EMPIR Call 2018 – Health, SI Broader Scope, Normative and Research Potential

Selected Research Topic number: **SRT-h13**
Version: 1.0

Title: Radiotherapy coupled with hyperthermia - adapting the biological equivalent dose concept

Abstract

Radiotherapy is a frontline cancer treatment that destroys or damages cancer cells to stop their proliferation. However, it can only be applied in limited doses as it is also toxic to normal tissue and this can affect the subsequent quality of life of patients. Therefore, novel multimodal techniques are under development including radiotherapy coupled with hyperthermia. This treatment locally increases tissue temperature and enhances radiosensitivity by an order of magnitude. A metrology framework needs to be developed for the evaluation and optimisation of the biological equivalent dose concept for a class of radiation-based therapies coupled with hyperthermia. This will require in-vitro and in-vivo experiments to be undertaken to establish the best combination in terms of equivalent dose and biological effect.

Keywords

Cancer therapies, radiotherapy, hyperthermia, ionizing radiation, electromagnetic radiation, therapeutic ultrasound, magnetic nanoparticles

Background to the Metrological Challenges

Despite improvements in cancer treatment, patient survival has not met expectations particularly for those who are diagnosed with advanced tumours. Therefore, cancer is still responsible for just over 1.3 million deaths in the EU per year. About 50 % of cancer patients have radiotherapy as part of their treatment. This approach uses radiation to kill cancer cells either directly by damaging their DNA or by creating charged particles (free radicals) within the cells that in turn damage the DNA. However, there are side effects which need to be reduced and its effectiveness needs to be enhanced in order to significantly improve the outcome for cancer patients. To meet this need multimodal techniques are being developed including radiotherapy coupled with hyperthermia. This treatment locally increases tissue temperature and enhances radiosensitivity, by an order of magnitude. It has been shown to be most effective when radiotherapy and hyperthermia are performed at exactly the same time. At present, the clinical uptake and use of this technique has been hampered by the lack of precision in treatment delivery and monitoring. Therefore, a reliable metrology framework needs to be developed for the evaluation and optimisation of the biological equivalent dose concept for a class of radiation-based therapies coupled with hyperthermia induced by therapeutic ultrasound (TUS), conventional electromagnetic radiation (EMR) and magnetic nanoparticles (MNP). To ensure that pre-clinical results are smoothly translated into future clinical practice, the properties of the radiation fields in in-vitro and in-vivo experiments needs to resemble the clinical situation as closely as possible.

The combined use of radiotherapy and hyperthermia is difficult to study in-vitro, although progress has been made on designing and testing a dedicated experimental set-up. An empirical cell survival model was recently tested with two cell lines for the quantification of heat induced radio-sensitisation and thermal dose. Other studies have focused on the quantification of the influence of treatment order and timing. Therefore, 2D and 3D measurement set-ups, and validated modelling tools, are needed for estimating the spatial-temporal distribution of energy deposition in in-vitro cellular systems and for the related temperature increase caused by the different methods of hyperthermia when coupled with radiotherapy. These numerical tools will then need to be tested in complex in-silico anatomical models, to ensure that temperature increases can be predicted, before in-vivo experiments can be undertaken.

A few trials that coupled TUS with radiotherapy have already shown promising results in-vivo. However, the repeatable and controllable clinical use of hyperthermia systems still needs to be demonstrated in in-vivo experiments, in order to guarantee treatments with a generated temperature distribution from 37 °C to 50 °C. This approach will require excellent knowledge of temporal and spatial distributions of temperature increase and radiation dose during and after treatment. Therefore, new measurement methods are needed for

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accurately assessing the spatial-temporal radiation field characteristics that are relevant for new combined modalities, including radioactive magnetic nanoparticles for simultaneous radiation and heating.

A number of factors are thought to contribute to the enhanced effectiveness of radiotherapy combined with hyperthermia: the inhibition of DNA repair mechanisms, immune stimulation, the induction of cell death, changes to the local perfusion environment etc. For these reasons the timing of the treatment and information on the spatial-temporal distributions of temperature are crucial. In addition, the treatment order may affect the biological response, depending on the tissue (normal vs. tumour), and the therapeutic window may need to be widened. Therefore, the biological effects need to be quantified in-vivo with and without dose reduction. The role of control parameters, such as energy deposition in tissues, the radiation dose and the duration of the treatment, also need to be quantified in order to establish the best combination of equivalent dose and biological effect.

In radiotherapy the biological equivalent dose concept has been successfully used as a surrogate for biological effects. Coupling radiotherapy with hyperthermia will require the biological equivalent dose concept to be extended to include the synergistic effect of heat on the radiation-induced biological effect using a dose modifying factor. This parameter will be a complex function of a number of factors, which include the local temperature distribution, the way heating is generated and delivered with respect to ionizing radiation, the heating duration, the temperature distribution within the tumour, the physical and biological characteristics of the tissue, the radiation dose, the dose rate and the fractionation.

Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the protocol.

The JRP shall focus on providing a reliable metrology framework for the evaluation of a class of radiation-based therapies coupled with hyperthermia induced by Therapeutic Ultrasound (TUS), Electromagnetic Radiation (EMR) and magnetic nanoparticles fed by Electromagnetic Radiation (MNP/EMR).

The specific objectives are

1. To determine the suitability of the methods of hyperthermia for use with radiotherapy. 2D and 3D measurement set-ups, and validated modelling tools, should be developed to estimate the spatial-temporal distribution of energy deposition and temperature increase in in-vitro cellular systems. The target uncertainty of the in-vitro determination of the temperature increase should be < 10 %.

2. To extend the assessment of the spatial-temporal distribution of energy, deposited from radiotherapy and hyperthermia, and of the related temperature increase, to in-vivo systems. In addition, to demonstrate the repeatable and controllable clinical use of the hyperthermia methods in in-vivo experiments, in order to guarantee treatments with a generated temperature distribution from 37 °C to 50 °C and a target fractional uncertainty below 15 %. Radiation dosimetry should also be demonstrated to have clinically fractional uncertainties less than 5 %. In-silico models should be adopted to estimate the ability of numerical dosimetry to predict temperature increases in complex anatomical models to within a fractional uncertainty of less than 10 %.

3. To extend existing and to develop new measurement methods for accurately assessing the spatial-temporal radiation-field characteristics that are relevant for the combined radiotherapy/hyperthermia modalities, including radioactive magnetic nanoparticles for simultaneous radiation and heating. This should focus on the translation of pre-clinical results into future clinical practice.

4. To exploit and quantify the biological effects of coupling the hyperthermia techniques with radiotherapy. In addition, to quantify the biological effects of dose reduction by performing in-vivo experiments that result in the same therapeutic outcome with and without dose reduction. The role of the control parameters, such as the energy deposition in tissues, the radiation dose and the duration of the hyperthermia and/or radiation treatment, should also be quantified.

5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (accredited laboratories, instrumentation manufacturers), standards developing organisations (CEN, ISO) and end users (e.g. hospitals

and health centres). This should include close interaction with clinicians to assess the applicability of the combined therapy for future trials on patients.

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical practitioners, hospitals and industry is strongly recommended, both prior to and during methodology development.

Proposers should establish the current state of the art, and explain how their proposed project goes beyond this.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.8 M€, and has defined an upper limit of 2.1 M€ for this project.

EURAMET also expects the EU Contribution to the external funded partners to not exceed 35 % of the total EU Contribution across all selected projects in this TP.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the “end user” community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the “end user” community (e.g. letters of support) is also encouraged.

You should detail how your JRP results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Transfer knowledge to the radiotherapy sector.

You should detail other impacts of your proposed JRP as specified in the document “Guide 4: Writing Joint Research Projects (JRPs)”

You should also detail how your approach to realising the objectives will further the aim of EMPIR to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. Specifically, the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work

Time-scale

The project should be of up to 3 years duration.