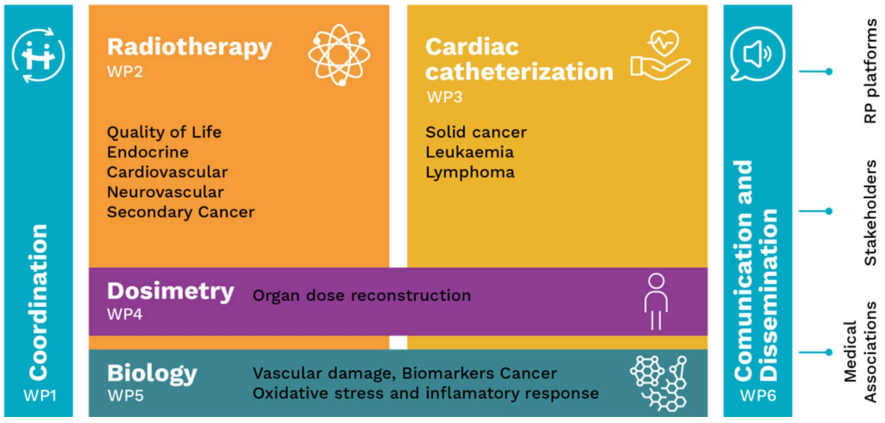

Fig. 1. Project organisation.

paediatric cohort by clinical investigations but also with the evaluation of serum markers, and cardiac echography data including ejection fraction and longitudinal strain.

2.1.3 Quantification of risks of neurovascular damages related to radiation doses

In study participants who received cranial irradiation, we will investigate the incidence of neurovascular events and correlate the findings with radiation doses to neurovascular structures. Early imaging changes on novel MRI sequences will also be investigated for any association with cerebrovascular disease. In addition, imaging changes will be correlated to the re-calculated doses to the cerebral arteries after photon or proton therapy.

2.1.4 Quantification of radiation-related risk of subsequent primary cancer (SPC)

We will assess associations between normal tissue radiation factors (i.e. total dose, dose fractionation, the irradiated volume of the organ, beam quality) and site- and histology-specific SPC incidence, while accounting for sex, attained age, time since exposure and other confounding factors. In this task, there is no a priori selection of patients based on first cancer diagnosis or EBRT characteristics. We will consider a wide range of factors which may bias or modify the radiation-risk relationship (systemic cancer treatments, certain non-cancer medications, genetic predispositions, lifestyle and hormonal risk factors). Given the long latency time between radiation exposure and radiation-related risks of (solid) SPC, the analyses on SPC will be performed once we reach a minimal median follow-up time in the study population of about 10 years, and register a sufficient number of cases. We anticipate that future analyses of SPC risk will focus on SPC of the CNS, thyroid gland, breasts, lungs, gastrointestinal organs and tracts, soft tissues, bones, and genital organs and tracts.

2.1.5 Evaluation of the Health-Related Quality of Life (HRQoL) of advances in medical therapeutic procedures

We will investigate patient/parent-reported outcomes to capture information on HRQoL, fatigue and academic achievement thus providing a comprehensive assessment of the burden of disease and treatment, and correlates between recorded late effects and patient/parent-reported outcomes [21]. HRQoL, fatigue and academic achievement are evaluated up to 10 years after the initiation of radiotherapy or age 25 years (whatever occurs first) among all study participants who were recruited prospectively (and agreed to respond to questionnaires) through questionnaires.

2.2 Cardiology

HARMONIC (WP3) builds the largest European pooled cohort of paediatric cardiac patients on the basis of two existing national cohorts previously established in France [22] and the UK [23]. HARMONIC expands and increases the follow-up of these two national cohorts, while also establishing new cohorts in Belgium, Italy, Germany, Norway, and Spain. Based on the estimated number of patients treated in participating hospitals, the pooled cohort will contain approximately 90 000 patients who underwent CFP, while aged under 22 years, providing a statistical power of the order of 80% to detect an odd ratio between 1.6 and 1.7. The information is obtained from hospital records and/or insurance claims data. To investigate the relationship between early-life exposure to IR from X-ray-guided diagnostic or therapeutic procedures and the development of cancer, doses to individual organs will be reconstructed (see below). The study design together with the strategy for dose reconstruction has been published with further details elsewhere [24].

A dose-response analysis is anticipated using appropriate regression modelling (either Cox or Poisson), with radiation dose-treated as a time-dependent variable. While, aside from the heart, the lungs, breasts and oesophagus receive the highest organ doses in cardiac fluoroscopy [25–27], the follow-up during the HARMONIC study period (up to 2024) will be too short to allow sufficient investigation of radiation-induced cancer at those sites because of the small number of expected cancer cases. Leukaemia and lymphoma will be the main outcomes studied in the project as they are among the most

frequent paediatric cancers [28], and are known to be associated with radiation exposure. Prolonged follow-up after the initial study period will be necessary and is foreseen to allow analysis for other sites, including thyroid and breast cancer.

Patients with heart defects are known to be at increased risk of cancer [29–33]. If the underlying disease is associated with both an increased risk of cancer and increased radiation exposure, the dose/risk relationship may be confounded. Down syndrome, for example, is associated with both heart disease and an increased risk of developing leukaemia [34]. In addition, a small proportion of individuals with congenital or acquired heart disease require a transplant, usually, the heart itself, though occasionally the heart and lungs. Transplantation, with associated immunosuppression, is a major risk factor for the development of several cancer types [35] creating the potential for confounding results. HARMONIC partners are therefore making all efforts to implement the framework to link patients with transplant and congenital disease registries, where available.

2.3 Dosimetry

The reliability and precision of results from epidemiological studies strongly depend on the accuracy of radiation dose estimates. HARMONIC (WP4) proposes methods and tools to improve the accuracy of organ dose data in photon and proton beam therapy and cardiac fluoroscopy. Substantial effort is devoted to developing patient-specific dosimetry methods to reconstruct individual radiation doses delivered to the organs of interest and assess the associated uncertainties.

2.3.1 Dosimetry for radiotherapy

Radiotherapy aims to deliver the prescribed dose according to clinical needs to a well-defined clinical target volume. Due to uncertainties in the daily set-up of the patient at the treatment machine, it is necessary to irradiate a larger volume called the planning target volume (PTV). In addition, the transit of multiple beams to the target and radiation scattering produced within the patient's body or the treatment head of the radiotherapy device results in the exposure of surrounding normal tissue. Therefore, the irradiation of cancer implies radiation doses to a relatively large volume of normal tissue. This exposure is unintended; it may be reduced by the use of particle therapy, but it cannot be fully avoided.

Current beam delivery techniques have evolved to deliver high tumour doses while minimizing the dose to adjacent organs-at-risk (OAR). However, out-of-field doses are still delivered. The treatment planning process aims at finding an optimal compromise between the dose that must be delivered to the PTV to control the disease, and the dose limits sought by the radiation oncologist to minimize the irradiation of critical tissues. Prevention of late sequelae of radiotherapy by reducing the dose during the treatment planning process remains challenging owing to two main reasons: (i) the lack of precise dose-volume constraints or prediction models for those low-dose-effects which can be applied to current techniques of external beam radiotherapy; (ii) the limitations of software tools applicable in the routine clinical practice for the accurate calculation of out-of-field doses. With modern treatment planning systems, high-dose regions and areas within the primary beam path are typically well described. However, the accuracy of the absorbed dose distribution computed already a few centimetres outside the irradiated field is usually poor [36].

For HARMONIC patients treated with EBRT, dose-volume risk estimates will be quantified for non-targeted organs/tissues according to the radiation delivery technique and beam quality factors. The main objective is to study whole-body absorbed dose distribution, with an emphasis on OARs. We are developing an approach based on Monte Carlo (MC) and analytical tools to quantify the out-of-field dose, and hence enable futures studies to optimise the out-of-field-dose and the dose delivered during imaging procedures undergone by the patient, including the initial X-ray and/or nuclear medicine diagnostics, the scans for therapy planning and re-planning, as well as patient positioning (CBCT) imaging.

2.3.2 Dosimetry for cardiology

Doses received by children in the course of CFP will be derived from the kerma-area product (P_{KA}, an indicator of the X-ray tube output), technical parameters of the procedure and patient features recorded at the time of examination. The methodology, published elsewhere [24], relies on a lookup-table-based dosimetry system containing coefficients relating the P_{KA} to organ doses. The coefficients are produced for combinations of beam geometry, X-ray energy spectra and patient features (i.e., height and weight), using MC radiation transport simulations and anatomically-realistic computational phantom models [37,38].

Uncertainties in doses retrospectively estimated are potentially large. These uncertainties are due to (i) errors in the MC simulations used to calculate conversion factors and (ii) lack of knowledge of patient features and technical parameters specific to a given procedure. The former can be minimised by using a well-benchmarked code such as MCNP [39] and running a sufficient number of particles to reduce simulation errors to $<1\%$. The latter is more difficult to reduce. We will assess these uncertainties using a 2-dimensional MC (2DMC) methodology [40,41], as previously implemented for the EPI-CT study [42]. The 2DMC simulation method maintains correlations of doses for persons within subgroups with similar attributes (e.g., patients at particular hospitals, time period, types of examination, age) and simulates uncertain dose-model parameter values that could otherwise lead to biases. The objective is to produce multiple 'realisations' of potentially true doses using probability density functions (PDFs) of procedure technical parameters such as machine type, beam angle and tube voltage. Briefly, the appropriate PDFs, representing the relative likelihood of use of technical parameters will be estimated from

data obtained from similar patients, procedure type, X-ray system and/or time period, using the available set of collected data in combination with expert judgement, historical data collected in the archives of the cardiology departments, and analysis of the literature. From these, the imputation of missing data will be performed to produce dose distributions characterising the uncertainty in the individual estimates. For each calculation of a cohort dose distribution, values of parameters will be selected from the appropriate PDFs, while maintaining proper correlations between parameters (for instance, the same X-ray system model will be used for reconstructing the dose for all patients treated in the same hospital during the same period). Sensitivity analyses are also planned to obtain a more accurate picture of the medical exposure from other radiological procedures than the CFPs (conventional radiology, CT, and nuclear medicine), which has to be accounted for in the epidemiological analyses since it adds to the accumulated dose.

2.4 Biology

HARMONIC integrates prospective sample collection of blood and saliva which is a unique opportunity to investigate biomarkers of exposure and effects before and after treatment (radiotherapy and CFP). The biological samples collected in the prospective part of the project, for 100 cancer patients (50 treated with photons, 50 treated with protons) and 50 cardiac patients, will be used for the analysis of differential responses by the use of biomarkers in the samples collected before, in conjunction to finishing the exposure and one year after the exposure. The results are planned to form the framework for future investigations identifying and validating predictive biomarkers for cancer risk and other adverse health effects after exposure to photons or protons as well as to promote a better understanding of the mechanisms involved.

HARMONIC (WP5) explores mechanisms and predictive biomarkers for oncogenic processes and vascular disease after radiotherapy and cardiac fluoroscopy procedures, using both blood and saliva as a non-invasive tool for sample collection. Additionally, a correlation between changes in blood/saliva markers and the presence of neurovascular effects after radiotherapy will be investigated. The neurovascular effects will be followed using clinical and imaging methods.

Several new approaches e.g., blood plasma protein profiling, miRNA analysis, reverse phase protein arrays (RPPA) for studying protein modifications and saliva protein profiling, are being implemented in order to understand the radiation-induced alterations at the biological level in samples. Additionally, changes in leukocyte telomere length, oxidative stress, inflammatory response and mitochondrial DNA copy number in blood cells will be analysed as they are considered important molecular mechanisms initiating and contributing to cancer risk.

3 Preliminary results

The HARMONIC project was launched in June 2019 with initial activities devoted to setting up its legal, administrative, and operational framework with particular attention paid to data protection and ethical issues associated with the vulnerable population of interest (paediatric patients). In the first years of the project, the main activities focused on:

- setting up the structure of the databases for inclusion of patients in both cohorts and starting data collection and patient inclusion
- developing simulation models for dose reconstruction and implementing measurement sessions for validation of these models
- pilot testing methodology and framework for analysis of biomarkers in both blood and saliva.

3.1 Radiotherapy

The WP2 partners identified the parameters to be collected at standardised points in time (baseline and follow-up). The study protocol was established to capture the required procedures. The consortium developed, tested, and validated the database, electronic Case Report Forms (eCRFs) for each task and the platforms used to collect, store and process clinical and physical data. Standard Operating Procedures (SOPs) have been developed and validated by the investigators to facilitate patient inclusion and standardise data collection and processing. For each task, partners agreed on a list of critical anatomical structures of interest. A delineation atlas of neurovascular structures was validated and has already been published [43]. A contouring guideline of the hypothalamus, pituitary, and thyroid and each of their substructures was defined. Data collection has already started and is anticipated to be completed by the end of 2023 with prospective and retrospective inclusion of patients. Prospective patient inclusion has started in Denmark (January 2021) and Germany (March 2022). Retrospective inclusion of patients has started in Germany. As of November 2022, 1148, and 121 patients have been included in the retrospective and prospective parts, respectively, (Tab. 1). Patient inclusion is planned to open in Belgium and France in 2023.

3.2 Cardiology

WP3 brings together the existing French and UK cohorts of paediatric patients with congenital and acquired heart defects treated with CFP and enlarges the binational cohort to include patients from Belgium, Germany, Italy, Norway, and Spain. In France and the UK, cohorts were built on a common collaborative protocol, specifically designed to provide a further understanding of the potential cancer risk associated with paediatric CFP [22,23,44,45]. The protocol was adapted to ensure the consistency of the data collected in all participating countries [24]. The structure of the common database was

Table 1. Patient inclusion in the radiotherapy registry, as of 30 Nov. 2022.

Country	Centre	Modality	Time period	No. patients	
				Already included	Anticipated
Belgium	KU Leuven	Photon	2008–2023	0	410
Denmark	DCPT Aarhus	Proton	2021–2023	24	90
France	CR F. Baclesse	Proton	2022–2023	0	90
	G. Roussy	Photon	2013–2023	0	560
Germany	UK Essen	Proton	2013–2023	1245	1348
	Overall			1269	2498

Table 2. Characteristics of national retrospective cohorts and status of data collection, as of 30 Nov. 2022.

Country	Age (Y)	N° of hospitals	Start accrual & follow-up	End		Cohort size	
				Accrual	Follow-up	Collected locally	Expected
Belgium	0–18	3	2004	2020	2020	2841	6000
France	0–16	15	2000	2020	2016	18 600	19 000
Germany	0–18	2	2004	2020	2020		4000
	0–18	Insurance claims	2004	2020	2020		20 000
Italy	0–18	2	2017	2021	2022	384	1000
Norway	0–18	1	1975	2022	2022	5400	6500
Spain	0–18	2 to 2	2005	2022	2021	None	5000
UK	0–22	6	1991	2020	2020	20 464	30 000
						47 000	90 000

agreed upon and data collection started in all countries but Spain. About half of the target population has been already included (Tab. 2).

3.3 Dosimetry

3.3.1 Dosimetry for radiotherapy

Within HARMONIC, we succeeded to adapt and validate the MC dose verification system PRIMO [46] for the routine computation of out-of-field dose distributions in IMRT and volumetric modulated arc therapy (VMAT), as described in [47]. In this article, an anthropomorphic phantom of a 5-year-old child was irradiated for a brain tumour and experimental doses were assessed using thermoluminescent detectors (TLD). The article also presents the dose values obtained from an analytic algorithm specifically designed to calculate out-of-field doses [48]. In general, the proposed computational methods for the routine calculation of the out-of-the-field showed an acceptable level of agreement with experimental data. Moreover, on average, the quality of results found with the current PRIMO version is similar to or higher than that obtained by the few existing analytical codes [49–52]. Interestingly it has been experimentally found that VMAT irradiation produces the smallest out-of-the-field dose when compared to IMRT for a given PTV.

PENELOPE [53], the MC engine of PRIMO, does not allow to transport of proton beams. However, its main author, recently published an extension aimed at the simulation of proton transport, called PENH [54]. Owing to the novelty of PENH, it was necessary to perform a set of benchmarks [55]. We observed that PENH yielded the best agreement with experimental data in the regions close to the proton pencil beam, while the general-purpose MC code TOPAS [56] (a wrap-up of Geant4 [57]) computed similar results. To evaluate the capacity of TOPAS to accurately calculate absorbed dose distributions far from the irradiated field during treatments, we recently modelled the West German Proton Therapy Center range shifters, the foci points of the scanning magnets and the treatment room for pencil beam scanning (PBS) proton therapy. In the corresponding recently published article [58], we considered the same brain tumour already described for the pediatric anthropomorphic phantom. A PBS treatment was applied with the same dose objectives set for IMRT and VMAT. The discrepancies found between the TOPAS-computed and experimental doses were smaller, around 18%, with respect to the photon case. This is due to the fact that the shielding geometry of the proton gantry is known and it was simulated in detail.

Fig. 2. Validation of the simulation framework with phantom measurements.

Further research will be aimed at improving the simulation speed of out-of-field dose computations in PRIMO, as well as expanding PRIMO capabilities to include proton beams. Research is also being conducted in the direction of improving the analytical models used for the computation of the out-of-field dose in photon [59] and proton treatments.

3.3.2 Dosimetry for cardiology

The estimation of absorbed dose to individual organs is an essential component of HARMONIC. Given the large inter-procedure variability in radiation exposures during CFP [26], patient- and procedure-specific dose estimates are essential. P_{KA} also known as Dose Area Product (DAP) has been recorded for the majority of procedures in the hospital Radiology Information System (RIS) for the last 20 years or more; while the main technical parameters necessary to accurately estimate organ doses for each procedure (beam angles, tube potential, added filtration, field size) are usually available in the Radiation Dose Structured Reports (RDSR) for recent years only.

A complete solution for dose reconstruction using the most recent data source available was established. It includes a data collection tool, and a fast dose reconstruction software tool.

The reconstruction tool relies on hundreds of thousands of pre-calculated dose conversion coefficients relating the P_{KA} to organ doses and provides rapid dose estimates for 16 organs of interest for epidemiology studies and radiation protection. The coefficients were produced using MC simulations implementing several realistic anthropomorphic phantoms and extended using advanced extrapolation methods. Seven series of phantom measurements were performed for validating the simulation framework using infant (newborn), 1- and 5-year child phantoms in a paediatric cardiologic clinic (see Fig. 2).

DICOMInspector, the software dedicated to extracting – DICOM meta-data from the Picture Archiving and Communication System (PACS), which stores the RDSRs and other less detailed technical procedure reports, has been developed and is being tested in some participating hospitals. Currently, the use is planned in Belgium, France, Italy, Spain, and Norway. A dataset of about 1000 patients with 17 different congenital heart disease diagnoses (ICD-10) is being analysed in Norway with respect to other radiological examinations made between 2000 and 2020. While data collection is underway, the structure of the dosimetry database is developed as complementary to the epidemiological database (see Fig. 3).

A Mixed Reality Prototype, based on 3DSlicer and Unity on the Software side and Microsoft Hololense and ARSpectra dedicated medical devices on the hardware side is being developed to contribute to the optimization of CFP through improved visualization.

3.4 Biology

WP5 is devoted to investigating mechanisms and identifying potential biomarkers that can be used (i) for molecular epidemiology to refine risk estimates for adverse health effects/disorders and (ii) for individualised therapy or providing a rationale for the selection of optimal diagnostic/therapeutic methods. To date, detailed protocols describing the collection, preparation and storage of saliva and blood samples have been established. While sample collection is ongoing, an official HARMONIC biobank was established at Stockholm University. This biobank will provide a unique opportunity to study biomarkers of exposure, susceptibility and effects in the context of different treatment modalities. Furthermore, two pilot studies have been carried out to test the quality of saliva samples following the protocols. A third pilot study was conducted to validate the study protocol with respect to the collection, isolation of blood cells, extraction of proteins and finally determination of the expression level of some proteins using the RPPA method. To date, more than 1300 aliquots of different biosamples were prepared and stored at −80°C.

3.5 Dissemination and communication

Communication and dissemination activities were devoted to establishing a detailed stakeholder list of radiation protection, medical and patient associations and preparing and disseminating the project's newsletter, in addition to presenting the project at international conferences. A dedicated area of the project website was designed for direct communication with participants and their families to provide them, in a form adapted to the patient's age, with general information about the treatments and about the project itself and presenting the legal framework and contact person. Direct contact between participating patients and clinicians remains the preferred channel for communication with the aim to provide useful complementary information for participants via this dedicated area of the website.

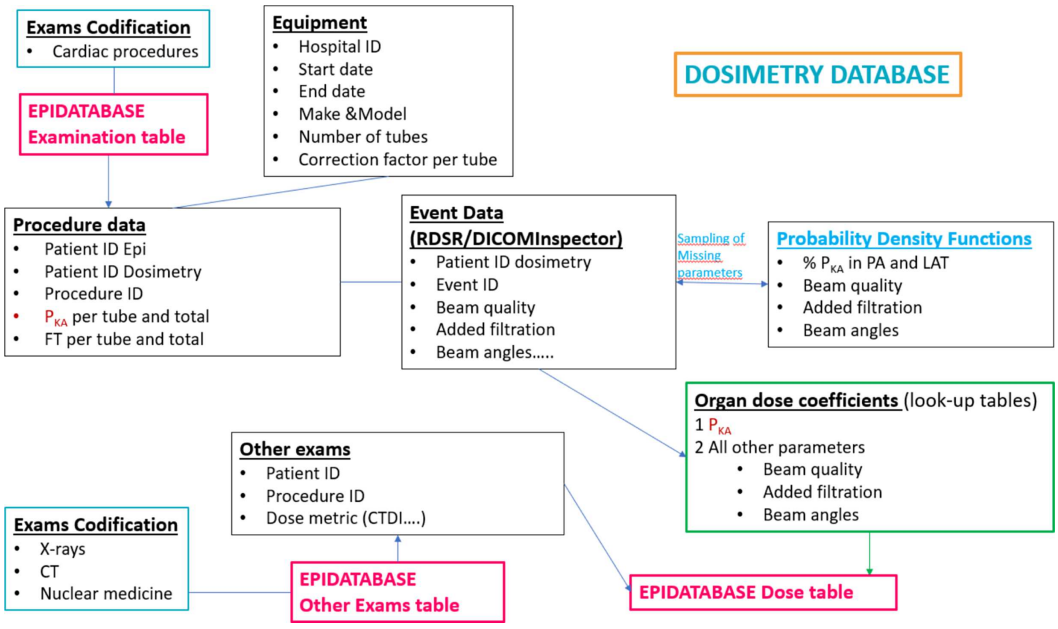

Fig. 3. Dosimetry database structure.

4 Discussion

The use of IR with advanced technology in medicine represents a tremendous benefit for the diagnosis and treatment of diseases in paediatric populations. HARMONIC aims to improve the knowledge of the health effects and associated biological mechanisms of medical exposure to IR in childhood and adolescence, providing evidence on the risk of cancer and non-cancer effects. Our project is multi-disciplinary by nature, aiming to further research into detrimental health impacts from exposure to medical IR early in life. The project will improve knowledge in the fields of radiation biology/mechanisms, epidemiology and dosimetry, and contribute to informing medical care.

The radiotherapy component of HARMONIC is dedicated to building the first European registry of paediatric patients treated with modern radiotherapy techniques (using protons or photons) outside clinical trials. Such a registry is an essential tool to gain knowledge as childhood malignancies are rare diseases, and the pooling of international data is crucial in order to establish cohort sizes large enough to attain the required statistical power for sound analyses. The potential health impact of IR treatments on endocrine, cardiovascular, and neurovascular systems as well as on HRQoL is investigated in an integrated, holistic approach. The registry data will allow quantification of radiation-related health risks in the short term but also implement tools for conducting future analyses for late effects evaluation. In addition, prospective data collection allows the possibility of collecting biological samples. As findings will be correlated to dose-volume effects of radiation, HARMONIC will provide healthcare providers and policymakers with an improved understanding of a large range of potential adverse effects of use to tailor and improve patient care. It aligns with the main mission of the North American initiative of the Paediatric Proton/Photon Consortium Registry (PPCR) to investigate adverse events and HRQoL of these patients after radiotherapy.

With its cardiology component, HARMONIC represents the largest study of long-term risks from CFP ever conducted. It will therefore provide unprecedented information on radiation doses, past and present, from cardiac fluoroscopy in children and young people and offer important information to stakeholders on the potential associated cancer risks. It will contribute important information on whether radiation-related risks from these procedures are being correctly predicted by existing risk models based on other populations (e.g., atomic bombing survivors) and will complement historical cohorts of childhood cancer survivors and ongoing studies of cancer risks following CT scans in childhood.

HARMONIC partners seek to develop harmonised methods for data collection which will not only contribute to long-term sustainable patient follow-up but also optimise diagnostic and treatment procedures and benefit European patients. It contributes to improving organ dose reconstruction from interventional cardiology procedures and estimation of patient-specific doses to non-targeted organs in radiotherapy. To do so, HARMONIC integrates the development of novel dosimetric tools providing the medical community with means to investigate the overall radiation burden in young patients. All of these actions are expected to lead to an improved patient outcome and raise awareness among healthcare professionals of out-of-field and imaging doses and the need for dose optimisation.

The study of predictive biomarkers aims at finding patients with an elevated risk of severe health effects due to genetic background. These will help define more effective radioprotection as well as more effective treatment strategies to reduce the risk of radiation-induced late toxicities and cancer.

HARMONIC registries and databases are meant to be maintained for long-term follow-up of these two paediatric populations and will expand (pending availability of funding) to include more patients from European countries with the potential to coordinate actions with registries from outside Europe. HARMONIC contributes to providing tools for an improved understanding of sequela to be considered and integrated in to patients' care and follow-up. Translation of the research results into improved practical measures for the effective protection of patients will lead to a more robust system of radiation protection in the medical sector.

5 Conclusion

HARMONIC is an international consortium that is building infrastructures to expand and pursue collaboration of experts to provide medical professionals and the radiation protection community with instruments to analyse the effects of IR exposure on children, adolescents and young adults, and thus improve the basis for radiation protection in medicine. HARMONIC provides insight into modifying factors (e.g., age at exposure, comorbidities, and medications) that may underlie differences in individual radiosensitivity for endocrine dysfunction, cardiac toxicity, neurovascular events, and cancer risk after radiation exposure, with the potential to establish dose planning recommendations and improved radiation protection measures to prevent radiation-induced events.

Biological studies will provide insights into the mechanistic understanding of radiation-induced adverse health effects with the potential to identify biomarkers indicative of vascular adverse effects and cancer, which could contribute to early diagnosis, treatment and prevention of these effects.

Clinicians, patients, parents, and carers will benefit from improved information on the potential radiation-related risks from both radiotherapy and cardiac fluoroscopy. This will aid the process of justification, balancing the benefits of the procedure with potential risks. Ultimately, we are producing evidence for the improved development of guidelines for the radiation protection of patients.

Conflict of interests

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

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Data availability statement

Data associated with this article cannot be disclosed due to legal and ethical reasons.

Author contribution statement

Isabelle Thierry-Chef, the coordinator of the project, took the leading role in proposing the strategy and overall organisation of the manuscript. All authors are partners in the project, they contribute to the different tasks and subtasks and they have read and contributed to this manuscript with very valuable inputs and comments.

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