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## Assessing late outcomes of advances in radiotherapy for paediatric cancers

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# Radiotherapy and Oncology

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## Assessing late outcomes of advances in radiotherapy for paediatric cancers: Study protocol of the “HARMONIC-RT” European registry (NCT 04746729)

### Background

Each year, approximately 35,000 children and adolescents are diagnosed with cancer in Europe [1]. Overall, the five-year survival rate now exceeds 80 % [2]. However, the burden of cancer and treatment-related sequelae is significant. Paediatric cancer survivors have a 5-times higher risk of developing severe, disabling or fatal health conditions by the age of 50 years compared to their siblings [3]. External beam radiation therapy technique (EBRT) is an important risk factor for sequelae such as second and subsequent primary cancer (SPC), cardio- and neurovascular diseases and endocrinopathies, which typically occur after some latency [4–8].

Over the last two decades, considerable technical progress in EBRT has been achieved, allowing a better dose conformality to the target volume and improved sparing of surrounding normal tissues. However, impact of modern EBRT techniques, such as intensity-modulated radiation therapy (IMRT) and particle therapy, on iatrogenic risks involving out-of-field structures remain unclear. Whereas IMRT causes larger irradiated volumes and out-of-field doses, proton therapy is associated with an increased biological effectiveness and secondary neutrons. In addition, radiation exposure from positioning and replanning imaging procedures have to be considered [9].

Current empirical evidence on late outcomes of modern EBRT remains limited [10,11], due to short follow-up times to ascertain and evaluate long-term sequelae (e.g. median latency reported for SPC varies between 10 and >30 years) and small sample sizes which prevent to reach sufficient statistical power [12]. In addition, harmonized dose-volume constraints specifically adapted to paediatrics, until recently, were lacking for most late effects, both for photon and particle therapy [13]. Following the QUANTEC consortium that summarized available data on iatrogenic risks and presented guidance for defining dose-volume constraints in adults [14,15], the equivalent mammoth effort for paediatric treatment planning (PENTEC) is reaching completion [16]. Comprehensive quantitative modelling of risk estimates was feasible for a number of side effects (e.g., [17,18]). Importantly, PENTEC delivers a review of knowledge gaps and recommendations for clinically-needed research. Cited limitations of underlying literature include short follow-up times and limited evidence on particle therapy and contemporary photon-beam techniques.

To address these issues and reach sufficient sample sizes to study rare diseases, such as paediatric cancers and complex treatment modalities,

the “HARMONIC-RT” study (ClinicalTrials.gov Identifier: NCT04746729) is setting-up a European registry of patient-level treatment data and outcomes. This registration information is complemented by a biobank, and procedures for long-term follow-up and evaluation of late health and social outcomes. Special effort is invested into evaluating in- and out-field dose burden.

HARMONIC-RT is the first multi-country registration system of paediatric patients treated with contemporary EBRT techniques (photons, particle) in Europe. It complements large cohorts of young individuals treated with older EBRT techniques [19], and registries on contemporary EBRT currently running outside Europe (e.g. [20,21]). This will build the ground for future international studies evaluating late outcomes of technical advances in radiotherapy for the management of paediatric cancers.

### Protocol summary

The main objective is to evaluate the late health and social outcomes of contemporary EBRT techniques in paediatric patients. HARMONIC-RT comprised two components: (1) a registry, defined as non-interventional research; and (2) ancillary sub-studies, which investigate subsets of participants and can be interventional, depending on whether the measurements needed are part of routine care.

The registry includes patients treated with first EBRT since 2000 at one of the participating centers, before the age of 22 years for a first neoplasm. Study participants are included either retrospectively (i.e., after EBRT initiation), or prospectively (i.e., before EBRT). These two approaches are complementary. Prospective registration allows a more detailed and standardized study-specific data collection methodology across the contributing centres, for exposures and outcomes which are not necessarily recorded in routine care and require extensive resources. Retrospective inclusion allows longer follow-up and information on long-term outcomes thus maximizing the statistical power and being less prone to selection bias.

The registry study is open to enrol patients for 10 years (2021–2031), and collect follow-up information for 10–20 years (2021–2041). The currently active investigating centers are: Katholieke Universiteit Leuven (Belgium), Aarhus University Hospital (Denmark), Centre Régional François Baclesse (France), Gustave Roussy (France), and Universitaetsklinikum Essen (Germany), where a total of 2670 patients are expected to be included by May 2024.

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**Table 1**  
Content of the HARMONIC-RT registry.

Category of data	Information collected	BO	FU	
Registration & Follow-Up	ID	X	X	
	Referral	X		
	Date and type of last information		X	
	Withdrawal		X	
	Date and causes of death		X	
Demographics and socio-economics	Date of birth, sex	X		
	Usual place of residence	X		
	Parent/guardian(s)'s education level	X		
	Participant's education level and occupational	X	X	
	Current weight and height	X	X	
General Health Information & risk factors	Predisposing factors for cancer (i.e., genetic predispositions, immunodeficiencies, bone marrow failure disorders)	X	X	
	Family history of cancer and other diseases	X	X	
	Current consumption of tobacco, alcohol, and drug	X	X	
	Certain medications, e.g. cardioprotector, hormones	X	X	
	Complete blood count	X	X	
	Lipid test, glycosylated haemoglobin, ferritin, creatinine	X	X	
	Codes for disease (ICD-O-3)	X	X	
Routine biological tests	Laterality	X	X	
	Grade, stage, molecular subgroup	X	X	
	Diagnostic procedures	X	X	
	Recurrence/progression (for first neoplasm only)		X	
	Extent with respect to the treated volume (for subsequent neoplasm only)		X	
First and subsequent neoplasms	Code for disease (ICD-10, CTCAE5.0, others)	X	X	
	Date, grade	X	X	
Surgeries	Cancer and non-cancer surgery: date, extent, localization, laterality	X	X	
	Organ/tissue transplantation: date, organ/tissue	X	X	
Systemic Cancer Treatments	Date, timing vs. EBRT, protocol or drug's code (ATC), administration route + cumulative doses	X	X	
Radiotherapy	Date, treated area	X	X	
	Protocol, intent of treatment	X	X	
	Number of target(s) <sup>1</sup> , by target: irradiated field <sup>1</sup> , beam quality <sup>1</sup> , delivery technique, total dose, dose per fraction or injection <sup>2</sup> , number of fractions or injection <sup>2</sup>	X	X	
	Conditions of irradiation: Imaging positioning verification, Positioning, Positioning Aids, Accessories <sup>1</sup>	X	X	
	Event during treatment: replanning, interruption		X	
	Initial tumor response		X	
	Total dose to critical structures (Dmean, D50, D02 and D98 as calculated by the treatment planning system) <sup>3</sup>		X	
	First EBRT and re-irradiation: CT, RT dose, plan + struct	X	X	
	DICOM-RT		X	X

BO: baseline FU: follow-up <sup>1</sup>for external beam radiotherapy only <sup>2</sup>for external beam radiotherapy or radioisotopes <sup>3</sup>for external beam radiotherapy or brachytherapy.

In the registry, any severe and/or chronic or fatal health condition, including SPC is recorded, as reported in the hospital records (active follow-up) or in national registries of cancer and vascular diseases, registries of vital status and causes of death, inpatient databases and health insurance claim databases (passive, long-term follow-up). The sub-studies investigate more specifically parent- and patient-reported outcomes (i.e. health-related quality of life, fatigue and academic

achievement), and early- and intermediate-term outcomes, by analysing endocrine hormone levels, blood/saliva markers of carcinogenesis (in relation to SPC) or vascular diseases, and imaging markers of vascular damages (on cardiac echography or neurovascular MRI), before EBRT and up to 5 years after EBRT.

Detailed information is collected about EBRT (including DICOM-RT files for all participants), surgeries and systemic cancer treatments, and possible confounding/modulating factors (e.g., genetic, hormonal, and lifestyle factors) potentially associated with outcomes after EBRT (Table 1). Pseudo-anonymized clinical data are centralized in a database supported by REDCap®, connected to an imaging-data repository in the Oncoplace platform (Aquilab, Inc.) designed to enable pooling studies with the US Pediatric Proton Photon registry [20].

**Limitations**

The study is currently limited by the short duration of follow-up and the restricted number of participating centres. Maintaining the registry to enable a long-term follow-up will require sustainable resources for data collection. Another challenge is to extend the registry to more centres to allow the investigations of the impact of radiation together with other risk factors, with sufficient statistical power. For this purpose, HARMONIC-RT can serve as a pilot phase of the European Particle Therapy Network (EPTN) registry for paediatrics [22,23].

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**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Appendix A. Supplementary material**

Supplementary material to this article can be found online at <https://doi.org/10.1016/j.radonc.2023.109972>.

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