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EURAMET EMPIR 18HLT06 RaCHy Project: Radiotherapy coupled with Hyperthermia (Induced by HITU)

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ABSTRACT

The main goal of external beam radiotherapy (EBRT) is to damage all cancer cells in a tumour in such a way as to stop their proliferation. Unfortunately, normal tissue toxicity can severely limit doses used, and thus it is useful to combine EBRT with other treatments. An interesting approach to improving local tumour control is to combine EBRT with hyperthermia (HT). The cell sensitisation induced by the heat is not completely understood, however evidence suggests that it impairs cellular DNA repair, thus rendering radiation damage more lethal. During hyperthermia treatments the temperature distribution generated is crucial. High Intensity Therapeutic Ultrasound (HITU) provides superior control of energy deposition, and thus can increase the tumour temperature to the target level homogenously. One of the main goals in the Radiotherapy coupled with Hyperthermia (RaCHy) project is therefore to improve the efficacy, safety and range of applicability of clinical HITU treatments by providing validated methods for ultrasonic field characterization, HITU system performance testing, quality assurance and patient exposure monitoring. The RaCHy project will address both the basic calibration and specification of equipment (and in particular characterisation of the acoustic pressure and temperature distribution in water and in-vitro and in-vivo experiments).

Keywords: External beam radiotherapy, EBRT, HITU, Ultrasound, Hyperthermia

1. INTRODUCTION

Cancer is responsible for just over 1.3 million deaths in the European Union per year. With the aging population, the incidence of cancer is rising. Furthermore, while cancer accounts for 22% of all deaths for those over 65, this figure grows to 38% for people younger than 65 and is the leading cause of premature death in 28 of the 53 regions in the Europe. Even though the current treatments available for cancer have improved response they have not improved the survival of patients, particularly of those diagnosed with advanced tumours. There is a need for integrated approaches,

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combining different expertise from different fields, to try to find innovative strategies able to significantly improve the outcome of cancer treatments, yet limiting the side effects.

Radiotherapy is one of the frontline treatments for cancer with about 50% of people with cancer having radiotherapy as part of their treatment, as stated by recent survey of ESTRO (European Society for Radiotherapy and Oncology) and HERO (Health Economics in Radiation Oncology). Radiotherapy uses radiation to kill cancer cells by damaging their DNA, either directly or by creating charged particles (free radicals) within the cells that can in turn damage the DNA.

In order to reduce the side effects, or to escalate the biological effects related to radiotherapy, multimodality techniques such as combination with hyperthermia have been shown to be effective through suppressing DNA repair mechanisms. However, clinical uptake has been hampered by lack of precision in treatment delivery and monitoring. The proposed strategy may also be a valuable alternative to chemoradiotherapy for advanced stage cancer patients for whom chemotherapy is contraindicated.

The main aims of EURAMET 18HLT06 - RaCHy - project are to demonstrate experimentally 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 detailed knowledge of temporal and spatial distributions of temperature increase and radiation dose during the treatment.

2. EURAMET EMPIR 18HLT06 -RaCHy- PROJECT

2.1 Project overview

Preclinical experiments have shown that the sensitising effects of heat are greatest when radiation delivery and heating are delivered at the same time, and that efficacy decreases as the time between the two increases. Recent in-vitro cell survival data (1) have described combination treatments as a function of radiation dose, heating temperature and duration, whereas other studies focus on quantification of the influence of treatment order and timing.

Combinations of hyperthermia with radiation are difficult to study in-vitro, although progress has been made on designing dedicated experimental set-ups. Also, combination treatments of partial HITU exposure with RT show promising results in-vivo. However, for both studies (in-vitro and in-vivo) quantification of the observed biological effects as a function of exposure conditions is still limited by the lack of dosimetric measures. An empirical cell survival model describing radiotherapy in combination with hyperthermia has recently been proposed and tested for two cells lines, with the objective of better quantifying heat induced radio-sensitization and thermal dose. There are a number of factors which are thought to contribute to the enhanced efficacy of radiotherapy and hyperthermia: inhibition of DNA repair mechanisms, immune stimulation, induction of cell death, changes to local perfusion environment etc. (2). For these reasons timing of radiotherapy and hyperthermia and temporal spatial distributions of temperature are crucial. Depending on the tissue (normal vs. tumour) the treatment order may affect the biological response with a further option to widen the therapeutic window.

2.2 Scientific objectives

The overall objective of the 18HLT06 RaCHy project is to develop the metrological framework and measurement techniques that underpin the adoption of combined therapies (radiotherapy and hyperthermia). The scientific objectives of the project are:

To determine the suitability of methods of hyperthermia 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 and temperature increase in in-vitro cellular systems. The target uncertainty of the in-vitro determination of the temperature increase should be < 10 %.

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 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 will 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 %.

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.

To exploit and quantify the biological effects of coupling 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 control parameters, such as energy deposition in tissues, radiation dose and duration of the hyperthermia and/or radiation treatment, should also be quantified.

2.3 Consortium

The consortium brings together 5 European National Metrological Institute, NMIs, 1 university, 1 health institute, 3 hospitals, 1 manufacturer. NMIs ensure that the methods and measurements are correctly and adequately characterised, see Figure 1.

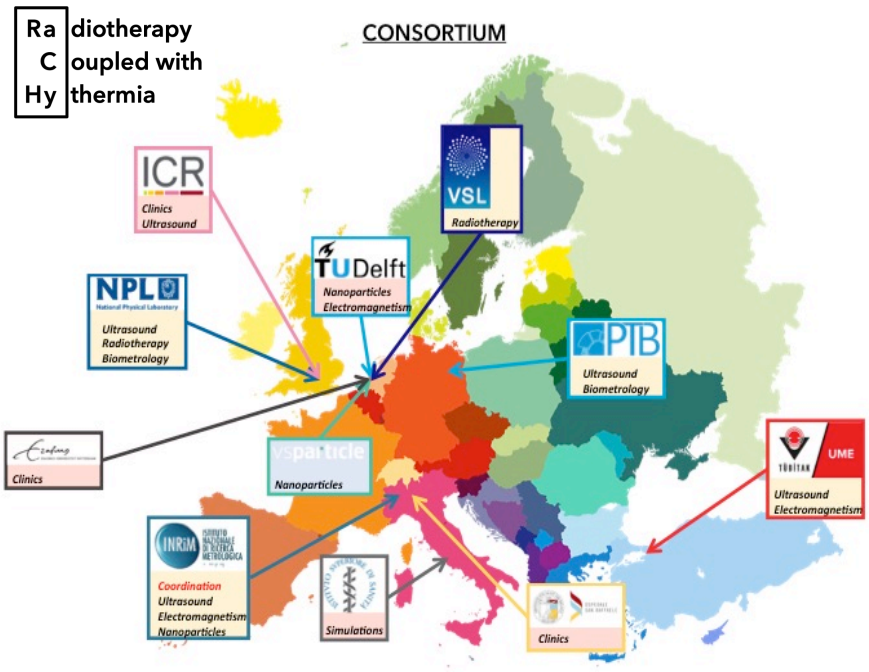

Figure 1. RaCHy Consortium

There are three partner categories:

Internal Funded Partner: National Metrological Institute (NMI)

INRIM	Istituto Nazionale di Ricerca Metrologica (Italy)
NPL	National Physical Laboratory (United Kingdom)
PTB	Physikalisch-Technische Bundesanstalt (Germany)
TUBITAK	TÜBİTAK UME Turkish National Metrology Institute (Turkey)
VSL	Dutch National Metrology Institute (Netherland)

External Funded Partner

ERASMUS MC	Erasmus University Medical Center (Netherland)
ICR	The Institute of Cancer Research (United Kingom)
ISS	Istituto Superiore di Sanità (Italy)
OSR	Ospedale San Raffaele S.R.L. (Italy)
TU Delft	Delft University of Technology (Netherland)

Unfunded Partner

VSPARTICLE	VSPARTICLE B.V. (Netherland)

The partners have experience and facilities, for the entire process of definition of scenarios, identification of critical parameters and required uncertainty, variability of operating conditions, selection of most significant configurations, especially for verification and validation of simulation models and results. The consortium has excellent links with standardisation bodies and end-users.

3. RADIOTHERAPY COUPLED WITH HYPERTHERMIA MEDIATED BY HITU

3.1 Radiotherapy coupled with HITU treatment

The direct experience with HITU for treating, for palliative purposes, bone metastases (3), led us to consider that the best way to do Radiotherapy is in combination with focused ultrasound.

In principle, if a tumor (of limited dimensions) were embedded in a homogeneous, water equivalent medium, the advantage of HITU would be so obvious (after ablation no malignant cells could survive) that we would not need the EBRT help. But the human body is a highly inhomogeneous medium and tumors are not homogeneous water equivalent media, and so HITU alone is not sufficient for treating, in particular, invasive local metastatic disease. The inhomogeneous tissues and organs surrounding a tumor mean that HITU has severe limitations due to:

(i) Absorption and scattering by bone;
(ii) Reflection by air;
(iii) The need to avoid/protect nerves and major vessels in the US beam path.

The treatment of larger volumes by starting with HITU ablation for debulking in the surgical sense and then EBRT, possibly with a reduced radiation dose, would be a suitable indication for EBRT plus HITU. That would reduce the ionizing radiation burden for treating large volumes. We will apply two techniques:

(i) Homogeneous treatment, with radiotherapy coupled with the whole tumor, or
(ii) Treatment with the addition of an ablative procedure in hypoxic regions.

This latter treatment is suggested when a significant hypoxic region is suspected. For this kind of experiment, HITU provides an ideal method giving the capability of effectively monitoring in near real time the distribution of the temperature field, see Figure 2.

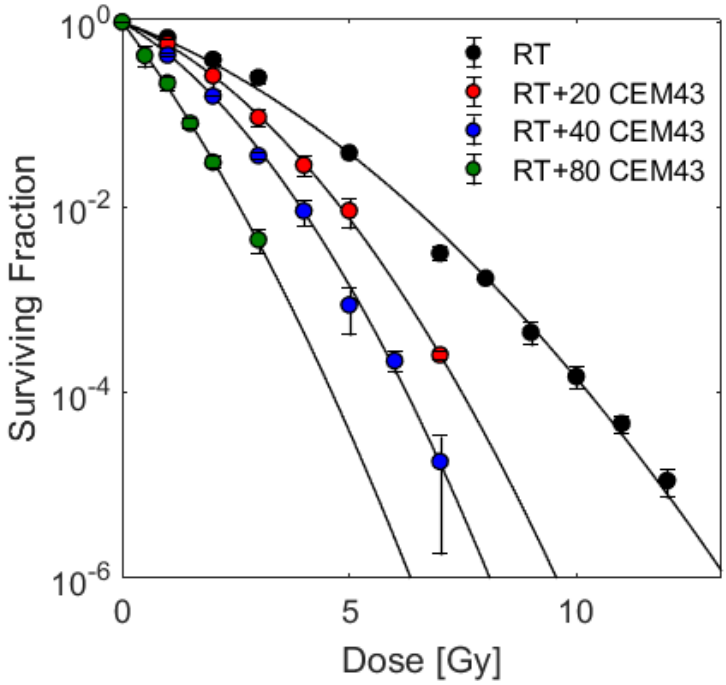

Figure 2. Radiotherapy coupled with hyperthermia mediated by HITU

3.2 Fast HITU Hyperthermia, FHH

The Sapareto equation, describes the equivalence between time and temperature for the same effect of cell killing with heat, without the possible synergistic effects (4). The relationship that links temperature, T, and time, t, is:

$$T_{43}(x,y,z) = \int_0^{t_{final}} R^{\left(\frac{43°C - T(x,y,z,t)}{1°C}\right)} dt \quad \text{where: } R = \begin{cases} 0.25 & T(x,y,z,t) \leq 43\,°C \\ 0.50 & T(x,y,z,t) > 43\,°C \end{cases} \qquad (1)$$

This means that, for $T > 43$ °C an increase of 1 °C of temperature is equivalent to reducing the exposure time by half. It has been verified that many living entities (cells, tissues) are completely "ablated" (protein denaturation, small vessels coagulation, cell inactivation) when they are exposed to a heat exposure of 240 min at 43 °C. The quantity T_{43} is called Thermal Dose (TD), or ,as the dimension of it is time, Thermally Equivalent Time (TET) (5,6).

Clinical Hyperthermia is administered to the patient (after EBRT treatment) by warming the region of interest to 42-43 ° C for 60-100 min, providing roughly a TD of about 0.25-0.30. We propose that FHH treatments could provide good results, by administering a thermal dose of 0.375 TD, corresponding to a Surviving Fraction (SF) of about 0.01 in the Sapareto survival curve (4).

3.3 Hyperthermia corrected Biological Equivalent Dose, BED

The Biological Equivalent Dose, BED, concept is very well recognised for radiotherapy and is based on its ability to carefully represent the expected biological effects of radiation. The growing interest in multimodality therapies combining hyperthermia and ionizing radiation is expected to extend this concept to include the synergistic effect of heat on the radiation-induced biological effect. To this aim, it is important to carefully measure the biological effect of EBRT coupled with hyperthermia mediated by HITU and to compare it to the case of ionizing radiation delivery without heat. This enables the quantification of a dose modifying factor (named K_{Heat}) taking into account the synergic effect of hyperthermia. The parameter K_{Heat} is expected to be a complex function of a number of factors including the local temperature, the way heating is generated and delivered with respect to ionizing radiation, the heating duration, the temperature distribution (homogeneous or heterogeneous) within the tumor or the considered organ, the physical and biological characteristics of the tissue, the radiation dose, dose rate and fractionation, etc.

4. CONCLUSIONS

As is clear from Figure 2, the proposed protocol, Radiotherapy combined with Hyperthermia, easily outperforms the traditional ones; it leads to low survival of tumor cells and a long offset time such that the patient is effectively cured. In order to maximize the synergistic effects, the two treatments, HITU and EBRT, should be applied at the same time or within a maximum10 min interval. For this reason, it could be necessary to develop a new integrated device, including real-time echography and CT imaging.

ACKNOWLEDGEMENTS

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