Publishable Summary for 18HLT06 RaCHy
Radiotherapy Coupled with Hyperthermia

Overview

The integration of radiotherapy with hyperthermia requires experimental studies to accurately assess the biological mechanisms involved at a cellular level (e.g. the inhibition of DNA repair mechanisms caused by heat exposure). The increased understanding of the involved biological mechanisms will allow clinicians to prescribe the required thermal and radiation doses (magnitude and homogeneity), according to the individual patient's needs. The project is aimed at providing metrological support to achieve the maximum synergistic advantages in the integration of radiotherapy (RT) oncology with different hyperthermia (HT) techniques, based on high intensity Therapeutic Ultrasound (TUS), Electromagnetic Radiation (EMR) and the use of magnetic nanoparticles (MNPs) excited by AC magnetic fields. One of the main aims of this project is to experimentally demonstrate how the use of different sources to generate hyperthermia, combined with radiotherapy, could result in a successful treatment of the whole tumour. This approach requires excellent knowledge and control of the temporal and spatial distributions of temperature increases, and of the radiation dose during and after the treatments.

Need

Cancer is responsible for just over 1.3 million deaths in the European Union per year. With the ageing population, the incidence of cancer is rising. While cancer accounts for 22 % of all deaths for those over 65, this figure has grown to 38 % for people younger than 65, and it is the leading cause of premature death in 28 of the 53 regions in Europe. Even though the current treatments that are available for cancer patients have improved, the survival of patients has not improved as desired, particularly in those diagnosed with advanced tumours.

The ability of hyperthermia to enhance the effects of radiotherapy has already been demonstrated, one benefit is its ability to double the local control and survival rates. **Different heat delivery systems for hyperthermia treatments, TUS, EMR and MNPs excited by AC magnetic fields need to designed, developed and characterised**.

In order to maximize the treatments' effectiveness, it is mandatory to define the characteristics of the spatial and temporal temperature profiles required for the enhancement of radiotherapeutic effects, in terms of the relevant parameters to be monitored. It is necessary **to extend and to better quantify the exposure to temperature** associated with the energy deposited from radiotherapy combined with hyperthermia methods (TUS, EMR and MNPs), in *in vivo*, *in vitro* and *in silico* systems.

With regards to biological optimisation of exposure, new innovative analytical tools for biological assessment need to be developed by using chemical metrology multimodal techniques such as vibrational spectroscopic techniques as suitable non-invasive and non-ionising tissue diagnosis tools, X-ray spectrometry traceable to the SI for elemental probing, and mass spectrometry combined with imaging modalities at nanometre resolution should be used for biological evaluations. A metrological approach, related to the delivery and the evaluation of the combined therapy, is required **to facilitate the review of Biological Equivalent Dose (BED) concept related to the radiotherapy combined with hyperthermia.**

Objectives

The overall objective of the project is to develop a metrological framework and measurement techniques that underpin the integration of clinical radiotherapy with hyperthermia treatments.

The specific objectives of the project are:

1. **To develop heat delivery systems for hyperthermia treatments (TUS, EMR and MNPs)** for use with radiotherapy. 2D and 3D measurement set-ups and validated modelling tools will be developed to estimate the spatial-temporal distribution of energy deposition.
2. **To extend and better quantify temperature exposure evaluation** associated with the energy deposited from radiotherapy combined with hyperthermia methods (TUS, EMR and MNPs), in *in vivo* (37 °C to 50 °C), *in vitro and in silico* systems with a target uncertainty of < 10 % (WP2).
3. **To determine by *in vitro* and *in vivo* testing, using a metrological approach,** the efficiency of combined therapies: radiotherapy plus hyperthermia and reverse combination. The spatial-temporal radiation-field characteristics are relevant for the combined radiotherapy/hyperthermia modalities, including radioactive magnetic nanoparticles for simultaneous radiation and heating.
4. **To develop innovative analytical tools for biological assessment** by using chemical metrology multimodal techniques as suitable non-invasive and non-ionising tissue diagnosis tools, and mass spectrometry combined with imaging modalities at nanometre resolution.
5. **To facilitate the review of Biological Equivalent Dose (BED) concept related to the radiotherapy combined with hyperthermia.** The role of control parameters such as the energy deposition in tissues, the radiation dose and the duration of the hyperthermia and/or radiation treatment will be taken into account.
6. **To facilitate the take up of the technology and measurement infrastructure developed in the project** by the measurement supply chain (accredited laboratories, instrumentation manufacturers), standard developing organisations (IEC, ISO) and end users (e.g. hospitals and health centres). This should include a close interaction with clinicians to assess the applicability of the combined therapy for future trials on patients.

Progress beyond the state of the art

The project will improve the state of the art in a number of different disciplines, for example: TUS, EMR, MNP based hyperthermia, radiation therapy, RT, biological assessment and in silico modelling.

Currently treatments that combine hyperthermia with radiation are difficult to study in vitro. The project will go beyond the start of the art by improving the efficacy, safety and range of applicability of clinical TUS treatments by providing validated methods for ultrasonic field characterisation, TUS system performance testing, quality assurance and patient exposure monitoring.

The safety and efficacy of Advanced Electromagnetic Field modelling to assist the design of novel RF applicators for in vivo characterisation, with the aim of generating uniform power deposition and temperature increase patterns, with limited off-target energy delivery has been proved in several clinical trials. However, currently, it still suffers from poor reproducibility and temperature distribution control, thus making the improvement of heating uniformity and target specificity a significant metrological issue. The project will go beyond state of the art by achieving increased selectivity in treating lesions thanks to the reduced formation of hot spots.

A promising approach to improve selectivity and thermal homogeneity is represented by magnetically mediated hyperthermia, where MNPs, typically superparamagnetic iron oxide nanoparticles, are employed as local heating sources after their injection into the tissue and exposure to external magnetic fields with frequencies from 50 kHz to 1.2 MHz. The project will go beyond state of the art by controlled hysteresis losses which allow a strong enhancement of specific loss power (SLP).

The integration of radiotherapy with hyperthermia requires experimental studies to accurately assess the biological mechanisms involved at a cellular level (e.g. the inhibition of DNA repair mechanisms caused by heat exposure). The project will go beyond state of the art by increasing understanding of the involved biological mechanisms. This will allow clinicians to prescribe the required thermal and radiation doses (magnitude and homogeneity) according to the individual patient's needs.

The growing interest in multimodality therapies that combine hyperthermia and ionising radiation is expected to extend the equivalent dose concept by including the synergistic effect of heat on the radiation-induced biological effect. The parameter is expected to be a complex function of several factors (e.g. local temperature, heating duration, temperature distribution, etc). The project will go beyond state of the art by providing a coherent set of experimental data to investigate the dependence of the linear quadratic

parameters on the hyperthermia exposures both *in vitro* and *in vivo*.

Results

Heat delivery systems for hyperthermia treatments (TUS, EMR and MNPs) combined with radiotherapy

New experimental and modelling methodologies will be developed in the medical ultrasound field to enable the prediction of power deposition and temperature profiles within biological media during TUS hyperthermia. The temperature profile will be measured during exposure, to ensure a safe and effective treatment.

A system based on HIFU transducers (Sonic Concepts SU-103) using the far field properties has been developed. With this approach it will be possible to treat by hyperthermia the cancer tissue with 10 mm diameter, without using the motorized positioning translator coupled with HIFU transducer. The system was tested by measuring the temperature induced by US field.

An ultrasound numerical tool, based on the Westervelt equation, for the simulation of the ultrasound propagation in heterogeneous media like fluids or tissues and the calculation of power deposition has been developed.

To extend and better quantify temperature exposure evaluation

Advanced Electromagnetic Field, EMF, modelling will be performed to assist the design of novel RF applicators for in vivo characterisation, with the aim of generating uniform power deposition and temperature increase patterns, with limited off-target energy delivery.

A finite element numerical tool was developed for the solution of the Maxwell equations in the presence of electromagnetic field sources, to be applied for both magnetic hyperthermia (low frequency regime) and EMR hyperthermia (high frequency regime). The code, validated by comparison to the commercial software CST Microwave Studio, was used for the preliminary design of the RF applicator. This has been used for a biological test and for the evaluation of possible eddy current effects in the frequencies of interest for magnetic hyperthermia.

An RF applicator based on a coaxial TEM system with variable aperture width, able to generate a uniform power deposition pattern in a target region with size of 1000 mm^3 at a frequency of 434 MHz has been designed. The applicator was developed through an extensive parametric analysis of the critical dimension of the antenna, which was designed to match with the standard amplification sources with 50 Ω impedance. One of the advantages of the setup is that it can also be used in *in vitro* experiments to heat cell cultures or tissue samples contained in test tubes or vials. Moreover, the designed applicator can be easily converted for application at 2.45 GHz, if more focused heating is required. The simulations of the antenna were previously performed with the electromagnetic numerical tool and then refined by using CST Microwave Studio and Sim4Life, with a cross-checking approach.

To determine the efficiency of combined therapies: radiotherapy plus hyperthermia by in vitro and in vivo testing, using a metrological approach

Novel heat nanomediators, such as NiFe and FePd nanodisks, whose heating contribution comes from hysteresis losses, and which allow a strong enhancement of specific loss power (SLP), will be developed.

A 2.5D and a 3D micromagnetic solver for the solution of the Landau-Lifshitz-Gilbert equation have been developed. The codes, validated by comparison to the OOMMF solver developed at NIST, were applied to calculate the hysteresis losses of $Fe_{70}Pd_{30}$ nanodisks and the Fe_3O_4 nanoparticles. In particular, the 2.5D code enabled the consortium to handle large numbers of magnetic thin-film objects (like the nanodisks) randomly distributed in a 3D medium. This was used to investigate the influence on hysteresis losses of concentration and local orientation with respect to the applied field, for the case of the $Fe_{70}Pd_{30}$ nanodisks. The 3D code was employed to calculate the specific loss power of the Fe_3O_4 nanoparticles with larger dimensions.

Monte Carlo models for the simulations of local dose distributions around MNPs have been developed in the codes Geant4 and PENELOPE. Simulations have been performed for various MNPs configurations, i.e. with different shell thicknesses and core diameters. These simulations demonstrate a strong local dose enhancement in the region of 0 - 100 nm around a single MNPs which depends on the configuration of the particle.

Three types of magnetic nanomaterials for magnetic hyperthermia application, namely Fe_3O_4 nanoparticles, $Fe_{70}Pd_{30}$ nanodisks and hybrid ^{103}Pd-FeO nanoparticles were prepared:

Fe_3O_4 nanoparticles with diameters variable in the range 10-200 nm were synthetized, calorimetric measurements have been perfomed for selection of the batches more efficient for magnetic hyperthermia, i.e. the largest size ones, which contribute to the heating with hysteresis losses.

$Fe_{70}Pd_{30}$ nanodisks by means of self-assembling nanosphere lithography were prepared. The three sets of nanodisks were characterised in terms of size (scanning electron microscopy) and static magnetic properties (vibrating sample magnetometry).

Non-radioactive Pd-FeO nanoparticles (Pd core and FeO shell) were prepared, with both spark-ablation and wet-chemistry methods; the latter seems to be more advantageous in terms of effective particle's size and yield that could be achieved.

To develop innovative analytical tools for biological assessment of the integration of radiotherapy with hyperthermia

The integration of radiotherapy with hyperthermia requires experimental studies to accurately assess the biological mechanisms involved at a cellular level (e.g. the inhibition of DNA repair mechanisms caused by heat exposure).

To facilitate review of the Biological Equivalent Dose (BED) concept

The project will extend the *in vitro* studies to 3D spheroid cultures, which better mimic the clinical conditions and therefore provide improved data on thermal enhancement. The water bath heating system will be replaced in the *in vivo* studies by TUS, MNPs and EMR based heating in the same way as in clinical practice, and this will result in a more reliable bench-to-bedside transfer of the outcome of the biological studies but will also offer the possibility of establishing whether thermal enhancement is device specific.

An in-depth literature review of the cellular response models (and associated data) used to quantify the synergistic biological effects of combined RT-HT treatments has been performed. This review has been discussed and the alpha-R model and the LQ model were selected.

Target uncertainties for physical quantities relevant to in-vitro experiments have been defined based on international recommendations (such as ICRU-24) and scientific literature. For the radiation dose distribution, a target uncertainty of 5% (k = 1) has been defined and for temperature a target uncertainty of 1˚C. It has been demonstrated that these uncertainties can be met in practice for external beam irradiations combined with a water bath heating system.

Impact

So far, 3 open access articles in peer-reviewed journals have been published. Project activities have been presented at 10 international and national conferences. One training activity has been carried out regarding the TUS application in hyperthermia (12 participants from one stakeholder of the project). Project updates have also been available on dedicated pages on Linkedin. In addition, more than 50 people, took part in the first project stakeholder workshop 'How the Metrology Can Support Radiotherapy Coupled with Hyperthermia' provided a great opportunity to share the results with the user community and to gather its needs. Feedback from the stakeholders (FUS Foundation, U.S. FDA, IRCCS Carlo Besta, UniTO, European Institute of Oncology) on the appropriate tumour lines and biological endpoints for in vivo testing of dose reduction have provided input into the project. The second stakeholder workshop has been scheduled in Autumn 2022 in Gothenburg, Sweden, joint with annual scientific meetings of the EUROPEAN SOCIETY FOR HYPERTHERMIC ONCOLOGY (ESHO). The project website (https://rachy-project.eu) is also updated regularly with the latest progress and a stakeholder committee has been established, the next meeting will take place in Berlin (PTB) or London (ICR) in autumn 2021. Last, four presentations of the project in scientific/technical events have been carried out.

Impact on industrial and other user communities

The first group of beneficiaries will be the cancer research community, who will be provided with metrological instruments that are able to perform reliable, repeatable and transferrable tests of nanoparticles and ultrasound-based methods for quantitative determination of temperature profiles. The next group of beneficiaries is the medical device industry, who will be provided with the knowledge and tools required to develop new medical equipment, such as US insonation system. Another group of beneficiaries are the

hospitals who will be provided with calibration devices to help measure the performance of the new equipment and a metrological framework for clinical trials to ensure the uniformity of trials and the application of trial-results of test temperature accuracy and reproducibility of TUS heating.

The regulation industries that are involved with Quality Assurance for HIFU devices and safety assessment for diagnostic devices will immediately obtain an advantage from the evaluation of temperature profiles during ultrasound exposure carried out in this project. An accurate measurement of the output of HIFU machines will reduce the maintenance costs of the equipment, allow defects to be detected quickly and prompt interventions to be made, thus reducing the shutdown times.

FDA U.S. Food & Drug Administration, Istituto Neurologico Carlo Besta and FUS, Focused Ultrasound Foundation, have demonstrated an interest in the RaCHy project activities on the development of techniques and methods for hyperthermia mediated by ultrasound have provided interesting opportunities for exploitation of the project results.

Impact on the metrology and scientific communities

Instruments and methods have been developed within the project, that will be useful both at metrological research level and in clinical settings. The main ones are (i) a new RF applicator based on a coaxial TEM system with variable aperture width, able to generate a uniform power deposition pattern at a frequency of 434 MHz; (ii) an ultrasound system based on HIFU transducers using the far field properties, that makes possible the treatment (by hyperthermia) of the cancer tissue up to 10 mm diameter. They will allow the power deposition and temperature increase in tissues during *in vivo* treatments. Ultrasound and Electromagnetic field exposure assessment will be beneficial for the metrology community and for preclinical studies.

The research activities and the comparison of different measurement methods are expected to benefit the US Technical Standard Committee working. The document: “Methods for the characterisation of the ultrasonic properties of materials” is expected during the second part of the project.

The EMR scientific community is also expected to benefit from the use of novel heat mediators prepared via advanced nanotechnology fabrication processes. An accurate characterisation of their magnetic properties, combined with a 2.5D and a 3D micromagnetic solver for the solution of the Landau-Lifshitz-Gilbert equation, developed in the project could also provide indications for their alternative use as new contrast agents in Magnetic Resonance Imaging, MRI.

Relevant scientific results, related to MNP field, are expected from the investigation of dual functional MNPs, made of a magnetic shell and a radioactive core, considering the complexity of evaluating their efficacy, due to the simultaneous delivery of heat and radiation. Understanding their behaviour could also have an impact on the design of novel Positron Emission Tomography, PET, or MRI agents.

In general, a rigorous assessment of different techniques, with the relevant uncertainties, could be exploited in different US and EM medical application fields, over and above those envisaged in this project, for example, diagnostics (US or Magnetic Resonance, MR, imaging and the related dosimetry aspects), high intensity ultrasound therapy and thermo-ablation treatments.

Impact on the relevant standards

The consortium has close links with IEC TC87 – Ultrasonics-, and the knowledge generated in the project will be immediately disseminated to this TC. The work in this project will influence the development of current technical specifications, such as “TS 63081: Methods for the characterisation of the ultrasonic properties of materials” and “TS 63900: Ultrasonics-: Measurement-based simulation in water and complex media”, as well as informing the generation of new standards.

ISO/TC229 WG4 has accepted the proposal for a standard for magnetic beads for DNA extraction formally as a new project in the committee's work programme. The current document numbering is ISO 22761, however, it is expected to change to ISO 19807-2, in the series of magnetic nanomaterials. The formal title is: Nanotechnologies -- Magnetic nanoparticles -- Part 2: Nanostructured superparamagnetic beads for nucleic acid extraction -- Specification of characteristics and measurements.

The two standards (ISO 22761 and ISO 19807-2) are mainly focused on measurements in Fe_3O_4 oxides nanoparticles. By measuring SLP, and more generally magnetic parameters in FePd and FeNi nanodisks using the standards used/assessed in the MagNastand project, this project will broaden scientific knowledge in order to pave the way for the exploitation of magnetic nanoparticles in biomedicine.

The work will also introduce robust methodology for quantifying the radiation enhancement. Recommendations on best practice will be drafted for the benefit of international technical committees. Principal activities of RaCHy project were presented during EURAMET Technical Committee for Acoustics, Ultrasound and Vibration, TC-AUV, plenary meetings and Subcommittee on Ultrasound and Underwater Acoustics meetings and EURAMET Technical Committee for Ionising Radiation, EURAMET TC-IR.

Longer-term economic, social and environmental impacts

It has been estimated that the total cost of cancer treatment and management in Europe is €126 billion/year, with the majority being used for healthcare expenses, including doctors' time and medicinal costs. The loss of productivity, due to sick days or people dying young, costs €52 billion/year, while the cost of providing care for bereaved families is estimated to be about €23 billion/year. The European external beam radiotherapy device market, which is mainly driven by the rapidly changing cancer treatment technology and the growing number of cancer patients, is expected to exceed €650 million by 2020.

Longer term, the clinical availability of the techniques developed in this project will be of benefit for the patients and society as a whole as Europe faces greater pressures from the increased number of patients that have to be treated as a result of the growing and ageing population. Survival rates and quality of life will improve, as it will be possible to reduce the radiation dose for patients without affecting the therapeutic outcomes, and this will result in reduced toxicity, which in turn will improve the patients' quality of life as well as reduce the burden of care. This is particularly desirable in cases of paediatric tumours. It will also be possible to reduce the dose, and as a result a greater number of patients will be admissible for treatment. On the other hand, it will be possible to deliver an increased effective dose with the same toxicity in order to target radio-resistant regions, such as hypoxic regions, thus improving the efficacy of treatments.

List of publications

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