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INVITED

LECTURES

INVITED LECTURES

IL-01
Radiobiological approach of combined hyperthermia with either radiotherapy or radio-chemotherapy

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There is extensive pre-clinical data demonstrating that in combination with radiation, hyperthermia is one of the most effective radiation sensitizers known. From in vitro cell culture studies, and tumour and normal tissue models in vivo, this enhanced affect was shown to be dependent on the time and temperature of heating, as well as being influenced by the time interval between applying the radiation and heat treatments. The in vivo tumour and normal tissue models also demonstrated that the sequence of the heat and radiation could play a role in determining a therapeutic benefit. A large number of randomised clinical trials, in a variety of tumour types, have now clearly shown the potential of hyperthermia to significantly improve both local tumour control and survival following radiation therapy, without a significant increase in side effects. Today, radiation is more often combined with chemotherapy, but the combination of hyperthermia with radio-chemotherapy has been less well investigated in both preclinical and clinical studies. Here we review the pre-clinical rationale for combining hyperthermia with radiation, with or without chemotherapy, for both in vitro and vivo studies, and summarise the clinical data showing its efficacy.

IL-02
Clinical indiations for superficial and deep hyperthermia – an updae of ESHO recommendations

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In general, hyperthermia is indicated when radiotherapy and/or chemotherapy effects need improvement. Experimental studies have shown that effects of hyperthermia, both direct cytotoxic, and radio and chemosensitizing effects, are seen in a large variety of tumour types. These findings are confirmed in clinical randomized studies.
We have analyzed the results of 54 randomized trials published between 1980 and 2017, including total 5099 patients. These studies investigated the addition of HT to RT (27), chemotherapy (11) or RT plus chemotherapy (15), or, in one study, to both RT and RT plus chemotherapy. Total 47 comparisons can be made between treatments with and without hyperthermia. A significant improvement by hyperthermia in any endpoint has been demonstrated in 34 of the 47 comparisons. In addition, in five of these comparisons, the difference, although not significant, was larger than 10% with the better results in the plus hyperthermia arm. A beneficial effect of hyperthermia was found in a large variety of tumour types: cancer of the bladder, breast, head and neck, uterine cervix, brain, esophagus, stomach, rectum, lung, and malignant melanoma and soft tissue sarcoma.

IL-03
Quality assurance in hyperthermia treatment

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Ample evidence can be found in literature showing that quality of the hyperthermia treatment is related to clinical outcome. Quality assurance (QA) guidelines are essential to provide uniform execution of clinical trials and treatment in the application of hyperthermia. The ESHO technical committee (ESHO-TC) has set out to provide QA guidelines for a number of different hyperthermia applications. The intention of the QA documents is to provide definitions for a good hyperthermia treatment and to identify which hyperthermia systems can adequately heat the tumor volume for different tumor sites. In other words, the guidelines are inclusive for all heating techniques, which have been demonstrated to be capable of adequate heating of the target.

In this way, participation in clinical trials is open for all participants providing they have **both** implemented the QA guidelines **and** strictly follow the specific requirements of the clinical study protocol to apply hyperthermia to the defined clinical target. Hence it is the responsibility of every institute to characterize its hyperthermia equipment and make the data available to the ESHO-TC. As a follow-up, the ESHO-TC will investigate the possibility to compose a public list of device types with a description of the potential tumor size, depth and location that can be heated.

IL-04
Current Technology for Hyperthermia Treatment

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Preferential heating of a tumor anywhere in the human body is a difficult task, as humans possess an excellent thermos-physiological system that is highly effective in removing a local energy surplus. Most excess energy is lost by evaporation at the tissue surface. Therefore, the best way to heat deep or subcutaneous located tumors is by depositing energy directly in the target, using electromagnetic (EM) fields or ultrasound (US).
Characteristic for EM-fields is that penetration depth increases with lower frequency, but also the focus size. To overcome the limitation of penetration depth and unfocused heating, constructive interference was introduced. Radiative and capacitive techniques are used to couple the EM-energy to the tissue. Over time multiple EM hyperthermia systems have been designed and build with which, tumors at nearly all locations and all sizes in the body can be heated.
A clear advantage of US is the small wavelength combined with a deep penetration in tissue. A disadvantage is however the inability to transfer energy though air and the very high absorption of US in bones. Therefore, heating of tumors with US is restricted to tumor location where the US path does not include air or bones. For such location the advantages of US, e.g. mm focus and deep penetration can be fully exploited to obtain a homogeneous temperature distribution. In practice with US heating there is a limit in tumor size (diam. 5-7 cm) that can be effectively heated.

IL-05
Pivotal position of modulated electro-hyperthermia in immuno-oncology

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Introduction - Hyperthermia in oncology is aiming to eliminate the malignancy in the body. Its definition allows wide range of interpretation centered on the points:

- higher temperature than normal, but how high?
- absorb heat selectively, but how to select?
- be safe and reproducible, but what is the dose?

Two main-stream solutions compete:

1. select by using the image of the tumor and heat it isothermally (as homogeneously as possible). The dose is conventionally the necrosis based artificial CEM43^{o}CTx.
2. select the malignant cells using the natural biophysical differences and heat the cancer-cells as high as possible. The dose is the absorbed energy in radiation units: Gy (J/kg).

Method - The modulated electro-hyperthermia (mEHT, trade-name oncothermia) makes cell selective impedance controlled capacitive coupling with amplitude modulated signal, by the time-fractal pattern. This definitive hyperthermia heats the membrane rafts and excites outer apoptotic signal transmission to the cell. It uses the high metabolism, the autonomy and the membrane raft properties of the malignant cells for selection, while heats up the complete tumor for mild temperature hyperthermia level.

Results - Reaching at least 3^{o}C higher membrane temperature than the anyway mild hyperthermia heated environment [i]. The cell-destruction mechanism is robustly apoptotic, [ii]. Damage associated molecular pattern (DAMP) formation is shown, which is a prerequisite of the immunogenic cell-death process (ICD) [iii]. The certain difference of mEHT from other kinds of conventional hyperthermia is well proven by immuno-histochemical methods [iv].

Discussion - The DAMP induced ICD has tumor-specific genetic information maturing the dendritic cells and producing antigen presenting cells (APC). The tumor-specific immune-reaction could be the basis of the systemic effects eliminating malignances, in far distant metastases too [v]; while the re-challenging of the tumor inoculation became impossible [v].

Conclusion – The mEHT method follows the legacy of hyperthermia by strict heating of the malignant cells, and directed to the modern trend of systemic immune-oncology.

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IL-06
Are there guidelines for clinical practice of WBH, based on clinical trials?

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Early phase I studies disclosed that most patients could only tolerate a systemic temperature of about 41.8°C for several hours before severe toxicity occurred . Most of the experience with the use of whole-body hyperthermia with systemic drugs is gained from phase I studies . In a phase III trial which included 44 patients with small cell lung carcinomas, standard chemotherapy with doxorubicin, cyclophosphamide and vincristine (ACO regimen) were given to the control group . The other group received, in addition, whole-body hyperthermia, 41.5°C for one hour, during the first three of the six ACO cycles. The median duration of response was 105 days in the normothermic arm and 130 days in the hyperthermic arm. No impairment of renal, cardiac or liver functional occurred. Toxicity was similar in both groups. The development of whole-body hyperthermia has been hindered by a tendency to include patients in very advanced stages of the disease. Currently, the procedure of applying whole-body hyperthermia is less burdensome for the patient and less demanding than procedures like high-dose chemotherapy with stem-cell support. The first Guidelines for application of WBH as we know it today were formulated by the collaboration of the Medical University of Lubeck and University of Wisconsin Medical School within the auspices of Systemical Hyperthermia Oncological Working Group(SHOWG). The application of WBH after the compilation of over 310 preclinical and clinical trials resulted in 28 state sponsored (Clinical Trials.Gov) clinical trials for studying the impact of WBH on cancer, and interestingly enough 6 trials studying the impact of WBH on Depression. This indicates the degree of interest that is evoked from the results. From this compilation of Trials a variation in the actual application protocols began to develop. The endpoints of the developing Extreme WBH temperatures reaching up to 42 C that were focused on maximizing cancer cell kill, and the Moderate WBH which focused more on the immunostimulation process that was incurred with the activation of Heat Shock Proteins (HSP). Also various modes of achieving these temperatures began to surface, with the most popular among these being the use of infrared energy to do the actual heating. As the technology advances, and more variations are being introduced, it is becoming obvious that new Guidelines are becoming imperative.

From the existing data we can conclude that : Achievement of more level I/II evidence, with more well-designed randomised clinical trials, and high quality prospective trials are a mandate,as well as Incorporation of translational research in clinical trials. Development of quality assurance guidelines must be implemented,as well as improvement of thermal dosimetry, when feasible, using non-invasive methods, and development of treatment techniques more user friendly for patients. Revision of the original Kadota consensus treatment techniques to incorporate the knowledge and clinical experience that has been compiled. Expansion of relationships with pharmaceutical and biotech companies, making a clear point that combination therapies with Hyperthermia esures better results, thus ensuring the tendancy for more targeted therapies through combinations. More agressive promotion of the benefits of hyperthermia in the medical community and to the general public are necessary.

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IL-07
Potentiation of chemotherapy by local and whole body hyperthermia from a clinical perspective

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In the last years hyperthermia has become an intensively discussed complementary treatment in cancer. Hundreds of publications show the mechanisms of action when heating up tumor tissue to 41°C - 42°C. These include a negative interference with several repair mechanisms, denaturation of p- glucoproteins, microthromboses in tumor vessels and increased perfusion/circulation of the tumor tissue.
Combining hyperthermia with chemotherapy a temperature dependent increase of activity of cytotoxic drugs was found.

The most important types of hyperthermia include local hyperthermia using infrared-A light or electromagnetic waves (microwaves or short waves) to induce a localized increase of temperature. For whole body hyperthermia techniques like whole body irradiation with high energetic infrared A light are used.

In some countries hyperthermia is considered as standard treatment, e.g. in Holland a combination of hyperthermia and radiation in patients with advanced cervical cancer or in Germany the combination of hyperthermia and chemotherapy in patients with advanced soft tissue sarcoma.

Hyperthermia has shown in frequent studies up to now positive effects against nearly every type of cancer.

In large solid tumors the efficacy of chemotherapy in general is limited.
In the presentation it will be shown that chemotherapy together with hyperthermia in different advanced cancers shows surprising results. These case reports are demonstrated in conjunction with international studies.

IL-08
Chemotherapy combined with regional hyperthermia - recent results and future activities

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Background Hyperthermia at clinical relevant temperatures (range 40 -43°C) shows synergistic or additiv effects with chemotherapeutic agents in vitro and in vivo. The goal is to translate this knowledge in clinical application . Methods For clinical translation , the methodology of clinical trial design is mandatory .The design must be based on the most recent findings and clinical results in the pre-specified group of patients without the use of hyperthermia. The medical need for improvement of outcome must be documented. The eligibility criteria must be well defined and adequate. According Good Clinical Practice (GCP) guidelines , the technology has to be proven in phase 1/2 trials by peer-reviewed results to be safe and sufficient to heat the target . Findings Based on stepwise performed clinical studies ,the recent up-dated results of a multi -center, randomised phase 3 trial in high-risk soft-tissue- sarcoma has led to the recommendation of hyperthermia combined neoadjuvant chemotherapy at specialized centers(ESMO guidelines } The multi -center, Hyperthermia- ESHO randomised phase 3 , Adjuvant Trial (HEAT) in R0 / R1 resected pancreatic cancer will be presented in order to demonstrate medical need , center cooperation , and requirement of a recent amendment. The HyperTET (HyperThermia Enhanced Trabectedin) randomised phase 2 trial in advanced soft tissue sarcoma will be presented in order to demonstrate a targeted approach of regional hyperthermia to enhance treatment efficacy by the principle of synthetic lethality and to evaluate abscopal effects by potentially induced immune mechanisms Interpretation Clinical cooperative studies are the most important issue for further implementation of regional hyperthermia in clinical practice . Results of randomised , first or second-line studies with proven clinical benefit in any of defined endpoints are the prerequisite for support by health authorities and spread of defined technology .

IL-09
Nanoparticle Based Hyperthermia: A Clinician's Perspective

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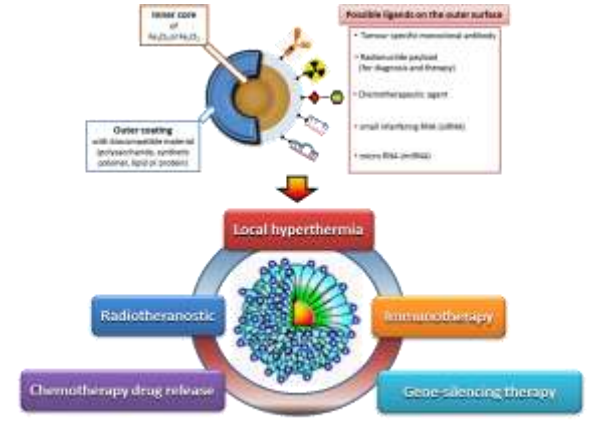
Effective multimodal cancer management requires the optimal integration of diagnostic and therapeutic modalities. Radiation therapy, chemotherapy and immunotherapy, alone or in combination, are integral parts of various cancer treatment protocols. Hyperthermia at 39-45°C is a potent sensitizer and has been shown to improve therapeutic outcomes in various tumours through its synergy with radiotherapy and chemotherapy. Two additional interventions - hyperthermia and more recently gene silencing therapies [small interfering RNAs (siRNAs) and microRNAs (miRNAs)] - are emerging as valuable additions to the therapeutic armamentarium against cancer. Cancer is a multi-factorial multi-genic disorder with complex interactive cellular and molecular pathways in a state of dynamic transition. This has led to the multimodality approach, either concurrently or sequentially in cancer management as may be indicated in a given case. Thus, therapeutic interventions for optimal cancer management involve an evidence-based interplay of surgery, radiotherapy, chemotherapy and immunotherapy tailored to tumour and host-related factors.

The application of nanotechnology in medicine – "nanomedicine", is based on nanosized particles, made from either organic or inorganic materials. For drug delivery, liposomes and polymeric vesicles filled with hydrophobic drugs are currently in clinical applications. Nanoparticles have been demonstrated to extravasate passively into the tumour tissues in preference to the adjacent normal tissues by capitalizing on the enhanced permeability and retention effect. Tumour targeting might be further augmented by conjugating tumour-specific peptides and antibodies onto the surface of these nanoparticles or by activation through electromagnetic radiations, laser or ultrasound.



Multifunctional magnetic nanoparticles: Potential for integrating multimodality therapy

Magnetic nanoparticles (MNPs) can induce hyperthermia in the presence of an alternating magnetic field, thereby multifunctionally with tumour specific payloads empowering tumour specific radiotheranostics (for both imaging and radiotherapy), chemotherapy drug delivery, immunotherapy and gene silencing therapy. The rapid developments in multifunctional nanoparticles provide ample opportunities to integrate both diagnostic and therapeutic modalities into a single effective cancer "theranostic" vector.

Such a (nano)bullet could realize the "magic bullet" conceived by Paul Ehrlich more than a century ago. This presentation from a clinician's point of view, would focus specifically on the multifunctional MNPs, their role as multimodal theranostic vectors and the future challenges that need to be addressed to enable these MNPs to be realized as the possible Paul Ehrlich's "magic (nano)bullet." This could possibly usher in a new paradigm in modern cancer diagnostics and therapeutics.

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IL-10

Nine indications for superficial and deep HT therapy jointly with radiotherapy reimbursed by Swiss health care insurances for outpatient therapy from 2017

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Introduction: Despite an increasing body of evidence, hyperthermia is seldom reimbursed by national health care systems either alone or combination with radio- and/or chemotherapy. A drawback a few years ago was the decision to stop reimbursement based on a report initiated by the ministries of health in Germany and Austria. Currently most indications are reimbursed only in combination with radiotherapy and/or chemotherapy, within study protocols. Additional requirements for reimbursement in some countries are patient registries and outcome analysis. In Switzerland, hyperthermia combined with radiotherapy was reimbursed for up to 10 indications until 2015 (1). The most frequent indications were chest wall recurrences and palliative re-irradiation for symptomatic patients. In 2015, one of the largest health insurance companies requested an investigation by the Ministry of Health for all hyperthermia indications jointly with radiotherapy in oncology, claiming lack of evidence and therefore, requesting cancellation of reimbursement for all indications.

Hyperthermia indications submitted to Swiss Ministry of Health for reimbursement by regular health care insurance: A detailed dossier was compiled and submitted to the Ministry of Health and requested full reimbursement for nine indications based on published evidence and/or own open clinical trials.

i. State of the art hyperthermia therapy conducted in our institution including workflow, planning, quality assurance and written standards.
ii. Overviews of clinical studies with curative intent initiated/submitted to our regional ethics committee -muscle invasive bladder cancer, locally advanced sarcoma, locally advanced pancreatic cancer (2-4).
iii. Published and submitted meta-analyses for three common treatment sites suitable for hyperthermia and radiotherapy – chest wall recurrence in breast cancer, head and neck and cervix cancers (5-7).
iv. Our research portfolio including the development of a novel superficial hyperthermia system with online SAR monitoring, temperature sensors, planning system and software packages. This includes also a novel joint care path for radiotherapy and hyperthermia integrated into our clinical information system.

Swiss Hyperthermia Network and Swiss Hyperthermia Tumor boards: In December 2016, the Ministry of Health decided to include four indications for superficial hyperthermia without any restrictions and five for deep hyperthermia for a 2-year period with reassessment by December 2018 in the compulsory health care insurance catalogue. All Swiss patients must be presented at the weekly Swiss Hyperthermia Tumor Board lead by us with participating institutions joining on WebEx. The Swiss Hyperthermia Network Society was founded in April 2017 by four Swiss radiation oncology institutions. The society is responsible for the proper registration of all Swiss hyperthermia patients and the proper conduction and reporting of the Swiss Hyperthermia Tumor Board. The first assembly will take place June 8, 2017 during the Swiss Radiation Oncology Annual Conference (SASRO). To date more than 10 radiation oncology institutions have expressed their interest to join.

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IL-11
THE ROLE OF THE THERMAL ABLATION

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The role of thermal ablation is an accepted alternative therapy in the treatment of selected patients with primary or secondary lung malignancies who are poor surgical candidates. Combining local therapies has also emerged as a possibility. Although outcomes are still early to judge, some have suggested that the use of RF ablation in combination with RT is safe and provides improved local survival versus conventional RT alone. Currently, thoracic ablative therapy has a role in treatment of primary lung cancer, treatment of lung metastases, and palliation of painful chest wall masses.
Hepatocellular carcinoma (HCC) and metastases from colorectal carcinoma are the two most common malignant tumors to affect the liver. Of all patients presenting with a malignant hepatic tumor, few are surgical candidates. A number of alternative therapies have been used for the treatment of malignant hepatic tumors. During the last years, considerable interest has developed in the thermal ablation techniques that produce heat. Radiofrequency and microwave ablation of the liver has been a promising technique. Differences in reported success rates are no doubt multifactorial.

IL-12
Ablation Bone Metastases

A.D.Kelekis
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Percutaneous techniques for painful osseous metastatic disease have evolved due to the often disabling pain these patients experience, despite the use of conventional therapies.

The **purpose** of this presentation is an overview of ablation for bone lesions. There is still an active dilemma on which lesions to use radiotherapy, thermal ablation and on which stabilization. Indications of treatment will be discussed, focusing on palliative versus curative treatment, as well as the relationship with radiotherapy and sequencing between therapies.

This presentation is an overview of bone ablation techniques used in the spine and the appendicular skeleton. Available **material** will be discussed, as well as possible combinations of treatments in order to yield maximum results, while reducing possible drawbacks. We will try to show the technical challenges of establishing safe and curative margins. Anatomic and positional landmarks will be addressed. Complications are analyzed, as well as techniques to minimize potential complications.

In **conclusion** bone ablation is a valid technique, standing alone or in combination with other treatments. The purpose of this presentation is to inform about ablation for the treatment of bone metastases. Patient management and limitations of the material at hand seems to be important for avoiding technical complications.

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IL-13
Technical aspects of MWA

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Introduction

Microwave thermal ablation (MWA) is a minimally invasive therapeutic technique used to destroy un-healthy tissue by way of a very high and localized temperature increase. Heat is obtained by the absorption of an electromagnetic field radiated by a minimally invasive microwave (MW) antenna. Tissue coagulation, and thus thermal ablation, is obtained almost instantaneously when the temperature of the tissue reaches a value of about 60°C [1].
Clinical applications of MWA include treatment of cardiac diseases and endometrium disorders. However, the most interesting application of MWA is the treatment of tumours, due to their widespread diffusion and the increasing number of inoperable cases, linked to e.g. co-morbidities, allergies to anaesthesia, etc.

Methods

MWA clinical set-up typically consists of a high power MW generator (usually operating at 915 MHz or 2.45 GHz) able to supply up to 150 W, a MW antenna, and a cooling system. The cooling system keeps the

antenna's shaft at safe temperatures, thus avoiding the heating of the tissue along the insertion path of the applicator.
The clinical procedure foresees the image-guided introduction of the antenna into the body and its placement in the centre of the tumour to be treated. Then, the cooling system and power generator are switched on, allowing the antenna to radiate the chosen MW power for the selected duration (typical values are up to 60 W for 10 min). Power and duration are determined according to the location and dimension of the tumour. Treatment goal is the ablation of the whole tumour plus a 5 mm safety margin all around it [1].
Although simple to describe, MWA is a technology to be handled with care because of the very high MW power used in the procedure, and of the very high temperatures reached by the tissue close to the radiating antenna. Actually, there are still unknowns about the non-linear effects occurring into the tissue during MWA and influencing the procedure's outcomes. As a consequence, sometimes neither not-reproducible nor predictable results are obtained [2].

Studies
Both ex vivo and numerical studies have been performed to characterize the interaction of the high-power electromagnetic field with the biological tissue [3,4]. The comparison between numerical and experimental data is fundamental to define the parameters that mostly influence the treatment outcomes, e.g. tissue's properties (dielectric, thermal, mechanical), and/or antenna's design, or cooling system's characteristics.

Conclusion
In this contribution, the technical aspects of MWA are presented and discussed, focusing on the recent studies as well as on the key issues which should be still investigated to make MWA procedures safe, reliable and reproducible. Comparison with radiofrequency ablation and hyperthermia is used to underline similarities and differences among the techniques.

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IL-14
HIFU Systems – Technology and Clinical Practice

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Focusing of ultrasound waves allows non-invasive heating of deep seated tissue structures without harming the surround tissue. With a focus point that has a dimension comparable to a grain of rice, this technique can be used as "a thermal knife" when tissue is heated to ablative temperatures above ca. 55 ˚C. Above possibility was recognized and already explored more than 100 years ago. Yet, high intensity focused ultrasound (HIFU) is still considered an emerging technology for clinical applications. While the non-invasive nature of HIFU is very attractive, it comes with the challenge to precisely target the tissue

and monitor the heating process. Thus, its combination with magnetic resonance imaging (MR-HIFU) in the 80-90'ties facilitated better and safer treatment leading to first approved clinical applications. In this talk, an overview of the HIFU technology and its use for thermal ablation including clinical examples will be given. Furthermore, the potential use of MR-HIFU for hyperthermia will be addressed together with new approaches of advanced control algorithms for point by point heating to ensure homogeneous heating.

IL-15
Chemotherapy and regional hyperthermia in soft tissue sarcoma - update of a phase 3 study

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Background
Chemotherapy for patients with localized soft tissue sarcoma (STS) is not currently viewed as standard practice, due to the lack of survival benefit. The preliminary report of our phase 3 study demonstrated that adding regional hyperthermia to neoadjuvant chemotherapy improved local progression-free survival as the primary endpoint of patients with high-risk STS. According to study protocol, we performed a final analysis of outcome including overall survival with long-term follow-up.

Methods
We randomly assigned adult patients with non-metastatic, high-risk (deep, ≥5cm, grade 2-3) STS to receive either pre- and postoperative doxorubicin + ifosfamide + etoposide chemotherapy alone, or this regimen + regional hyperthermia. Patients were stratified according to site (extremity vs. non-extremity) and presentation of tumor (primary vs. recurrent vs. prior surgery).

Results
Of the 341 patients randomly assigned, 329 (94%) were eligible and started study treatment. Compared with the neoadjuvant chemotherapy-alone group, the addition of regional hyperthermia improved objective response rate (12.9% vs. 29.8%; P=0.002), prolonged local progression-free survival (29.2 months vs. 67.3 months; hazard ratio (HR) 0.65; log-rank P=0.002), disease-free survival (17.4 months vs. 33.3 months; HR 0.71; log-rank P=0.013), and overall survival (6.2 years vs. 15.4 years; HR 0.73;log-rank P=0.037). Hyperthermia-related adverse events were rare and without signs of late toxicity.

Conclusions
After a median follow-up of 11 years, the addition of regional hyperthermia to neoadjuvant chemotherapy improved clinical outcome which translated into a significant overall survival benefit. These findings strongly support the use of regional hyperthermia in this setting for patients with high-risk STS.

IL-16
Which are the best nanoparticles for hyperthermia?

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Introduction
Magnetic particle hyperthermia attempts to treat cancer following the modality Hippocrates suggested around 2500 years ago: "What medicine cannot cure, iron cures; what iron cannot cure, fire cures; what fire does not cure, is to be considered incurable". Its proof of principle relies on the fact that cancer cell are more vulnerable to temperature variations when compared to normal ones, while the heat cargo is delivered by especially designed magnetic nanoentities under the guidance of an external magnetic field. Although, it is authorized for cancer treatment since 2011, after passing a phase II clinical trial, as adjuvant therapy with conventional radiotherapy,,[1] it still needs further elaboration prior to routine clinical application. As in most biomedical applications, several constraints both in carriers and therapy scheme have to be successfully addressed.

Results and Discussion
The first general question that naturally arises is why use magnetic nanoparticles in modern theranostics? The answer is multifold and has to do with their flexibility, selectivity and effectiveness. Magnetic nanoparticles may be remotely (i.e. externally) and effectively stimulated by the adequate magnetic field. Since they are only a few tens of nanometer in size and therefore, they may manoeuvre around, for example, find easy passages into several tumors, whose pore sizes are for example in 100 nm range.
To advance magnetic particle hyperthermia applicability, three critical puzzles have to be solved:
a).Which particles? Reproducibility, is the first milestone, for a synthetic approach, which should be self-consistent and reproduce its outcome under standard conditions. Then, synthetic controls should be tuned to provide control over size and shape (uniformity and morphology) within a homogenous (stability) in time and varying conditions dispersion. Eventually, scalability to greater length scales may be examined in an effort to create microscale or even mesoscale objects.
b).Which conditions? Magnetic Particle Hyperthermia treatment utilizes high frequency magnetic field and is excellent paradigm for discussion of field application safety in biomedicine. The generated temperature depends on the magnetic properties of the nanoparticles, and it increases with magnetic field frequency and amplitude. In order to minimize possible risks, the dosage of nanoparticles administered during the hyperthermia treatment should be kept as low as possible together with clinical constraints for the magnetic field intensity and frequency values.
c).Will it perform under bio-conditions? Nanoparticles due to their multivalency and multifunctionality, pose challenge for understanding their pharmacokinetics because different components will have different features that affect their performance, toxicity, distribution, clearance. The 3Ds: Dose, Dimensions and Durability provide the set of parameters to be fine-tuned in order to have optimum performance together with minimum side-effects within a biological environment.

Conclusions
Magnetic particle hyperthermia is a unique multifunctional platform since its carriers can be remotely and non-invasively employed not only as heat mediators but as imaging probes, carrier vectors and smart actuators as well.

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IL-17
Nanoparticle-mediated drug delivery to treat cancer

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Chemotherapy one of the pillars in cancer therapy, but suffers from lack of activity, severe dose limiting side effects and resistance seriously impairing it potential. Important is to get more in the tumor and less in healthy and sensitive tissues. For this purpose nano-particles may be used as smart drug delivery devices or nanobots, which can be steered, controlled, monitored and facilitate through that optimal delivery with strong clinical outcome. Different methods will be presented and compared showing that local delivery can be impressively augmented, while side-effects are controlled. This may result in the patient in shifting the balance and irrespective of resistance produce a favorable outcome.

IL-18
Targeting nanoparticles for cancer: Immune microenvironment of tumours determines uptake and retention of nanoparticles.

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Nanoparticle-based cancer therapy and drug delivery has advanced significantly in recent years, providing new opportunities. Significant deficiencies in knowledge remain to explain nanoparticle delivery and distribution to (solid) cancer tumours. Results of clinical trials often fail to recapitulate preclinical experience, implying that model-specific features, which do not accurately reflect clinical realities, are unknowingly incorporated into nanoparticle design. It has been recognized for some time that the unique properties of nanoparticles lead to interactions with components of host immune systems; but, less understood is how these interactions affect uptake and distribution in cancer tumours. We sought to systematically study the impact of the host immune system, targeting, and tumour biology on the distribution of ferrite nanoparticles in mouse models of HER2 overexpressing breast cancer by varying the tumour and immune status of the host. We show that tumour-associated immune cells play a major role in the uptake and distribution of antibody conjugated nanoparticles across xenograft models, with implications that host immune status is also a factor. We also developed an allograft model of human HER2 overexpressing breast tumor that spontaneously develops in immunocompetent transgenic mice (FVB/N background). Using this model we compared the uptake and retention of a given nanoparticle construct in different immune stratified mouse models, using the same tumour, ranging from most immunocompromised to fully immune-competent models. Results of these studies will be presented indicating a passive uptake mechanism is unsupported by our results.

IL-19
Design and application of temperature sensitive liposomes for hyperthermia induced drug delivery

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Hyperthermia-induced local drug delivery using temperature sensitive liposomes (TSLs) has been shown in several studies to increase local drug concentrations by a factor of approximately 5 to 15. One of the most important factor is the stability and the release kinetics of TSLs to provide high drug plasma concentrations and sufficient release while the TSLs pass through the heated tumor, which requires optimization of the TSL formulation. However, above approach is mostly suited to treat well vascularized tumor areas, as perfusion is a key factor to ensure supply of TSLs during hyperthermia. Recent studies showed that poorly perfused and partly necrotic areas remain undertreated. Here, thermal combination protocols can provide an improved therapeutic option. As a first step, well vascularized areas are treated with hyperthermia and temperature induced drug delivery, followed by an ablation of the necrotic area. One requirement for performing above protocol is a method that allows both hyperthermia of larger tumors but as well ablation of smaller, necrotic or poorly perfused tumor volumes in one treatment session. Here, high intensity focused ultrasound under MRI guidance (MR-HIFU) emerged as a very suitable method. In this talk, design and testing of TSLs will be discussed and presented in the context of thermal combination protocols to treat tumors using MR-HIFU.

IL-20
Non-Thermal Effects of Radiofrequency Radiation

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Introduction:
Since the 1970s, clinicians have reported the importance of hyperthermia in the treatment of cancers. In most cases the method to obtain hyperthermia was by radiofrequency radiation, usually due to the problematic application of other means, such as conductive heating and ultrasound. Recent discoveries, however, suggest that radiofrequency has non-thermal effects which are selective to cancer cells.

Discussion:
Since 2014, articles pinpointing the effect of RF (isolated from its thermal effect) selectively on malignant cells have started to emerge. These effects include microporing of their membranes, loss of adhesion in cancerous tissue, and changes in topography, morphology, motility and proliferation, all of which point out to phenotypical and metabolic changes.
This partially explains the different pharmacokinetics and clinical findings between RF-Induced Hyperthermia and Hyperthermia without RF – some of which are especially evident in Non-Muscle Invasive Bladder Cancer.
In addition, RF generates Foucault currents, which electrically charge and mobilise molecules. RF-application could be used for different indications - achieving active diffusion, homogenous distribution, and adding activation energy to administered agents to potentiate their efficacy.

Conclusion:
In order for us to keep adding to our knowledge, perfecting protocols and for the sake of future generations, it is imperative to mention the method in which hyperthermia is achieved (once thermal registry proves tissue is efficiently heated otherwise). In addition, a paradigm shift in the interest in RF is emerging, and it would be interesting to learn more about the effects and importance of RF on cancer.

IL-21
Our initial experience on hyperthermic intravesicular chemotherapy (HIVEC)

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Introduction: Preventing the recurrence of non-muscle invasive bladder cancer (NMIBC) post-transurethral of the bladder (TUR-B) remains challenging. The aim of this study was to investigate the effectiveness and safety of recirculating hyperthermic intravesical chemotherapy (HIVEC™) with epirubicin, using Combat's BRS system in such patients.
Patients and Methods: From October 2016 to April 2017, N=10 patients with intermediate and high risk NMIBC received adjuvant HIVEC™ treatment with a Combat BRS system using epirubicin (50mg/25ml). Epirubicin was recirculated at 200 mL per minute at a stable pressure and the temperature inside the bladder was maintained for 60 minutes at 43 °C. N=3 of these patients had previously received BCG and had exhibited tumor recurrence under BCG.
The patient's protocol was six instillations (weekly), control cystoscopy with bladder biopsy if required, and then six instillations (monthly) and control cystoscopy with bladder biopsy if required. Recurrence rates (according to cystoscopy or new bladder biopsy) and adverse effects were evaluated.
Results: All patients tolerated HIVEC™ excellent and no side-effects were observed. N=3 patients who had previously received BCG and exhibited recurrence underwent a new bladder biopsy after the 6 weekly instillations were concluded, but did not exhibit new evidence of tumor recurrence. The remaining N=5 patients at cystoscopy controls did not exhibit tumor recurrence. N=2 of the patients have not yet undergone cystoscopy evaluation.
Conclusion: The use of recirculating hyperthermic intravesical chemotherapy with epirubicin using Combat's BRS system seems to be safe and effective in such patients. Although or patient cohort is small and or follow-up period short, the oncologic results seem promising.

IL-22
Closed technique with CO2 agiation, an innovative solution for HIPEC

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HIPEC with closed technique and CO2 agitation represents a significant enhancement to the procedure which optimizes the therapeutic effect. The following improvements have been seen clinically and can be discussed.:

- Homogeneous and constant intra-abdominal targeted temperature
- Complete distribution of the drug across the visceral and peritoneal surfaces

- Recirculation of drug performed under controlled and targeted pressure
- Use of individualized volumes to ensure complete abdominal cavity filling

This new innovative technology offers specific solutions for minimally invasive or even laparoscopic approach providing methodological and technical support to future potential indications of extended HIPEC roles and modalities currently under investigation, as neoadjuvant and/or prophylactic therapy.

IL-23

Cervical cancer and modulated electro-hyperthermia: What we have learnt from our clinical trial so far

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INTRODUCTION: The aim of the study is to determine the effects of the addition of modulated electro-hyperthermia (mEHT) to treatment protocols for HIV positive and negative locally advanced cervical cancer patients in South Africa. The study objectives are to assess the effects of the addition of mEHT on quality of life, safety and toxicity, local disease control and 2 year survival. We report on the first 175 participants to reach 6 months post treatment.
MATERIALS AND METHODS: This is an ongoing phase III randomised clinical trial at the Charlotte Maxeke Johannesburg Academic Hospital. The study aims to enrol 236 participants of which 227 female participants with FIGO stage IIB to IIIB cervical cancer have been enrolled. Participants have been randomised into a "Hyperthermia" group (mEHT plus chemoradiation) and a "Control" group (chemoradiation alone), based on HIV status, age and stage of disease. Treatment protocols for both groups are 25 fractions of 2Gy external beam radiation, 3 doses of high dose rate brachytherapy (8Gy) and up to 3 doses of cisplatin. The Hyperthermia group is receiving two 55 minute local Oncothermia treatments per week during radiation therapy. Local disease control is being assessed by Positron Emission Tomography (PET) CT scans. Adverse events, quality of life and overall survival are being recorded and the data is being analysed. **RESULTS:** There has been a dropout rate of 26%. 51% of the participants enrolled so far are HIV positive and 61% are in FIGO (International Federation of Gynaecology and Obstetrics) stage III of disease and 39% are in stage IIB locally advanced (defined by the invasion of the distal half of the parametrium). 50% of participants are between the ages of 30 and 50 years and 47% of participants are between the ages of 50 and 70 years. 3% are below 30 years of age. There is a positive trend in the six month survival rates and local disease control in the Hyperthermia group. There is an expected slight increase in early adverse events in the Hyperthermia group, however this difference disappears six weeks post treatment. Late side effects and survival will be assessed with continued follow up.
CONCLUSION: Preliminary results appear to be confirming the benefit of the addition of modulated electro-hyperthermia to treatment protocols for cervical cancer. Final conclusions can be drawn on completion of data collection.

IL-24

Hyperthermia and current oncological guidelines: Indications and technical capabilities for selected tumor entities

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The rationale and potential to add hyperthermia to an oncological standard treatment depends on various conditions such as on the established oncological standard and kind of available treatments, tumor location and heating accessibility, perfusion behavior of the tumor and others.
The highest evidence for hyperthermia has been found for locally advanced *soft tissue sarcoma (STS)*, if heat is added to pre- and postoperative chemotherapy (CTX), surgery and adjuvant radiotherapy (RT). STS are considered as easy-to-heat tumors and now the optimal sequence of all four modalities is under debate.
The prognosis of *abdominal tumors* (pancreatic, gastric, ovarian cancer) is still unsatisfactory in terms of local and systemic control, even if all available modalities (e.g. surgery, adjuvant radiochemotherapy (RCT)) are employed. *Abdominal* hyperthermia, if properly applied, can heat the entire peritoneal cavity as well as tumor bed and in addition the liver via pre-heating. In combination with cisplatin, abdominal hyperthermia might be effective in all clinically relevant risk areas (liver metastases, peritoneal carcinosis, local recurrence). However, adequate heating of the complete abdomen and its monitoring are challenges, which require dedicated applicators and MR-thermometry.
Pelvic tumors can only be adequately heated in the lower pelvis covering cervical, bladder, prostate, anal and distal rectal cancer. The heating capabilities of regional hyperthermia (RHT) can be evaluated by clinical MR-thermometry and planning studies. Clinical studies are running upon prostate cancer (salvage RT plus RHT), bladder cancer (RCT plus RHT), anal cancer (RCT plus RHT) and rectal cancer. For the latter it is important to exclude proximally located tumors, which are known as difficult-to-heat. Current data support beneficial effects of RHT particularly for distally located rectal carcinoma.

IL-25

Phase II Study: Hyperthermia as a useful tool for bowel protection in radiation therapy

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Radiation doses are generally limited for the tumors adjacent to gastrointestinal tract because of severe radiation bowel toxicity even with high precision technique such as intensity modulation. In this respect, some hyperthermia techniques may have a significant role as a complementer with their capacities of high-frequency, micro-heating energy transfer, and possible non-thermal effects. Additionally, there might be a chance to promote regional lymph node control by the use of hyperthermia, which is associated with a favorable immunogenic microenvironment or apoptotic capacity, etc. For many cases, increased tumor controllability is being reported when hyperthermia is combined with radiation therapy. It is expected that concurrent hyperthermia in radiotherapy plays a role in partially escalating the radiation effect without increasing related toxicity. Further investigation for biophysical mechanism and various succeeding clinical results may strengthen hyperthermia as a significant part of multimodality management. Hear we present our treatment experiences for this situation with interim

results of non-inferior phase II study to explore the hyperthermia-mediated synergistic capacity of partially replacing the radiation dose for preoperative radiotherapy for locally-advanced rectal cancer.

IL-26
Need for multi-centric European trials for combined hyperthermia-radiotherapy

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Background: Hyperthermia as a therapeutic option in the multimodality approach for cancers has yet to gain widespread acceptance in clinical oncology. At 39-43°C, hyperthermia is one of the most potent radiosensitizer and is also synergistic to a number of chemotherapeutic agents. Furthermore, recent evidence also indicate a favorable immunomodulatory effect at moderately raised temperatures. There have been marked improvements in the hardware, software, thermometry developments and last but not least quality assurance. Despite this impressive progress numbers of clinical hyperthermia related abstracts in major (radiation) oncology conferences, e.g. ESTRO and ASTRO are very small and enthusiasm among academically oriented clinical oncologists remains tempered, well below 39 degrees.

Current status: One of the reasons for the lack of enthusiasm is the absence of well-designed randomized clinical trials for curative treatment indications with adequate sample size. Although there have been randomized trials in hyperthermia, these are mainly from locally advanced head and neck cancers, recurrent breast tumors and locally advanced cervical cancer. Recently published systematic review and meta-analysis have shown that hyperthermia significantly improves the outcomes in each of these tumor sites. Other randomized studies reported in malignant melanoma, rectum and other pelvic tumors have also indicated improved outcomes with hyperthermia along with radiotherapy compared to radiotherapy alone. The well conducted, prominently published and so far largest multi-centric phase III randomized trial in soft tissue sarcoma has demonstrated that therapeutic outcome significantly improves by adding hyperthermia to standard chemotherapy treatment.

Future action: To bring hyperthermia in the mainstream of oncology management, there is an urgent need to carry out prospective phase III randomized studies jointly with radiotherapy and/or chemotherapy with adequate sample sizes in key tumor sites like locally advanced pancreatic cancer, locally advanced head and neck cancer, muscle invasive urinary bladder cancer, locally advanced anal and rectal cancer and in soft tissue sarcomas. The key endpoints in most studies should be local contral, functional organ preservation, cancer specific and overall survival for efficacy. On the other hand toxicity, quality of life assessment and cost-efficacy analysis are needed.

As ESHO is the leading organization and globally engaged in clinical hyperthermia, it is essential now that all academically oriented hyperthermia centers form an alliance to actively take part in randomized phase III multi-centric clinical trials. This could be conducted under the umbrella of ESHO, which should form an “ESHO Clinical Trial Group (ESHOCTG)”. The ESHOCTG should select appropriate study proposals, support the PI to write a full study protocol, actively recruit interested centers and help national centers to monitor the studies using stringent QA criteria (data monitoring, technical quality assurance, reporting). Multidisciplinary oncology societies conducting clinical studies for decades like EORTC or NRG could advise ESHO and provide start up- and maintenance support. Selected studies might become EORTC and/or NRG endorsed studies.

IL-27
Hyperthermia on regulation of cancer cell metabolism

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Recently, cancer metabolism is getting more and more attention as a therapeutic target. Hyperthermia had a general effect on cancer cell proliferation, further supporting the hypothesis through modulation of cancer metabolism. There are several kinds of hyperthermia (HT) machines currently available, including the conventional HT (cCHT) and the modulated electro-hyperthermia (mEHT). In our previously study, we conducted a direct comparison between water bath, cCHT, and mEHT methods with regards to their biological effect. Under isothermal conditions (42°C for 30 min), we found that mEHT resulted in significantly higher apoptosis rate than other HT methods at the same temperature. The engineering and physical properties on mEHT produce an enhanced electrical effect in additional to the thermal effect. In this study, we further investigated the ability of mEHT on cell membrane stimulation and disruption. The consequence of these membrane effects were also evaluated. mEHT could induce the phosphorylation of EGFR and this phosphorylation could be inhibited by tyrosine kinase inhibitor, gifitinib. The apoptosis effect that induced by mEHT treatment was impaired by gifitinib. The metabolic pathway after conventional HT and mEHT was compared. c-Myc was activated after cCHT treatment. cCHT induced a significantly cell death under lack of glucose condition. mEHT inhibited the expression of pyruvate pehydrogenase and decreased the intracellular ATP value. The results imply that mEHT probably causes deposition of energy in cancer cell. In conclusion, mEHT could be considered as a new treatment modality involving the cell metabolism.

IL-28
Combined Oncothermia and Immune Checkpoint Inhibitor Therapy -from Bench to Bedside

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Tuning noimmunogenic tumor microenvironment (TME) into an immunogenic TME is the key step for successful immunotherapy. Immunotherapy treatment frequently fails due to being unable to evoke immunity in a poor tumor microenvironment (TME). Modulated Electro-hyperthermia (mEHT) introduces autofocusing electromagnetic power on the cell membrane to create massive apoptosis. Despite the antibody block PD-1 (immune checkpoint inhibitor, ICI) had led to some durable response in 15 to 25% of patients, most patients do not respond to anti-PD1 therapy. We aimed to investigate the immune-potentiation effect of combined oncothermia and anti-PD1 therapy on mice model. We also reported our preliminary experience on combined oncothermia and anti-PD1 containing regimen in clinical cases.

mEHT significantly induced apoptosis and enhanced the releasing of heat shock protein 70 (Hsp70) in murine colon cancer (CT26) cells. mEHT effectively inflamed the TME through a multi-step link of cancer-Immunity cycle. For the combination of ICI therapy and mEHT, we also observed a significant inhibition of tumor growth in compared to control groups. Immunohistochemistry-staining showed marked tumor infiltrating lymphocytes (TIL) and macrophages increased after mEHT. mEHT also leads to marked expression of PD-L1 on tumor cells within the tumor tissues through Interferon-gamma release from TIL.

mEHT could create a favorable tumor microenvironment for an immunological chain reaction to enhance the last step (anti-PD1) role of T cells. Clinically, we observed autoimmune response after oncothermia and radiation treatment on a locally advanced breast cancer patients. We identified 3 patients reversed resistance to anti-PD1 treatment after the introduction of weekly oncothermia. We demonstrated another 4 out of 9 patients showing some degree of response to anti-PD1 containing regimen with oncothermia. Our laboratory and clinical experience suggest that oncothermia is likely to become a vital part of 8CI treatment strategy.

IL-29

Tumor specific stress and immune response induced by modulated electro-hyperthermia in relation to tumor metabolic profiles

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Selective heating (to ~42°C) and destruction of cancer can be achieved using modulated electrohyperthermia (mEHT) induced electromagnetic field due to elevated glycolysis (Warburg effect), ion concentration and permittivity of malignant tumors. *In vivo*, mEHT caused significant apoptosis in colorectal cancer models generated in mice through either caspase dependent (C26) or apoptosis inducing factor (AIF) mediated (HT29) pathways depending on the genetic makeup of treated tumors. Activation of cleaved-caspase 3 was mediated by both the extrinsic pathway through upregulating cleaved caspase-8, and the intrinsic pathway through mitochondrial accumulation of bax and release of cytochome C in grafted tumors. Cell death response was accompanied by the occurrence and release of DAMP (damage associated molecular pattern) signals including chaperons such as calreticulin, Hsp70 and Hsp90 and the high mobility group1 (HMGB1) protein. In line with this, accumulation of CD3 positive T cells including granzyme B+/CD8+ cytotoxic cells (granzyme B+/CD8- NK cells) and S100+ antigen presenting dendritic cells (APC) were observed suggesting an mEHT related immune stimulation relevant to immunogenic cell death (ICD). Furthermore, the treatment response of tumors to mEHT could be associated with elevated levels of glycolytic enzymes *in vivo*, and increased lactate production and reduced buffer capacity (and pH) in cultures.

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IL-30

Smart drug delivery by use of lipid based devices, tumor manipulation and alteration of tumor pathophysiology

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Chemotherapy is one of the main treatment policies in cancer. While (acquired) resistance is a major hurdle and therefore an important subject of study, adequate and sufficient delivery to the site of action is crucial to inflict an effect of importance. Here in particular the possibilities at hand to improve drug delivery to tumors is discussed. For this purpose the focus will be on nanocarrier-based drugs (i.e.

liposomes encapsulated) and the use of mild hyperthermia. Nanocarriers are used to tune pharmacokinetics and to modulate logistics in the body as well as in the target site. Hyperthermia is applied to manipulate tumor microenvironment and to control release and availability of the nanocarrier-born chemotherapeutic. By combining the beneficial characteristics of liposomes with the possibilities hyperthermia provide a better drug delivery and tumor response are anticipated.

IL-31

Concurrent Pencil Beam Scanning Proton Therapy and Hyperthermia: rational and clinical experience

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Concurrent hyperthermia (HT) with radiotherapy is known to increase efficacy through multiple mechanisms including radiosensitization of hypoxic cells and inhibition of DNA-repair. HT reduces the oxygen enhancement ratio of "low"-linear energy transfer (LET) radiation (photon/proton) and increases radiobiologic effect (RBE), potentially mimicking high-LET particle therapy (^{12}C ion) [Datta et al. 2014]. Naturally, both enthusiasm for improved outcomes and concerns regarding increased toxicity have arisen, yet limited data exists to date. At the Maryland Proton Treatment Center, over 200 patients have been treated with pencil beam scanning proton therapy (PBSPT). Eighty-seven patients have been treated with HT in 4 years. All HT has been delivered on the BSD-500 platform with the 40-42^{o}C target tumor temperature. Clinical experience with combination of PBSPT and HT will be presented and discuss. In general, all patients completed their courses of proton and hyperthermia treatment without substantial acute complication suggesting concurrent PBSPT and HT appears safe, effective, and promising treatment option for selected patients. Further investigation and expansion of clinical experience is warranted amongst institutions with technical capabilities.

IL-32

Hyperthermia Enhances the Efficacy of Stereotactic Body Radiation Therapy

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Stereotactic body radiation therapy (SBRT) precisely irradiates tumors with 15-50 Gy in 1-5 fractions. The high-dose hypofractionated SBRT has been suggested to be highly effective to control various tumors because it causes massive tumor cell death by inducing DNA double strand breaks and also by causing secondary cell death via induction of vascular damages. Furthermore, the massive cell death by SBRT acts as an in situ vaccine, thereby inciting anti-tumor immune reactions. Little attempt has been made to elucidate the potential effects of combination of hyperthermia with SBRT for human tumors. Nevertheless, followings may be envisioned to occur when hyperthermia is combined with SBRT in treating human tumors. First, both hyperthermia with temperature higher than 42-43^{o}C and SBRT damage tumor vasculatures. Therefore, hyperthermia and SBRT may complement each other or even react synergistically in destroying tumor vasculatures, thereby causing massive indirect/necrotic cell death. Second, both hyperthermia and SBRT have been shown to enhance anti-tumor immune response. The anti-tumor immune response elicited by SBRT in combination with hyperthermia may be

greater than that by either of them alone. Third, regional hyperthermia using presently available external heating devices elevates temperatures not only in tumor mass, but also in the adjacent normal tissues. Given that SBRT is able to precisely deliver radiation energy only to the tumor, unlike conventional radiotherapy, interaction between radiation and heat may be confined to tumor, minimizing heat-induced radiosensitization in normal tissues. Fourth, SBRT upregulates HIF-1α in tumors that activate various survival factors including VEGF leading to promotion of revascularization essential for recurrence and metastases. Importantly, mild temperature hyperthermia induces degradation of HIF-1α via increasing tumor oxygenation. In conclusion, hyperthermia may be a potent enhancer of the efficacy of SBRT.

IL-33
Radiofrequency-Hyperthermia in medical oncoloty - Current status

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RF-hyperthermia induces pleiotropic effects on tumor tissue which synergize with medical tumor therapy. In addition, RF-hyperthermia potentiates the antitumor effect of certain cytotoxic drugs and can be used as trigger mechanism for heat sensitive drug delivery systems. Concerning recent developments in Immune Oncology with the use of check-point inhibitors, RF-hyperthermia might play an important role to further boost anti-tumor immune responses by increasing tumor antigenicity or attraction of immune cells. A comprehensive overview of phase II and phase III trials with RF-Hyperthermia in medical oncology will be given including recent developments in the field of heat sensitive nanocarriers and immune oncology.

IL-34
Chemo-hyperthermia with MR-thermometry in pediatric ovarian germ cell tumors

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Propose: In girls and young women with advanced or recurrent ovarian germ cell tumors after repeated and incomplete resection have an unfavorable prognosis. This also applies for patients who were treated according to the MAKEI therapy-optimization clinical trials. In such circumstances additional regional hyperthermia (RHT) has been used in order to facilitate a complete tumor resection and to improve the prognosis.
Patients and methods: Chemo-hyperthermia with MR-thermometry at temperatures of 40-43°C for 60 minutes on days 1+4 is performed in combination with PEI-chemotherapy (cisplatin 40 mg/m², days 1+4, etoposide 100 mg/m², days 1–4 and ifosfamide 1800 mg/m², days 1–4). According to response the patients received 4-6 treatment courses with time intervals of approximately 21 days. On suspicion of residual tumor the possibility of a complete surgical tumor resection (provided as 2nd-look operation) was investigated after the 3rd or 4th course.
Results: A total of 22 girls/young women at 8;5-24;8 years of age (median:16;2 years) with recurrent or primary refractory ovarian germ cell tumors were treated according to the Hyper-PEI-protocol in the

context of our interdisciplinary tumor board. The histological examination yielded different, mostly mixed germ cell tumors with following quantitative dominated subtypes: Yolk sac tumors (n=12), teratomas (n=6), embryonal carcinomas (n=3), and choriocarcinoma (n=1). In addition, in six tumors a malignant transformation was found.
Results: In 15/22 patients with a measurable tumor in diagnostic imaging and increased levels of tumor markers before RHT clinical treatment response was assessed: CR (n=4); PR (n=4); SD (n=6); PD (n=1). After 3-4 Hyper-PEI courses a 2nd-look operation was performed in 13/22 patients: R0 (n=9), R1 (n=3); R2 (n=1). Overall survival in this patient population with an unfavorable prognosis was 71% (95% CI 46-86). The median follow-up of surviving patients is 55 months (range 18–248).
Conclusion: Chemo-hyperthermia with MR-thermometry according to the Hyper-PEI-protocol has led to a long-term remission in the majority of patients with advanced refractory or recurrent ovarian germ cell tumors.
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POSTER

PRESENTATIONS

POSTER PRESENTATIONS

TOPIC: TECHNOLOGY / DOSIMETRY

PP-01

In vitro and vivo temperature measurements invasively and minimal invasively in capacitative hyperthermia at 13,56 Mhz

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Background:
capacitative hyperthermia is still regarded by some experts as not capable of achieving sufficient temperature rise in the depth of a body. On the other side this heating technology is wide spread in numbers among clinicians. This paper is about show that, if application is correctly operated, sufficient temperatures in the range of effective temperature can and will be reached.
Methods:
Temperature measurements were performed by invasive and minimally invasive placement of temperature sensors, attached to the tip of a flexible fiber optic cable. Accuracy +/- 0.3° C as total system accuracy
Results:
Measured temperature in vivo in depth of the body do range from 39 to 46 ° C. Applied technology and adjusted operating procedures determine the desired effect and are able to overcome the limiting factor of patient tolerance to the impact of higher powers.
Temperature rises/ SAR of 1 degree Celsius per 5 minutes / 10-12 degree Celsius in 60 minutes can be met.
Conclusion:
Capacitative Hyperthermia at 13,56 Mhz as a technology is principally capable of "doing the job". As with all technology it depends in detail on its engineering and on part of the users on its operational handling.

PP-02

Predictive modeling of regional hyperthermia

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Introduction. The model prediction of human functional state during RF hyperthermia is the actual task as it helps to find necessary approach in use of radiofrequency hyperthermia without hazard to human health.
The purpose of this study is to develop computer multicompartmental model for prediction of temperature dynamics during regional RF-exposure.

Methods. Human body is approximated by composition of multilayered cylinders related to trunk, arms, forearms, hands, thighs, calves and feet, head is sphere. Each cylinder and sphere is divided by ij-compartments related to core, muscle, fat and skin. Human body is approximated by 38 compartments.
Model describes metabolic heat production, absorbed heat by RF-exposure, heat transfer by blood flows, heat conduction through compartments, heat-exchange with environment through evaporation, radiation and convection. Controlling system describes thermoregulatory responses that provide stabilization of core temperature as impact of environmental challenge. Dynamic model of thermoregulation is implemented as computer simulator of RF hyperthermia [3]. Simulator can predict dynamics of body temperatures, heat fluxes, blood flows, total and local thermoregulatory responses during regional RF-impact.
The electromagnetic radiation absorbed by a layer of tissue is the difference between incident and transient power of waves. Specific absorption rate (SAR) in each compartment depends on biophysical properties of biological tissues and depth of a flat layer. The choice of electromagnetic frequency depends on dimension of the irradiated area and the depth of required therapeutic heating.

Simulations & Conclusion.
Simulations.
The developed multicompartmental model was used to simulate the regional impact at frequency of 40 MHz [1] and 433 MHz [4]. It was simulated regional exposure of leg.
Modeling results showed effective hyperthermia in both cases.
1. During 40 MHz and initial intensity 100 mW/cm² exposure SAR is equal to 243 W/kg, to the end of exposure (35 min) calf muscle temperature increases to 42 °C.
2. During 433 MHz and initial intensity 70 mW/cm² SAR attained 300W/m², calf muscle temperature increases to 43.2 °C.
Comparison of modeling results with experimental and model data [1, 2] resulted in conclusions.

Conclusions
- A multi-compartment model of human thermoregulation was developed, that can be used as computer tool for analysis of thermo-physiological state during of RF exposure.
- This computer model allows for prediction of dynamics of body temperatures during total and regional hyperthermia.

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TOPIC: PHYSICS & ENGINEERING FOR HYPERTHERMIA

PP-03

A standardized procedure for QualityAssurance of superficial applicators

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Introduction
The success of clinical trials including hyperthermia treatments depends greatly on a comparable application of heat to the tumour at the participating centres. The Thermal Effective Field Size (TEFS) and Thermal Effective Penetration Depth (TEPD) of the applicator can be measured in a homogeneous phantom and are related to the maximum Specific Absorption Rate (SAR) of the applicator. A standardized procedure is proposed to measure these characteristics of the applicator.
The aim of this study is to test the procedure on six 915 MHz hyperthermia applicators (Pyrexar Medical, Salt Lake City, UT) and the practicability of using the resulting transparent Thermal Effective Field Size (TEFS) sheet (one per applicator) in the clinic.
Methods
A vertically split flat muscle equivalent agar phantom (35 cm x 35 cm x 6 cm) and a removable 1 cm thick agar top layer placed on a revolving frame were used to determine the TEFS (i.e. area within the 50% of max temperature rise (TR)) and the TEPD (i.e. depth at which the TR is 50% of the max TR at 1 cm depth). The phantom is constructed to characterise heating in the chestwall. The applicator with water bolus was positioned on top of the phantom. An infrared camera (Optris-PI 160, Optris GmbH, Berlin, Germany) mounted on the frame at 95 cm from the phantom surface measures the two heat patterns before and after a 6 min power pulse in accordance with ESHO technical Committee guidelines [1]. The heat patterns were analysed using a MATLAB evaluation program, yielding TEFS and TEPD graphs, and the heat patterns transferred to transparent TEFS sheets for use in the clinic.
Results
The TEFS and TEPD of the six applicators were determined (table) and measurement procedure and reproducibility was evaluated. The TEFS depends strongly on the contact between bolus and phantom and is on average 40% smaller than the physical inner size of the applicator. The elaborated transparent TEFS sheets are used in the clinic.
Conclusion
An effective technique was developed to perform QA measurements for superficial applicators. The transparent EFS sheet appears to be an effective tool to select an applicator for optimal SAR coverage of the tumour.
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Table. Results of the measurements.

Applicator	Type	Physical (inner) appl. size (cm)	TEFS (cm)	TEPD (cm)
SA308	3 spiral	8.6 Ø	7.7 Ø	3.0
SA812	8 spiral	12 Ø	11.8 Ø	3.1
SA248	24 spiral	16 x 23	11.9 x 20.0	2.5
MA151	waveguide	6.2 Ø	3.4 x 3.7	2.7
MA100	waveguide	10 x 13	8.4 x 10.1*	2.9
MA120	waveguide	17.7 x 24	12.4 x 18.7	3.1

* MA100 has 2 maxima

TOPIC: NANOPARTICLES & HYPERTHERMIA

PP-04

Tunable spatial focus of Magnetic Particle Hyperthermia effect

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Introduction
A typical problem of the application of hyperthermia is its difficulty to locate its therapeutical heating solely the targeted malignant cells without damaging the potentially healthy surroundings. Thus, we propose a simple upgrade of a magnetic particle hyperthermia device which localizes the heat on very small tunable regions with the adequate combination of a static and an alternating field. The main objective of this work is to control heating effect through the application of a static and an alternating magnetic field in order to localize the heating in the central region of a specimen.
Methods
Magnetic particle hyperthermia experiments were carried out for magnetic nanoparticles of different size in order to examine superparamagnetic and ferromagnetic particles possessing different magnetic heating mechanisms and thus interacting at a variable degree with the external magnetic field. The sample was placed in the center of a typical induction coil (100-800 kHz) and (5-60 mT). An additional static magnetic field was generated by using two permanent NdFeB magnets placed symmetrically, facing each other, outside the coil, resulting to magnetic gradient field from 0.4 to 2.8 T/m and field intensities from 4 to 40 mT depending on the type of the magnets and the distance between them. To start with, we estimated numerically the total magnetic flux density and the corresponding gradients at the central region of the coil i.e. the sample area, by using Comsol Multiphysics 3.5a, showing that around the sample's center an area with zero static magnetic field is created, the so called, field free region. Experiments, verified that in the absence of static field, i.e. nanoparticles inside the field free region, are able to freely align with the alternating field giving rise to their best performance concerning

heating efficiency. Outside the field free region, where the static field exists, nanoparticles may be found in two possible states. First, when the alternating field and the static field are antiparallel, the static field's torque is competing the one of the alternating field attenuating its effect. Second, when the static and alternating fields are in the same direction, two torques are additive, speeding up nanoparticles' saturation process. Eventually, in both states, yet for different reasons, the nanoparticles do not respond at a maximum extent to the alternating magnetic field, thus are unable to activate their power loss mechanisms.

Conclusions

In this study, we propose a facile upgrade of a typical magnetic hyperthermia system able to focus its magnetic heating effect in the center of the sample by adequate combination of a static and an alternating magnetic field. Through the simulation and experiments of magnetic particle hyperthermia, we can see that in present of the static magnetic field the heat release was selectively focused in the central region, for example, the malignant cells location. The advantage of such an application scheme is the minimization of the heat side-effects to surrounding healthy tissues. Thus, the magnetic particle hyperthermia can be a much more effective method with focusing capabilities better and tunable heat localization.

PP-05

The development and in vitro research of novel hypoxia-targeting gold nanospheres

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Purpose: Cancers can over-express Carbonic Anhydrase-IX (CA-9) under hypoxia This study investigated the novel conjugated procedures of modification of gold nanoparticles and pharmacokinetics of hypoxia-specific antibody-mediated active targeting gold nanoparticles (AuNP) in HT29 under hypoxia.
Materials and Methods: AuNP-NOTA were synthesized by p-SCN-Bn-NOTA (from Macrocyclics Inc. Dallas, Texas, USA), sphere AuNP, Anti-CA-IX polyclonal antibody (from EMD Millipore) and labeled with 67GaCl3 (from Institute of Nuclear Energy Research, Taiwan) in room temperature. HT29 cellular uptake of anti-CA-IX-AuNP-NOTA-Ga-67 was tested under hypoxia/normoxia.
Results: The radiochemical purity (RCP) of anti-CA-IX-AuNP-NOTA-Ga-67 was over 90%. However, the RCP reduced to about 75% at 4 hour within fetal bovine serum (FBS). After 2 h incubation, the cellular uptake of anti-CA-IX-AuNP-NOTA- Ga-67 was 15.62 ± 1.85 and 10.11 ± 0.54 %dose/106 cells (n=4) under hypoxia and normoxia, respectively.
Conclusions: In this study, anti-CA-IX-AuNP-NOTA-Ga-67 was developed with an acceptable radiochemical yield and high radiochemical purity. The results of cellular uptake confirmed that anti-CA-IX-AuNP-NOTA-Ga-67 could be uptake by over-expression of CA-IX in HT29 under hypoxia. The biodistribution and thermo-therapeutic effect with RF-8 were executed.

PP-06
A numerical study of magnetic nanoparticles: Application to magnetic hyperthermia

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In the clinical application of magnetic hyperthermia, the heat generated by magnetic nanoparticles in an alternating magnetic field is used as a cancer treatment. The heating ability of the particles is quantified

by the specific absorption rate, an extrinsic parameter based on the clinical response characteristic of power delivered per unit mass. At the crossover between the hysteretic and superparamagnetic regimes of magnetic nanoparticles direct calculations of the specific absorption rate become much difficult. Rosensweig theory has been applied to a non-interacting assembly of magnetic nanoparticles, close to equilibrium, in order to describe its dynamic response using the Néel-Brown relaxation time but is not valid in the hysteretic regime while Carrey et. al. have introduced analytical expressions in order to estimate the specific absorption rate of ferromagnetic nanoparticles. This work presents an accurate numerical magnetic method for the estimation of the specific absorption rate of single domain ferromagnetic nanoparticles based on the quantification of their characteristic magnetic properties, such as coercive field and energy, validated by the model proposed by Carrey et al.
For the nanoparticle magnetic characterization, we conducted numerical simulations based on the Monte Carlo method which is a stochastic numerical technique used to simulate physical systems that have a high phase space. We simulated an assembly of magnetic nanoparticles, taking into account their size dispersity, subjected to an alternating magnetic field that invests electromagnetic energy from the field in magnetization reversal processes. Its internal energy is then first increased and afterwards released as heat. The field amplitude and frequency were set to 30 mT and 765 kHz respectively which are typical for the parameters used in magnetic hyperthermia. The relationship between the heat generated and the magnetic response of the magnetic nanoparticles makes possible the determination of the specific absorption rate which is calculated from the area entrapped within the magnetization versus magnetic field curve, the so-called hysteresis loop. This area determines the amount of heat released by the magnetic nanoparticles during one cycle of the magnetic field. By integrating the magnetization curve, occurred through Monte Carlo simulations, we computed the specific absorption rate. The influence of MNPs' anisotropy and external temperature in a range between 2000 J/m³ to 11000 J/m³ and 150 K to 350 K, respectively, on hysteresis loop area was examined. We found that the area was increased with anisotropy while it was decreased with temperature. This behavior is in agreement with the predictions of theoretical models found in literature and also with the results of the corresponding experiments.
We investigated the dependence of the hysteresis loop area from the magnetic nanoparticle anisotropy and temperature. The specific absorption rate is also calculated as a function of these parameters leading to power law relationships. Furthermore analytical expressions derived from theoretical models, available in literature, are used in their domains of validity for the verification of our results and for a theoretical study of magnetic hyperthermia. This study helps in the determination of suitable materials for magnetic hyperthermia and provides accurate formulas to analyze experimental data.

PP-07

An in-vitro study of the effect of gold nanoparticle in cancer cells treatment with modulated electro-hyperthermia

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Introduction: Modulated electro-hyperthermia (mEHT) uses a capacitive-impedance coupled 13.56 MHz radiofrequency to selectively generate the heat production on malignant cell membrane. Metal-based nanoparticles, such as gold nanoparticle (AuNP), have been reported to promote the heat generation

and therapeutic efficacy in radiofrequency-induced hyperthermia cancer therapy in vitro and in vivo. This study aimed to investigate whether AuNP would alter the heat generation and cell viability in combination with mEHT.

Methods: Spherical gold nanoparticle (sAu) with various sizes (10, 20, 30 and 50 nm) and an urchin-like gold nanoparticle (uAu, 50 nm) were synthesized by using Turkevich method and/or hydroquinone-reduction method. All nanoparticles were characterized by UV-VIS absorption spectrometry, dynamic light scattering (DLS) and transmission electron microscope (TEM). Oncotherm EHY-100 was employed in the heat generation of solution containing different AuNPs and in the cellular studies. HepG2 cells incubated with and without sAu (50 nm, sAu_{50}) or cells pre-treated with sAu50 for 24 h were subjected to mEHT. The cell survival was analyzed by MTT assay.

Results: When treating with mEHT, the heat generations in solution containing 100 ppm of gold nanoparticles, with a size of 10-50 nm, were found reduced compared with that in the deionized water. Among these, the solution of sAu_{50} showed the lowest temperature rising. Compared with water bath (42°C, 30 min) treatment, treating with mEHT at 42°C for 30 minutes significantly reduced the HepG2 cell survival in vitro. However, less cell death at 24 and 48 h after mEHT treatment was noticed for the HepG2 cells incubated or pre-treated with 50 ppm of sAu_{50} (Figure 1). mEHT alone exhibited more HepG2 cell killing (cell survival rate 60.0±0.6 %) compared with that of co-incubated with sAu50 group (67.2±2.3 %) and pre-treated group (70.0±0.3 %) at 24 h post mEHT treatment.

Conclusion: Our results indicated that applying AuNP in HepG2 hepatoma cell treatment with mEHT exerts no synergic or additive effect in cell killing. The metal-based nanoparticle, AuNP, may disperse the energy of electromagnetic current during mEHT treatment and result in lower heat generation and higher cell survival.

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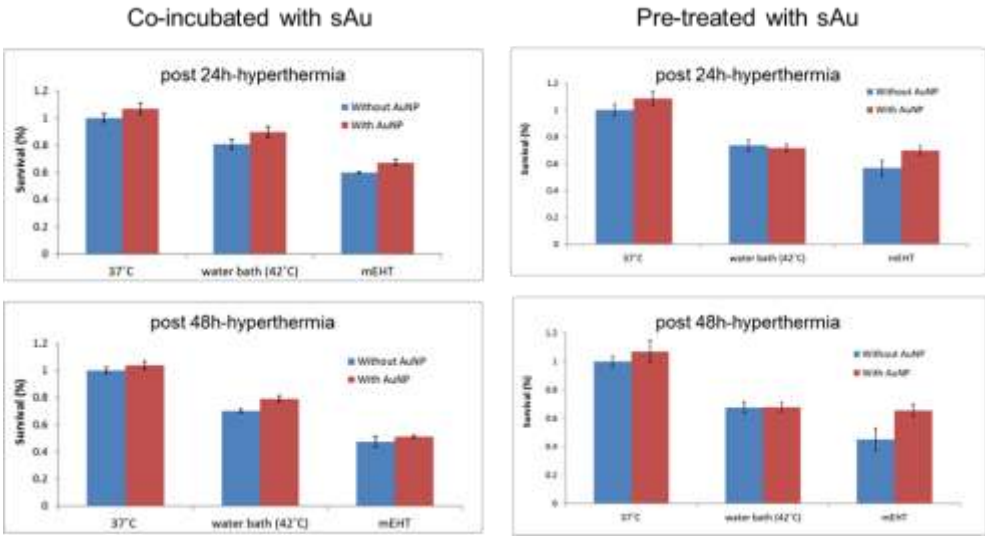

Figure 1. HepG2 cell lines co-incubated sAu (50 nm, 50 ppm) or cells pre-treated with sAu (50 nm, 50 ppm) for 24h were subject to control (37°C), water bath (42°C) and mEHT. The cell survival ratios were analyzed by MTT assay.

TOPIC: CHEMO-THERMOTHERAPY

PP-08

Chemotherapy with concurrent hyperthermia for breast patient with metastatic lung disease: A case report

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Introduction
Some patients with breast cancer suddenly develop lung metastases, despite conventional appropriate treatment. In such cases the initial prognosis is overriden. The present case study offers some new perspective for such cases, by demonstrating the value of adding hyperthermia to chemotherapy in breast cancer patients with lung metastases.
Method
A female patient has been diagnosed with breast cancer (stage III, ER-, PR-, c-erb 3+). She had undergone three cycles of induction chemotherapy with Docetaxel and Transtuzumab before right mastectomy with axillary node dissection, followed by reconstructive surgery. After surgery, she underwent three more cycles of chemotherapy (Docetaxel and Transtuzumab) and external beam radiation therapy of 50Gy in 25 fractions to the chest wall, supraclavicular and internal mammary lymph nodes. Maintenance chemotherapy with Transtuzumab was also administered.
Two years later, she was diagnosed with lung metastasis with enlarged lymph nodes (right hillar and subcarinal lymph nodes) with the largest measuring 2.5cm diameter. She was treated with concomitant chemotherapy (FEC) and two hourly sessions of hyperthermia per week, for three months. Modulated Electrohyperthermia (mEHT) was performed with model 2000 plus (Oncotherm), at max output 150W; a mean 1490.5kJ were administered per 60 min session. In this study we used the 30cm applicator, directly to the thorax.
Results
Three months later, complete remission of enlarged lymph nodes was observed on CT imaging. No toxicities developed and the patient was alive and well, with no evidence of disease, 18 months after completion of treatment. We postulate that, given the fact that metastatic disease in this case developed under dual conventional treatment, the observed full remission that ensued is attributable to the addition of mEHT.
Conclusion
The present case report suggests that the addition of mEHT to chemotherapy might be a better choice, promising longer survival and good quality of life, with no adverse effects, in breast cancer patients with metastatic lung disease. It is tempting to hypothesize that the addition of mEHT might even be a better *initial* therapeutic choice, before metastatic disease manifests itself.

PP-09

Does upfront therapy with cytoreductive surgery and HIPEC confer a survival benefit in patients with synchronous gastric peritoneal carcinomatosis when compared with patients with metachronous gastric peritoneal carcinomatosis?

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BACKGROUND: Patients with peritoneal carcinomatosis (PC) of gastric origin have an extremely bad prognosis with a median survival estimate at 1–3 months. Peritoneal carcinomatosis is present at the diagnosis in 5-20% of the patients, and almost 60% of them will present it after curative treatment. Peritoneal carcinomatosis from gastric cancer (GPC) responds poorly to systemic chemotherapy. We studied the efficacy of the upfront treatment with cytoreductive surgery (CRS) and HIPEC in patients with synchronous gastric peritoneal carcinomatosis and in patients with metachronous gastric peritoneal carcinomatosis.
METHODS: We retrospectively analyzed 14 patients with GPC undergoing CRS/HIPEC the last 10 years. Six patients already presented GPC at the time of the diagnosis and eight of them presented metachronous GPC.
RESULTS: CRS/HIPEC was performed for synchronous GPC in 6 patients and metachronous GPC in 8 patients. Kaplan-Meier survival curves demonstrated that survival times between two groups were not statistically different.
CONCLUSION: Upfront treatment with CRS/HIPEC doesn't seem to confer a survival benefit in patients with synchronous gastric peritoneal carcinomatosis.

TOPIC: LOCO-REGIONAL HYPERTHERMIA

PP-10

Thermoradiation in muscle invasive bladder cancer (MIBC): A Valuable therapeutic option for elderly or inoperable patients

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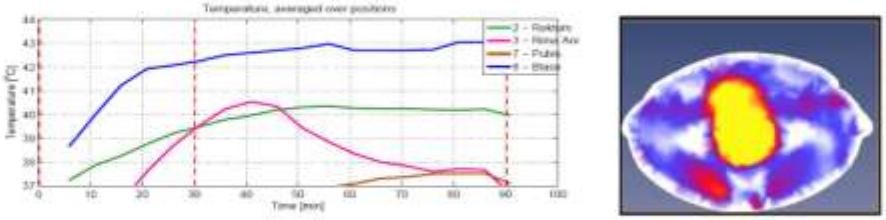
Aim: Chemoradiotherapy (CTRT) is an established treatment option for patients with muscle invasive bladder cancer unsuitable for radical cystectomy. But often some elderly patients are ineligible for chemotherapy. We treated this specific population with hyperthermia (HT), a valuable radiosensitizer, in addition to radiotherapy (RT) and expected comparable local control rates as with radio-chemotherapy and low toxicity with preserved bladder function.
Methods: Between 02/2011 and 03/2017, 15 consecutive elderly patients (median age 80y) received short course hypofractionated thermo-radiotherapy (within 4 weeks) after transurethral tumor resection. Patients unsuitable for, or who refused, radical cystectomy or were ineligible for chemotherapy according to the multidisciplinary urology tumor board, were considered for this departmental protocol. Patients received 16 x 3Gy / 4x weekly (for solitary lesions) or 20 x 2.5Gy / 5x weekly (for multiple lesions). HT (41° - 43°C for 60 minutes, Fig.1) with intravesical online thermometry was applied once weekly before radiotherapy. Follow-up included repeated cystoscopies and urine cytology by the referring urologist.
Results: All patients completed prescribed therapy and tolerated the combined bimodality treatment well. At a median follow-up of 13 months (range 1 – 48), 14 patients were in local complete remission with well preserved bladder function. In one patient, the first follow up is still pending. No grade 3 or 4 late toxicities were reported.

Conclusion: These preliminary data show excellent clinical results. The combined therapy is well tolerated in the elderly. Continuing interdisciplinary collaboration with urologists is necessary to provide further evidence in the context of such clinical studies.

Fig.1 Thermal dose distribution in bladder



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PP-11

Deep regional hypethermia combined with chemotherapy: Experience of the Greek Society of Hyperthermic Oncology.

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Introduction: Hyperthermia has been used to treat a number of different types of localized cancer, including liver metastases, lung metastases, cervix, rectum, and bladder. This procedure in combination with chemotherapy or radiotherapy, or with both, may help to improve the effectiveness of these treatments.

Patients and Method

Between July 2012 and February 2016, 40 patients underwent combined chemotherapy and modulated Electrohyperthermia (mEHT), using model EHY 2000 plus (Oncotherm), with output carrier frequency

13.56 MHz, max output power 150 W. mEHT was performed at hourly sessions. Anatomical regions included 17 cases of metastatic liver disease (mean energy delivery 1517kJ/h), 13 cases of lung metastases (mean 1483kJ/h), 6 cases of cervix (mean 1506kJ/h) and 4 cases of bladder primaries (mean 1446kJ/h). Patients were followed up for at least twelve months post combined RT+HT.
Results
In terms of 12 months follow-up, complete radiological response was achieved in 84% of cases with liver metastases, 68% of those with lung metastases, 77% of cervix and 52% of bladder patients.
Conclusion
mEHT combined with chemotherapy is able to enhance the response of the latter, thus achieving high rates of local control of disease. All patients are still alive; follow up is ongoing. Life extension should not be extrapolated on the basis of good local control of disease. More patients are needed, comprising focused disease type, and longer follow ups.

PP-12

Modulated Electro-Hyperthermia in Oligometastatic Cancer Patients: initial experience and clinicopathologic evaluation

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Introduction: Modulated electro-hyperthermia (mEHY) has gained support in the treatment of cancer patients as supplementary method besides the standard treatment or for those who exhausted conventional treatment.

Patients and methods: Seventeen eligible patients were recruited based on clinical rounds decision since SEP-2, 2016. Primary tumors of patients originated from the locations as follows: 7 pancreas, 4 colorectal, 3 breast, 2 lung and 1 kidney. Patients who attended one treatment occasion and multiple primary tumors were excluded. EHY-2000 instrument (Oncothermia Ltd., Budaörs, Hungary) was used and initial power of 60-150 W was applied. The increments were set to 5-10 W in 5 minute steps. Tumor markers CEA and CA19-9 and imaging studies were reviewed in light of duration of mEHY therapy.

Results: The patients' data was evaluated on APR-7, 2017. Average number of metastases of the tumors were 2. Various chemotherapeutic protocols were administered to the patients as per guideline recommendations. Average treatment time of each mEHY occasion was 59.5 minutes. From the initial power to the final power on average 50W power increment was reached. The patients underwent 18.7 cycles on average (range: 2-45).
Eight patients (4 pancreas, 1 colon, 1 breast and 1 kidney) had to discontinue the therapy due to progression, especially hydrothorax, ascites and severe pain, their treatment lasted on average 58.6 days. Upon analyzing pancreatic tumor patients' data, elevated CEA ($p=0.050$) but not CA19-9 levels correlated with progression of disease as confirmed by CT scans and eventual outcome. There was no significant difference in the duration of mEHY treatment between those possessing elevated CEA level and subsequently going into progression and those who remained free of symptoms and staying on mEHY therapy ($p=0.417$).

Conclusion: Seventeen patients were treated at our mEHY therapy unit, which was established in the past months. Patients with oligometastatic/inoperable tumors are likely the target population of this treatment approach, especially supplementing systemic therapy. CEA and CA19-9 levels in pancreatic

cancer patients are not predictive for response to mEHY therapy (yet patient numbers are low), thus, identification of better biomarkers is warranted. In the next phase, we plan to recruit pancreatic cancer patients and identify predictive markers for response to mEHY therapy combinations.

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PP-13

Quality Control of the SAR distribution for Deep Hyperthermia Applicators with a 3D Scanning Phantom

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Introduction
Hyperthermia of the tumour volume at 41-43°C has shown to be a valuable sensitizer for radiation- and chemo-therapy in cancer treatment. To monitor the heated volume in annular antenna array applicators regular checks of the specific absorption rate (SAR) focus and its steering by phase shift are recommended in the quality management guidelines [1].
In this study a method and results for monitoring the 50% iso-SAR ellipsoid are presented for the SigmaEye and Sigma60 applicators used with the BSD-2000 3D deep hyperthermia equipment (both Pyrexar Medical, Salt Lake City, USA).
Methods
The phantom used is an elliptical tube inserted in the Sigma applicators. The tube is filled with 0.2% saline simulating average intra-pelvic tissue (σ = 0.4 S/m at 20°C) [2]. Inside the tube a SAR probe (EASY4/MRI, SPEAG, Zürich, Switzerland) can be moved in 3 spatial directions. By scanning the probe through the centre of the applicator profiles of the relative SAR strength are measured. From the full width half maximum (FWHM) distance of the recorded profiles the 50% iso-SAR ellipsoid described by: $x^2/a^2 + y^2/b^2 + z^2/c^2 = 1$ where a, b and c are the semi-principal axes of the ellipsoid inside the applicator are determined using a MATLAB program.
Results
The 50% iso-SAR volume was determined for the Sigma60 from 47 and for the SigmaEye Applicator from 115 individual scans. The semi-principal axes a (lateral), b (dorso-ventral) and c (cranio-caudal) of the ellipsoid are given in table 1. Figure 1 shows an example for the 50% iso-SAR ellipse in the saggital plane of the Sigma-Eye applicator.
Conclusion
With the elliptical scanning phantom the 50% iso-SAR volume of a deep hyperthermia applicator can be determined with high resolution in the millimetre range. Uncertainties were found to be small including positioning errors and water bolus variations. The 3D SAR scanning phantom has been shown to be a versatile tool for investigations of the electrical field inside the applicators.

	a – lateral	b – dorso-ventral	c – cranio-caudal
Sigma60	10.4 ± 0.75 cm	6.9 ± 0.25 cm	13.2 ± 0.55 cm
Sigma-Eye	8.7 ± 0.45 cm	6.4 ± 0.95 cm	13.1 ± 0.55 cm

table 1: semi-principal axes of the 50% iso-SAR ellipsoid for the Sigma60 and Sigma-Eye applicator

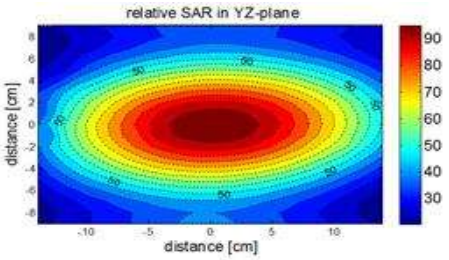

figure 1: relative SAR and 50% iso-SAR line in the saggital plane of the Sigma-Eye applicator with 1cm resolution

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PP-14

The thermo-enhanced effect of Iron dextran as thermosensitizer for maximizing cancer treatment efficacy with the radiofrequency-induced hyperthermia

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Treatment of cancer has been one of the toughest challenges that human race has been faced. Past 100 years of intensive researches on cancer treatment have developed surgery, chemotherapy, radiotherapy, hyperthermia, etc, for treatment of cancer. Among the current methodologies for cancer treatments, surgery, chemotherapy, and radiotherapy are dominated, and thermotherapy is used only in supportive care although the 13.56 MHz radiofrequency-induced hyperthermia recently is getting attention in clinics recently. Because the therapeutic efficacy of the 13.56 MHz radiofrequency-induced hyperthermia for cancer treatment is very marginal, the 13.56 MHz radiofrequency-induced hyperthermia is currently used mostly in combination therapy with chemotherapy or radiotherapy. Therefore, development of a method to amplify the therapeutic efficacy of the 13.56 MHz radiofrequency-induced hyperthermia is required for the 13.56 MHz radiofrequency-induced hyperthermia to become another therapeutic option for cancer. Metal ions such as ferric ion have very strong dipole moment, which means that metal ions can interact well to generate heat. Considering the characteristics of metals ions, it would be an ideal thermos-sensitizer for radiofrequency-induced hyperthermia if non-toxic biological metal ion such as ferric ion could be specifically delivered to cancer. Here, we report that iron dextran can be used as an ideal thermos-sensitizer for the 13.56 MHz radiofrequency-induced hyperthermia. Ferric ions in iron dextran are actively absorbed by apo-transferrin to become transferrin. Because natural tendency of cancer cells strongly absorbs transferring, iron dextran were 1.9 times more actively transferred into cancer cells than non-malignant normal cells in vitro. As is the case of in vitro experiment, ferric ions loaded in iron dextran was specifically accumulated in the tumor tissue of tumor xenografted mice so that the concentration of

ferric ions were 1.2 ~ 3.3 times higher than normal tissues. Because ferric ions were specifically accumulated in the tumor tissue of tumor xenografted mice, ferric ions reacted with the electromagnetic wave-dependent hyperthermia to generate high heat. Therefore, increase in the temperature of the tumor tissue was 2.4 fold higher in the tumor xenografted mice under the 13.56 MHz radiofrequency-induced hyperthermia after injecting iron dextran, compared to the 13.56 MHz radiofrequency-induced hyperthermia without iron dextran injection. Surprisingly, the overall anticancer efficacy of the 13.56 MHz radiofrequency-induced hyperthermia using iron dextran as a thermosensitizer was much better than paclitaxel's efficacy, and completely eradicated cancer in the tumor xenografted mice.

PP-15

Superficial radio-hyperthermia with 433MHz: the University of Athens experience.

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Introduction
Superficial hyperthermia has been used to treat a number of different types of localized cancer, including recurrent breast cancer, skin metastases and metastatic lymphnodes of SCC. This procedure in combination with chemotherapy or radiotherapy, or with both, may help to improve the effectiveness of these treatments.
Patients and Method
Between July 2012 and February 2016, 88 patients undergone combined radiotherapy and hyperthermia (RT+HT) for the treatment of superficial carcinomas. Hyperthermia was performed with a 433MHz circular applicator with emitted power up to 80Watt for one hour 30 minutes after radiotherapy. The radiotherapy dose ranged from 30-50 Gy. In every session, temperatures were monitored with a multipoint sensor (thermocouple). Tmin was 42.7oC. Anatomical regions included 35 metastatic lymphnodes SCC (head and neck), 38 relapses from mastectomy, 8 cases of melanoma and 7 cases of sarcoma. Patients were followed up every three months post combined RT+HT for one year.
Results
During follow up, complete response was achieved in 68% (head neck), 88% (thoracic wall), 82% (melanoma) and 78% (sarcoma) of patients, concerning 6 months of follow-up data. Grade 3 acute skin RTOG/EORTC toxicity was observed in 7.9% of patients.
Conclusion
Simultaneous hyperthermia combined with radiation is able to enhance response and local control rates. Follow-up is ongoing every three months.

PP-16

Inoperable multifocal intrahepatic cholangiocarcinoma treated with modulated Electrohyperthermia (mEHT), IV Vitamin C and ozonated blood autotransfusion

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Introduction: Intrahepatic cholangiocarcinoma is a rare (3/1,000,000) malignancy with a very poor prognosis. Even in the rare cases that are resectable (30%), more than half of them have lymphatic spread at the time of diagnosis. Chemotherapy (CT) and radiation therapy (RT) have a purely paregoric role. In extensive disease, there is no more than 4% one year survival, and the mean survival is 8.5 months from the time of diagnosis.

Case Presentation: This case is a 75 yr. old woman that presented with weight loss, anorexia, weakness, and intermittent low grade fever. MRI results depicted a lesion covering half her liver, with concurrent satellite lesions. Lung CT showed no metastatic disease. Her blood tests were also normal. Her CEA levels were normal (0.53ng/ml). Her monoclonal antibodies indicated the presence of the disease: CA 125: 121.8 U/ml, CA 19.9: 387.3 U/ml , CA 15.3: 24.98 U/ml. Due to her age, she refused standard treatment modalities (CT, RT etc). She was finaly treated with hyperthermia alone (mEHT), IV Vitamin C and autotransfuion of ozonated blood .

Methods: Phase I: Treatment from 18/11/17 – 27/12/17 with

mEHT: 60 min sessions, twice weekly, abdominal field covering all the liver area, mean energy delivery 458KJ, total duration of treatment 6 weeks.

Phase II: Treatment from 9/2/17 – 23/3/2017.

Parametres same as previously.

The patient was tested for G6PD and TSH. Having secured normal values, IV 7gr. Vitamin C with Magnesium, alternating with Selenium 200μg and Zn, during mEHT sessions. Previous to this autotransfusion of ozonated blood was performed (125ml of her blood was taken, ozonated, and autotransfused).

Follow up was with MRI GE Sigma Infinity 1.5 Tesla with EXCITE at the same diagnostic center with Transverse, Coronal and Saggital planes with T1-W pulse in and out of phase GRE, T2-W Fat Sat, 3D FAME with dynamic study and rapid IV infusion of radiopaque substance.

Results: MRI results 18/1/17 : The findings are same as the original MRI:

25/4/17 : The same findings of the primary tumor with differentiation of the satellite lesions, which show slight increase of diameter (3mm) with RO uptake in peripheral ring and necrosis in the middle.

The patients QoL was significantly improved after therapy and she was able to return to normal life. Her fever stopped and her weakness receded, her anorexia stopped with result of weight gain due to normal eating habits.

Conclusions: Hyperthermia (mEHT) may play a significant role in improving patients QOL, and may offer objective results in disease stabilization. We should consider various non-toxic protocols which may enhance patients immune systems and increase healthy tissue resistance to disease dissemination in conjunction with Hyperthermia. Further investigation is warranted into the best combinations for this purpose.

PP-17

Complete and durable remission in a stage IV prostate cancer patient with multiple lung metastases(without bone involvement) treated solely with androgen deprivation and modulated Electrohyperthermia

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Introduction: Multiple pulmonary metastases of prostate cancer are difficultly managed and almost impossible to eradicate completely, even with chemotherapy (CTh). Solitary metastatic nodules have been successfully managed with metastasectomy. Effective management with androgen deprivation has only given partial results in patients from Japan as indicated by respective studies. Besides, multiple pulmonary metastases without previous bone mets is very rare.
Case Presentation: Our patient is a 75yr old man that was diagnosed with prostate cancer almost simultaneously with metastases in both lungs (CT scan of 12/9/14). Biopsies were performed for both sites, verifying the diagnosis. Initial PSA was 104.085ng/ml with Gleeson score 3+3. The biopsies were histologically and immunophenotypically identical. Upon verification, the patient was free of bone involvement. Although CTh was indicated, the patient refused it. Subsequently, androgen deprivation was started. Parallel to this he was started on modulated Electrohyperthermia (mEHT).
Methods: The therapeutic regimen consisted of Degarelix injections every 28 days and mEHT on two sites (primary site and on the pulmonary metastases). mEHT was administered twice weekly; duration of sessions was 60 minutes at the primary site, delivering a mean energy of 416KJ; at the pulmonary field duration was 90 minutes and a mean energy of 627KJ was delivfered. The patient was followed up with PSA readings, chest radiograms and CTs.
Results: Within four months, the PSA values went dramatically down (from 104.085 to 0.202ng/ml) and stayed at about that level (0.198ng/ml on 18/2/17). Complete remission of lung metastases was first documented by CT scan at 13 months (21/10/15), and holds until today; the same applies to the intermediate chest X-rays.
Conclusions:. The combination of mEHT and androgen deprivation treatment gave unexpectedly good results, with long lasting complete remission of this rare expression of metastatic disease from prostate cancer. This warrants further study of the interaction of Hyperthermia on multiple pulmonary metastases from prostate cancer and its impact on therapeutic response in various regimens.

PP-18

Full eradication of metastatic site in cerebellum in 28year old patient with triple negative breast cancer by radiation & hyperthermia and partial remission in liver and pulmonary mets and stability in bone mets using integrative therapeutic strategy

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Introduction. Cancer is a complex and multi-facetted disease, but the overwhelming complexity of poly-metastatic malignancy necessitates extra-complex, multi-modal treatment approaches, if it is to be successful at all. In this case report we present the usefulness of modulated Electrohyperthermia (mEHT) in the treatment of a Stage IV triple negative, invasive ductal Ca of the left breast, Grade 3, treated in our facility in 2015.
Case presentation. Status post L. mastectomy with metastatic disease at the time of diagnosis (operated elsewhere). When presenting, the patient also had multiple liver and pulmonary metastases. Molecular

profile was established, including sensitivity tests for chemotherapy (CT), radiation therapy (RT), mEHT, propensity for neo-angiogenesis and cell cycle rate. CT based upon molecular sensitivity (quantitative) was administered, along with RT/mEHT combination for brain metastases, and mEHT for liver and pulmonary metastases.

Methods. The molecular profile was established, based on molecular/genetic sensitivity test (R. G . C . C: Research Genetic Cancer Centre). Cell harvest count was 6.7 cells isolated /7.5ml (disease stability count at 5cells/7.5ml). High level of neo-angiogenesis was established through VEGFr, FGFr and PDGFr markers. Resistance to CT, as determined by ABCG2 resistance pump mechanisms (markers MDR1 and MRP), was established at 50% and 40% respectively.

Sensitivity to RT and mEHT were established by measuring levels of HSP 27, HSP 72, HSP 90; respective values were 5%, 15%, and 25% down-regulation). Sensitivity to conventional CT agents was established. Sensitivity was also established for a wide range of biological molecules (vitamins, anti-oxidants etc). The patient was submitted to RT to brain, delivered through linear accelerator (6 mV) and received 6.5Gys, a complex, personalized CT scheme, based on her molecular/genetic profile (including resistance pump inhibitors to reduce cancer cell resistance), and mEHT on metastatic sites (cerebral, hepatic and pulmonary) with two sessions/week and mean 350KJ/site, except for brain which received 250KJ/session for a total of six weeks.

Results. Computerized tomography showed complete eradication of brain lesions compared with the initial examination. MRI examination corroborated these findings. The quality of life of the patient was improved.

CA 15.3 tumor marker: 453.0 IU/ml initially, 199.0 IU/ml intermediately, 28.4 IU/ml finally.

Conclusions. The personalization of treatment, which is achieved through the integrative oncological approach with inclusion of mEHT to the enriched standard CT and RT protocols, can give us surprisingly good results even on the most aggressive and disseminated tumors.

mEHT can safely be applied to the brain, without fear of edema and its complications. In similar cases without the use of Hyperthermia , with only the conventional modalities of treatment, the literature has very disappointing results.

PP-19

Combining different local-regional deep hyperthermia devices for the optimum results of treatments.

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Introduction

The modern deep local-regional hyperthermia offers excellent complementary treatment for complex conventional therapy for solid malignancies. Its remarkable clinical additions are the synergy with almost any gold-standard therapies, its resensitizing ability of the refractory medication and its rare side-effects.

Method

The endpoints of many local therapies are the local control, which is not enough in advanced metastatic cases. The locoregional or even the part-body treatments are mostly limited to treat far distant metastases simultaneously. In consequence of this limited treatment ability, the clinical results are sometimes controversial: together the shrinking of the treated primary site the distant, not-treated metastases have progression. The metastatic developments are often life-threatening situations, drastically limiting the survival time and the quality of life of the patients.

I would like to report my few years clinical practice with a new facility of large field treatment of the advanced metastatic cases. My primary choice to solve the whole-body treatment was earlier the

conventional WBH, but the results were not satisfactory. The clinical application of WBH was complicated, toxic, unpleasant and risky for the patients in definitely advanced metastatic tumors.
Then I treated simultaneously the distant metastases together with the primary tumor with a new facility (EHY3010, Oncotherm, Germany). The capacitively impedance coupled hyperthermia electrode covers the patient. The method systemically induces only mild hyperthermia, but (according to research results) it selectively heats up the tumor-cells all over the volume under the extended large electrode at least 3°C higher temperature than their environment, causing apoptotic cell-death. This effect is expected to be active in the non-visible micro-metastases and suppresses the disseminated circulating cells as well.
Results
The collected cases are all far advanced, they need high line treatments. In fact no evidence-based curative protocol exists for these patients, only limited number of palliative therapies are available. I applied the combination of the large-field electrode hyperthermia together with personalized complex supportive complementary treatments, and in many cases additional local hyperthermia (EHY2000, Oncotherm, Germany) was in combination, boosting the effect on the most life-threatening lesion. Patients had shown reasonable improvement of the quality of life, and sometimes surprising curative results were achieved.
I would like to present far advanced cases like colon cancer with abdominal spread to lymphatic nodes, omental and peritoneum, and with liver metastasis with certain curative results, with good quality of life. Another case to show is a breast cancer, locally advanced with distant bone metastasis, treating the whole skeletal areas with the large-field hyperthermia facility and the local breast disease with addition of the local hyperthermia boosting. The results were: disappeared symptoms, and good partial remission in all the lesions. Also other cases of such combined treatments will be presented.
Conclusion
The multilocal, large-field hyperthermia treatment is a feasible active part of a complex therapy of advanced, metastatic malignancies.

PP-20

Intra-articular application of pulsed radiofrequency for knee osteoarthritis: efficacy and safety during 1 year follow-up

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PURPOSE: The purpose of the study is to prospectively evaluate the effectiveness of intra-articular application of pulsed radiofrequency (PRF) in patients with knee osteoarthritis suffering from chronic pain refractory to conservative therapies.
METHODS: During a 30-month period, PRF was performed on 53 cases of knee osteoarthritis (45 patients, 8/45 with bilateral knee osteoarthritis). A 20G/10cm cannula was percutaneously inserted from the antero-lateral region of the knee joint under fluoroscopy. Coaxially, a RF electrode (10-mm ‘‘active tip’’) was introduced and neurolysis session was performed with PRF (1,200 pulses at 50 V with 10-ms duration followed by a 480-ms silent phase). Following, intra-articular injection of hyaluronate was performed. Pain, prior, one week/ one, 6 and 12 months post were compared by means of a numeric visual scale (NVS) questionnaire.
SIMULATION: Mean pain scores prior to PRF WAS 8.19± 1.4 NVS units. This score was reduced to a mean value of 2.47 ± 2.5 NVS units at 1 week after, 2.55±2.6 at 1 month, 3.1 ± 2.8 at 6 months and 5.02± 3.09

at 12 months of follow-up ($p<0.01$). Overall mobility improved in 47/53 (88.6%) patients. No complication was observed.
CONCLUSION: PRF seems to be an effective and safe technique for palliative management of chronic pain in patients with knee osteoarthritis. Results seem to be reproducible and lasting longer that intra-articular injection of hyaluronate solely performed. There seems to be a need of repeating the session at 1 year.

PP-21

A unifying cell survival model for hyperthermia, radiation and combination treatments

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Introduction: Hyperthermia (HT) induced radio-sensitization is believed to be due to a combination of impaired cellular repair mechanisms and enhanced cellular damage. For optimized treatment planning, quantification of these biological effects is essential. Although cell survival modelling approaches exist for HT and radiotherapy (RT) treatments on their own, a framework applicable to both treatment modalities is needed. Such a model is proposed and experimentally validated.
Methods: The AlphaR model is motivated by the observation that heat induced radio-sensitization may be explained by a reduction in the DNA damage repair capacity of heated cells. We assume that repair is only possible up to a threshold (thermal) dose above which survival will decrease exponentially. These effects are accounted for by a two case description of the surviving fraction as a function of (thermal) dose using three parameters. α_o, a measure of the initial damage, characterizes the slope of the survival curve at high doses. Repair is expressed as a first order Taylor expansion with parameters, αR, and β. These are used to reflect repair potential and the reduction of repair, respectively, and provide a smooth transition of the curve from an exponentially linear-quadratic to an exponentially linear function of dose.
Experimental cell survival data from two cell lines (HCT116, Cal27), along with two taken from the literature (BHK, CHO) were considered to compare the AlphaR model to approaches routinely applied for RT (linear quadratic model), and HT (Arrhenius model). For RTHT combination treatments, a wide range of thermal and radiation doses was fitted (43-48°C, 0-80 CEM43, 0-12 Gy), including different heating profiles for the same thermal dose. Moreover, cell survival as a function of radiation dose (fixed thermal dose), or heating time (fixed radiation dose) was considered. The resulting fitted model parameters were assessed for time-temperature, cell line and treatment modality specific dependencies.
Results: The proposed model fits survival curves with equivalent, or better, coefficient of determination than the linear-quadratic approach, independent of the treatment technique used ($R^2 > 0.95$ for all fits, fig.1l). For HT data, the model delineates the shoulder of the curves and gives equal values for α_o and αR, which reduces the number of free parameters to two. These parameters have an exponential relationship with temperature yielding an expression of the relative biological effectiveness of treatments at different heating temperatures that can be related to the classical thermal dose concept. This allows an interpretation of cellular damage in terms of chemical reaction kinetics as described by Arrhenius equations.
Combined RTHT treatments are well fitted by the linear quadratic case of the AlphaR model assuming a constant value for β. Under this assumption, all three cell lines displayed a linear increase in $\alpha=\alpha_o-\alpha R$ as

a function of thermal dose (fig.1r). Within the temperature range tested, the heating profile used to obtain a specific thermal dose did not influence the overall shape of the survival curve.
Conclusion: The proposed model accurately describes cell survival curves from hyperthermia, radiotherapy, and combined HT-RT, and holds great potential for planning clinical combination therapies.

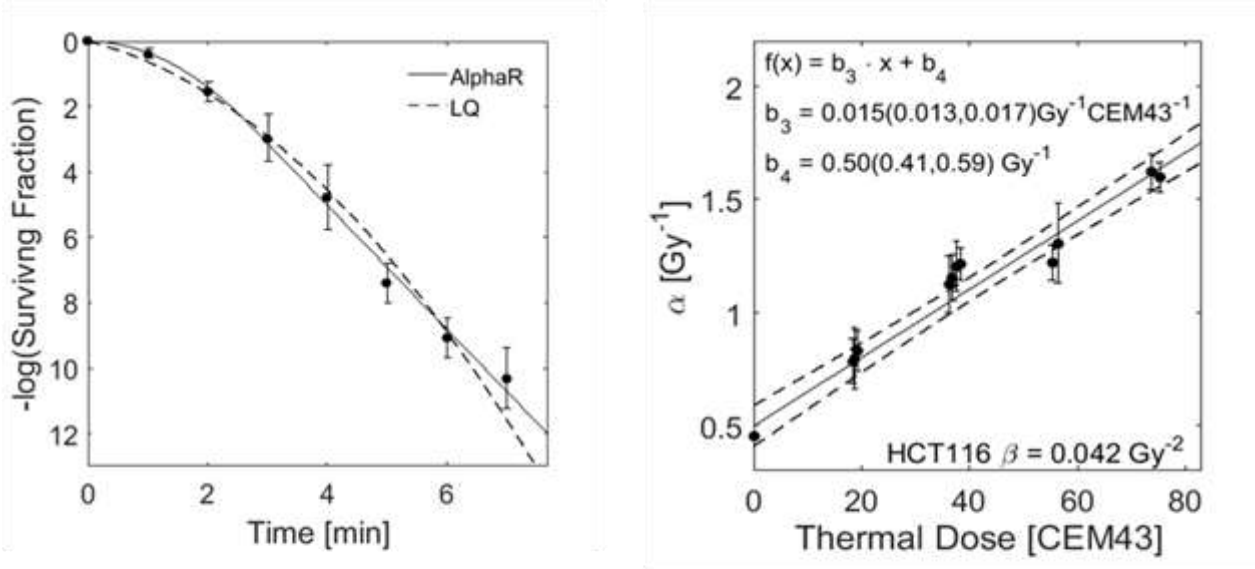


Figure 1. *Left*: Comparison of the fit of HT (48°C) cell survival data of HCT116 cells by the AlphaR (solid line) and LQ (dashed line) model. Shown are mean survival data with standeard deviations. In contrast to the LQ model, the AlphaR model follows the initial shoulder and exponentially linear decay of the data. The corresponding coefficients of determination (R^2_{AlphaR} = 0.99, R^2_{LQ} = 0.98) further support this observation. *Right:* Fitparameter α (with 95% confidence bounds) as a function of thermal dose given in addition to RT treatment. The parameter roughly follows a linear increase with thermal dose. The fit was performed under the constraint of a constant value β.

PP-22

Multimodality therapy concept of classical and complementary procedures as retrospectively reviewed over six years on patients with brain tumors (GBM; AA).

Dr. Med. Hüseyin Sahinbas[1]
[1]*Dayclinik for Hyperthermia*

Multimodality approach including hyperthermia
Detailed comprehensive documentation and its retrospective analysis enable us to critically evaluate proceedings and their clinical results in GBM and Astrocytoma (AA). Both are quite susceptible to hyperthermia treatment and to our experience an extended multimodal concept (traditionally entailing surgery, radiation, chemotherapy) including hyperthermia allow for success in quality of life and in overall survival that are markedly better than expected.

Treatment plan and experiences

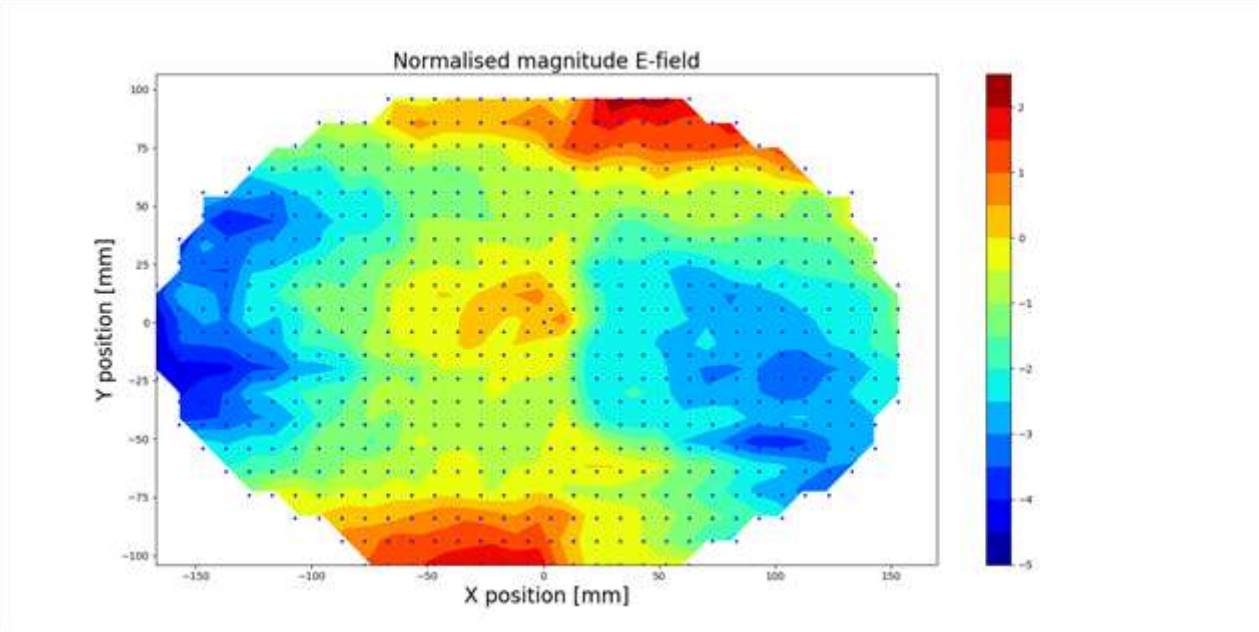
Ideally a patient may receive all three classical therapies: surgery, chemotherapy plus radiation. In more than 80% our patients did receive all these therapy options with newly progress. All this patients received additionally loco regional hyperthermia.
For this delicate entity we shall cover timing aspects within the therapy proceedings on a daily perspective as well as over the course of the treatment series. In summary we present our therapy protocols and experience on our brain tumour patients (n= 53) within the last six years.
Results
We compare results in this tumour entity relating to overall survival compared to recent international trials.

PP-23

Comparison of the performance between AMC4 and ALBA 4D for loco regional hyperthermia treatments

ing. Remko Zweije[1], Dr. Hans Crezee[1], Dr. Petra Kok[1]
[1]*Amc Amsterdam*

Background
In the late 1980s the AMC has developed the 70 MHz AMC4 system, a loco regional hyperthermia system with 4 rectangular waveguide antennas designed for heating deep seated tumours. The four antennas are positioned in dorsal, ventral, left and right position around the pelvis of the patient. The amplitude and phase control of each antenna enables steering of the focal point. Since then this system has been in clinical use with good clinical results, also in the framework of successful randomised trials. ALBA has now commercialised this system as the ALBA 4D. The ALBA 4D utilises the same 70 MHz waveguides and has the same geometric layout. To ensure identical clinical performance, it is important to verify whether both systems generate identical electric field (E-field) and specific absorption rate (SAR) distributions and whether phase and amplitude control of the focal point is similar. Goal of this study was to compare the performance of the AMC4 and ALBA 4D locoregional hyperthermia systems.
Methods
The performance of both systems was tested by measuring the amplitude and phase of the E-field distribution in a liquid elliptical tissue-equivalent phantom (93 x 37 x 25 cm) using an optical E-field sensor and by measuring the SAR by means of temperature rise in a solid phantom (86 x 37 x 25 cm). For both systems E-field measurements were performed in the transversal, coronal and sagittal mid-planes with different phase settings causing the focal point to shift in predetermined directions. The E-field measurements were performed automatically with measurements taken every 10 mm in each direction with RF power set at a constant level. The SAR measurements were taken in the transversal mid-plane with RF power set for one minute at a constant level.
Results
Both systems performed equally well. Phase shifts of 20°, 40° and 60° in each direction resulted in equal shifts of the focal point in both systems. The magnitude of the E-field corresponds to the SAR measured with the solid phantom in both systems. Figure 1 shows the E-field distribution of the ALBA 4D with centred focal point.
Conclusions
The electric field and SAR distributions generated by the ALBA 4D system are similar to the distributions generated by the AMC4 system. Phase and amplitude control of the focal point is similar for the ALBA 4D and the AMC4 system. Therefore, similar clinical performance can be expected with the ALBA 4D and with the AMC4 system for hyperthermia treatments for deep seated tumours.



TOPIC: SUPERFICIAL HT

PP-24

Influence of a silicon breast implant on the temperature distribution during superficial hyperthermia

MSc Akke Bakker[1], Sandy Loopeker[1], MSc Remko Zweije[1], BSc Linda Korshuize-van Straten[1], dr Geertjan van Tienhoven[1], dr Hans Crezee[1]
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Introduction. During hyperthermia the tumor temperature is increased to 41-43°C for one hour. The addition of hyperthermia to reirradiation increases the tumor response from 41% to 59% compared to reirradiation alone for recurrent breast cancer in previously irradiated area (Vernon et al., 1996). Patients with recurrent breast cancer in previously irradiated area often have a reconstructed breast with a silicone breast implant (SBI). We investigated the influence of a SBI on the temperature distribution and whether there was an association between the temperature near the SBI, skin temperature and the distance of the sensor to the skin and the implant.
Methods. A phantom study and retrospective patient study were performed. The in-house built phantom was filled with superstuff and was based on the anatomy of a patient with a SBI (Figure 1). Eighteen catheters were placed one centimeter below the surface. A refurbished SBI was inserted in the phantom immediately beneath these catheters. Multisensory thermocouple probes were used for temperature measurements. A treatment was simulated by placing the 1H applicator (ISTOK, Russia) on the phantom and giving 20 Watt with the 434 MHz ALBA 4000 Double-ON system (Medlogix, Italy). The invasive temperature close to the implant (Tsbi) was compared using paired t-tests to the invasive temperature more than 5 cm away (Tinv) and the skin temperature (Tskin). Linear regression was used to examine associations between the invasive temperature and the distance of the sensor to the breast implant (dsbi) and the distance between the implant and the skin (dskin).

A retrospective analysis was performed in patients with recurrent breast cancer in previously irradiated area with a SBI treated in the AMC from 2014 – 2016. Patients were treated with 23x2Gy and hyperthermia for one hour once per week. Under ultrasound guidance one or more catheters were placed invasively as close as possible to the SBI. Multisensory thermocouple probes were placed in the catheters and on the skin during treatment. Superficial hyperthermia was applied with the 434 MHz ALBA 4000 Double-ON system (Medlogix, Rome, Italy) combined with ISTOK (Russia) applicators. Statistical analysis was carried out in SPSS version 24.
Results. In the phantom study Tsbi was significant higher than Tinv ($\Delta T=5,6^{o}C$, $p<0.001$). There was a relation between the distance to the implant (dsbi) and the temperature of an invasive sensor (Tsbi and Tinv, p=0.003). Furthermore, Tsbi was related to dskin (p=0.003).
Three patients that had both invasive catheters close to the SBI and more than 5 cm from the SBI during multiple treatments, were included for analysis. Tskin had higher temperatures than Tsbi ($\Delta T=0,6^{o}C$, p=0.067) and a possible relation was found between Tskin and Tsbi (p=0.096).
Conclusion. A phantom study and retrospective patient study showed that a silicon breast implant influences the temperature distribution during superficial hyperthermia, both on the skin above the implant as invasively close to the implant. The closer the invasive temperature sensor is to the SBI, the higher the temperature. Skin temperatures and skin thickness are related to invasive temperatures near the implant.

PP-25

Hyperthermia with water-filtered infrared A sensitizes breast cancer spheroids to hypofractionated irradiation, but not normal epidermal cell cultures

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Introduction
Mild hyperthermia in the range of 42°C has been shown to cause a radiosensitization of cancer cells, without causing relevant damage to normal tissues. To treat superficial tumors, locoregional hyperthermia may be applied in a non-invasive, contact free way by irradiation with water-filtered infrared A (wIRA).
Recently, a study of >70 patients with locally recurrent breast cancer in previously irradiated regions reported a high rate of complete locoregional remissions after hypofractionated re-irradiation (5 x 4 Gy; 1 fraction per week), combined with superficial wIRA hyperthermia (1). Despite this successful cancer cell inactivation, only mild skin toxicities were observed.
The biology underlying the favourable outcome of such uncommon treatment protocol remains poorly understood. Therefore, this work aimed to reproduce the clinical protocol in vitro, using 3D cultures of breast cancer cell lines and explant cultures of normal skin.
Materials and Methods
Human breast cancer cell lines T47D, MCF7 and MDA-MB-231 were cultured as multicellular aggregates in arrays of agarose microwells and treated weekly with hyperthermia at 42°C for 1 hour +/- irradiation of 4 Gy to a cumulative dose of 16-20 Gy.

Response to treatment was monitored by repeated cell aggregate volume measurement for a total of 8 weeks. Growth curves were plotted from data of 200 cancer cell aggregates for each treatment condition. Paraffin histology was used to examine treatment effects in terms of cell morphology.
As a normal tissue model, skin biopsies of 0.5 x 1 mm were treated with a single dose of hyperthermia +/- irradiadiation and subjected to a wound healing assay. Keratinocyte outgrowth was quantified after histochemical staining and measurement of area covered by cells.
Results
Growth of normal tissue cells and tumor cell aggregates was not significantly impaired by hyperthermia and wIRA treatment alone. A combination of hyperthermia and irradiation enhanced 'cell aggregate cure rate' of all three breast cancer cell lines, compared to irradiation alone.
In skin explants, area of cell outgrowth showed a decline with increasing irradiation doses, but was not significantly reduced by addition of hyperthermia.
Conclusion
Mild hyperthermia +/- wIRA is shown to radiosensitize 3D cultures of breast cancer cells. Interestingly, in a wound healing model function of normal epidermal keratinocytes was not impaired by addition of hyperthermia. The applied in vitro models could reproduce the clinical findings and therefore may help to reveal the differential effect of radiohyperthermia on malignant and normal tissue.

(1) Notter et al. (2016) Hypofractionated re-irradiation of large-sized recurrent breast cancer with thermography-controlled, contact-free water-filtered infra-red-A hyperthermia: a retrospective study of 73 patients. Int J Hyperthermia 28: 1-10

ORAL

PRESENTATIONS

ORAL PRESENTATIONS

TOPIC: HYPERTHERMIA & CHEMO-RADIOTHERAPY

OP-01

Chemo radiation with hyperthermia in Head and Neck Cancer- Update of a single institution study

Doctor Nagraj Huilgol[1], Dr. B C Sridhar[1], Dr. Ajith Nair[1], Ms. Neela Pai Dhungat[1]
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Objective : It is a retrospective analysis of patients undergoing chemo-radiation with hyperthermia . The study looks at initial response time to recurrence and overall survival.

Introduction : Chemo radiation has emerged as a standard of care in the management of head and neck cancer. Pignon has demonstrated an improvement in survival by 6-8% though at a premium of acute side effects. Hyperthermia as a known sensitizer of radiation and chemotherapy has the potential to enhance the effects of both modalities.

India and Asia-Pacific suffer from the scrounge of locally advanced head and neck cancer. There is an unmet need. The survival figures have stagnated may change this scenario.

Materials and Methods:

Patents with head and neck cancers treated with chemoradiaiton and hyperthermia from 2004 to 2013 have been retrospectively analysed for initial response, disease free survival and over all survival. Patients received either cisplatinum or pactitaxel every week besides conventional fractionated radiation therapy. Hyperthermia was delivered once a week on Thermatron 8, a RF at 8.2MHz. It comes with impedance tuning and pre-cooling facility. Patients received 60-70GY of radiation within six to seven weeks. Patients were evaluated periodically during the treatment for a mucosal and dermal toxicity. Patients were assessed for response within a week of conclusion of radiation.

Results:

A total of 195 patients were assessed. The patients have been staged according to TNM staging . Patients were predominantly grouped as stage III, IV. They constituted 84.7% of all patients analysed. Nearly all patients received radiation to a total dose of 50-70Gy of which 22.6/- received between 50-60Gy on 6MV accelerator. All patients received hyperthermia for 30-40 minutes after pre-cooling. The initial response as assessed clinically was CR in 92.5% in stage III, 78% in IVa and 54.7 in stage IV A. Mucosal and cutaneous reactions were acceptable. No dose limiting thermal burns were observed.

Discussion:

Hyperthermia is toxic to hypoxic tumour cells suffused in low PH. Hyperthermia can also promote inhibition of DNA repair. Hyperthermia also can increase perfusion or increases intra tumour transit time of Cyto toxic drugs. Addition of hyperthermia to radiation has shown distinct survival benefits in various randomized trail. This retrospective of further addition of chemotherapy not only feasible but beneficial as well. The draw back of this study is lack of robust survival data.

OP-02

A Phase II Randromized study of concurrent hyperthermia and chemoradiotherapy vs Chemoradiotherapy alone in locally advanced pancreatic cancer (HEATPAC): First information and call for participation (ClinicalTrials.gov Identifier: NCT02439593)

Prof. Dr. Med. N. R. Datta[1], Prof. Dr. med. B. Pestalozzi[2], Prof. Dr. med. P. Clavien[3], Dr. A. Sienbenhüner[2], Dr. E. Puric[1], Prof. Dr. med. C. Mamot[4], Dr. O. Reisterer[5], Dr. J. Knuchel[6], Dr. C. Reiner[7], Prof. Dr. med. S. Bodis[1,5], HEATPAC Trial Group[8]

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Introduction:

Pancreatic cancer has a dismal prognosis with 5-year overall survival rate of just around 5%. The outcome has remained grossly unchanged despite the advances in chemo-radiation and advent of newer systemic agents. Although, complete surgical resection is still the only curative treatment option, merely 10-20% of cases are suitable for surgical resection, with only 4% expected to finally undergo radical surgery. Novel approaches, are therefore needed for the management of the around 80% of the inoperable patients of locally advanced pancreatic cancers (LAPC). Hyperthermia, a potent radiosensitizer also enhances the action of gemcitabine, a known radiosensitizer. Thus, a combination of hyperthermia, radiotherapy and gemcitabine could be expected to improve the therapeutic outcomes in LAPC. This phase II randomized trial attempts to explore the feasibility and efficacy of a concurrent thermochemoradiotherapy in comparison to chemoradiotherapy alone following neoadjuvant FOLFIRINOX.

Primary objectives:

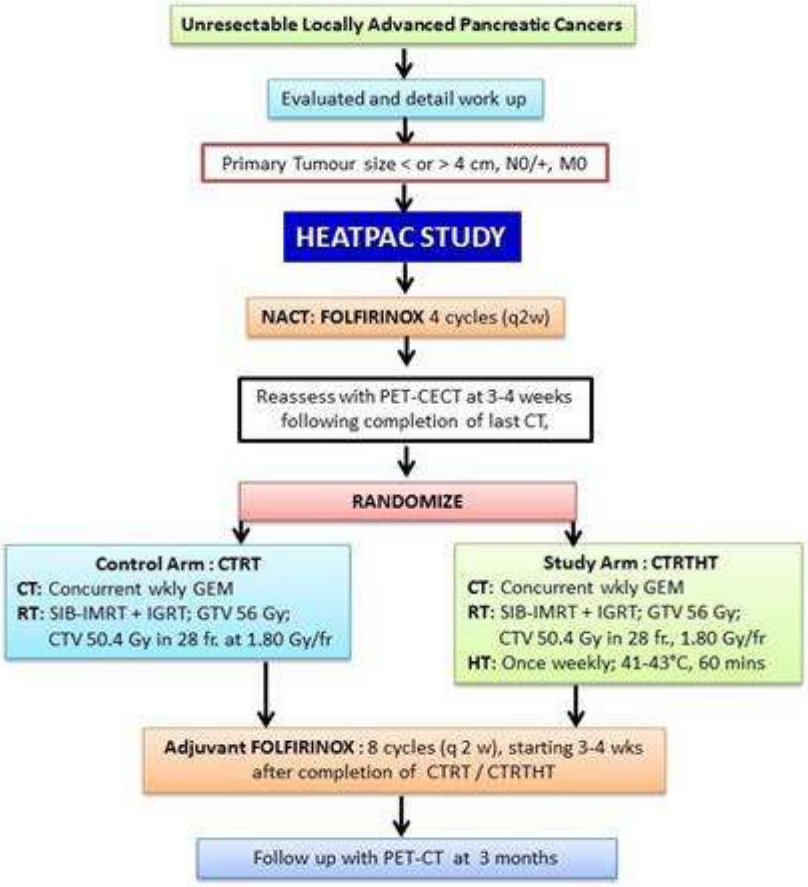
These are (a) to determine if local hyperthermia along with concurrent chemoradiotherapy (study arm) in LAPC following neoadjuvant chemotherapy with FOLFIRINOX would show an improvement of overall survival from 40% to 60% at 1 year compared to concurrent chemoradiotherapy (control arm) and (b) assess the acute and the late morbidities associated with hyperthermia and chemoradiotherapy in concurrent chemoradiotherapy compared to concurrent chemoradiotherapy alone.

Study outline:

All patients of LAPC fulfilling the following criteria of "Unresectable LAPC" as defined by Callery et al (Callery et al, 2009) would be considered to be eligible for enrolment in the study. Patients would be considered for 4 cycles of neo-adjuvant FOLFIRINOX. At 3-4 weeks of completion of neo-adjuvant chemotherapy, patients would be evaluated by PET-CECT (triple-phase). All patients with no metastasis and no gross peritoneal carcinomatosis would be randomized into the treatment arms of either (a) Control arm: concurrent chemoradiotherapy with gemcitabine (400 mg/m2, weekly for 6 weeks of radiotherapy) or (b) Study arm: locoregional hyperthermia (once weekly during radiotherapy) with concurrent chemoradiotherapy with gemcitabine (same as in control arm) (Fig). Radiotherapy would be delivered using IMRT with 56Gy to gross target volume and 50.4 Gy to clinical target volume in 28 fractions. Hyperthermia to 41-43°C would be administered weekly with intraduodenal temperature monitoring with a multi-sensor temperature probe at each session. Following the completion of above therapy, all patients of both groups would receive an additional 8 cycles of FOLFIRINOX chemotherapy.

The expected 1-year survival rate with chemoradiotherapy is considered as 40% (p0=40%). With hyperthermia along with chemoradiotherapy, an overall survival advantage of +20% is expected (p1= 60%) in LAPC. A total 86 patients, divided equally into the two groups would be required as per the Simon's two-stage minimax design (Simon, 1989) considering one-sided alpha of 0.05 and power of 80%.

The study has been approved by the Ethical Commissions of Basel and Zurich and is open for patient recruitment since January 2017. We welcome all centres with deep hyperthermia facilities having adequate in-house facilities for management of pancreatic cancers to join the study. Further information could be obtained from https://clinicaltrials.gov/ct2/show/NCT02439593. Interested participants may contact niloyranjan.datta@ksa.ch or bernhard.pestalozzi@usz.ch.



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TOPIC: LOCO-REGIONAL HYPERTHERMIA

OP-03

Ssytematic review of brain glioma and lung cancer trials with modulated electro-hyperthermia with meta-analysis and economic evaluation (Level IIA Evidence)

Dr. Sergey Roussakow[1]

[1]Galenic Research Institute, Moscow

INTRODUCTION: Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor. Despite the recent advances, the prognosis of GBM remains dismal with the median survival time (MST) limited by 15 – 18 months and 3 – 6 months after the virtually inevitable recurrence (RGBM). Standards of care are not yet defined for RGBM. Treatment options include surgical resection, re-irradiation and chemotherapy, all having significant limitations. All the modern chemotherapies (CTX) like temozolomide (TMZ) and anti-angiogenic agents are not cost-effective. Lung cancer (LC) is in the top three of the most common cancers worldwide. Having one of the least 5-year survival among all cancers (14-17% in USA and 12-14% in EU), LC is typically the first reason of cancer-dependent mortality. Current treatments show low efficacy and can't change the trend of high mortality. Thus, study of possibilities to improve the prognosis of RGBM and LC is of outstanding significance for oncology. Modulated electro-hyperthermia (mEHT, Oncothermia®) is one of the promising novel methods of the cancer treatment. The relevance of the present study is determined by the possibility to improve the quality of treatment of RGBM and LC while reducing health care costs.

OBJECTIVE: To assess the safety, efficacy and cost-effectiveness of mEHT in the combined treatment of RGBM and LC.

MATERIAL AND METHODS: Systematic review with effect-to-treatment analysis (ETA) and meta-analysis (PRISMA). Economic evaluation (CHEERS) by cost-effectiveness analysis (CEA), budget impact analysis (BIA) and cost-benefit analysis (CBA).

RESULTS: Nine original cohort studies on mEHT treatment were identified, five for RGBM and four for LC. Strong and significant enhancement of RGBM CTX with mEHT is suggested. Typically, mEHT allows to attain the same or better survival with 2-3 times shorter treatment course and appropriate decrease of toxicity (no grade III-IV toxicity versus 45% – 92% in regular CTX, $p<0.001$) with the maximal attainable MST of about 10 months. Combination of mEHT with TMZ is suggested cost-effective versus the cost-effectiveness threshold 25,000 €/QALY (quality-adjusted life year), unlike TMZ alone, and provides a significant budget economy of about €8,500,000 with 25 – 38.5 QALY gained per 1000 patients per year versus TMZ alone.

Concurrent mEHT in the 3rd-4th line complex treatment of LC is suggested to provide the better 1-3 year survival compared to any 1st line conventional treatment except of surgery. mEHT provided virtually the same utility as the best concurrent chemoradiation treatment (+0.04 QALY/patient) and the better utility than the standard treatment in the USA and Europe (+0.42 QALY/patient versus Eastern Europe). mEHT showed better cost-utility compared to radiation therapy (ICER = -3,000 — -50,000 $/QALY) and to CTX (ICER = -10,000 — -250,000 $/QALY).

CONCLUSIONS: This IIa level evidence suggests that mEHT strongly and significantly improves survival in RGBM and LC versus not mEHT-containing regimens, with favorable toxicity. Economic evaluation suggests that mEHT is cost-effective, budget-saving and profitable versus all modern CTXs. mEHT is suggested for the treatment of RGBM and LC as a cost-effective enhancer of CTX regimens and the method of choice of the salvage therapy.

TOPIC: SUPERFICIAL HT

OP-04

Re-irradiation and wIRA-hyperthermia for superficial widespread breast cancer recurrences: an up date

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Introduction: Locally recurrent breast cancer after previous radiotherapy is a challenging clinical situation since initial RT considerably limits the level of re-irradiation (re-RT). Under these conditions, the combination with superficial hyperthermia offers the possibility of achieving local control even with lower RT doses as recently shown by Notter et al. (IHJ, 2016). An up-date after an additional year of follow up should investigate, whether the obtained local control is maintained.
Methods: We report now of 102 patients with large-area, locally recurrent breast cancer (57 patients with lymphangiosis included), which were treated in this retrospective study from Sep 2009 to Feb 2017 with combined hypo-fractionated, low-dose re-RT (4 Gy 1x/week up to a total dose of 20 Gy), delivered 1-4 min after thermography-controlled water-filtered infrared A hyperthermia (wIRA-HT). 24 patients had tissue transfer, 18 patients presented with microscopic disease.
Results: Overall response was: CR: 63/102 (62%), PR: 35/102 (34%), NC: 3/102 (3%), PD: 1/102 (1%). Response rates in patients with macroscopic disease were: CR: 45/84 (54%), PR: 35/84 (42%), NC: 3 /84 (3%), PD: 1/84 (1%). Local control throughout life time after obtained CR-s is presented in the table.
Out of 17 patients with re-recurrences, 30 manifestations were observed: 5 infield (17%), 13 at the border (43%) and 12 outside (40%).
Conclusions: Good local control of heavily pretreated, large-area breast cancer recurrences can be obtained and is maintained in 73% of patients throughout life time. Most of the re-recurrences are observed at the border of or outside former treatment fields. Irradiances up to 150-200 mW/cm2 were applied without generation of heat pain and thus limited patient compliance.
The clinical wIRA/HT-setting used offers a series of advantages over other techniques currently applied in clinical oncology. These include: contact-free heating (e.g., of ulcerated, bleeding tumors) and treatment of irregularly shaped, widespread lesions. No patchwork technique is required for larger sizes (diameter of treatment field is 23-26 cm per applicator with approx. 7% inhomogeneity of irradiance, circular field area = 420-530 cm2). Adaptation to larger areas can be achieved by a twin-applicator system. wIRA is independent of individual body contours. While thermal dosimetry for HT is generally performed with fiberoptic probes that sample only a small number of set locations, in the system applied real-time thermography is used which assesses large surface temperature distributions allowing for the observation of dynamic developments during HT sessions. Thermography also enables the instant and easily achievable protection of heat-sensitive tissue structures (e.g., scars) and can thus avoid hot spots and grade 2 - 4 skin toxicities. Because of low toxicity with this treatment schedule, wIRA-RT can be used for re-reRT-settings (e.g., in 17 patients in our study).
Limitations for wIRA-HT are tumor lesions with depth extensions >20 mm.
Outlook: wIRA-sHT/re-RT is ready to be prospectively tested against standard schedules.
Ref.: Notter et al, IJH Sept. 2016

	all	**macroscopic total**	**macroscopic with L***	**macroscopic Ø L***	**microscopic**

no. patients with CR	63 (100%)	45 (100%)	25 (100%)	20 (100%)	18 (100%)
local control (life time)	46 (73%)	28 (62%)	9 (36%)	19 (95%)	18 (100%)
Re-recurrences	17 (27%)	17 (38%)	16 (64%)	1 (5%)	0

Table 1: Local control & re-recurrences after CR. Legends: L* = lymphangiosis

OP-05

Water-filtered infrared-A (wIRA) in superficial hyperthermia – physical and photo-biological basics

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Introduction

There is an increasing interest in the use of water-filtered infrared-A (wIRA) for superficial hyperthermia, especially because of its suitability for large-sized area treatment, for contact-free real-time thermographic control of the irradiated region and for both major reduction of side effects and complete exclusion of burn risks.

Methods

wIRA radiators are technically realized by filtering of the emission spectrum of a halogen lamp radiator by a water layer of 7 mm thickness. In order to control skin surface temperature during the exposure, an IR-camera is used integrated in a closed control loop.

Results

wIRA radiators show a structured spectrum in the spectral range of 780 - 1400 nm with strong reduction of the emission within the included water absorption bands. Penetration of radiation into the tissue is mainly influenced by absorption which causes primary generated heat. Mie-scattering supports penetration by forward orientation and diverges the incident radiation. Main chromophores of skin and tissue show relatively small absorption coefficients within the spectral range of wIRA as a part of the "optical window" of tissue for interaction with optical radiation. Therefore, maximum spectral penetration depth was found at 1080 nm yielding a depth of about 28 mm (1 % of incident irradiance), to about 8 mm (10 % of incident irradiance), and to about 5.6 mm (1/e of incident irradiance), whereas mean penetration depths of the whole wIRA spectrum range between 15 mm (1 % of incident irradiance), 5 mm (10 % of incident irradiance), and 1.3 mm (1/e of incident irradiance).

Primary generated thermal energy is dissipated effectively by conduction and by convection creating a much larger heated target volume as compared with the range of absorption.

Data of in vivo measurements and of model calculations are provided which show the effects of incident irradiance on generation of both surface temperature and tissue temperature, and of individual variability which is considered in practical use by thermographic control during the treatment.

Conclusions

wIRA is an effective radiation in superficial hyperthermia with contact free thermographic control of the irradiated area creating the therapeutic temperatures required for therapy of superficial tumour lesions.

TOPIC: CHEMOTHERAPY & HYPERTHERMIA

OP-06

Perioperative Chemotherapy versus Cytoreductive Surgery & HIPEC alone for Peritoneal Mucinous Carcinomatosis from Appendiceal Cancer

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Aim: The aim of this study is to identify the role of systemic chemotherapy in the management of appendiceal malignancies.

Material & Methods: Over a ten-year period, 52 patients with appendiceal neoplasms were treated at our Peritoneal Surface Malignancy Unit (14 DPAM (26.9%), 30 PMCA (57.7%), 8 PMCA-I (15.4%)). All patients (100%) underwent cytoreductive surgery & HIPEC, while 20 (38.5%) of them also received perioperative systemic chemotherapy.

Results: Mean Peritoneal Cancer Index (PCI) was 23.6. Completeness of Cytoreduction Score (CC-S) was: CC-0 in 26 patients (50%), CC-1 in 20 patients (38.5%) and CC-2 in 6 patients (11.5%). High grade malignancy was reported in 27 patients (51.9%) and low grade malignancy in 25 patients (48.1%). More than half of the patients had a recurrence (n=36, 69.2%), while death was reported in 40.4% (n=21). Median OS in all histologic groups was 24 months for patients who received perioperative systemic chemotherapy and 14 months for patients who did not (p = 0.048). Median DFS in all histologic groups was 19 months for patients who received perioperative systemic chemotherapy and 10 months for patients who did not (p = 0.034).

Conclusion: We suggest that perioperative systemic chemotherapy serves as a helpful therapeutic tool in the management of peritoneal mucinous appendiceal carcinomas treated with cytoreductive surgery & HIPEC.

TOPIC: HYPERTHERMIA FOR PELVIC TUMORS & CLINICAL PRACTICE

OP-07

A COMPARISON BETWEEN RADIATIVE AND CAPACITIVE SYSTEMS IN DEEP HYPERTHERMIA TREATMENTS

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Introduction
Hyperthermia (HT) treatments aim at inducing temperatures in the range of 41-45°C for about 60 min in the treatment region to increase the efficacy of chemotherapy (CT) and radiotherapy (RT) [1]. Clinical outcomes of the combined HT-CT and/or HT/RT are critically linked to the quality of the hyperthermia treatment, i.e. to the ability of reaching and maintaining the hyperthermia temperatures for the needed time [2].
For this reason, in the last years several studies posed their attention on the quality of the treatment, developing treatment planning procedures and looking for possible treatment standardizations [3,4].

Several devices are on the market to induce the temperature increase by way of electric and/or electromagnetic currents induced into the tissue. In particular, according to the frequency of the electromagnetic source, these devices can be divided into capacitive systems, or radiative ones. Capacitive systems operate in the radiofrequency range of the electromagnetic spectrum, i.e. at 8 MHz, 13.56 MHz o 27.12 MHz, and are substantially made by two electrodes placed at opposite sides of the patient body. Radiative systems operate at higher frequencies, i.e. about 70 MHz in case of deep hyperthermia and at 434 MHz or 915 MHz in case of superficial hyperthermia, and are constituted by an array of antennas which are opportunely fed to focus the electromagnetic field into the target region.
In this contribution the performances of three different systems, a capacitive one and two radiative systems, will be studied and compared with reference to deep hyperthermia, i.e. considering as possible targets the bladder, the cervix, and the rectum.

Methods
Simulations were performed using CST MW Studio^{TM} software. Models of the radiative applicators BSD-2000 - Sigma 60, and Alba 4D as well as of the capacitive system Celsius TCS were realised and validated comparing the obtained data with literature ones.

Studies
The electromagnetic field absorbed by simple phantoms as well as an inhomogeneous anatomically correct model of a woman was calculated for the three considered devices. The simple phantoms were cylinders (height 850 mm) with an elliptic base (semi-axes 120 mm and 180 mm) and constituted by different layers. At first an homogeneous phantom made by muscle was considered, then a fat layer (of the same thickness all around the muscle or with different thicknesses on the front and on the back of the phantom) was added. Finally, the skin was introduced. Comparison was made among the different electromagnetic field distributions, as well as the SAR values obtained in the centre of the phantoms and in specific locations to simulate the presence of a tumour in the bladder, the cervix, or the rectum.
As an example of the obtained results, Figure 1 shows the SAR distribution obtained on the axial section of the skin-fat-muscle phantom without any type of focalization. From the figure it is evident the very different interaction between the electromagnetic field generated by the hyperthermia devices and the phantom's layers. These differences can be easily interpreted by way of electromagnetic field theory.

Conclusion
Very different electromagnetic field distributions are obtained into the human body from radiative or capacitive hyperthermia systems. These differences should be taken into account when planning an hyperthermia treatment.

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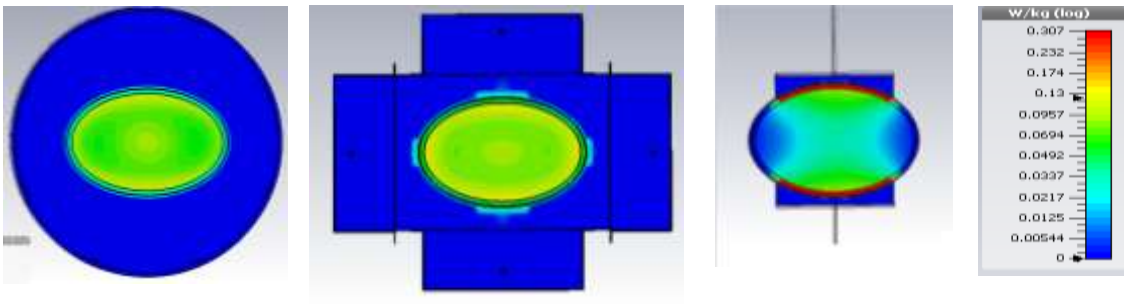

BSD 2000 ALBA 4D CELSIUS CTS

Fig. 1 SAR distribution obtained from the three considered devices in a 3-layers phantom (skin, fat, muscle)

TOPIC: TREATMENT PLANNING

OP-08

Performance evaluation of helmet-like hyperthermia applicators for brain tumors

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Introduction
Modern treatment methods for brain tumors in children has long-lasting side effects. In this paper, we explore the side effects of radiation therapy in children by adding hyperthermia and limiting radiation dose to the brain. However high power absorption in the brain makes the heating challenging and requires a good control of heating pattern. We have already designed an applicator for heating brain tumors in children which is not efficient enough in heating large tumors in cerebellum [1]. The aim of this paper is investigating the performance of new designs using high frequencies and high number of antennas to heat large tumors in the brain.

Methods
The antenna element in our applicators is the self grounded bow-tie antenna immersed in a water bolus of truncated cone shape [2]. The operational frequency range for this antenna is 430 MHz-1 GHz. In initial designs, the phantom was considered as a spherical and homogeneous phantom with properties of the brain tissue. A water layer of thickness 10 mm was placed on top of the phantom.
We evaluated the performance of different antenna set-ups in helmet-like applicators to heat most difficult positions in the brain. In the first set-up 26 antennas were arranged in a 3-ring setup. Second applicator consisted of 58 bow-tie antennas immersed in reduced size water bolus. In the last applicator, regular bow-ties were combined with large-scaled antenna elements in a set-up with a total of 25 antennas.
For performance evaluation we compute tumor coverage 25%, which is defined as the volume percentage of the tumor covered by 25% of the maximum SAR (specific absorption rate) in the whole patient model.
Results
The tumor coverage 25% was computed for 3 lowest frequencies in the operational range and tumor radii of 20, 30 and 40 mm. Tumors were positioned in the center of the phantom and a non-center

position. For a tumor in center of the phantom and at each frequency, the tumor coverage decreased as the radius of the tumor was increased. For the tumor in non-center location, the tumor coverage values were lower than the ones for the tumor in center position. For example in the applicator with 26 bow-tie antennas, 95% tumor coverage was obtained for a tumor of radius 20 mm in the center of the phantom while only 22% tumor coverage was achieved for the same tumor size in the non-center location.
Conclusion
Array with the most number of antennas, 58 antennas, performed the best to heat large tumors in central brain however we still have limitations to heat tumors in cerebellum.

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OP-09

Hyperthermia treatment planning with fluid simulations for a novel brain applicator.

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Introduction— Treatment of brain tumours may benefit from adjuvant hyperthermia. Radiotherapy is known to lead to serious late toxicities. As one of the most potent radiosensitizers known, hyperthermia allows for lower radiation doses with equal treatment outcome and reduced late toxicities. Chemotherapeutic agents often fail to pass the blood brain barrier. Hyperthermia has also been known to temporarily open the blood brain barrier, allowing access for chemotherapeutic agents. However, hyperthermia treatment of tumours in the brain is very challenging with currently available applicators.
To solve this, the Chalmers Hyperthermia Helmet was developed, a microwave antenna applicator specifically for brain tumours. Temperature simulations using Plan2Heat indicate that proper heating may be challenging. One of the reasons is the role of cerebrospinal fluid (CSF). Because of its high electric conductivity ($\sigma \sim 2.17$ S/m), CSF absorbs EM radiation very efficiently and is thus easily heated. As Plan2Heat models CSF as a solid, heat removal is relatively inefficient, leading to hot spots. Taking into account the fluid nature of CSF, this heat may be transported over relatively large distances, affecting a wide area. The aim of our current research is to investigate by numerical simulation the role of CSF in the temperature distribution in the human brain during microwave hyperthermia treatment using the Chalmers Hyperthermia Helmet.
Methods— We simulated a hyperthermia treatment of a patient with medulloblastoma, both with Plan2Heat without detailed fluid modelling, and with proper fluid modelling. For both simulations, we determined the temperature metrics Tmin, T90, T50, T10, and Tmax. We also studied the correlation between both simulations, with special emphasis on potential hot spots. We modelled three different cases to investigate the influence of properly taking the fluid properties into account on the temperature distribution. First, we used a patient with a large medulloblastoma. Second, we studied the same patient post-operatively, when the tumour had been removed and the resulting volume filled with CSF. Third, we used the same patient with a more centrally located artificial tumour. We compared the temperature

distribution simulated with the properly modelled fluid and with CSF modelled as a solid, as is done in Plan2Heat and other commercially available treatment planning systems (Fig.1).
Results— Hot spots predicted by Plan2Heat in the CSF disappear when fluid modelling is added, except when they occur in small isolated CSF pockets. Hot spots at some distance from the major CSF regions, however, remain practically unchanged. Overall, tumour temperatures tend to be a little higher when fluid modelling is taken into account. Reoptimizing might improve the thermal dose to the tumour, but is not feasible with the current set-up.
Conclusion— Although locally, incorporating the fluid model for the brain hyperthermia treatment planning yields results that are noticeably different from those obtained with a solid-only model, these differences are mostly limited to the regions close to the major CSF regions. The fluid model will now be applied to other clinical cases to determine in which cases the Chalmers Hyperthermia Helmet can obtain clinically relevant temperatures.

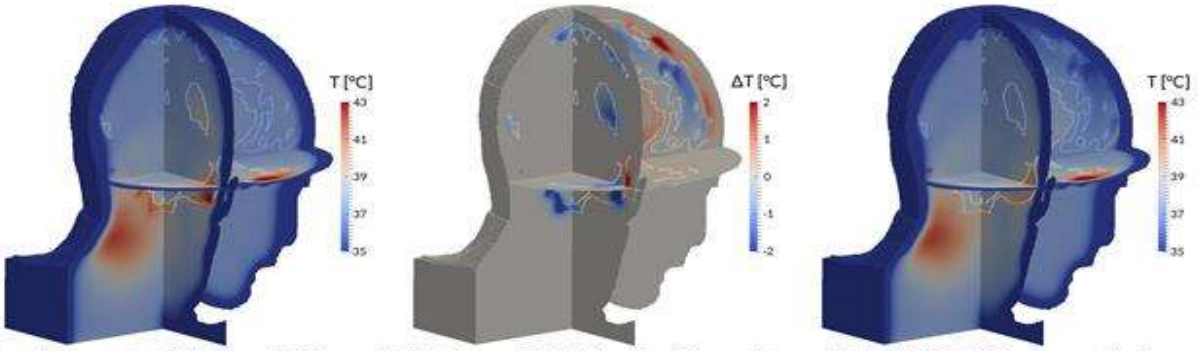

Figure 1: Temperature distribution with CSF as a solid (left), CSF as a fluid (right), and the difference between both (middle). The CSF has been outlined.

TOPIC: WHOLE BODY HYPERTHERMIA

OP-10

Low-dose checkpoint inhibitor therapy with interleukin-2 (IL-2) and fever range hyperthermia in stage IV cancer: a retrospective analysis with single case presentations

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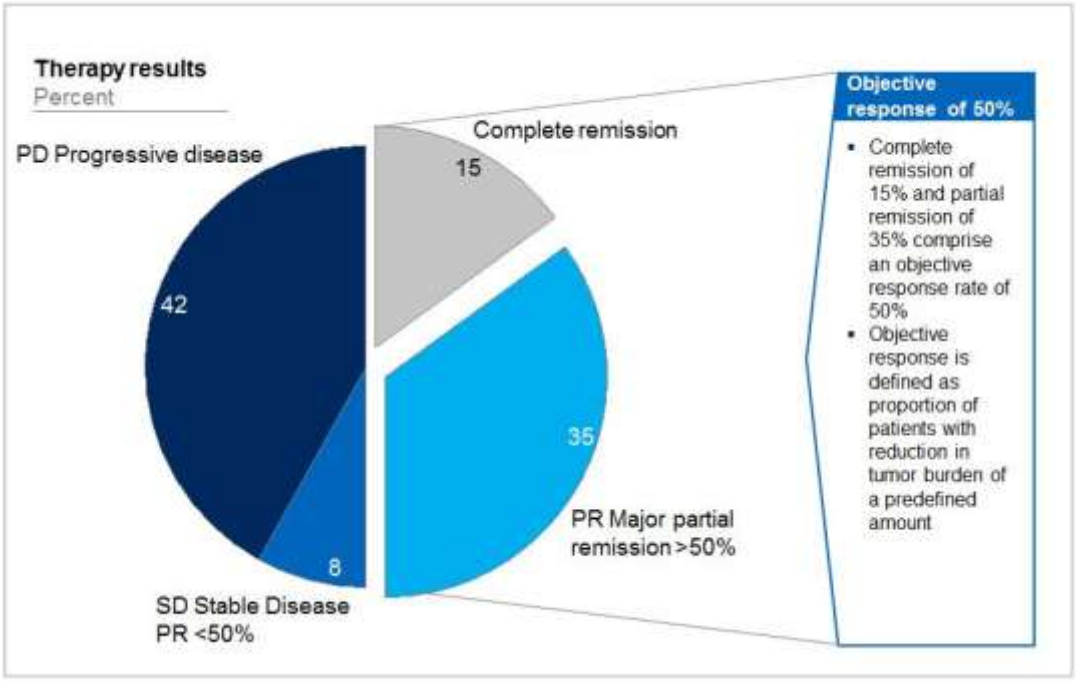
Introduction: Advanced inoperable Stage IV cancer has a poor prognosis and patients rarely enjoy durable complete response to treatment; progression free survival often is limited. We previously reported complete remission of far advanced lung metastasis in triple negative breast cancer at ITOC3 (Munich) 2016 and of inoperable stage UICC IIIB esophageal cancer at ITOC4 (Prague) 2017 following the complex immunotherapy protocol as described at ITOC and in this ESHO 2017 abstract. Here we report for the first time preliminary statistical evaluation as well as presentation of single best cases.
Materials and methods: Patient description: all patients were stage IV metastatic inoperable cancer patients most of them heavily pretreated. Different cancer types were: stomach=3, melanoma=3, SCC tongue=1, breast=20, bladder=1, prostate=5, ovaries=4, colon=6, liposarcoma=1, pancreas=2, TUO=1, mesothelioma=1, oligodendrioglioma=1, carcinosarcoma=2 (1 ovarian, 1 uterus), cervix=2, esophagus=2, Ewing sarcoma=1, lung=3, kidney=2
The immunological and hyperthermia treatment was identical in all patients; many patients also received metronomic low-dose chemotherapy and/or hormonal therapy.

Therapy consisted of administration of the following combination protocol: Low-dose PD-1 immune checkpoint (IC) inhibitor nivolumab (0.5 mg/kg) with CTLA-4 IC inhibitor ipilimumab (0.3 mg/kg) administered weekly, over three weeks. This was accompanied by loco regional hyperthermia with radiofrequency fields (13.56 MHz) using the Syncrotherm, Oncotherm or Andromedic device 3 times per week (max output 400 w) over the tumor region in combination with high dose vitamin C (0.5 g/kg) and alpha lipoic acid (600mg) over three weeks. This was followed by long duration fever range whole body hyperthermia (using the Heckel device) in combination with low dose chemotherapy using cyclophosphamide 300 mg/m² to down modulate Treg cells. Next, moderate dose i.v. interleukin 2 (IL-2) under Taurolidine protection was administered for five days with careful titration to daily fever hyperthermia of max 39.5°-40.0°C.
Results: 60 patients underwent this treatment protocol; 48 are currently evaluable. The others were too early to evaluate with follow-up time < 3 months. Resist Response criteria were met with restaging using CT and/or MRI as well as clinical and laboratory evaluation. Subgroups were as follows:
Progressive disease PD: n=20; 2 stomach, 1 melanoma, 1 SCC tongue, 2 ovarian, 1 colon, 9 breast, 1 TUO, 2 carcinosarcoma, 1 lung
Stable disease SD: n=4; 1 liposarcoma, 1 melanoma, 1 pancreas, 1 ovarian,
Partial remission PR: n=17, 1 NSCLC, 7 breast, 2 colon, 1 ovarian, 1 Ewing sarcoma, 1 cervical, 1 Prostate, 1 Pancreas, 1 renal, 1 stomach
Complete remission CR: n=7; 1 melanoma, 1 bladder, 2 prostate, 1 esophageal, 1 breast, 1 Cervical

Preliminary evaluation of 48 patients with 3 month to 2 years follow-up (median 6 months):
Progressive disease: 42%
Overall clinical benefit 58%
Overall response Rate = objective response rate: 50%

Conclusion: This complex combined immunotherapy treatment of advanced stage cancer patients achieving an objective response rate of 50% and overall clinical benefit of 58% seems to be very promising. Clearly, this combination immune treatment warrants further clinical studies.



TOPIC: NANOPARTICLES & HYPERTHERMIA

OP-11

Combination of hyperthermia and radiosensitizer-loaded thermosensitive liposomes improves efficacy of radiotherapy: an in vitro proof of concept study

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Introduction: The efficacy of radiotherapy (RT) can be improved by combining RT with drugs to increase the sensitivity of radiation (concurrent chemoradiation). Combining RT with these drugs, so called radiosensitizers, results in significant clinical improvement in many tumor types[1]. Still, further improvement is desired since these drugs are not tumor specific and thus cause systemic toxicity as well as toxicity to the healthy tissue in the beam path[2].
Even if the toxicity can be reduced by encapsulation of the drug into a nanosystem, such as liposomes[3], the anticipated enhanced efficacy is compromised due to low bioavailability and poor tissue penetration of the drug in the tumor. These drawbacks can be overcome by using trigger-sensitive nanosystems, such as thermosensitive liposomes (TSL) with local-hyperthermia as stimulus. TSL combined with hyperthermia results in an increase in both drug concentration and drug penetration in the tumor[4]. In addition, hyperthermia is a powerful radiosensitizer by itself. Thus, hyperthermia-triggered local radiosensitizer delivery by TSL may improve the efficacy of RT while reducing normal tissue damage.
The objective of this study is to investigate in vitro if i) triggered release of a radiosensitizer, doxorubicin (DOX), from a TSL (ThermoDox) by hyperthermia improves the efficacy of RT and ii) if the radiosensitization effect of DOX is concentration dependent.
Methods: HT1080, human fibrosarcoma, cells were used. Cells were exposed to ThermoDox (0.02 µg/ml) or DOX (0.01, 0.02 or 0.06 µg/ml) for 1 hour in a water bath of 37°C or 43°C. 45 minutes after incubation with ThermoDox or DOX, cells were irradiated by a linear accelerator (Elekta, 6MV). Subsequently cell viability was measured by clonogenic assay.
Results: RT combined with ThermoDox at 37°C showed similar efficacy compared to RT as a single treatment, due to retention of DOX in the liposomes at 37°C[5], Figure A. ThermoDox and DOX at 43°C showed equal efficacy. However, ThermoDox at 43°C resulted in less radiosensitization at high RT doses when compared to DOX at 43°C, a difference that is not yet understood. DOX shows a radiosensitization effect, however it is not concentration dependent, Figure B.
Discussion/conclusion: ThermoDox in combination with hyperthermia improves the efficacy of RT in vitro, whereas in the absence of hyperthermia efficacy was similar to that of RT alone. This provides a first indication that local heating of only tumor tissue will reduce systemic toxicity as well as toxicity to healthy tissue in the beam path. Unfortunately, the radiosensitization effect of DOX is not concentration dependent, higher local concentrations will not lead to an extra sensitization boost in the tumor. In summary this study provided the first proof that local radiosensitizer delivery may improve efficacy, while reducing systemic toxicity.
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Acknowledgment: ERC Sound Pharma – 268906 (CM)

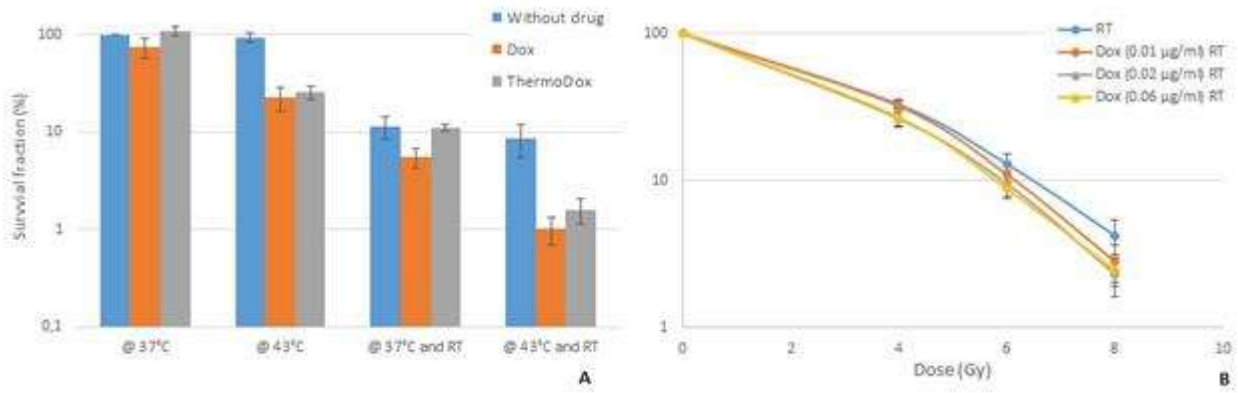

Figure A. Treatment without and with dox or ThermoDox at a concentration of 0.02 µg/ml at 37°C or 43°C in a water bath with or without RT at 6 Gy. Figure B. Treatment with DOX at 37°C followed by RT.

OP-12

Hyperthermia-triggered release of hypoxic cell radiosnsitizer from temperature sensitive liposome improves radiotherapy treatment in vitro

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Introduction: Radiotherapy has a significant contribution to the successful treatment of many cancer patients. However, it is also accompanied by a risk of serious damage to normal tissue surrounding the tumor or present in the radiation path. Besides technical developments, such as intensity modulated radiotherapy and charged particle therapy, the addition of radiosensitizers has further improved the efficacy of radiotherapy. However, since these drugs are not tumor specific, the maximum radiosensitizer concentration that can be reached in the tumor is limited by systemic toxicity1.

By encapsulating cytostatic drugs in nanosystems, such as liposomes, the systemic toxicity can be significantly reduced2. Though, due to limited and heterogeneous penetration of liposomes in tumor tissue and the low bioavailability of the drug in the tumor the anticipated enhanced efficacy is compromised3. Stimuli-responsive nanosystems can overcome these drawbacks by triggered release of their contents upon applying a tumor confined stimulus4.

Here, a concept is introduced (i.e. Image-Guided Radiosensitizer Delivery (IGRD)) in which radiosensitizers are released from temperature sensitive liposomes (TSLs) by local heating of the tumor, followed by conventional radiotherapy. As a first step to demonstrate feasibility of this concept, we developed pimonidazole (i.e. hypoxic cell radiosensitizer) loaded TSLs and tested them in combination with hyperthermia and radiotherapy in vitro.

Methods: TSLs were prepared by the lipid film hydration and extrusion method. Liposomes were composed of DPPC, MSPC and DSPE-PEG2000 in a molar ratio of 86:10:4. Pimonidazole (PMZ) was loaded actively into the aqueous lumen of the TSLs. The TSLs were characterized by measuring particle size, phase transition temperature (Tm), particle charge, drug loading efficiency and temperature

dependent release kinetics of PMZ. The radiosensitizing effect of PMZ on FaDu cells under hypoxic conditions (i.e. pO2 = 0.1%) was assessed as function of concentration using a clonogenic assay. Finally, the temperature triggered PMZ release combined with radiotherapy was tested in vitro.
Results: PMZ loaded TSLs were formulated, with a mean diameter of 100 nm and a Tm of 41.3 °C. The final PMZ concentration in the TSLs was 4.4 mM. The TSLs showed fast release of PMZ upon heating (i.e. more than 80% after 1 minute at 42 °C). The radiosensitizing effect of PMZ under hypoxic conditions increased with drug concentration. Temperature triggered PMZ release from TSL followed by conventional radiotherapy showed increased efficacy compared to radiotherapy alone and PMZ loaded in non-temperature sensitive liposomes.
Conclusion: PMZ loaded TSLs in combination with hyperthermia improved the efficacy of radiotherapy in vitro (fig 1b). Moreover, the radiosensitizing effect was clearly dose dependent (fig 1a) and therefore may benefit from increased drug concentrations as can be obtained using triggered release from TSL5. This is the first indication that Image-Guided Radiosensitizer Delivery (IGRD) may improve the efficacy of radiotherapy, while reducing normal tissue damage.

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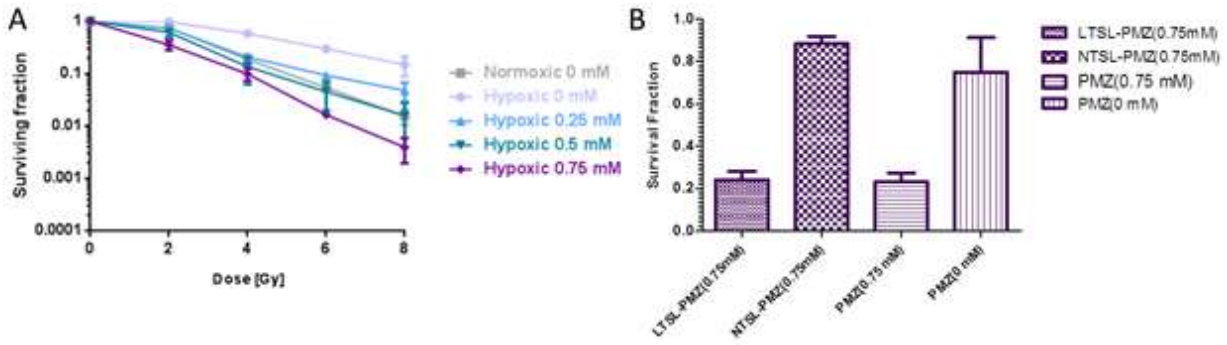

OP-13

Uncertainty and error minimization in magnetic particle hyperthermia evaluation

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Introduction
Measurement of specific loss power (SLP) of magnetic nanoparticles (MNPs) is crucial to assert their heating potential in magnetic particle hyperthermia (MPH). The SLP estimation is a multi-parameter problem, significantly affected not only by particle properties and experimental conditions but also by the computational routine followed, as well. In this work, we attempt to define and record sources of uncertainty and errors in each step of a hyperthermia process and examine their impact on concluding SLP values.
Methods
Typically, SLP index evaluation is based on the rate of change of temperature of a sample that is magnetically heated by the effect of an alternating magnetic field on MNPs. The intrinsic uncertainties in

such a process derive from the sample itself (dimensions, volume, concentration, magnetic properties), the field application (frequency, amplitude, homogeneity), the temperature (recording process, distribution, external heat exchanges) as well as from measurement errors, naturally occurring in every experimental procedure, transmitted through each estimation step. More specifically, the contribution of different sample's concentrations and volumes in MPH evaluation are thoroughly studied in this work using magnetic iron oxides showing that reducing the sample's volume by a factor of two (from 1 mL down to 0.5 mL) may lead to an underestimate SLP value by half. In contrast, sample's concentration change (0.25 to 3 mg/mL) seems not to have any crucial effect in the SLP values (change less than 10 %). Moreover, variations in magnetic field homogeneity (different coil geometry), in the frequency (100 – 800 kHz) and also in the amplitude (5 - 60 kA/m) of the magnetic field are also determinant parameters affecting the ultimate SLP value. Additionally, regarding the temperature rise, the measurement conditions, the non-magnetic origin heat exchange as well as the heat dissipation are also examined in detail for their contribution in MPH heating evaluation. Finally, the most widely used SLP evaluation methods (namely, the Initial Slope and Box-Lucas data manipulation methods[1], together with Hysteresis[2] and Rosenweig[3] theoretical models) are examined against the Modified Cooling Law[4] we are routinely employing for SLP evaluation outlining the importance of temperature data manipulation for the final thermal efficiency evaluation.

Conclusions

In principle, MPH application has a multi-parametric nature. In this work, we split the parameters incorporated to four major categories: sample, field, temperature and estimations and try to unravel each one's role and significance to ultimate goal which is SLP evaluation. By studying each factor separately, a specific uncertainty in SLP occurs. All these uncertainties are included in SLP evaluation to provide a reliable and error-free under certain conditions SLP index value. Such a process is expected to be useful not only for MPH but for any type of regional magnetic hyperthermia where similar parameters are affecting heating efficiency in such a way that a desirable heat transfer and temperature distribution could be achieved.

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OP-14

Modulated-Electro-Hyperthermia Enhanced Liposomal Drug Uptake by Cancer Cells

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Modulated Electro-hyperthermia (mEHT) stands for a significant technological advancement in the hyperthermia field, which has autofocusing electromagnetic power on the cell membrane to create massive apoptosis. Since mEHT expressed the unique ability to excite cell membrane, we hypothesized that mEHT could enhance the uptake of liposomal drug by enhancing the phagocytosis activity. Cancer cells were visualized for doxorubicin (DOX) fluorescence to investigate the uptake of the drug in the cells. The uptake of liposome encapsulated DOX (Lipo-DOX) was compared under 42°C water bath and mEHT treatment. mEHT treatment showed a significant enhancement of Lipo-DOX uptake of DOX fluorescence(the mean fluorescence ratio to untreated control is 11.94) in compared with 37°C or 42°C control(4.85 and 6.25). To investigate whether the macropinocytosis is involved in the mEHT-induced high intracellular retention of DOX, Wortmannin was used to inhibit the micropinocytosis effect and 70kDa Dextran-FITC was served as uptake substance. Cancer cells uptaked Dextran significantly after

mEHT treatment whereas this enhancement was significantly inhibited by Wortmannin. This result showed mEHT-induced particles uptake thought micropinocytosis. BALB/c mice bearing CT26 colon carcinoma were given a single i.v. dose of 3 mg/kg of Lipo-DOX, and the tumors were then heated to either 37°C, 42°C water bath or 42°C mEHT for 30 min. To confirm drug concentrations based on fluorescence intensity in the tumor, indeed, tumor tissue sections were evaluated for DOX fluorescence to examine the local distribution of the Lipo-DOX. mEHT treatment achieved the highest DOX concentration (1.44ug/g of mEHT group and 0.79 ug/g of 42°C water bath group). In conclusion, mEHT-enhanced uptake of Lipo-DOX may effectively increase the therapeutic effect of liposomal drug. This novel finding warrants further investigation clinically.

OP-15

Magnetic Particle Hyperthermia: Multifunctional modes for effective cancer treatment

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Introduction
Magnetic particle hyperthermia attempts to treat cancer following the modality Hippocrates suggested around 2500 years ago: “What medicine cannot cure, iron cures; what iron cannot cure, fire cures; what fire does not cure, is to be considered incurable”. Its proof of principle relies on the fact that cancer cell are more vulnerable to temperature variations when compared to normal ones, while the heat cargo is delivered by especially designed magnetic nanoentities under the guidance of an external magnetic field. Although, it is authorized for cancer treatment since 2011, after passing a phase II clinical trial, as adjuvant therapy with conventional radiotherapy,,[1] it still needs further elaboration prior to routine clinical application. As in most biomedical applications, several constraints both in carriers and therapy scheme have to be successfully addressed.
Results and Discussion
The first general question that naturally arises is why use magnetic nanoparticles in modern theranostics? The answer is multifold and has to do with their flexibility, selectivity and effectiveness. Magnetic nanoparticles may be remotely (i.e. externally) and effectively stimulated by the adequate magnetic field. Since they are only a few tens of nanometer in size and therefore, they may manoeuvre around, for example, find easy passages into several tumors, whose pore sizes are for example in 100 nm range.
To advance magnetic particle hyperthermia applicability, three critical puzzles have to be solved:
a).Which particles? Reproducibility, is the first milestone, for a synthetic approach, which should be self-consistent and reproduce its outcome under standard conditions. Then, synthetic controls should be tuned to provide control over size and shape (uniformity and morphology) within a homogenous (stability) in time and varying conditions dispersion. Eventually, scalability to greater length scales may be examined in an effort to create microscale or even mesoscale objects.
b).Which conditions? Magnetic Particle Hyperthermia treatment utilizes high frequency magnetic field and is excellent paradigm for discussion of field application safety in biomedicine. The generated temperature depends on the magnetic properties of the nanoparticles, and it increases with magnetic field frequency and amplitude. In order to minimize possible risks, the dosage of nanoparticles administered during the hyperthermia treatment should be kept as low as possible together with clinical constraints for the magnetic field intensity and frequency values.
c).Will it perform under bio-conditions? Nanoparticles due to their multivalency and multifunctionality, pose challenge for understanding their pharmacokinetics because different components will have

different features that affect their performance, toxicity, distribution, clearance. The 3Ds: Dose, Dimensions and Durability provide the set of parameters to be fine-tuned in order to have optimum performance together with minimum side-effects within a biological environment.

Conclusions

Magnetic particle hyperthermia is a unique multifunctional platform since its carriers can be remotely and non-invasively employed not only as heat mediators but as imaging probes, carrier vectors and smart actuators as well.

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OP-16

PET-MFH Hybrid System Feasibility Study

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1. Introduction

Dynamic PET imaging can monitor the transient and spatial distribution of radiopharmaceuticals during their delivery in the vascular system, as well as during the later metabolic phase. Significant differences have been reported in ^{18}F-FDG uptake in studies regarding anti-angiogenic cancer treatment efficacy. Thermotherapy is reported to prevent angiogenesis in the tumor region by blocking the expression of associated genes. Considering the effect of hyperthermia on physiological mechanisms and the utilization of Magnetic Nanoparticles (MNPs) as drug carriers, an investigation on the feasibility of a PET-Hyperthermia hybrid system, is of interest. Magnetic Fluid Hyperthermia (MFH) premises the presence of an Alternating Magnetic Field (AMF) which would affect PET radionuclides' positron routes. Consequently, further error would be transferred in the localization of the positron-electron annihilation event. Employing a pulse magnetic field would allow sampling of PET data during the inactive phases of the field without introducing additional errors. The feasibility of such a system has been investigated.

2. Methods

Superparamagnetic magnetite MNPs were fabricated via co-precipitation method and their magnetic and physical properties were determined, upon proper characterization via a series of experimental processes. Magnetic fluid was prepared and heated to obtain experimental hyperthermia curves for different configurations of the AMF. Numerical models were developed in Comsol Multiphysics to reenact the AMF and predict the volumetric power dissipation for the magnetic fluid. The models were validated against analytical calculations and experimental data.

3. Simulations

A 2D-Axisymmetric numerical model was developed in Comsol Multiphysics, using the "Bioheat Transfer" module, governed by the Pennes Bioheat Equation (PBHE). A simplified geometry was designed to represent a composite consisting of MNPs accumulated in a low-grade cerebral glioma, surrounded by healthy tissue. Thermal properties of tissues and corresponding blood perfusion rates were retrieved from the literature. The variables and parameters associated with the magnetic fluid were imported from the validated models described above. The time-dependent temperature profiles, as well as the min and max temperatures within the 90% of the tumor volume were calculated for 4 different configurations of the AMF and the most suitable set up for an ideal thermotherapy in terms of thermal dose ($CEM_{43}T90$) delivery optimization was specified. To enable a homogenous temperature distribution during an intercepted heating process several accumulation zones were tested and upon

determination of the most efficient, an "Events" module was added to the model to emulate the activation and inactivation of the AMF when predefined temperature conditions are met. The min and max temperatures within the 90% of the tumor volume were monitored and maintained within a selected range, which determined the duration of the heating phase, as well as the duration of PET data acquisition phase.

4. Conclusion

The results of this study are indicative of the feasibility in developing a PET-MFH hybrid system. Further research is required, to optimize the PET data acquisition phase to heating phase ratio and ensure both a sufficient sampling time and a high temperature distribution for clinically acceptable concentrations of MNPs and AMF configurations.

OP-17

Oprimization of in vivo imaging and hyperthermia procedures for quality assured theranostics

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Introduction

Nanoparticle based drug delivery is considered as a new, promising technology for the efficient treatment of various diseases including, but not limited to cancer. Nanoparticles can penetrate biological barriers, carry drugs on the target site, while minimizing dose in other organs. When nanoparticles are radiolabelled it is possible to image them, using standard molecular imaging SPECT (Single Photon Emission Tomography) or PET (Positron Emission Tomography) techniques [1].

The use of magnetic nanoparticles in hyperthermia is one of the most promising nanomedicine directions and requires the optimization of magnetic induction devices, as well as the accurate, non-invasive, monitoring of temperature increase. The combination of imaging and therapy has opened the very promising Theranostics domain [2]. Simultaneous nuclear imaging during hyperthermia can provide insights in the biological process that occur when nanoparticles are heated [3]. In this way, it is possible to monitor the successful organ/tumor targeting, drug release and/or real time response to therapy. This approach is by far superior when compared to the use of conventional anatomic or functional modalities, which can monitor the long term therapeutic effect.

Methods

The project THERAQ will develop, validate and provide procedures and support for Quality Assured Theranostics and has been recently funded by the Greek Scholarships Foundation. It is an ambitious project aiming to provide new approaches, tools and knowledge in the emerging field of Theranostics. The main objectives of THERAQ are (Figure 1) the (i) Development of a PET prototype system for use inside the coil of hyperthermia systems; (ii) Design of a hyperthermia coil, in order to be combined with the PET system for in vivo imaging; (iii) Differentiation of active and passive targeting through the spatial distribution of the pharmaceutical measured in tumor and (iv) Imaging of drug release during hyperthermia, using radiolabelled pharmaceutical or radioisotope entrapped inside nanoparticles. The proposed detector will be based on magnetic compatible Silicon Photomultipliers (SiPMs), a technology that has been well tested in the field of combined PET/MRI. The authors have several publications on the design and evaluation of SPECT and PET detectors based on SiPMs and this experience will be used for the proposed integrated system [4], [5].

Conclusions

The added value of THERAQ can be summarized as Technical improvements in hyperthermia and temperature measurement equipment; Construction and evaluation of the first Theranostic imager for hyperthermia and New protocols for quality assured theranostics.

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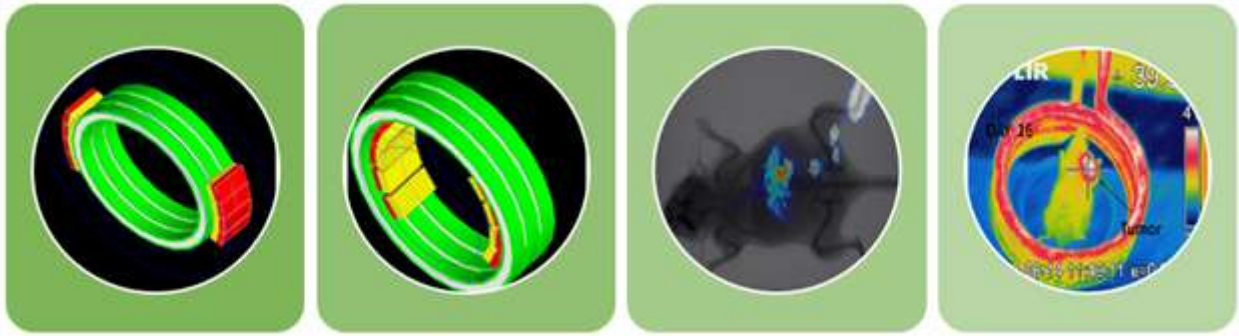

OP-18

Paramagnetic liposomes form hyperthermia-induced MR-Guided drug delivery

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Hyperthermia-induced local drug delivery using temperature sensitive liposomes (TSLs) has been shown in several studies to increase local drug concentrations by a factor of approximately 5 to 15. Co-loading of a paramagnetic MR contrast agent such gadoteridol (Prohance) together with the drug doxorubicin (dox) into the lTSLs allows to visualize and to some extend quantify dox release using MRI. Though promising, the approach copes with two challenges. First, encapsulation of gadoteridol inside the TSLs is changing its biodistribution leading to a high concentrations in liver and spleen due to clearance of the liposomes, which could present a potential toxicity risk. The subsequent long term fate and eventual redistribution or excretion of gadoteridol has so far not been studied. Second, gadoteridol has very different pharmacokinetic properties compared to the encapsulated dox, leading to different tumor uptake upon release of the two compounds. If gadoteridol release is quantified only at the end of an hyperthermia session, the correlation between gadoteridol and dox concentrations in the tumor tissue can be obscured by differences in uptake, retention and washout, deteriorating the MR-based quantification. Here, intermittent monitoring of gadoteridol release during hyperthermia is highly warranted. To investigate the first question, we performed in vivo studies to test the biodistribution of gadoteridol encapsulated in TSLs in comparison to free gadoteridol, or gadoteridol encapsulated in non-temperature sensitive liposomes (NTSLs) and liposomes carrying a gadolinium chelate conjugated to a lipid. For the second question, we performed an in vivo study, where a new MRI method using an interleaved scanning approache was used to follow release of gadoteridol from TSLs during hyperthermia. Local hyperthermia was induced in a R1 rat model using high intensity focused ultrasound (MR-HIFU).
The results showed that gadoteridol encapsulated in TSLs and NTSL leads after injection to high uptake in liver and spleen, but that it is cleared to the same extend as free gadoteridol after weeks leading to comparable residual amounts of gadolinium in organs. Covalent conjugation of a a gadolinium chelate to a lipid that is incorporated into a liposome increases retention of gadolinium in liver and spleen and

leads to higher gadolinium concentrations in all organs throughout the study. The second study showed that interleaved MR scanning allows to follow release of gadoteridol during MR-HIFU hyperthermia enabling simultaneous mapping of temperature and relaxation times. The latter allow a direct correlation with doxorubicin concentrations in the tumor leading to improved MR-based quantification of dox.

TOPIC: TECHNOLOGY / DOSIMETRY

OP-19

Impact of magnetic resonance imaging on hyperthermia treatment quality assurance

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[1]*Erasmus Mc*

Quality assurance (QA) is defined as the systematic evaluation of system performance. In general the objective is to perform QA with the most advanced measuring tools available in order to allow a quantitative decision based on objective criteria whether a system operates according to specifications. HT applicators require formal QA to ensure accurate, precise and consistent treatments.
Most commonly used HT QA measurement techniques to evaluate hyperthermia system performance rely on temperature probes, infrared (IR) cameras, Diode E-field sheets, single E-field sensors and lamp phantoms. Although, these techniques in principle provide objective, quantitative information they have serious drawbacks for pre-treatment quality control. Limitations include invasiveness (all), a limited set of points or single plane measurements (temperature probes and single E-field sensors), poor spatial or temporal resolution (IR cameras, E-field sheets, lamps), long sampling time (scanning devices) and a limited dynamic range (lamps). As a result the decision whether a system meets the QA assurance demands, is often based on either a low number of data points covering only a small volume of the whole energy distribution or at best on a qualitative 2D registration of the E-field distribution in one of the major cross-sectional planes of the phantom.
In contrast, magnetic resonance thermometry (MRT) offers a non-invasive 3D view of temperature distribution, thereby being the only system that provides the ability to register 3D energy distribution in solid anatomical phantoms.
For the introduction of the Pyrexar BSD2000 3D MR HT applicator in combination with the GE 450w MR scanner at the Erasmus MC Cancer Institute in Rotterdam, the proton resonance frequency shift (PRFS) method was used to acquire temperature maps. We made an anthropomorphic phantom as well as several cylindrical phantoms to check different properties of the system and to match the HTP simulations to the MRT. By carefully controlling positioning the phantom in the applicator we were able to verify phase and amplitude steering resolution with the MR-compatible Sigma Eye applicator and to demonstrate it to be accurate at sub-cm level. Further, the 3D imaging of the temperature distribution in anthropomorphic phantoms with MRT facilitates investigating the sensitivity of translating hyperthermia treatment planning settings to clinically relevant conditions and resembles a major step forward in adaptive image guided hyperthermia.

OP-20

On-line adaptive treatment planning during locoregional hyperthermia to suppress treatment limiting hot spots

Petra Kok[1], Linda Korshuize - van Straten[1], Akke Bakker[1], Rianne de Kroon - Oldenhof[1], Debby Geijsen[1], Lukas Stalpers[1], Hans Crezee[1]
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Introduction: In clinical hyperthermia adequate tumor temperatures are essential for good response, but excessive heating of normal tissue should be avoided. This makes locoregional heating using phased array systems technically challenging. On-line application of hyperthermia treatment planning could help to improve the heating quality. The aim of this study was to evaluate the clinical benefit of on-line treatment planning during treatment of pelvic tumors heated with the AMC-8 locoregional hyperthermia system.
Methods: For on-line adaptive hyperthermia treatment planning a graphical user interface was developed (Figure 1). Electric fields were calculated in a pre-processing step using our in-house developed finite-difference based treatment planning system. This allows instant calculation of the temperature distribution for user-selected phase-amplitude settings during treatment and projection onto the patient's CT scan for on-line visualization. On-line treatment planning was used for 14 treatment sessions in 8 patients to reduce hot spot complaints. One of these sessions involved a patient with a deep-seated melanoma at an eccentric location in the pelvis, different from our mainstream of patients with pelvic malignancies. During this session on-line treatment planning was also used to increase the tumor temperature.
Results: In total 17 hot spot complaints occurred during the 14 sessions and the alternative settings reduced complaints while maintaining at least 95% of the achieved tumor temperature rise. For the melanoma patient steady state tumor temperatures were disappointing and using treatment planning the tumor temperature rise was increased more than 15% without inducing hot spot complaints.
Conclusion: On-line application of hyperthermia treatment planning is reliable and very useful to reduce hot spots without affecting tumor temperatures Additionally, planning can help to increase the tumor temperature rise for sites with little clinical experience.

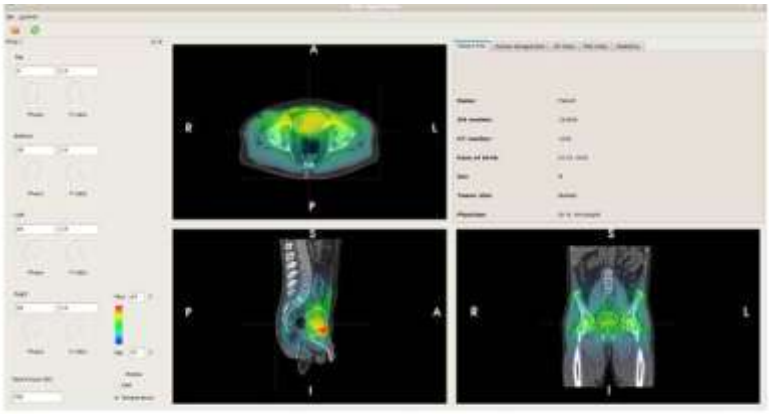

Figure 1: Screenshot of the graphical user interface as used for on-line adaptive hyperthermia treatment planning

OP-21

Regional deep hyperthermia: Determination of patient misalignments and its impact on SAR and temperature distribution using MR thermometry

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Introduction

Magnetic Resonance Imaging (MRI) has emerged from a diagnostic imaging modality to a powerful intervention guidance tool. The capability to image temperature is a very attractive property of MRI and has been actively used for non-invasive thermometry in regional deep hyperthermia. Among serval MR-based temperature-sensitive methods, proton resonance frequency (PRF) thermometry provides the advantage of excellent linearity of signal with temperature over a large temperature range.

Methods

In this study, the MR images used for the thermometry were utilized to assess inter-fractional patient mispositioning between hyperthermia treatment fractions, as well as intra-fractional mispositioning during one single hyperthermia treatment. In order to determine the possible clinical patient misalignments, a landmark-based rigid image registration was performed by placing ten landmarks in total on bone structures distributed across the patient body. For inter-fractional mispositioning, the MR images of the first hyperthermia treatment fraction were taken as a reference, while the first MR imaging at the begin of treatment was taken a reference scan for the image registration. The results of the inter-fractional patient mispositionings were taken as input for analytical simulation studies to systematically investigate the influence of possible clinical patient misalignments on specific absorption rate (SAR) and temperature distribution. Since the results of the intra-fractional patient mispositionings showed relatively small patient movements and rotations, this was excluded from the simulation study. For electromagnetic and thermal simulations, the finite element (FE) approach was used to obtain SAR and temperature distributions for six patients at 312 positions. Patient displacements, rotations as well as the combination of both were considered inside the Sigma-Eye applicator. Position sensitivity is assessed for hyperthermia treatment planning (HTP)-guided steering, which relays on model-based optimization of the SAR and temperature distribution. The evaluation of the patient mispositioning was done with and without optimization. The evaluation without optimization was made by creating a treatment plan for the patient reference position in the center of the applicator and applied for all other positions, while the evaluation with optimization was based on creating an individual plan for each position. The parameter T90 was used for the temperature evaluation, which was defined as the temperature that covers 90% of the gross tumor volume (GTV). Furthermore, hotspot tumor quotient (HTQ) was used as a goal function to assess the quality of the SAR and temperature distribution.

Results & Conclusion

The T90 was shown considerably dependent on the position within the applicator. Without optimization, the T90 was clearly decreased below 40 °C by patient shifts and the combination of shifts and rotations. However, application of optimization for each positon led to an increase of T90 in the GTV. Position inaccuracies of less than 1cm in X and Y directions and 2cm in Z-direction, resulted in an increase of HTQ less than 5%, and do not significantly affect the SAR and temperature distribution. Current positioning precision is sufficient in the X (right–left)-direction, but higher position accuracy is required in the Y and Z directions.

OP-22

Simulation of prostate tumor hyperthermia-induced cell death via microwave electromagnetic radiation: a computational work.

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Introduction

Microwave-induced hyperthermia (MIH) is governed by physical mechanisms and effects that can be easily modeled because of the good knowledge of electromagnetism and heat transfer effects.

Here we present case studies for prostate cancer tumor that is treated with endorectal MIH. For the simulation, we modeled the positions of prostate and the microwave antenna. We assumed that the microwave antenna emits electromagnetic waves at 433 MHz and the total input power can be set up to 100 W [1]. Furthermore, we used three-state mathematical models to estimate the cell death due to hyperthermia.

The results help us determine the optimal thermalization time in which a minimum thermally-induced damage (cell death) of healthy tissue and a maximum damage of cancerous tissue can be achieved. Finally, we estimate the possible tumor shrinkage over time with the help of mathematical models.

Materials and methods

The equations that were used to model the electromagnetic waves are described in [2, 3]. The equations that were used for the prediction of the hyperthermic cell death are described in [4]. In order to minimize the computing requirements, we projected the geometry in 2-Dimensions.

Results

The results show (Figure 2) that with an initial antenna configuration at frequency of 433MHz and power 100W, a severe damage is achieved in the tissue that is closer to the antenna and a minor damage in the prostate region that is far from the antenna. The results are compared with an antenna configuration that comes at 2.4GHz and 20W during 30 minutes of heating. Assuming that the tumor has volume ~113 mm^3 and stabilizing the temperature at 50 ^oC for 15 minutes, we observe the results of the hyperthermic cell death model, showing in Figure 3. The model has been calibrated with experimental data of Huang et. al. [6]. Sequencing the therapy with these configurations, we observe the tumor shrinkage by the time as shown in Figure 4.

Conclusions

Concluding, our methodology and first results must be considered a proof of principle for the significance of simulating realistically the hyperthermia-induced cell death and prostate tumor treatment. By this approach, we envision in the future more application of our methodology in real cases of prostate or other tumor tissue treatment in order to optimize the treatment and more importantly minimize damage to neighboring healthy tissues.

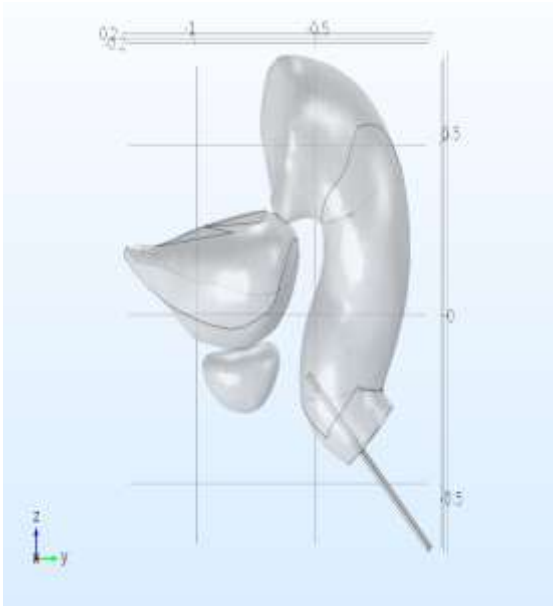

***Figure 1**. Initial 3D geometry. Here we can see the rectum, the bladder, the prostate and the antenna.*

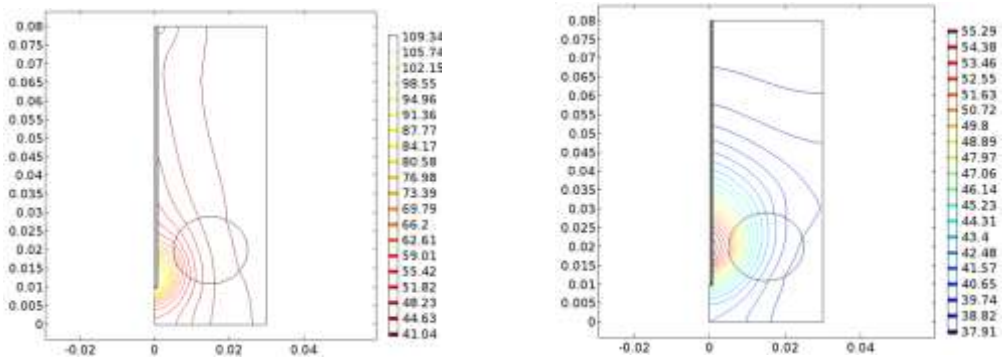

***Figure 2.** Left: 433Mhz and 100W for 30 minutes. Right: 2.4GHz and 20W for 30 minutes*

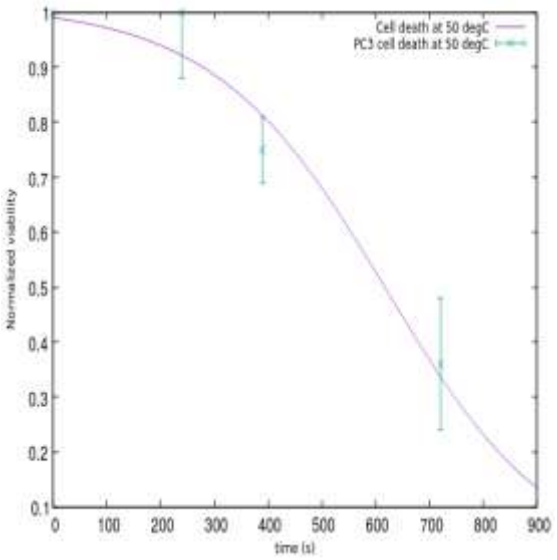

Figure 3. Hyperthermic cell death at 50 degrees Celsius.

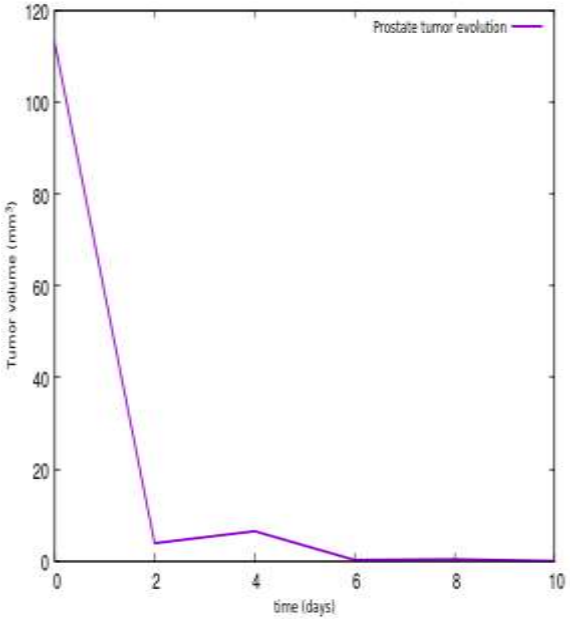

Figure 4. Estimation of prostate tumor shrinkage.

Acknowledgments
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OP-23

Simulation guided design of an MR compatible head and neck hyperthermia applicator: assessment of B1+ distortion

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Introduction: Over the last decade, we developed the HYPERcollar and HYPERcollar3D applicators. The applicators consist of 12 and 20 patch antennas placed in rings and operating at 434MHz. Although, good focused heating in a number of sites in the head and neck region is possible, thermal dose control remains challenging as placement of interstitial thermometry catheters in this region is difficult and temperature information is always limited to a few locations. Hence, we are currently working towards an MR compatible HYPERcollar for 3D temperature measurements using MR thermometry. The initial applicator setup was redesigned leading to a laboratory prototype ("MRlabcollar") [1]. The purpose of this study was to determine the influence of the MRlabcollar on the radiofrequency B1+ field of the MR scanner.
Methods: Experiments and simulations were done for two experimental setups in the MR scanner bore: 1) fat-muscle phantom and 2) fat-muscle phantom inserted into the MRlabcollar prototype. For both setups, we ensured that the height to the center is identical. Flip angle maps (proportional to B1+) were acquired using an SPGR sequence (TE=5ms, TR=6000ms, FA=α, 2α, FOV 40cm, matrix 128x128, NEX 1, axial slice 10mm, at 5mm spacing and processed by taking the arc-cos of the ratio of signal intensities at the α and 2α flip angles. Simulations were done using a generic 1.5T 16-rung high-pass birdcage RF body coil model (radius=355mm, rung length=670mm) constructed using the birdcage tool in SEMCAD X (Speag, Zürich, Switzerland). The coil was excited by two edge sources (64MHz, quadrature mode, 60 periods) and tuned by 32 capacitors placed in two end-rings.
Results: Figure 1a) and b) show flip angle maps for phantom with and without MRlabcollar. Results indicate a similar uniformity of the B1+ transmit/receive field, yet in the MRlabcollar setup less power is required to generate a 90 degree flip angle, as shown in figure 1b by the over-flipped spins in the phantom at a lower transmit gain. In the simulations, the peak difference in |B1+| at the center of the body coil with the phantom (figure 1c) compared to the unloaded coil was 5.8%, and a 1.8% difference was found when antennas were added to the MRlabcollar simulation setup (figure 1d).
Conclusion: No significant changes in B1+ field caused by the metallic parts of the MRlabcollar were observed. In this study, we also showed the suitability of modeling to study the impact of the hyperthermia device on the RF characteristics of the MR scanner.

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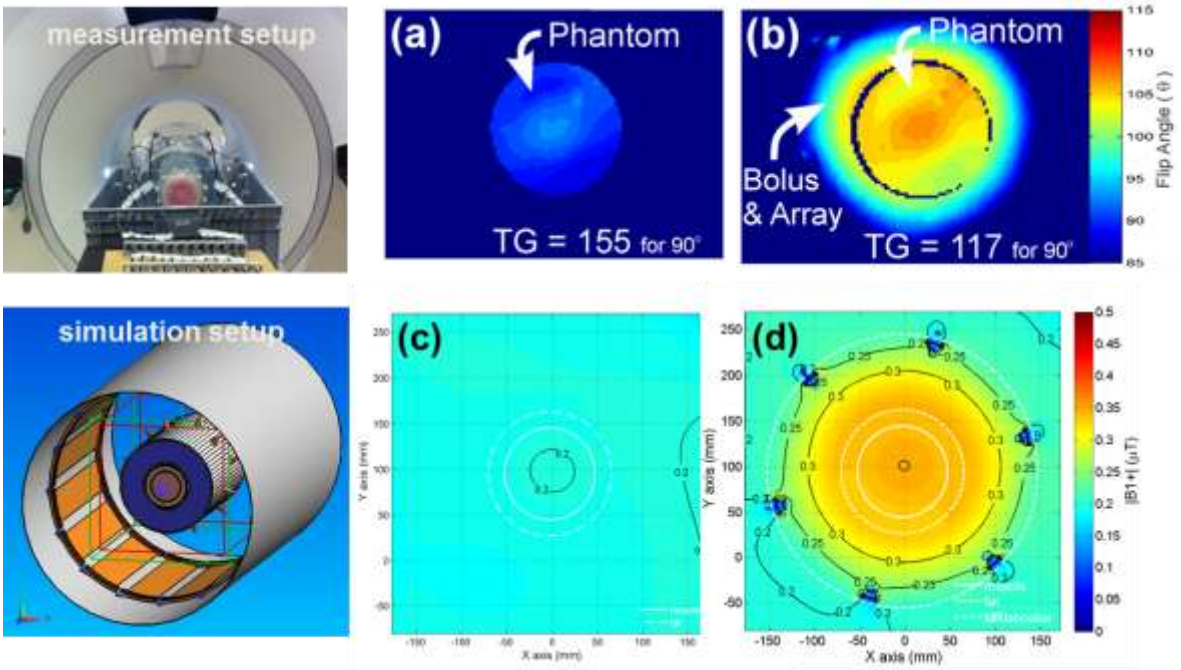
Acknowledgement: This study was supported the Dutch Cancer Society, grant EMCR2012-5472.



OP-24

Optimization of Tumor Therapy by Combination of Focused Ultrasound and Ionizing Radiation Guided by (PET-)MRI

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Introduction:

The two ZIK-Centers for Innovation Competence, ICCAS in Leipzig and OncoRay in Dresden, have joined forces to start a new multidisciplinary 6.3 million Euro research project: SONO-RAY - Tumor therapy combining image-guided (PET-MR and MR) focused ultrasound (FUS) and radiation therapy (RT). The hypothesis underlying this approach is that the combination of two tissue-destroying energies is more effective in cancer treatment than the effect of employing one of the above two energy forms alone[1].

Facilities, Materials and Methods:

In vitro FUS and RT: A high throughput in vitro 96-well sonicator was designed and allows individual sonication for each of the wells in a 96-well plate. It consists of 96 single transducers at an operating frequency of 1 MHz and a maximum energy of 0.05 W/cm². A 150 kV X-ray machine (DARPAC 150-MC) was employed for irradiation at doses of 0 – 20 Gy. The analysis was conducted by using three different cell lines for prostate cancer (PC-3, Vcap, LNcap), glioblastoma (LN405, U87MG, T98G) and head/neck

tumor (FaDu, UT-SCC 5, UT-SCC 8). Effects at the cellular level on metabolism (WST-1), proliferation (BrdU), membrane integrity (LDH release) and apoptosis (Annexin V) were detected after treatment.
In vivo: PET-MR and MR guided FUS system allows precise sonication treatment for small animals bearing tumors, under real-time MR-thermometry[2]. Small animal PET-MR system (nanoScan, Mediso) will be integrated with a FUS transducer (11×11 matrix array) which allows the function of beam forming to achieve hyperthermia treatment. Local tumor irradiations under normal blood flow conditions will be given with 200 kV X-rays (0.5 mm copper -filter) and 20 mA at a dose rate of ~ 1.1 Gy/min (X-ray machine type Yxlon Y.TU 320-D03)[3].
Robot installed in PET-MR: An MR-compatible robotic arm system (INNOMOTION™, Innomedic)[4] was installed with Biograph mMR MR-PET (Siemens Healthineers) in the Department of Nuclear Medicine of the University Medical Center Leipzig to investigate the effects of a combination of FUS and RT. The robotic arm will reposition the ultrasound transducer during the sonication treatment. It is possible to detect residual tumor tissue after the treatment by using PET-MR imaging to provide an optimal treatment outcome.
MR guided FUS-Sonalleve: The Philips Sonalleve MR-FUS system was installed in Leipzig University Hospital at the beginning of 2017, introduced a new approach for uterine fibroids and bone metastasis. The Sonalleve system also offers solutions of hyperthermia platform[5] in combination with radiation and chemotherapy in cancer treatment.
MR guided FUS-prostate system: The TULSA-PRO System (Profound Medical) is a transurethral MR guided FUS system for whole gland ablation of the prostate. A test system was installed at the university hospital Dresden to perform the world's first compatibility tests on a Philips Ingenuity TF PET-MR scanner. The system comprises a transurethral ultrasound applicator with 10 FUS elements working at 4 or 14 MHz to heat the rim of the prostate up to 55 deg Celcius. The power and frequency of the 10 ultrasound transducers are individually steered by real-time MR-thermometry.

OP-25

Longitudinal preclinical study of the 'breakthrough' Vectron thermal treatment (TTx) system: safe and effective noninvasive heating of deep porcine abdominal organs in vivo using a novel RF inductive electromagnetic field design

WITHDRAWN

OP-26

"Quality assurance protocol for superficial and deep tissue hyperthermia systems established by the Hellenic Association of Medical Physicists (HAMP) in cooperation with the Hellenic Society of Oncologic Hyperthermia (HSOH)"

Sotiria Triantopoulou[1], Christos Antypas[1], Kalliopi Platoni[1], Pantelis Karaiskos[1], Christina Armpilia[1], Nikolaos Uzunoglou[2], Vassilis Kouloulias[2]
[1]Hellenic Association of Medical Physicists, [2]Hellenic Society of Oncologic Hyperthermia

INTRODUCTION
Hyperthermia is a therapeutic modality that is applied in conjunction with radiotherapy and/or chemotherapy. Superficial Hyperthermia is applied for tumors of depth less than 5cm within the human body, while deep tissue hyperthermia is applied for tumors located deeper inside the human body. Correct operation of the hyperthermia system should ensure the selective heating of the tumor with the

minimum toxicity to the surrounding healthy tissues. Therefore, quality assurance procedures are essential in order to provide an effective hyperthermia treatment. The purpose of this study is to describe the quality assurance protocol for superficial and deep tissue hyperthermia systems established in Greece.

METHODS

A working group of Medical Physicists in Greece was created for the proposal of quality assurance guidelines for superficial and deep tissue hyperthermia systems. An analysis of the existing protocols in other European and international centers, as well as protocols suggested by European or International organizations, was performed. Then a protocol was suggested, describing procedures for quality assurance according to the current technology and the existing equipment used in Greece.

SIMULATIONS

A protocol describing the procedures for the quality assurance of superficial and deep tissue Hyperthermia systems was proposed. The required equipment consists of a calibrated thermometer, two waterbaths, a tissue equivalent phantom, a calibrated digital counter, a calibrated power meter, a 50-Ohm load and a calibrated isotropic radiation survey meter.

The procedures described aim to evaluate the correct operation of the device, of the thermometric system, the generator, the incorporated power meter and the applicators. It will also ensure the electrical safety.

CONCLUSIONS

A protocol is proposed for the quality assurance of superficial and deep tissue Hyperthermia systems in order to be followed by medical physicists in Greece. This protocol will ensure an efficient treatment with safety and minimum adverse effects. This protocol has been approved by the Hellenic Society of Oncologic Hyperthermia and the Hellenic Association of Medical Physicists.

OP-27

Quality benchmarking in hyperthermia treatment

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Introduction: The development, in the hospital environment, of performance indicators in the field of certification/accreditation systems and quality benchmarking is evolving. The aim of this work is to propose a set of quality indicators for hyperthermia treatments in order to provide a continuous quality improvement.

Methods: A preliminary set of indicators was selected on the basis of evidenced critical issues. Three structure, six process and two outcome quality indicators were obtained. A multidisciplinary team involving different professional profiles as Radiation Oncologist, Medical Physicist and Radiation Technologists, was assembled in order to take advantage from different professional figures and to underline main critical issues in the use of hyperthermia.

Results: A final set of 11 indicators has been developed. They concern general structural, processing and outcome operational features. For each indicator, topic, type of indicator, numerator (parameter value),denominator (reference population), standard (reference value), time period for data collection and frequency of analysis have been proposed. Numerical values for the standard were selected from the international literature, when available, and from guidelines on hyperthermia/radiotherapy, or empirically on the basis of the experience of the Italian Institutes. Briefly, in the table 1, we reported

the list of hyperthermia indicators. Data on some of these indicators were collected in a number of Italian hyperthermia Institutes and medical physics Services.

Indicator	Topic	Type of indicator	Numerator	Denominator	Standard	Frequency of analysis
1. Equipment	Kind of hyperthermia equipment (superficial/deep-hyperthermia)	structure	Number of hyperthermia equipment	Total number of radiotherapy machines	At least 1 for equipment	At least 1 year, every 3 years
2. Quality control equipment	Quality assurancy (QA)	structure	Number of test equipment performed before patient treatment	Total number of the treated patients with hyperthermia	100%: each plan should be checked prior to delivery	To be checked at least once a year
3. workload	Human resources productivity	structure	Total number of patients treated in 1 year	Number of workers: 1) technician 2) physician 3)physicist 4) nurse	At least 1 person for each figure (also part-time)	1 year, repeated every 2 years
4. Approved protocols	Quality improvement of patient management	Process	Number of patient enrolled in clinical protocol for hyperthermia	Total number of treated patients	100% the standard proposed is the average percentage value considering the centers data	1 year, every two years
5. multidisciplinary work	Multidisciplinary approach to patient care	Process	Number of patients discussed in multidisciplinary meeting	Total number of treated patients	80%	1 year, repeated every 2 years
6. Input image (TC,eco, RM,PET)	Information accuracy	Process	Number of patients undergoing hyperthermia treatment receiving multi-parametric imaging (TC/eco/RM/PET)	Total number of treated patients	15%	1 year, or at least 6 months; repeated every 2 years
7. Temperature measurement	Hyperthermia treatment accuracy	Process	Number of treatments in which temperature measurement is performed (yes/no)	Total number of hyperthermia treatment	100%: each plan should be checked during treatment	To be checked at least once before a new treatment
8. Treatment planning	Hyperthermia treatment control	Process	Number of hyperthermia treatment performed with treatment planning	Total number of hyperthermia treatments	100%: each hyperthermia course should be performed with treatment planning	Six months every 2 years
9. Thermal Dose Calculation	Quality improvement of hyperthermia treatment	Process	Number of treatments in which thermal dose calculation is performed (yes/no)	Total number of hyperthermia treatments	100%	1 year, every year
10. Treatment outcome and toxicity	Quality improvement of patient management	Outcome	Number of complete response (CR)/ No patients showed toxicity ≥ G2 at 12 months after the treatment	Total number of treated patients	CR=40% (late response); Toxicity G2 (12 months after the treatment): 0%	1 year, every year
11. Patient compliance	Treatment compliance	outcome	Number of the patients that complete total hyperthermia treatment	Total number of treated patients	100%: total number of patients complete hyperthermia treatment	1 year, every 1 year

TABLE 1: Hyperthermia Indicators

Conclusion: The proposed indicators are available to be investigated and applied by a larger pool of the Institutes, especially at European level. Consequently, it will be possible to conform this type of the treatment in terms of operational procedures in order to compare different data derived from different Institutes.

Acknowledgments
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OP-28

Feasibility of MR thermometry improvement by combining coils into the hyperthermia applicator

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Introduction: Temperature during hyperthermia treatment (HT) is usually measured using intraluminal or interstitial temperature sensors. This technique provides limited temperature data and often suffers from tissue contact (intraluminal) or discomfort and/or infection risk for the patient (interstitial). Noninvasive 3D thermometry by magnetic resonance imaging (MRI) solves these issues, but its accuracy is strongly dependent on the signal-to-noise-ratio (SNR) of the radiofrequency (RF) measurements. Since SNR decays quickly with increasing distance to the imaging region in MRI often (close-tissue) surface coils are used instead of the body-coil to improve the SNR (up to 3-fold improvement). In this work, we studied the feasibility and potential of surface receive coils inside a hyperthermia applicator to increase the signal to noise ratio (SNR) with respect to the currently used body-coil, aimed at improving MR thermometry accuracy.

Methods: For the experiments, two 3T surface coils were designed, tuned for 128MHz and placed around a 2x2 Yagi-Uda 434MHz hyperthermia antenna array [1]. Yagi-Uda antennas were inserted into the structure containing the coil elements. Tuning of antennas and coils was done in SEMCAD X: v. 14.8.6 (Speag, Zürich, Switzerland). The 4cm water bolus was modelled by two layers of agar mixed with deionized water and the patient was mimicked by agar, water and combination of copper sulfate (1g/liter) and salt (3.2g/liter) ("phantom" in figure 1a). A GE 750w 3T scanner was used, and RF receive was by the body coil and the new surface coil. SNR (figure 1a) was determined using a fast spoiled gradient echo (FSGRE) sequence with extended dynamic range: flip angle = 20°, TE=3.2ms, TR=68ms, slice thickness = 6mm and in plane = 256x256.

Results: Figure 1b shows the SNR improvement, both at the center and under the antennas, at a depth from 1 to 4 cm into the phantom. In comparison to the body coil, the surface coils provided a substantial better SNR (under the antenna: +30% to 80%; at center 0% to 40%) for both locations confirming the benefit of using surface coils.

Conclusion: Our initial results confirm the benefit of using MRI surface coils. We expect that SNR can be further improved by better antenna-coil integration and exploitation of coil-array operation.

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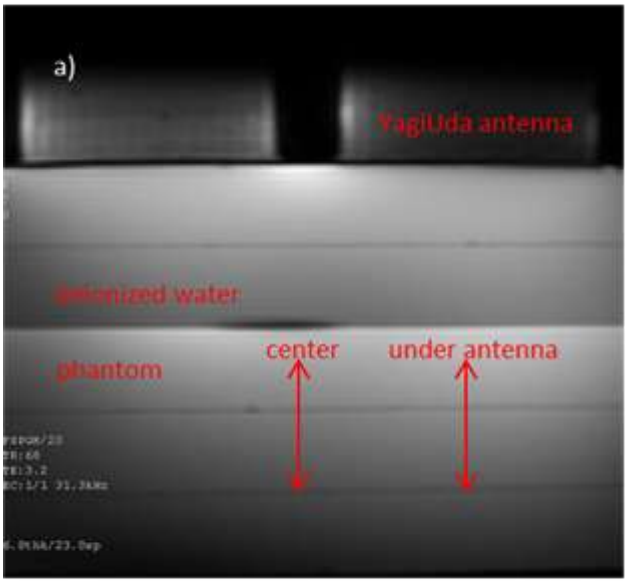
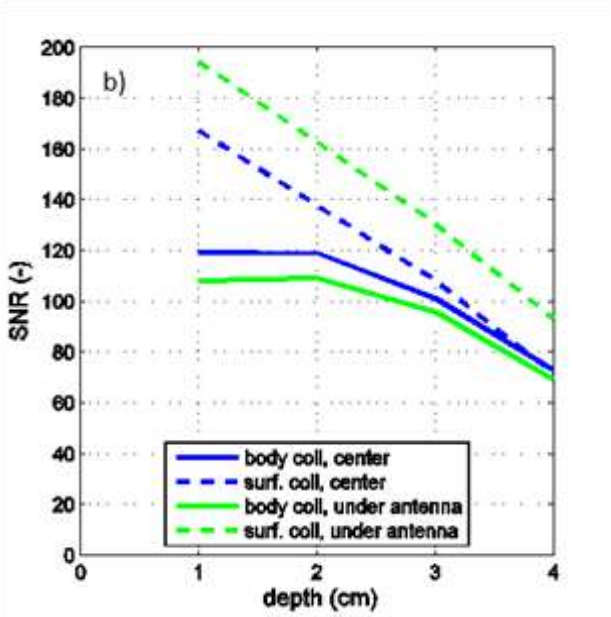
Acknowledgement: This study was supported by COST action BM1309 EMF-MED, the Rene Vogels foundation and the Dutch Cancer Society, grant EMCR2012-5472.





TOPIC: BIOLOGY & BASIC RESEARCH

OP-29

Comparison of thermal dose concepts in human and animal patients

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Introduction
Thermal dose concepts are crucial for the planning and evaluation of hyperthermia (HT) treatments. In this study, a physiologically motivated thermal dose concept (Transient Thermal Dose Equivalent, TTDE) is compared to the established CEM43 concept. The comparison is conducted with data of human and animal patients treated with different modalities.
Methods
Thermal dose values are computed from data obtained from human bladder cancer patients (n=12, 58 acquisitions) as well as with data from canine and feline oral melanoma and soft tissue sarcoma patients (n=8, 51 acquisitions). All patients underwent moderate hyperthermia treatment followed by radiotherapy (RT); human patients were treated at the KSA with a BSD 2000 device, animal patients

were treated at the Vetsuisse Faculty of the University of Zurich with a newly designed applicator prototype operating at 433.92 MHz.
For thermal dose calculation, time resolved temperature measurements during and after heating are used. The TTDE is calculated according to the biophysical model proposed by Scheidegger et al. [1,2] and calibrated to the fraction of non-functional repair protein (1 for complete thermo-induced inactivation and 0 for full repair capacity). Since TTDE is a dynamic quantity and is decaying after heating, it can be determined at the peak value (TTDE_peak) or when starting RT (TTDE_gap, after the time gap between the end of HT and the start of RT).
Results
The relationship between CEM43 and TTDE_peak is displayed in Figure 1a. The plot shows a strong correlation between CEM43 and TTDE and a saturation effect of the TTDE not observed in CEM43 values. This effect is stronger in animal patients because higher temperatures were reached during some treatments. Acquisitions which exceeded 43°C are marked with triangles. The plots show a wide diversity regardless of the measure used.
The relationship between CEM43 and TTDE_gap is shown in Figure 1b. The pattern is similar, although with a lower TTDE and a larger fan-out. This is due to the decay of TTDE during the time gap, and due to variations in the duration of the time gaps, respectively.
Conclusion
This study shows that the different dose concepts exhibit comparable patterns in both human and animal patients despite the inhomogeneities in patients and tumors and the differences in applicator design and treatment protocol. Yet, the HT treatments have a wide spread of dose values for both TTDE and CEM43. The TTDE dose concept shows results similar to CEM43, but incorporates the time gap between HT and RT and the saturation effect, both of which cannot be modeled by CEM43. Correlations between thermal doses and clinical outcome are unclear yet and are monitored as the trials progress.

Figure 1: Comparison between CEM43 and TTDE_peak (left) and TTDE_gap (right). Blue: human patients, red: animal patients, triangles: T>43°C.

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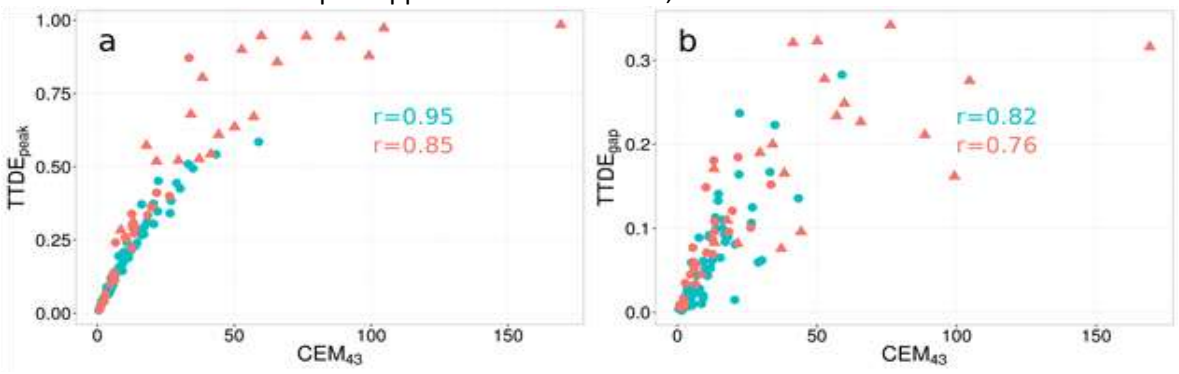

OP-30

Testing modulated electro-hyperthermia using C26 colorectal carcinoma cell line in vitro

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Introduction. By inducing heat shock at ~42°C, modulated electro-hyperthermia (mEHT) can selectively damage malignant tumors. For rapidly testing molecular changes we set up an in vitro tumor model and optimized mEHT treatment conditions.
Methods. Confluent coverslip cultures of C26 mouse colorectal adenocarcinoma cell line were treated with mEHT at 42°C for 2x60 min, 60+30 min, 2x30 min or for 30 min, respectively leaving 120 min intervals between interventions. After 24 h, stress response, apoptosis and growth signaling related markers were detected compared to untreated control cultures.

Results. Tumor damage rate of ~50% (LD50) was achieved after 2x30 min mEHT treatment, while other combinations killed the majority of tumor cells. Significant translocation of phosphatidyl-serine to the outer cell surface detected with annexin V flow cytometry indicated massive apoptosis. Elevated levels of heat stress induced Hsp70 and calreticulin, as well as cleaved caspase-3 and cytoplasmic phospho-ERK1/2 proteins were also revealed in situ.
Conclusion. Our results indicate that molecular changes related to cell stress, apoptosis and growth regulation upon mEHT treatment in C26 colorectal carcinoma cultures can be best analyzed after 2x30 minutes interventions. Repeated, as opposed to single intervention, better simulate human mEHT treatment used complementarily, either to radio- or chemotherapy

OP-31

Simulating response to multimodality therapies in vitro - towards modelling of virtual patient treatments

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Introduction: Combined radiotherapy and hyperthermia offer great potential for the successful treatment of radio-resistant tumours through thermo-radiosensitisation. Tumour response heterogeneity, due to intrinsic-, or micro-environmental induced factors, may greatly influence treatment outcome but is difficult to account for using traditional treatment planning approaches. Systems oncology simulations [1,2] provide a powerful tool for analysis and optimisation of combined treatments, using mathematical models designed to predict tumour growth and treatment response.
Methods: We present a simulation framework that models combination treatments of hyperthermia and radiotherapy on a cellular level. This multiscale model is a high-performance C++ implementation of a hybrid cellular automaton which simulates large cell populations (≤107 cells) in vitro while allowing individual cell cycle progression, proliferation, and treatment response. Based on physical heat and/or radiation dose distributions, the local surviving probability for each cell is calculated using the recently developed AlphaR model. In contrast to previous implementations [3], the framework allows for the simulation of radiation-induced mitotic cell death, as well as immediate cell kill in response to heating. A variance-based sensitivity analysis was used to rank the simulation parameters by their influence on the overall uncertainty of the simulation outcome.
Results: Cellular growth curves, cell cycle distribution measurements by flow cytometry, and clonogenic assays, were performed to calibrate the simulation framework to model the response of HCT116 cells.

Based on this calibration the dynamic growth response of these cells treated with radiation, hyperthermia, or combinations thereof was predicted for single and multiple treatment fractions and compared with experimentally measured growth data. Within the range of (thermal) doses tested (0-40 CEM43, 0-5 Gy), model predictions agreed very well (R2 > 0.95) with experimental data (see figure 1).
It was shown that it was essential to consider delayed mitotic cell kill and the relevant simulation parameters to correctly simulate the dynamic growth of the cell population in response to irradiation. In particular, for fractionated radiation or combination treatments, simulating immediate cell death would allow for a fast repopulation of a confluent cell layer and therefore underestimate the overall number of cells surviving the whole course of the treatment. For hyperthermia treatments alone, cell kill may be simulated as an instantaneous effect making the calculated surviving fraction the most influential factor for as confirmed by sensitivity analysis. For treatments involving irradiation, the sensitivity analysis showed that in addition to the overall surviving fraction, the simulation parameters controlling the cell death response were highly influential.
Conculsions: The proposed framework offers great flexibility in modelling treatment combinations in different scenarios and may now be used to compare different treatment schedules for combination treatments of radiotherapy and hyperthermia. It may therefore provide an important step towards the modelling of personalized therapies in a virtual patient tumour.

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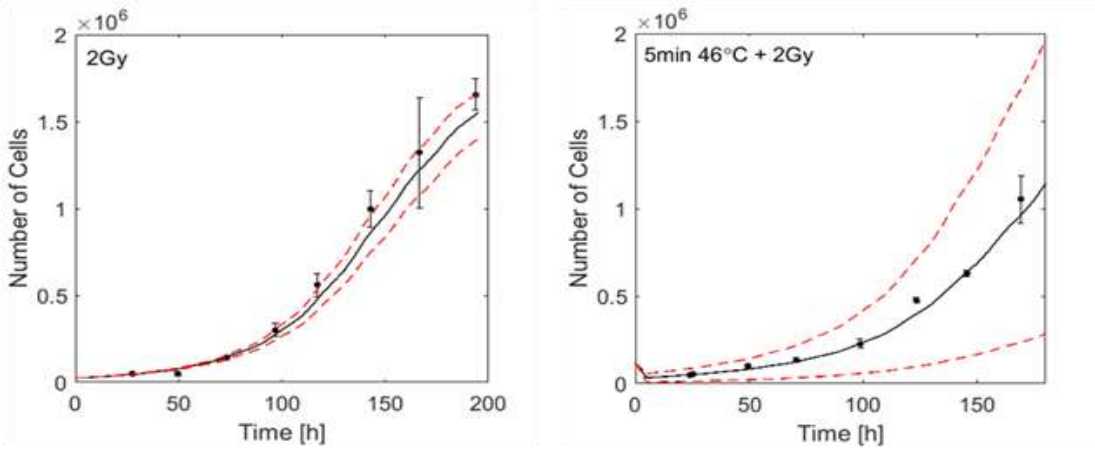

Figure 1. Simulation verification by comparing experimental and simulated growth curves for HCT116 cells treated with radiation ± heat. The mean experimental cell counts (with standard deviations) are shown, as are the simulated total cell numbers (solid lines), along with the 95% confidence bounds of the surviving fractions used (dashed lines). *Left:* 2Gy radiation (24000 cells seeded in 24-well plates, surviving fraction S_{2Gy} = 0.31(0.25, 0.37)). *Right:* Combination of 2Gy radiation and heating for 5min at 46°C (120000 cells seeded in 6-well plates, $S_{2Gy+5min,46C}$ = 0.03(0.01, 0.05)).

OP-32

The mitochondrial thermogenic Uncoupling Protein UCP1 is expressed in lung cancer and exhibits kinetics that parallels resistance to fever-range hyperthermia and hypothermia.

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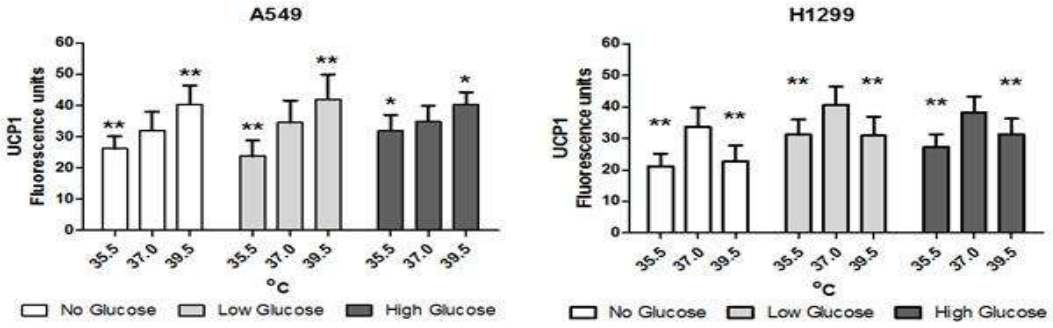
Uncoupling Proteins (UCPs) are a group of mitochondrial proteins residing in the inner membrane, aside to ATP synthase. While this latter generates ATP from ADP, UCPs generate heat. The role of thermogenesis in cancer cells is a new field of research. The response of UCPs to hyperthermia or hypothermia and how this may affect cancer cell thermo-resistance is unknown. Here we investigated the expression of UCP1 in two non-small cell lung cancer cell lines, namely A549 and H1299. In previous studies we had shown that A549 is thermophilic, sustaining its proliferation under fever-range hyperthermia (39.5oC), whilst H1299 is thermophobic and suffers a profound suppression of cell viability and growth. The proliferation ability of these two cell lines is strongly suppressed under hypothermia (35.5oC) UCP1 expression, as studied by confocal microscopy, was significantly induced in the A549 thermophilic cell line, whilst this was suppressed in the thermophobic H1299 one (Figure). Of interest, both cell lines exhibited a down-regulation of UCP1 under hypothermia, which parallels a strong suppression of cell proliferation. These findings were persisted under conditions of glucose deprivation or high glucose availability. To investigate the expression of UCP1 in human tumors, we performed immunohistochemistry in a series of 99 non-small cell lung cancer surgical specimens. Lack of UCP1 expression was noted in 55/99 (57%) of cases while expression in 10-40% of cells was noted in 33/99 (33%) and in 50-100% of cells in 10/99 (10%) cases. A significantly higher expression was noted in the squamous cell histology (p=0.04). In this preliminary study, we provide evidence that UCP1 is expressed in non-small cell lung carcinomas and, in in vitro studies, we provide evidence that resistance of cancer cells to fever-range hyperthermia goes along with the ability of cells to intensify this thermogenic mitochnondrial enzyme. Studies are in progress to investigate an eventual direct role of UCP1 in abrogating death pathways exploited by hyperthermia.



OP-33

Inhibition of proliferation, induction of apoptotic cell death and immune response by modulated electro-hyperthermia in C26 colorectal cancer allografts

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Introduction: Non-invasive modulated electro-hyperthermia (mEHT) can induce selective heat shock (at 42°C) and damage in tumors. Earlier we showed mEHT provoking significant apoptosis inducing factor (AIF) mediated cell death and immune cell infiltration in HT29 colorectal cancer xenografts of immunocompromised mice. In this study, we tested mEHT related damage responses using tumors grown in immunocompetent mice.
Methods: C26 colorectal cancer allografts were treated for 30 minutes using single shot mEHT. The expression of heat shock, growth-, damage signaling and immune response associated proteins was measured in situ and in vitro.
Results: Loco-regional mEHT treatment caused significant caspase-dependent apoptosis in C26 colorectal cancer allografts with reduced phospho-Raf 1; and elevated phospho-ERK1/2 protein levels of dominantly cytoplasmic localization. Ki67 protein expression disappeared completely from mEHT affected tumor cell nuclei. mEHT promoted the release of damage-associated molecular pattern (DAMP) proteins such as Hsp70, calreticulin and HMGB1. In line with this, the number of tumor infiltrating S100+ antigen-presenting dendritic cells and CD3+ T-cells showed major increase.
Conclusions: In immunocompetent mice, mEHT treatment interfered both with cell cycle progression and the MAP kinase related downstream growth pathway. Increased expression and translocation of phospho-EKR1/2 might contribute to caspase dependent apoptosis, which induced DAMP signalling and elevated immune response in C26 colorectal cancer allografts.

OP-34

The efficiency of modulated electro-hyperthermia may correlate with the tumor metabolic profiles

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Introduction: Elevated glycolysis (Warburg effect), lactate and ion concentration in cancer can contribute to selective tumor destruction by modulated electro-hyperthermia (mEHT) at ~42°C. In this study we correlated mEHT treatment efficiency and the glycolytic profile in 3 tumor cell lines.
Methods: Levels of glycolytic enzymes, metabolites of glycolysis and oxidative phosphorylation, as well as pH and buffer capacity were tested in mouse (C26) and human colorectal carcinoma (HT29), and in human hepatocellular carcinoma (HepG2) cell cultures. These cell lines were also grown in mice and treated with mEHT.
Results: Intracytoplasmic lactate levels measured using mass spectrometry were 58% higher in C26 than in HT29, and 37% higher than in HepG2 cells. Citrate levels were 119 % higher in C26 than in HepG2, while only 32% higher than in HT29 cells. Buffer capacity was the lowest in the medium of C26 cell line, suggesting the most acidic environment. In line with this, in vivo tumor destruction ratio 24h after

treatment showed also a similar tendency: HT29 ≥C26>HepG2. Immunohistochemistry demonstrated high glycolytic enzyme levels.
Conclusion: Glycolytic profile, particularly elevated acidification and ion concentration supports the accumulation of electric field in tumors and the effectiveness of mEHT treatment.

OP-35

Hyperthermia induced by ultrasound combined with radiation therapy to improve treatment of cancer

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Introduction
Hyperthermic temperatures (40-45°C) can be precisely generated in tissue by the use of ultrasound (US)[1],[2] and can be controlled in real time during the treatment. The aim of SONO-RAY project is to use the synergistic effect of heat and mechanical effects produced by sound waves as well as ionizing radiation (RT) in order to improve the results of radio-oncological treatments of malignant solid tumors and metastases. Combination success of hyperthermia with radiation therapy and chemotherapy was shown in the literature but very few have reported by using ultrasound for hyperthermia[3]. Regarding poor availability of data which shows the impact of acoustic waves on tumor cells and tissue in detail, physical and biological effects are being investigated and the synergy of US and RT will be quantified in simulation, cell, and small animal studies. The project aims at developing a proof-of-concept system and workflow for the translation into clinical use.
Methods
An in vitro cell sonicator with 1.14 MHz single transducer made by piezoelectric ceramic material was employed and allows individual sonication for wells in a 96-well plate. T98G glioma cells were exposed to intensities of 71 W/cm² and 109 W/cm² with hyperthermia duration of 134 sec and 65 sec, respectively. A 150 kV X-ray machine (DARPAC 150-MC) was employed for irradiation at doses of 0-20 Gy to investigate the radiation dose curve of T98G cells. For US and RT combinations, 5 and 10 Gy were used to treat T98G cells 24h post sonication. Effects at the cellular level on metabolism (WST-1), proliferation (BrdU) and membrane integrity (LDH release) were detected after treatment.
Results
The preliminary RT results showed dose dependent loss in cellular NAD(P)H levels of 60 % for T98G cell lines at 20 Gy. A release of LDH indicating membrane damage was observed from 4 % (0 Gy) to 17 % (20 Gy). The highest impact of RT was detected during analysis of DNA synthesis (BrdU) which nearly stopped at dosages above 5 Gy. In terms of the first US and RT combination experiment, there is no higher LDH release in the combination therapy group in comparison to US or RT single treatment groups. In contrast, cells treated by combination of US hyperthermia at 40-45 °C for 65 sec with 10 Gy irradiation treatment suggested lower cell viability of 81 % (WST-1 assay) in comparison to treatment of US hyperthermia only (97 % viable cells) and RT only (90 % viable cells).
Conclusion
In conclusion, longer US hyperthermia duration from 100 sec to 1000 sec should be further investigated in combination with RT treatment. The interval between US hyperthermia and RT treatment will be

examined within 8 h according to literature[3]. A fitted treatment for different cell lines will be necessary based on the different radiosensitivities[4]. Future in vitro investigations of effects of US hyperthermia as well as of a combined therapy on other tumor cells need to be conducted.

OP-36

PARP1-inhibitor improves the synergistic effect of thermal radiotherapy in breast cancer cells

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Background: As Poly(ADP-ribose)polymerase1 (PARP1) is a key player in regulating DNA replication, inhibition of PARP1 can cause collapsed DNA forks resulting in genomic instability. Therefore, PARP1 inhibition makes DNA more susceptible to the development of fatal DNA double strand breaks. DNA damage induced by PARP1-inhibitors (PARP1-i) is generally repaired by homologous recombination (HR), for which BRCA2 proteins are essential. As a result, BRCA2-deficient tumor cells are susceptible to treatment with PARP1-i. Recently BRCA2 was shown to be temporarily downregulated by hyperthermia (HT), thereby inactivating HR for several hours and therefore PARP1-i's might be a good sensitizer for hyperthermia treatment.
Methods: In this study we investigated whether HT exclusively interferes with HR by testing the hyperthermic radiosensitization on BRCA2-proficient and deficient cells. After elucidating the equitoxicity of PARP1-i on BRCA2-proficient and deficient cells, cell survival, apoptosis, DNA damages (γ-H2AX foci and comet assay) and cell cycle distribution after different treatments were investigated.
Results: Results confirmed that sensitivity to PARP1-i strongly depends on the BRCA2 status. Both BRCA2-proficient and deficient cells show radiosensitization by HT, indicating that HT does not exclusively act by inhibition of HR. In all cell lines, the addition of HT to radiotherapy and PARP1-i resulted in the lowest cell survival, the highest levels of DNA damages and apoptotic levels compared to duo-modality treatments.
Conclusions: Concluding, HT not only inhibits HR, HT is also capable of radiosensitizing BRCA2-deficient cells. Therefore, combining HT with PARP1-i not only boost the effectiveness of treatments of BRCA2 proficient tumors but is also beneficial for BRCA2-mutation carriers. The combination therapy would be effective for all patients with PARP1-i regardless of their BRCA status.

TOPIC: THERMAL ABLATION

OP-37

Percutaneous microwave ablation of renal cell carcinoma using a high power microwave system: focus upon feasibility, safety and efficacy

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INTRODUCTION: Small- to medium sized renal masses are increasingly imaged as incidental findings requiring a treatment strategy which preserves renal function and minimizes procedural morbidity. Percutaneous ablation is an expanding, minimally invasive approach. The purpose of this study is to review feasibility, safety, and mid-term efficacy of percutaneous microwave ablation (MWA) for Renal Cell Carcinoma (RCC) treatment using a high power microwave system.
METHOD: Institutional database research identified 48 consecutive patients with a single RCC lesion (biopsy proven) who underwent percutaneous microwave ablation using a high power microwave system. All patients had undergone biopsy on a different session using an 18 G semi-automatic soft tissue biopsy needle. Contrast-enhanced computed tomography or magnetic resonance imaging was used for post-ablation follow-up. Patient and tumor characteristics, microwave technique, complications, and pattern of recurrence were evaluated.
SIMULATION: Mean patient age was 74 years (male-female: 31-19). Average lesion size was 3.1 cm (range 2.0-4.3 cm). The 3-year overall survival was 95.8% (46/48). Two patients died during the 3-year follow-up period of causes unrelated to the MW ablation and to the RCC. Minor complications including hematomas requiring nothing but observation occurred at 3% (6/50) of the cases. Local recurrence of 6.25% (3/48) was observed with 2/3 cases being re-treated achieving a total clinical success of 97.9% (47/48 lesions).
CONCLUSION:
Percutaneous microwave ablation of RCC using a high power microwave system is a feasible, safe, and efficacious technique for the treatment of small- to medium sized renal masses.

OP-38

High power microwave platforms for ablation of hepatocellular carcinoma lesions in challenging locations

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Introduction: Purpose of the study is to evaluate clinical efficacy/safety of CT-guided percutaneous microwave ablation for HCC lesions in challenging locations using high-power microwave platforms.
Methods: A retrospective review was conducted in 26 patients with 36 HCC lesions in challenging locations (hepatic dome, subcapsular, close to the heart/diaphragm/hepatic hilum, exophytic) undergoing CT-guided percutaneous microwave ablation in a single centre since January 2011. Two different microwave platforms were used both operating at 2.45 GHz: AMICA and Acculis MWA System. Patient demographics including age, sex, tumor size and location, as well as technical details were recorded. We evaluated technical success, treatment response and complication rate.
Simulation: In this retrospective review treated tumours were located in the hepatic dome (n=14), subcapsularly (n=16), in proximity to the heart (n=2) or liver hilum (n=2), while two were exophytic lesions (n=2). Mean tumor diameter was 3.30 cm (range 1.4-5 cm). In 3/26 patients due to tumor size (diameter >4cm) an additional session of DEB-TACE was performed. Technical success rate was 100%; complete response rate was recorded in 33/36 lesions (91.6%). Overall survival rate was 92.3% over 24 months of follow-up. There were no major complications; two cases of minor pneumothorax and two cases of small subcapsular hematoma were resolved only with observation requiring no further treatment.

Conclusion: CT-guided percutaneous microwave ablation for challenging hepatocellular carcinoma lesions including subacpsular or exophytic lesions and those located in the hepatic dome or in proximity to heart/diaphragm/hepatic hilum can be performed with high efficacy and safety rates.

TOPIC: CHEMOTHERAPY & BIOLOGY

OP-39

Boosting cervical cancer thermo-sensitivity to radiochemotherapy with Parp-inhibitors

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ORAL SESSION 5, Parallel Conference Hall, June 23, 2017, 8:40 AM - 10:30 AM

Introduction: DNA double strand breaks (DSBs) are a cytotoxic type of DNA lesion caused by ionizing radiation and chemotherapeutic drugs. The crucial pathways for repairing such lethal damages are the homologous recombination (HR) and non-homologous end joining (NHEJ) repair pathway which involves proteins like BRCA2, Rad51 and Ku70 , DNA-PKcs proteins respectively. Thermotherapy interferes with the HR pathway by deactivating BRCA2. Cisplatin (cDDP) works by interrupting the NHEJ pathway. And, adding a Parp-inhibitors(Parp-i) , blocks the activity of Parp1 , which is an essential protein in the NHEJ, back-up NHEJ and the single strand break repair mechanisms. The purpose of this study is to enhance the thermal sensitivity of therapy resistant cervical cancer cells with the support of Parp-i, which would consequently augment their response to radio- and / or chemotherapy in clinics.

Methods: Cervical cancer cells were treated with Parp-i, thermotherapy was given at 42˚C, with radiation doses (0-8Gy) and cDDP. Cell reproductive death was determined by the clonogenic assay. Comet assay was performed to measure the DNA damage, and the DNA double strand breaks were analysed by the γH2AX staining. To interpret the mechanisms of action expression levels of different DNA repair and apoptotic proteins were investigated by the western blotting.

Results: The combinatorial treatment of Parp-i and thermotherapy increased the efficacy of radio and chemotherapy as compared to thermo-radiotherapy and thermo-chemotherapy. It significantly decreased the reproductive cell death, increased DNA damage and γH2AX phosphorylation which was retained even after 24hr as observed in the comet assay and γH2AX staining. Western blotting revealed in the understanding the mechanism of action of Parp-i induced thermo-sensitivity.

Conclusion: Thermal sensitivity of cervical cancer to radiotherapy and chemotherapy is significantly enhanced by Parp-i incorporation.

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