Publishable Summary for 18HLT06 RaCHy
Radiotherapy Coupled with Hyperthermia

Overview

The integration of radiotherapy with hyperthermia, which has been demonstrated to improve survival rate for patients with cancer, requires experimental studies to accurately assess the biological mechanisms involved at a cellular level. An increased understanding of the biological mechanisms involved will allow clinicians to prescribe the required thermal and radiation doses, according to an individual patient's needs. This project has developed and provided metrological support to achieve maximum synergistic advantage in the integration of radiotherapy (RT) oncology with different hyperthermia (HT) techniques, based on high intensity Therapeutic Ultrasound (TUS), Electromagnetic Radiation (EMR) and magnetic nanoparticles (MNPs) excited by AC magnetic fields. Heat delivery systems able to generate a uniform power deposition pattern in the target region with a closed-loop control which would maintain the defined temperature indefinitely have been developed and used for *in vitro* and *in vivo* tests. New systematic metrological approaches by using chemical metrology techniques such as FTIR spectroscopy as suitable non-invasive and non-ionising tissue diagnosis tools regarding chemical species combined with hyperspectral imaging (HSI) modalities at micrometre resolution have been used for the biomedical evaluations. The techniques and methods have been tested in preclinical cases and they are now available for clinical evaluation.

Need

Cancer is responsible for more than 1.3 million deaths in the European Union every year. With an 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 current treatments available for cancer patients have improved, the survival of patients has not improved as desired, particularly for those diagnosed with advanced tumours.

The ability of hyperthermia to enhance the effects of radiotherapy has already been demonstrated, with results that include 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 be designed, developed and characterised**.

In order to maximise treatment efficacy, 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 improve quantification of the temperature exposure** obtained using hyperthermia techniques (TUS, EMR and MNPs), in combination with the energy deposited from radiotherapy, in *in vivo*, *in vitro* and *in silico* systems.

With regards to biological optimisation of exposure, the development of new innovative analytical tools for biological assessment 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 is needed. A metrological approach, related to the delivery and the evaluation of the combined therapy, is required to facilitate the **review of Relative Biological Effectiveness (RBE)** concept related to the radiotherapy combined with hyperthermia.

Objectives

The overall objective of the project is to develop measurement techniques and a metrological framework and 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 improve temperature exposure quantification** 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 %.
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 Relative Biological Effectiveness (RBE) concept related to radiotherapy combined with hyperthermia.** The role of control parameters such as energy deposition in tissues, radiation dose and 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

Treatments that combine hyperthermia with radiation are difficult to study *in vitro* and *in vivo*. The project has gone beyond the state of the art by improving the efficacy, safety and range of applicability of clinical therapeutic ultrasound treatments by providing validated methods for ultrasonic field characterisation and temperature measurements, oriented towards monitoring patient exposure during treatment.

Several studies have demonstrated that the combination of hyperthermia with radiotherapy can lead to an enhancement of radiation effects, mainly because of the inhibition of DNA-repair processes, the triggering of the immune response and modifications of the tumour microenvironment, following a local temperature increase up to 42°C – 44°C. Ultrasound hyperthermia delivery systems for *in vitro* testing, based on HIFU transducer has been developed and successfully tested. The system developed was capable of increasing the temperature of the target volume by 6 °C above body temperature, and of maintaining the temperature to within ±0.5 °C indefinitely.

Non-invasive temperature measurement during hyperthermia treatments, typically temperature distribution between 42 °C and 45 °C, is an ongoing issue that greatly limits the reproducibility and consequently the acceptance of such therapies in clinical practice.The effectiveness of advanced electromagnetic field modelling in assisting the design of novel RF applicators for *in vivo* characterisation, with the aim of generating uniform power deposition and temperature increase distributions, with limited off-target energy delivery, has been proven in several clinical trials.

A high dose estimation accuracy level is also needed for contemporary combined RT-HT treatment, and it should also be feasible to achieve this level in TUS and EMR-based HT. Ultrasound hyperthermia delivery systems based on acoustic hologram lenses that produce a more uniform thermal dose over complex in vitro and in vivo biological targets than a single geometric focus HIFU transducer have been developed and successfully tested.

The biological effect is often measured by looking at cell survival curves in *in vitro* experiments or at clinical effects, in terms of tumour control and normal tissue side effects. New systematic metrological approaches using chemical metrology multimodal techniques such as vibrational spectroscopic techniques, SI-traceable X-ray spectrometry for probing elemental compositions, combined with hyperspectral imaging, HIS, modalities at micrometre resolution have been used for biological evaluations.

The *in vitro* experimental assessment of the thermal enhancement of radiotherapy has predominantly been performed using 2D and 3D layered cell cultures. The project has improved the state of the art by increasing understanding of the biological mechanisms. The concepts for Relative Biological Effectiveness (RBE) based

on different modalities for radiotherapy combined with hyperthermia methods which take into account energy deposition in tissues, the radiation dose and the duration of the hyperthermia and/or radiation treatment have been evaluated thanks to *in vitro* and *in vivo* test results.

Results

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

New experimental and modelling methodologies were developed to enable the prediction of power deposition and temperature profiles within tissue-mimicking materials and biological media during TUS, EMR and MNP-based hyperthermia.

A system based on HIFU transducers (Sonic Concepts SU-103) using their far field properties was developed. With this approach it is possible to treat tumour tissue up to 10 mm diameter with hyperthermia, without using the motorized positioning translator coupled to the HIFU transducer. The system was tested in vivo by measuring the temperature induced by US fields. Ultrasound hyperthermia delivery systems based on acoustic hologram lenses that produce a more uniform thermal dose over complex in vitro and in vivo biological targets than a single geometric focus HIFU transducer have been developed. The *in vitro* set up was designed for simultaneous treatment of 3D cell aggregates (spheroids) using an absorbing phantom with multiple wells, each holding a tumour spheroid.

An RF applicator based on a coaxial TEM system with well-focused heating was designed and fabricated for EMR hyperthermia. This system is able to generate a uniform power deposition pattern and a controlled temperature rise in a 1 cm^3 target region size, at a frequency of 434 MHz and has been shown to be suitable for use as a calibrated setup for hyperthermia tests on tissue-mimicking materials, 3D cell cultures and tumour organoids.

Magnetic hyperthermia experiments were conducted in a custom-built laboratory setup on a set of samples, comprising Fe_3O_4 nanoparticles and $Fe_{70}Pd_{30}$ nanodisks suspended in liquid. The heating properties were determined by the magnetic single- or multi-domain configuration and by the competition between magnetocrystalline and shape anisotropies. The results demonstrated that a larger concentration of MNPs in phantoms is needed to obtain a temperature rise than in liquid.

The project successfully met this objective.

To extend and better quantify temperature exposure evaluation

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 and EMR hyperthermia in the temperature range from 37°C to 50 °C. In parallel, a finite element thermal solver for the bio-heat equation was implemented to determine the temperature increase in tissues, during hyperthermia pre-clinical tests. 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 was developed. The results were successfully compared with commercial k-wave code.

Methods for the evaluation of temperature resulting from ultrasound exposure using thermocouples were developed. Different models and approaches were considered, for evaluating the effect of positioning, sensor size and sensor artifacts. A method of non-invasive temperature measurement using diagnostic ultrasound was developed that ensures an uncertainty less than 10%. The results were compared with thermocouple methods with good agreement. A thermochromic phantom which changes colour at hyperthermia relevant temperatures was also manufactured and evaluated.

Thermocouples were used to assess the accuracy and repeatability of measurements using MR Thermometry in a commercial device. The results of the comparison have been published on the International Journal of Hyperthermia.

The project successfully met this objective.

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

A 2.5D and a 3D micromagnetic solver for the solution of the Landau-Lifshitz-Gilbert equation was developed. The codes were applied to calculate the hysteresis losses and the associated specific loss power of nanodisks and nanoparticles, thus providing support to the interpretation of the results from thermometric measurements.

Simulations were 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 MNP which depends on the configuration of the particle.

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

A complete set of *in vivo* tests have been performed using RT combined with HT mediated by TUS. A mechanical cone adaptor has been developed to allow use of the HIFU far field. Two thermocouples were placed between the mechanical cone and the skin mice to measure and control the temperature during the HT treatment. Radiotherapy was carried out by using a dedicated small animal image guided radiotherapy system (SmART, PXI). The dose planning was based on the CT scan of the animal and performed using the Monte Carlo treatment planning system.

Acoustic hologram lenses that produce a more uniform thermal dose over complex *in vitro* and *in vivo* biological targets than a single geometric focus HIFU transducer has been developed and tested. The *in vitro* system was designed for simultaneously treating 3D cells aggregates (spheroids) by using an absorbing phantom with multiple wells each holding a tumour spheroid. Holograms allow a simultaneous targeting providing a uniform thermal dose.

The project successfully met this objective.

To develop innovative analytical tools for biological assessment

New systematic metrological approaches using chemical metrology multimodal techniques such as vibrational spectroscopic techniques, FTIR, as suitable non-invasive and non-ionising tissue diagnosis tools regarding chemical species, and SI-traceable X-ray spectrometry for probing elemental compositions, combined with hyperspectral imaging, HIS, modalities at micrometre resolution have been used for biological evaluations. This includes the development of non-destructive metrological strategies and the establishment of reliable measurement procedures (combined with chemometric tools) for the characterisation of biological effects arising from radiotherapy treatments at lateral resolutions on a μm scale. The FTIR-HSI has been widely implemented for detecting and differentiating tumour tissues from benign regions via biomarkers, as well as its potential for tumour grading.

The project successfully met this objective.

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

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 and LQ models were selected.

The Biological effective Dose (BED) offers a quantitative indication of the biological effect induced by any combination of dose per fraction and total dose to a particular tissue characterized by a specific α/β ratio. Its purpose is to compare different fractionation regimes using a common numerical score. It uses a generic α/β ratio = 10 for the early-responding tissues and tumours and α/β ratio = 3 for the late-responding tissues such as normal tissues.

Different modalities have been employed for the radiation treatment and the hyperthermia. The purpose has been to find which RT-HT protocol would be the most favourable to have a synergistic effect. To quantify the comparison of the different modalities the investigation has mainly used the linear quadratic model in order to obtain a fitting of the parameters α and β.

A glioblastoma (GBM) xenograft nude mouse model obtained by injecting luc+ cells was used to study the combination of hyperthermia (HT) and radiotherapy (RT) on tumour growth. Mice were divided into four groups of six mice each:

1. Control (No treatment)
2. RT alone (6 Gy)
3. HT alone (7.5 or 15 CEM)
4. Combination of 6 Gy RT and HT for either 7.5 or 15 CEM (RT was delivered approximately 30 minutes after hyperthermia).

Daily measurements of tumour volume performed with a calliper show a 50% reduction for the HT+RT group with respect to the RT or control groups. A similar trend has been found using optical BLI, however in this case the differences between the groups is less (15%).

Despite the complex dependency of the alpha and beta parameters on the Temperature (T) and temperature exposure time (t), a clear trend in the Relative Biological Effect (RBE) values for cell survival has been observed. A second phenomenological model was therefore developed and tested based on the observed RBE values. This model was based on the hypothesis that RBE dependence on Temperature (T) and

temperature exposure time (t) can be parametrized according to the formalism: RBE = 1+w(T-37), with w being fitting parameters. An independent and linear relationship for both T and t is hypothesized.

The project successfully met this objective.

Impact

14 open access articles have been published in peer-reviewed journals. The project has been presented at 52 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). An e-learning course has been completed and it is available on the RaCHy project website: https://rachy-project.eu/e-learning-course/. The course is titled: Temperature measurements under ultrasound exposure, consisting of four modules: Introduction, Background, Technical Solutions for laboratory measurements and Technical Solutions for clinic measurements. The project website (https://rachy-project.eu) is updated regularly with the latest progress, project updates have also been made available on dedicated pages on Linkedin.

There were more than 50 attendees at the first project stakeholder workshop (VSL, February 2020) '*How the Metrology Can Support Radiotherapy Coupled with Hyperthermia*'. More than 70 attendees (including15 in person), participated at second project stakeholder hybrid workshop (PTB, 23rd November 2021) '*A combined approach for the treatment of tumours*'. Both workshops provided a great opportunity to gather the needs of the stakeholders and share results, or potential results, with the user community. Using input from stakeholders, appropriate tumour lines and biological endpoints for *in vivo* testing of dose reduction were selected during the project stakeholder workshops. A third stakeholder workshop was organized in September 2022 in Sweden, jointly with the annual scientific meeting of the European Society for Hyperthermic Oncology (ESHO). The focus of the workshop was the presentation of the project results, there were around 30 attendees mainly from clinical institutes.

During the Italian celebration of World Metrology Day 2021, the project was presented and discussed to a wide non-technical audience. In addition, three PhD students have presented their studies about HIFU application mechanisms, phantom production, ultrasonic power measurements and temperature investigations in phantoms to researchers.

As an alternative to the 2021 European Researchers' Night at the Istituto Superiore di Sanità (ISS), which was suspended due to Covid-19, the consortium gave an informal presentation of the project at the entrance of the ISS (PlanISSfero, which stands for ISS research planisphere).

Two Special Session have been organised: "Materials characterisation, SPM techniques and European project highlights" within E-MRS ALTECH 2021 - Analytical techniques for precise characterization of nano materials and "Hyperthermia techniques - Update from the EMPIR RaCHy Project" within Mathematical and Statistical Methods for Metrology (MSMM 2021).

The project results have been presented during the EURAMET TC-AUV and TC-IR annual meetings. Thanks to a strong collaboration with IEC TC 87 Ultrasonics, project outcomes have been shared with the members of the technical committee. During the 13th BIPM Consultative Committee for Acoustics, Ultrasound and Vibration (CCAUV) virtual meeting the project progress was presented by the TC-AUV Chair to the CCAUV delegates and experts.

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 a laboratory 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. 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 shutdown times.

FDA U.S. Food & Drug Administration, Istituto Neurologico Carlo Besta, FUS, Focused Ultrasound Foundation ESHO, European Society for Hyperthermic Oncology and stakeholders have demonstrated an interest in the development of techniques and methods for hyperthermia mediated by ultrasound. They provide interesting opportunities for exploitation of the project results. The solution based on acoustic holograms can be helpful on getting uniform thermal doses for large volume in vivo tumours, when constant temperature over a wide area is needed. In this case, patient-and-target-specific holograms should be designed, because the acoustic field should be tuned to compensate the balance between heating rate and heat transport along the therapeutic acoustic image. Project results demonstrate that tunned holographic lenses coupled to single-element transducers can be applied to obtain uniform thermal doses over wide areas or complex targets, using a low-cost but robust system. Further work can be done to optimize thermal uniformity in complex 3D targets, for example, applying optimization and machine learning algorithms to tune the holograms for uniform thermal dose. Other strategies for a deep control of the acoustic field include broadband phase-and-amplitude holograms, locally resonating metamaterials, or spatial sound modulators, to engineer the acoustic wavefront and produce uniform thermal patterns for ultrasound hyperthermia systems.

Impact on the metrology and scientific communities

The interaction with metrological and standardisation bodies is ongoing, and is implemented through the involvement of consortium partners in EURAMET technical committees (TC-AUV, Technical Committee for Acoustics, Ultrasound And Vibration, TCAUV SC-U, TC-AUV subcommittee Ultrasound and Underwater Acoustics, TC-IR, Technical Committee for Ionising Radiation, 19NET04 MIRA, Support for a European Metrology Network on the medical use of ionising radiation) and in national and international standardisation bodies (CEI TC29/87 Electroacoustics/Ultrasound, CEI SC 62C -Equipment for radiotherapy, nuclear medicine and radiation dosimetry-, IEC TC87 -Ultrasonics-, U.S. FDA, Food and Drug Administration).

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

Hyperthermia is the process of raising tissue temperatures in the range 40°C - 45°C for a prolonged time (up to hours). The ability to maintain a certain temperature in a target region is key to a hyperthermia delivery system.

The research activities and the comparison of different measurement methods are expected to benefit the US Technical Standard Committee working groups. Material and phantoms developed and tested in the project were designed with the following criteria: to simulate biological tissue acoustically and thermally, to provide real-time feedback of the temperature, and to include a thermochromic material to provide both an indicator of exposure area and the temperature reached in a biologically relevant environment. A report has been sent to IEC TC 87-Ultrasonics- chair to evaluate the application on technical specifications.

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 micromagnetic modelling, could also provide indications for their alternative use as new contrast agents in Magnetic Resonance Imaging, MRI, or tracers in Magnetic Particle Imaging, MPI.

Relevant scientific results, related to MNP design 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 contrast 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. In this framework, a strong support can be also provided by *in silico* models, able to guide the development of the hyperthermia applicators towards a more controlled heat release and temperature rise.

Impact on the relevant standards

The impact within the clinical community is strengthened by the involvement of EU oncology research institutions in the consortium. These partners and some stakeholder committee members are also active members of relevant scientific associations including ESHO, European Society of Hyperthermic Oncology and ESTRO, European Society for Radiotherapy and Oncology. Thanks to these links, the consortium was able to identify the best research strategy and, at the same time, maximize impact to the end user (in this case the oncology research centres and hospitals).

In particular the consortium has close links with IEC TC 87 – Ultrasonics. A report on the results of a comparison between different techniques for the measurement of temperature based on thermochromic phantoms and ultrasound-based techniques was prepared. The report was sent to IEC TC 87 chair to evaluate the application on technical specifications, TS-63081: *Methods for the characterisation of the ultrasonic properties of materials* and TS-62900: *Measurement- based simulation in water and complex media*.

ISO/TC 229 has accepted the proposal for a standard for magnetic beads for DNA extraction formally as a new project in the committee's work programme. Static hysteresis loops have been measured following the protocol indicated in the first standardization documents on Magnetic NP, ISO/TS 19807-1 “Magnetic nanosuspensions”. However, this document contains the basic terms for characterisation of magnetic nanomaterial and lists measurement methods, without giving any detailed prescription on how to perform measurements.

There are two standards (ISO 22761 and ISO 19807-2) that are mainly focused on measurements in Fe_3O_4 oxides nanoparticles. By measuring SLP, and more generally magnetic properties also of other types of MNPs, like FePd nanodisks, using the standards implemented/assessed in the EMPIR 16NRM04 MagNastand project, RaCHy project will broaden scientific knowledge to pave the way for the exploitation of MNPs in biomedicine.

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 to 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 a 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. 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

[1]. G. Durando, P. Miloro, V. Wilkens, B. Karaboce, J.De Pooter, G. Van Rhoon, G. Ter Haar, B. Caccia, A. Spinelli, A. Denkowa, R. Dijkema, EURAMET EMPIR 18HLT06 RaCHy Project: Radiotherapy coupled with Hyperthermia (Induced by HITU), Proceedings of the 23rd International Congress on Acoustics, DOI: https://doi.org/10.18154/RWTH-CONV-238838

[2]. M. Marschall, A. Hornemann, G.Wubbeler, A.e Hoehl,1 E.Ruhl, B. Kastner, C. Elster1, Compressed FTIR spectroscopy using low-rank matrix reconstruction, Optics Express, Vol. 28, Issue 26, pp. 38762-38772 (2020), DOI: https://doi.org/10.1364/OE.404959

[3]. G. Ulrich, E. Pfitzner, A. Hoehl, J.-W. Liao, O. Zadvorna, G. Schweicher, H. Sirringhaus, J. Heberle, B. Kastner, J. Wunderlich, D. Venkateshvaran, Thermoelectric nanospectroscopy for the imaging of molecular fingerprints, Nanophotonics, Volume 9: Issue 14, DOI: https://doi.org/10.1515/nanoph-2020-0316

[4]. Minutoli, D., CACCIA, B., Campa, A., Durando, G., Pozzi, S. and Valentini, S. How to make FAIR a project: open access to research data and the RaCHy - Radiotherapy Coupled with Hyperthermia, Notiziario dell’ISS, Volume 34, Issue 1, DOI: https://doi.org/10.5281/zenodo.5728941

[5]. A.Manzin, R. Ferrero, M. Vicentini, From Micromagnetic to In Silico Modeling of Magnetic Nanodisks for Hyperthermia Applications, Advanced Theory and Simulations, Volume 4, Issue 3, DOI: https://doi.org/10.1002/adts.202100013

[6]. Ferrero, R., Barrera, G., Celegato, F., Vicentini, M., Hüseyin, H., Yıldız, N., Atila Dinçer, C., Coïsson, M., Manzin, A. and Tiberto, P. Experimental and Modelling Analysis of the Hyperthermia Properties of Iron Oxide Nanocubes, Nanomaterials, Volume 11, Issue 9, DOI: https://doi.org/10.3390/nano11092179

[7]. F. Foglietta, G. Gola, E. Biasibetti, M.T. Capucchio, I. Bruni, A. Francovich, G. Durando, E. Terreno, L. Serpe, R. Canaparo, 5-aminolevulinic acid triggered by ultrasound halts tumor proliferation in a syngeneic model of breast cancer, Pharmaceuticals, Volume 14, Issue 10, DOI: https://doi.org/10.3390/ph14100972

[8]. F. Foglietta, V. Pinelli, F. Giuntini, N. Barbero, P. Panzanelli, G. Durando, E. Terreno, L. Serpe, R. Canaparo, Sonodynamic treatment induces selective killing of cancer cells in an in vitro co-culture model cancers, Volume 13, Issue 15, DOI: https://doi.org/10.3390/cancers13153852

[9]. P. Miloro, S. Ambrogio, F. Bosio, R.M. Baêsso, B. Zeqiri, F. Fedele, and K.V. Ramnarine, A standard test phantom for the performance assessment of magnetic resonance guided high intensity focused ultrasound (MRgHIFU) thermal therapy devices, International Journal of Hyperthermia, Volume 39, Issue 1, DOI: https://doi.org/10.1080/02656736.2021.2017023

[10]. A.Manzin, M.Vassallo, R. Ferrero, M. Vicentini, In silico experiments as a tool to reduce preclinical tests of magnetic hyperthermia, Proceedings of Third Centro 3R Annual Meeting (Biomedical Science and Engineering), Volume 4, Issues s1, DOI: https://doi.org/10.4081/bse.2021.199

[11]. Librizzi, L., Uva, L., Raspagliesi, L., Gionso, M., Regondi, M.C., Durando, G., DiMeco, F., de Curtis, M. and Prada, F. Ultrasounds induce blood–brain barrier opening across a sonolucent polyolefin plate in an in vitro isolated brain preparation, Scientific Reports, Volume 12, Issues 1, https://doi.org/10.1038/s41598-022-06791-7

[12]. Manzin A., Ferrero R., Androulakis I., Martino L., Nadar R., van Rhoon G.C. Design and characterization of an rf applicator for in vitro tests of electromagnetic hyperthermia, Sensors, Volume 22, Issues 10, DOI: https://www.mdpi.com/1424-8220/22/10/3610

[13]. A. M Ivory, R. de Melo Baesso , G. Durando , S. Rajagopal , P. Miloro Development and testing of a system for controlled ultrasound hyperthermia treatment with a phantom device, Transactions on Ultrasonics, Ferroelectrics, and Frequency Control, DOI: https://ieeexplore.ieee.org/document/10012378

[14]. M. Vassallo*, D. Martella, G. Barrera, F. Celegato, Marco Coïsson, R. Ferrero, E. S. Olivetti, A. Troia, H. Sözeri, C. Parmeggiani, D. S. Wiersma, P. Tiberto, A. Manzin Improvement of Hyperthermia Properties of Iron Oxide Nanoparticles by Surface Coating, ACS Omega DOI: https://doi.org/10.1021/acsomega.2c06244

This list is also available here: https://www.euramet.org/repository/research-publications-repository-link/

Project start date and duration:	01 June 2019, 42 months	
Coordinator: Giovanni Durando, INRIM Tel: +39 011 3919 353 E-mail: g.durando@inrim.it Project website address: www.rachy-project.eu		
Internal Funded Partners: 1 INRIM, Italy 2 NPL, United Kingdom 3 PTB, Germany 4 TUBITAK, Türkiye 5 VSL, Netherlands	External Funded Partners: 6 ERASMUS MC, Netherlands 7 ICR, United Kingdom 8 ISS, Italy 9 OSR, Italy 10 TU Delft, Netherlands	Unfunded Partners: 11 VSPARTICLE, Netherlands
RMG: INRIM, Italy (Employing organisation); VSL, Netherlands (Guestworking organisation)		