L01
The Atzelsberg Circle study group for hyperthermia (ACSGH)

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The Atzelberg Circle study group (ACSGH) is an interdisciplinary meeting of experts working in the field of hyperthermia (HT). The aim of the meetings is to create a platform for interdisciplinary exchange to optimize treatment of cancer patients through the use of HT. The multicentric approach provides the opportunity to set up multicenter studies and maximizes chances of implementing HT as treatment standard for a broader range of indications. Input from different HT centers helps to improve clinical as well as preclinical data analyzing and improves understanding of the mechanisms underlying HT helping in the set-up of new scientific models. Participants come from different HT centers in Germany as well as from Italy, the Netherlands and Switzerland. The inclusion of further centers or institutions such as the ESHO is strongly intended. The possibility of interdisciplinary discussion offered by the collaboration not only fosters the generation of high-quality data for publication in high impact journals enhancing acceptance among different clinical specialties and by insurance companies but will also ensure acceptance of the jointly discussed protocols by the different disciplines involved.

The agenda of the meetings not only includes discussion of active studies as well as their actual recruitment but also addresses problems like endorsement, a major issue that can only be addressed with an improved body of evidence. The international character of the meeting is well suited for the adaption of protocols to the peculiarities of individual countries. One major technical topic currently under discussion is the improvement of MRI planning and MRI guided HT. The elaboration of guidelines for different modalities and for quality assurance is planned for the future.

Ongoing studies include the use of HT in bladder-, cervical-, rectal cancer as well as recurrent breast cancer. Successful studies supervised by the ACSGH include the Hyrec study initiated in Erlangen and the Rektum HT01 trial study from Tübingen. New studies looking at the role of HT in sarcoma treatment are currently in the planning stage. Further projects include improvements in documentation, joint agreements on aspects of quality assurance such as staff requirements, minimum training, treatment delivery, minimum technical requirements as well as the investigation of thermometric parameters and the evaluation of predictive values.

L02
Radiative deep hyperthermia in combination with radiotherapy: The current practice in Switzerland

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Introduction: Moderate hyperthermia is a potent and evidence-based radiosensitizer but the availability of hyperthermia facilities in Europe is low. Several indications are reimbursed for the combination of deep hyperthermia with radiotherapy (dHT+RT) in Switzerland if the indication is confirmed by the national Swiss Hyperthermia Network tumorboard (SHN-TB).

Objectives: To evaluate the patient flow through the SHN-TB, current practice and the patterns of care for dHT+RT in Switzerland.
Patients & methods: All indications presented to the SHN-TB for dHT+RT between January 2017 and June 2021 were evaluated and treatment schedules were analyzed using descriptive statistics.

Results: Of 183 patients presented for dHT at the SHN-TB, finally 51.9% (95/183) received dHT. At this time, only one center provided moderate radiative dHT based on ESHO guidelines. Patients showed a median age of 65 years (range 18-88). The most frequent reimbursed dHT indications were "local tumor recurrence and compression" (20%; 19/95), rectal (14.7%; 14/95) and bladder (13.7%; 13/95) cancer, respectively. For 25.3% (24/95) of patients, an individual request to the insurance company was necessary. 47.4% (45/95) of patients were treated with curative intent and 42.1% (40/95) received dHT combined with re-irradiation. 7.4% (7/95), 23.3% (22/95) and 69.5% (66/95) of patients were treated within a clinical study, analogous to a clinical study or in routine practice, respectively. 36.8% (35/95) were in-house patients and 63.2% (60/95) of patients were referred from other hospitals with a mean travel distance of 61.5 km (range 23-238km). The median number of dHT sessions was 6 (range, 1-10). DHT adherence was high with only six patients (6/95) not receiving the complete planned dHT sessions.

Conclusion: About 2/3 of patients receiving dHT+RT were referred from external hospitals indicating a general demand for dHT in Switzerland. The most common indications of these patients were re-irradiation, complex palliative situations, organ-preserving treatment combinations (bladder and rectal cancer, soft tissue sarcoma) and inoperable, bulky or radioresistant tumors. The patterns of care were diverse with respect to treatment indication. To the best of our knowledge, this is the first pattern of care study in a national cohort treated with dHT+RT. This insight will serve as a basis for a national strategy to standardize dHT+RT treatment schedules, evaluate and expand the evidence for dHT.

L05
The clinical benefit of hyperthermia in pancreatic cancer: a review of selected clinical trials

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Objective: Pancreatic ductal adenocarcinoma (PDAC) is the second leading cause of cancer death in the next decade. The aim of this presentation is to review whether hyperthermia added to radiotherapy and/or chemotherapy offers new aspects to improve outcome for pancreatic cancer patients.

Methods and materials: Selected clinical studies involving hyperthermia in pancreatic cancer patients will be presented. Primary outcome of treatment efficacy evaluated response rate and survival, and compared these effects between hyperthermia and control groups whenever reported in these studies.

Results and conclusion: Overall patients were treated with regional, intraoperative or whole-body hyperthermia, combined with chemotherapy, radiotherapy or both. Some studies including a control group showed better results in the hyperthermia group than in the control group. In summary, hyperthermia may positively affect treatment outcome for patients with PDAC. However, the quality of these studies is limited and future randomised controlled trials are needed to establish efficacy.
Tetramodal therapy for muscle-invasive bladder cancer with transurethral resection followed by radiochemotherapy in combination with regional hyperthermia: Early results of a multicenter phase IIB study

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Background Trimodal therapy consisting of transurethral resection of bladder tumor (TUR-BT) followed by radiochemotherapy (RCT) is a reasonable treatment option for patients with muscle-invasive bladder cancer (MIBC).

Objective The present study aims to investigate the efficacy of tetramodal therapy including regional hyperthermia (RHT).

Patients and methods Patients with stage T2-4 MIBC were recruited in two institutions, Cantonal Hospital Aarau and Charité Universitätsmedizin. Planned treatment consisted of TUR-BT followed by radiotherapy at doses of 55.8 to 58.2 Gy, weekly concurrent with platinum-based chemotherapy and weekly deep RHT sessions (41-43°C, 60 min). The primary endpoint was complete response six weeks after the end of treatment. Further endpoints were cystectomy-free rate, progression-free survival (PFS) and overall survival (OS). Acute and late toxicity was evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) v.4.03. Furthermore, quality of life (QoL) was assessed by the EORTC-QLQ-C30 and QLQ-BM30 questionnaires. The study was planned with a Simon’s two stage minimax design. Due to slow accrual an unplanned interim analysis was performed after the first stage.

Results Altogether 27 patients were included in the first stage of the study. Of these 27 patients, two patients had to be excluded because they did not meet the study’s inclusion criteria and four patients withdrew their consent during follow-up. In total, 21 patients with a median age of 73 years were assessable. Compliance with RCT was 95% and 85% received RHT with a median of 6 sessions (range: 3-7). Patients received a median thermal dose expressed as cumulative equivalent minutes at 43°C (CEM43°C) of 3.71 minutes (range: 0.31-25.56). Based on the imaging, cystoscopy and cytology results, the complete response rate of evaluable patients at 6 weeks after therapy was 14/15 (93%; 95% CI: 0.81-1.0). The 2-year cystectomy-free, PFS and OS rates were 95%, 76% and 86%, respectively. Tetramodal treatment was well tolerated with acute and late G3-4 toxicities of 10% and 13%, respectively. One year after therapy, a trend to a decrease in symptom scores was observed, indicating an improvement of various aspects of QoL.

Conclusion Tetramodal therapy of T2-T4 MIBC is promising with an excellent local response rate, very moderate toxicity and a good QoL in patients with locally advanced MIBC.
Towards deep hyperthermia for locally advanced head and neck cancer patients

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Hyperthermia in the head and neck (HN) region potentially increases the local control/cure of HN tumors. However, due to the low-availability of hyperthermia equipment and finance for hyperthermia studies, the number of studies and patient numbers are limited. In addition, in older studies superficial heating devices were used, which is suboptimal as not the whole tumor can be warmed up. We have therefore in-house developed and tested an applicator to apply deep hyperthermia, which is better suited to treat HN tumors. Although in earlier studies no adverse effects of HN hyperthermia were observed, the question is valid whether this also is true for deep hyperthermia in the HN region. The feasibility and safety of deep hyperthermia was tested by us in HN patients who were heavily pretreated. These patients had a recurrent or second primary tumor and hyperthermia was added as a last resort adjuvant to a second course of radiotherapy. We observed unexpected acute trismus, maximal grade II, in 4/22 patients, but no other acute or late toxicities related to deep hyperthermia in the HN region were observed. To further bring deep hyperthermia treatment in the HN region to the clinic, we are preparing a phase I-II trajectory in patients with radiotherapy for a newly diagnosed HN cancer. First, a dose finding phase I part is prepared, with the aim to find the dose limiting toxicity of deep hyperthermia in the HN region. Following this dose finding part, we aim to test for efficacy in subsequent phase II trial.

Salvage-Radiation Therapy and regional Hyperthermia for biochemical recurrent prostate cancer after radical prostatectomy

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Introduction: Patients with biochemical recurrence of prostate cancer (PC) after radical prostatectomy commonly undergo salvage radiation therapy (SRT) of the prostate bed as only curative treatment option, but still a significant proportion of patients develop further progression after SRT. Regional hyperthermia (HT) is well-known to improve tumor sensitivity to RT in several entities.

Objectives: Here we report cancer outcome data after recruitment of the first 65 patients of the single arm HTProlate Phase II trial combining SRT and HT compared with mature cancer outcome data from the dose intensified arm of the randomized Phase III trial SAKK 09/10.
Patients and Methods: Comparable PC patients with early biochemical recurrence after radical prostatectomy without macroscopic recurrence were recruited for both trials and SRT to the prostate bed without irradiation of the pelvic lymph node regions and without additional antiandrogen deprivation was performed. In the HTProstate trial a SRT dose of around 70 Gy and 7-10 sessions of HT were used. We conducted a preliminary matched pair analysis comparing the first 65 patients from the HTProstate trial to patients treated receiving 70Gy SRT alone within the SAKK 09/10 trial with respect to the endpoint freedom from biochemical progression.

Results: The analysis is still ongoing and the results will be presented at the ESHO 2022 annual meeting.

Conclusion: The final analysis of the total HTProstate sample size of 100 patients has to be awaited but the present preliminary analysis may serve as a first estimation of the potential effectiveness of the combined SRT and HT approach for PC patients with biochemical recurrence after radical prostatectomy.

L10
Four year survival results with a cost effectiveness analysis for locally advanced cervical cancer treated with chemoradiotherapy and modulated electro-hyperthermia

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INTRODUCTION: We have previously reported local disease control (LDC) and 3yr survival results from our ongoing Phase III randomised controlled trial in South Africa investigating chemoradiotherapy (CRT) + modulated electro-hyperthermia (mEHT) for the management of locally advanced cervical cancer. Here we present 4yr survival results with a cost effectiveness analysis (CEA).

METHODS: 210 participants were randomised (stratum: HIV; accounting for age and stage of disease), to receive CRT (external beam radiation; HDR brachytherapy; cisplatin), with/without mEHT. The mEHT treatments were administered twice per week (total 10 treatments), immediately before EBRT. Participants with FIGO stage IIB to IIIb disease, staged clinically, with adequate renal function and haematological values, and who signed an informed consent, were included. HIV-positive patients on antiretroviral therapy >6months/a CD4 count >200 cells/µL were included. Hazard Ratios (HR) and Odds Ratios (OR) are reported for overall survival (OS) and disease free survival (DFS), and a Markov model was used for the CEA. Approval was obtained from the local ethics committee (M120477; M704133) before recruitment began.

RESULTS: 198 participants were eligible for the OS analysis (mEHT: n=97; Control: n=101), and 200 were eligible for the DFS analysis (mEHT: n=98; Control: n=102). 60% of the participants who achieved LDC at 6 months post-treatment, achieved 4yr OS, while only 25% of the participants who did not achieve LDC survived 4yrs post-treatment (Chi squared: p<0.0002). The rate of OS was not significantly different between the two groups (mEHT: n=38[39%]; Control: n=31[31%]; HR:0.75; [95%CI]:0.53-1.07; p=0.112), however when the sample was analysed according to stage of disease, the difference between the two groups was significant for participants with Stage III disease (HR:1.59; [95%CI]:0.39-1.02; p=0.039). The DFS was more than doubled with the addition of mEHT (mEHT: n=36[36%]; Control: n=16[16%]; HR:0.65; [95%CI]:0.45-0.96; p=0.029), with an OR of 3.1 of achieving DFS status at 4yrs with the addition of mEHT ([95%CI]:0.1.59-6.12; p=0.001). The baseline CEA showed that CRT+mEHT was more effective and less costly over a three year cycle, compared to CRT alone.

CONCLUSION: These results continue to confirm the long term clinical benefits of the addition of mEHT to CRT, and demonstrate the feasibility of the technique, even in a resource-constrained setting.
L11 The combination of non-invasive ultrasound imaging and a 4-inflow preclinical HIPEC setup to ensure a thermal stability and uniform drug delivery during HIPEC treatments in a peritoneal metastasis confirmed rat model

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Introduction Cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC) is the only treatment with curative intent for patients with peritoneal metastases (PM) of colorectal cancer origin. There is a large variation in clinical application of HIPEC. Therefore, thorough investigation of HIPEC protocols is required, accounting for both effectivity and possible risk of systemic toxicity. To ensure this, a well-controlled and uniform flow and temperature are essential, as well as a representative preclinical model. A major challenge for these models is defining and quantifying the total tumor burden of PM prior to treatment.

Aim Evaluation of ultrasound as a simple and easy-to-handle imaging method to define and quantify tumor lesions in the peritoneal cavity and realization of well-controlled uniform flow and temperature distributions during HIPEC treatment in small animals.

Methods PM were established in WAG/Rij rats by i.p. injections of the colon carcinoma cell line CC-531. Using ultrasound, location, number and size of PM were determined by two independent observers. Tumor outgrowth was followed using ultrasound until the peritoneal cancer index (PCI) was ≥8. Interobserver variability and ex vivo correlation were assessed. When tumors reached 2-5 mm, rats were treated with PBS using our newly developed HIPEC setup using two different catheter setups (1 vs. 4-inflow) for 90-min with an inflow temperature of 42°C. Extensive peritoneal thermometry was performed during the treatment.
**Results** In most animals, tumor nodules reached a size of 4-6 mm within 3-4 weeks, with total PCI scores ranging from 10-20. Predicted PCI scores using ultrasound, ranged from 11-19 and from 8-18, for observer 1 and 2, respectively, which was quite similar to the ex vivo scores. The inflow temperature was higher in the 4-inflow setup compared to the 1-inflow (41.5°C vs. 42.3°C). Tail cooling proved an adequate technique to prevent rats from overheating during 90-min treatments. Using tail cooling, core temperatures remained stable and rarely exceeded 39°C.

**Conclusion** Ultrasound is a reliable non-invasive method to detect intraperitoneal tumor nodules and quantify tumor outgrowth in a rat model. The use of 4 instead of 1-inflow catheters increases temperature homogeneity and stability during HIPEC. This validated HIPEC setup combined with the rat PM model can improve accuracy in future in vivo experiments investigating the efficacy of HIPEC treatments.

**Fig. 1**

*Figure 1. Tumor growth over time in three regions in a rat using ultrasound. Tumor lesions are indicated with white arrows and organs are named (A). Total PCI, lesion size and lesion quantity scores predicted on ultrasound by 2 independent observers, as well as the ex vivo scoring are shown in these graphs (B).*
Intercomparison of temperature measurements during ultrasound exposure

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Introduction

Ultrasound-based therapies continue to develop and show promise as non-invasive tools for cancer treatments. High-intensity focused ultrasound (HIFU) can be used for both thermal ablation and hyperthermia. However, measuring the temperature during HIFU exposure can be quite challenging if the final aim is to measure it accurately.

Objectives

The aim of this work was an intercomparison between different ultrasound laboratories. With different experimental set-ups and different temperature probes the measurements obtained during an exposure to HIFU were compared. The comparison between laboratories investigated the role that metrology plays when reproducing the same experiment in various locations while changing some components of the measurement system.

Materials & methods

The ultrasound exposure system was reproduced by 3 laboratories. A HIFU transducer (H-101, Sonic Concepts, Washington, USA) was characterised (acoustic power and pressure) by all 3 institutions. The 1.1 MHz focused transducer was driven at 1.06 MHz using different acoustic powers (1 W, 2 W and 3 W) and exposure time (2 min, 3 min and 4 min). The sine wave was triggered using a gate with a period of 4.1 s and 97.6% duty cycle. The measurements were performed at the focal distance and 20 mm from the front surface of the tissue mimicking material (TMM), Figure 1. Four K-type thermocouples (T0, T1, T2 and T3) were placed in parallel, 2.5 mm apart from...
each other. The TMM was prepared according to Annex DD of IEC 60601-2-37 Edition 2:2007/2008 and acoustically characterised.

Figure 1 – HIFU sonication system for temperature comparison

Results

The system was reproduced by all partners with each one using a different size of thermocouple. The maximum temperature for each configuration increased with the power and the exposure time. Initial comparison showed results with an average of 24% difference in temperatures between laboratories.

Conclusion

The system was proven to be easily reproducible even when replacing some of the components. The first results demonstrated that the temperature measurements are comparable and that some aspects of the system (i.e. sensor size, temporal resolution, alignment) are crucial to obtain accurate results.

Fig. 1

L13
Quantitative analysis of trace elements in pancreatic carcinoma and pancreas sections by reference-free X-ray Fluorescence analysis

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To assess innovative medical therapeutic approaches the physical and chemical analysis of organic tissues with reliable and physically traceable methods is essential. The high complexity of biological samples requires a multimethod approach for complete characterization. Due to its non-invasive nature, reference-free X-ray Fluorescence (XRF) analysis is a suitable method in various applications. It allows to monitor treatment effects via the spatial distribution of the absolute elemental mass depositions of trace elements within samples. Here, the elemental sensitivity and detection sensitivity provided by XRF are crucial.

Within the RaCHy program malignant and benign pancreatic tissue sections of mice were analysed to assess radiotherapy treatment induced changes. Pancreas of healthy mice, mice with pancreatic cancer treated with radiotherapy or with untreated pancreatic cancer were extracted and sectioned. The dried tissue sections were fixated on glass slides and analysed by reference-free XRF to investigate differences and changes of the spatial absolute elemental mass depositions distribution of P, S, Cl, K and Ca between samples. The advantage of the reference-free XRF approach is the access to quantitative results by using radiometrically calibrated instrumentation.
and reliable knowledge of atomic fundamental parameters such that representative reference or calibration samples mimicking the biological samples under investigation are not required.

It was found that malignant tissue sections display an overall high tissue homogeneity as well as K and Cl gradients towards the periphery. Within the benign tissue sections, spatial differences of elemental mass depositions indicate the presence of various tissue types. Hence, discrimination capabilities between the benign and malignant tissue types have been confirmed allowing therapeutic effects to be evaluated and growth factors for tumorous tissue to be identified. As it is important to be aware of changes inflicted on biological samples during probing, repetitive measurements allowing the investigation of X-ray irradiation-induced changes in binding states of carbon and nitrogen compounds were conducted. In addition, over-time binding state degradation of carbon and nitrogen compounds of the tissue samples were observed.


L14 Therapeutic effects of radiotherapy and hyperthermia treatment on 3D tumor spheroids of three different cancer cell line

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INTRODUCTION: Conventional two-dimensional in vitro cell culturing of cancer cells do not represent the complex interactions of highly interconnected communication networks observed in three-dimensional tumor growth in vivo. Therefore, two-dimensional cell monolayers do not accurately represent a suitable in vitro tool to characterize cancer treatment’s therapeutic effects. Here, we investigate the viability of U87, MDA-MB-231 & FaDu tumor spheroids as a response to individual and combined hyperthermia and radiation treatment.

MATERIALS & METHODS: 3D spheroids were prepared using the liquid-overlay method at 2000 cells per 200 µl medium in U-shaped 96-well plates. The spheroids were exposed to external hyperthermia using a temperature-controlled water bath (Grant TX150) and radiation treatments using an X-ray beam (Xylon, Y.TU 320-D03). Spheroid growth was measured using a 12MP camera mounted on the binocular microscope using automated imaging software (SampleScan). Glo3D assay was performed to confirm the cell viability.

RESULTS & DISCUSSION: Increased radiation and hyperthermia doses decreased spheroids’ viability and growth. However, the effect was not apparent for the lowest hyperthermia doses (41˚C, 30 CEM43). Comparing the viability effects from different treatments on 2D and 3D cell cultures, the viability results were significantly lower for monolayer cultures than the spheroid cultures (20-30 % lower cell viability).

CONCLUSION: These results support the known fact that the treatment response for spheroids is different from monolayer cultures, with significantly higher resistance to radiation treatment for spheroids. Finally, the in vitro spheroids’ responses to combination treatment can be summarized as given below,

1. U87 cell lines are sensitized irrespective of treatment order.
2. MDA-MB-231 cell lines are sensitized by combining hyperthermia doses of 30 CEM43 followed by radiation doses of 6 Gy
3. FaDu cell lines are sensitized by combining radiation doses followed by hyperthermia doses of 120 CEM43
Development and implementation of a HIFU transducer-based system for a closed-loop controlled focused hyperthermia treatment

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Introduction

The ability to maintain a specific temperature in a target region is key to any hyperthermia delivery system, to achieve the desired effects, ensure necrosis is not induced (due to increased temperatures consistent with thermal ablation) or healthy tissue treated (requiring sufficient treatment localisation to avoid sensitising healthy tissue).

Objectives

The aim of this work was to design and characterise a heat delivery system using a HIFU transducer for focused ultrasound hyperthermia able to generate a uniform power deposition pattern in the target region with closed-loop computational control which would maintain hyperthermia at a defined temperature indefinitely.

Materials & methods

The hyperthermia delivery system was designed with an adapted HIFU transducer (SU103 S/N 101, Sonic Concepts, Washington, USA), fully characterised by NPL. The 3.57 MHz focused transducer, and a deionised-degassed water filled stand-off cone, sealed with a 12 µm thick Mylar layer, was attached to the face designed to achieve an exposure area of 10 mm² at the contact surface. A novel phantom device was designed to test the system performance, the main body of which was an IEC agar with 5 K-type thermocouples (SSRTC-TT-KI-40-1M, Omega, UK) placed across the phantom and a thermochromic layer placed on its surface. 100 exposures were performed, with the temperature achieved recorded over the heating phase for 4 minutes and the cooling phase for 4 minutes. Using both thermocouples and thermochromic tissue mimicking material, the temperature achieved, stability and localisation of the treatment were assessed. The system was transferred to a preclinical laboratory and initial studies were performed on small animals, monitoring the temperature increase at the face of the transducer standoff cone.

Results

The system was fully characterised and tested on tissue-equivalent phantoms containing embedded thermocouples. The recorded temperature increase was compared to the RGB colour-change in the thermochromic material. Initial tests on small animals were successful.

Conclusion

The system allowed the temperature of the phantom to be increased by 6 ºC above body temperature and maintained indefinitely. The increase in temperature correlated with the RGB analysis of the thermochromic TMM. The developed system has been used for phantom and small animal proof-of-principle studies. The developed phantom test device may be used for testing other hyperthermia systems.
Combination of ultrasounds hyperthermia and radiotherapy on a preclinical glioblastoma model

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Introduction
Glioblastoma (GBM) is one of the most malignant brain tumours, with a short life expectancy and an elevated mortality because of the lack of effective therapies and, thus, innovative treatments need to be developed. In this work a combined ultrasounds (US) hyperthermia (HT) with radiotherapy (RT) using a preclinical GMB model has been investigated.

Material and methods
A GBM xenograft nude mouse model obtained by injecting 2x10⁶ U87 luc+ cells was used to study the combination of HT and RT on the tumour growth. Mice were divided into three groups of five mice each. The groups received respectively: PBS treatment (control group), a combination of RT 6 Gy and HT 43 degrees for 7 min, RT 6 Gy (RT alone group). The HT treatment was delivered 1 minute after RT. The ultrasound field was generated by a closed-loop computationally controlled system, consisting of a HIFU, High Intensity Focused Ultrasound, transducer with centre frequency 3.57 MHz, a power amplifier, a function generator and a MATLAB® controller developed at NPL. A mechanical cone adaptor has been developed to use the HIFU beam at a pre-defined post-focal distance. Two thermocouples were placed between the mechanical cone and the skin mice to measure and control the temperature during the HT treatment. Radiotherapy was carried out by using a dedicated small animal image guided radiotherapy system. The dose planning was based on the CT scan of the animal and performed using a Monte Carlo treatment planning system. RT has been delivered in a single fraction using 2 opposite beams. Bioluminescence imaging (BLI), calliper measurements and CT imaging were performed before and after treatments in order to monitor the tumour growth.

Results
Daily measurements of tumour volume performed with a calliper show a 25% reduction for the HT+RT group with respect to the RT or control groups. A similar trend has been found using optical BLI, however in this case the differences between the groups is lower (10%). Ex vivo analysis will be performed on the tumour regions.

Discussion and Conclusion
Preliminary results show that the combination of HT+RT allows a better tumour control over a period of two weeks with respect to RT alone. In particular these data suggest that the use of HT as a radiosensitizer can reduce the RT dose delivered to the animal and, thus, limit the side effects on normal tissues.
Design and characterization of an RF applicator for in vitro tests of electromagnetic hyperthermia

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Question

The study of the biological effects of therapeutic hyperthermia in oncology and the precise quantification of thermal dose, when heating is coupled with radiotherapy or chemotherapy, are active fields of research [1]. The reliable measurement of hyperthermia effects on cells and tissues requires a strong control of the delivered power and of the induced temperature rise [2].

To this aim, we have developed a radiofrequency (RF) electromagnetic (EM) applicator based on a coaxial TEM design [3], consisting of an open-ended coaxial line with a hollow inner conductor operating at 434 MHz and specifically engineered for in vitro tests on 3D cell cultures.

Methods

The RF applicator has been designed with the aid of an extensive modelling analysis, which combines EM and thermal simulations. Subsequently, the heating performance of the built prototype has been validated by means of temperature measurements carried out on tissue-mimicking phantoms and aimed at monitoring spatial and temporal variations of temperature. Temperature was acquired with both an array of fiber-optic thermometers and IR thermal camera.

Results

As schematized in Fig. 1, the built RF applicator consists in an outer cylindrical conductor connected to the metallic shield of the feeding coaxial cable and a hollow inner cylindrical conductor, connected to the coaxial cable core. The inner conductor is engineered to irradiate the EM field in a specific target region, centered in the aperture. Thermal measurements on agar gel phantoms have proved that the RF applicator is able to guarantee a strong uniformity of the temperature in the target region (Fig.2) and a stable maintenance of the desired temperature, achieved with a simple tuning of the supplied power.

Conclusion

We demonstrated the RF applicator ability to reliably deliver heat in a localized and controlled manner, guaranteeing strong uniformity and stability of the temperature increase in the target region. The tuning of the supplied power also enables to precisely modulate the heating transient duration and the rate of temperature change over time. After characterization on phantoms, the applicator has been successfully employed in in vitro tests, confirming again its effectiveness.

Fig. 1

Fig. 2
In silico experiments as a tool to guide magnetic hyperthermia preclinical tests

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\textbf{Question} In magnetic hyperthermia, the temperature increase in diseased tissues is achieved after the administration and activation of magnetic nanoparticles (MNPs), which release heat when exposed to AC magnetic fields with frequency of 50-500 kHz. The evaluation of MNP efficacy involves preclinical studies, generally conducted on murine models [1]. During \textit{in vivo} tests, several factors have to be considered to optimize heat deposition and reduce side-effects, like hot spots caused by eddy currents. These factors comprise the fulfilment of biophysical limits when selecting field parameters [2], the dependence of MNP specific heating power on experimental conditions, the field applicator geometry and positioning, and the spatial distribution of MNPs within the tumor, strongly influenced by administration route. This scenario requires the development of methodologies able to guide the experiments on animals and support the result interpretation, for a possible translation to humans.

\textbf{Methods} In this context, we developed \textit{in silico} models to support \textit{in vivo} tests of magnetic hyperthermia [3]. We focused on the evaluation of the possible eddy currents induced in the body during hyperthermia sessions and the calculation of thermal effects, consequent to MNP excitation. The simulations were performed on digital phantoms of murine models (mice and rats), with a high-resolution reproduction of tissues and organs.

\textbf{Results} Different applicators were compared, studying the role of geometry and position on the magnetic field distribution within the target tissue. To avoid adverse eddy current effects, we considered the Herg-Dutz limit for selecting field frequency and amplitude. \textit{In silico} experiments were then performed to evaluate the heating effects produced by MNPs, versus MNP dose and spatial distribution. The figure shows the results obtained for a 500 g rat, when treating tumor with iron oxide NPs activated by a 150 kHz magnetic field, generated by a solenoid placed in close proximity to the target region.

\textbf{Conclusions} The obtained results showed the utility of \textit{in silico} experiments in guiding magnetic hyperthermia preclinical tests, enabling a proper selection of treatment parameters, the prediction of possible adverse effects and the estimation of temperature increase in target region, versus MNP type, dose and distribution.

L20

Immune infiltrates in patients with localised high-risk soft tissue sarcoma treated with neoadjuvant chemotherapy without or with regional hyperthermia: A translational research program of the EORTC 62961-ESHO 95 randomised clinical trial

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**Background:** The EORTC 62961-ESHO 95 randomised trial showed improved long-term survival of patients with high-risk soft-tissue sarcoma by adding regional hyperthermia to neoadjuvant chemotherapy. We hypothesised that immune infiltrate of patients treated with neoadjuvant therapy associate with clinical outcome.

**Methods:** Tumour infiltrating lymphocytes (TILs) and CD8, FOXP3, PD-1, and PD-L1 were evaluated in sequential biopsies of patients after four cycles of therapy.

**Results:** From a subgroup of 109 patients who had been randomised between July 1997 and November 2006 to neoadjuvant chemotherapy (53 patients) or neoadjuvant chemotherapy with regional hyperthermia (56 patients), 137 biopsies were obtained. TILs increased in paired second biopsies independent of treatment allocation (p < 0.001). FOXP3 regulatory T cells decreased (p = 0.002), and PD-L1 expression of tumours became undetectable. In the multivariate analysis, post-treatment high TILs correlated to LPFS (HR: 0.34; 95\% CI 0.15–0.75; p = 0.008) and DFS (HR: 0.38; 95\% CI 0.17–0.82; p = 0.015). In comparing post-treatment immune infiltrate between treatment arms, tumour response was associated with neoadjuvant chemotherapy with regional hyperthermia (p = 0.013) and high TILs (p = 0.064). High CD8 cell infiltration was associated with improved LPFS (HR: 0.27; 95\% CI 0.09–0.79; Log-rank p = 0.011) and DFS (HR: 0.25; 95\% CI 0.09–0.73; Log-rank p = 0.006). Improved survival at 10 years was associated with immune infiltrate after neoadjuvant chemotherapy with regional hyperthermia.

**Conclusion:** Preoperative therapy re-programs a non-inflamed tumour at baseline into an inflamed tumour. The post-treatment immune infiltrate became predictive for clinical outcomes. The combination with regional hyperthermia primes the tumour microenvironment, enabling enhanced anti-tumour immune activity in high-risk soft tissue sarcomas.
Does hyperthermia and radiation therapy sequence influences cell death and the immune phenotype of breast cancer cells?

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Hyperthermia treatment (HT) is a very potent sensitizer for radiotherapy (RT) and its combined use is effective in recurrent breast cancer. Additionally, HT has broad effects on the innate and adaptive immune system, and potentially strengthen systemic antitumor immune responses. However, currently little is known about how HT of distinct temperatures and in particular how the sequence of HT and RT affects the immunophenotype of breast cancer cells. Also, the effect of HT and RT on the activation of dendritic cells needs further elucidation as well. Therefore, human MDA-MB-231 and MCF-7 breast cancer cells were treated with HT of different temperatures (39, 41 and 44 °C) alone and in combination with RT (2 x 5 Gy) in different sequences, with either RT or HT first followed by the other. Tumor cell death forms and the expression of immune checkpoint molecules (ICMs) were analyzed by multicolor flow cytometry. Human monocyte-derived dendritic cells (moDCs) were differentiated and co-cultured with the treated cancer cells, then the expression of DC activation markers was analyzed.

Our experiments showed that in both cell lines RT was the main inducer of cell death with apoptosis being the most prominent cell death form in MCF-7 cells, and both apoptosis and necrosis in MDA-MB-231 cells. The sequence of the combined treatments was not significantly different in case of inducing cancer cell death. The expression of suppressive immune checkpoint molecules (ICMs) namely PD-L1, PD-L2, and HVEM was significantly increased after 120h of RT and HT treatment in MCF7 cells. In MDA-MB-231 cells, PD-L2 was upregulated after the treatment of RT with HT of 41 and 44°C. Likewise, generally high dynamics of ICM expression is observed after combined RT and HT, however there was no significant difference between the different sequence of combined treatments regarding ICM upregulation. Additionally, the co-culture of moDCs with tumor cells of any treatment had no impact on the expression of DC activation markers.

In conclusion, the sequence of HT and RT doesn’t strongly affect the immune phenotype of breast cancer cells. However, the combined treatments result in upregulation of particularly immune suppressive ICMs. This matter should be considered in multimodal treatment settings by including immune checkpoint inhibitors in combined treatment of HT and RT. Lastly, RT and HT combination affects the immune system in the effector phase rather than in the priming phase.
The thermal and immunogenic potential for PBNP-based ablation of solid tumors

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Photothermal therapy (PTT) is a thermal-based therapy in which laser light is absorbed by photothermal agents, such as light-absorbing nanoparticles, to generate heat in tumors. While the leading effects of PTT are tumor cell death and ablation, PTT can also activate an antitumor immune response that could be harnessed for robust and durable treatments against solid tumors. Our group has implemented Prussian blue nanoparticles (PBNPs), an FDA-approved material, for PTT with immunotherapies, including TLR agonists,1,3 checkpoint inhibitors,2,4 and agonistic antibodies,5 to potentiate the PTT-induced antitumor effects against syngeneic models of neuroblastoma, melanoma, and breast cancer. Through these studies, we seek to treat tumors with PBNP-PTT thermal doses that 1) elicit maximal tumor ablation/regression without recurrence while 2) simultaneously inducing an immunogenic PTT-generated in situ vaccine for enhancing the effective immune response against cancer. In our recent work, we demonstrate that interstitially administered PBNP-PTT (I-PTT) expands the treatment zone by generating heating patterns that differ from superficially administered PTT (S-PTT), resulting in effective tumor ablation (Fig1). In syngeneic neuroblastoma murine models, the heating with I-PTT improved the tumor-free survival and reduced the therapeutic thermal dose, while presenting some protection against tumors in rechallenge models. We have also shown the upregulation of immunogenic markers on PTT-treated human neuroblastoma cells that could enhance the tumor’s susceptibility to T cell-mediated killing (Fig2).6 which is essential as T cells are critical to observe therapeutic antitumor responses in PBNP-PTT and immunotherapy combinations.2,4 Thus, our group’s findings demonstrate the promising potential of PBNP-based ablation to thermally eliminate tumors while eliciting therapeutically favorable immune responses highly receptive to immunotherapies for robust cancer elimination. Fig1. Tumor-free survival after I-PTT with PBNPs (Ledezma, et al. under review).Fig2. PBNP-PTT stimulated T cell-mediated killing of neuroblastoma cells (Sekhri, et al. 2022). 1. Cano-Mejia, J., et al. Biomater Sci, 2019, 7 (5), 1875-1887. 2. Cano-Mejia, J., et al. Transl Oncol, 2020, 13 (10), 100823. 3. Shukla, A., et al. Adv Nanobiomed Res, 2021, 1 (8). 4. Cano-Mejia, et al. Nanomedicine, 2017, 13 (2), 771-781. 5. Balakrishnan, P.B., et al. Nano Res, 2021. 6. Sekhri, P., Cancers (Basel), 2022, 14 (6):1447.
Fig. 1

Fig. 1.

[a) Fig. 1. (a) Temperature (°C) over time (minutes) for S-PTT and I-PTT treatments.

[b) N2A and 9464D cells under S-PTT and I-PTT treatments.

[c) N2A tumor-free survival over 80 days after inoculation for Control, S-PTT, and I-PTT treatments.

[d) 9464D tumor-free survival over 80 days after inoculation for Control, S-PTT, and I-PTT treatments.

Fig. 2

Fig. 2.

[e) Fig. 2. (a) Schematic diagram of PINP-PTT and SH-SYSY cells coculture with LAN-1 and T cells.

[b) SH-SYSY and LAN-1 cell killing under different thermal dose treatments.

Please be aware that all abstracts are printed as submitted. Editorial deadline: 5 September 2022
Epithelial ovarian cancer (EOC) is the most lethal gynecologic cancer with an average survival of two years. In 2022, it is estimated that 19,880 cases of EOC will be diagnosed and that 12,810 patients will succumb to their disease in the U.S. Hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a treatment paradigm that significantly increases the survival of EOC patients and is being adopted as a standard clinical approach for management of these tumors. While the clinical results are encouraging, there is a need to understand the cellular and molecular mechanisms underlying the HIPEC response to develop biomarkers and new therapeutic strategies to extend overall patient survival. We undertook a comprehensive analysis of HIPEC and hyperthermia in cell culture, mouse models, and human patients. We employed an innovative clinical strategy to harvest matched tumor specimen from high grade serous ovarian cancer patients at time of interval debulking surgery before and immediately after HIPEC to define the cellular and molecular alterations in the tumor microenvironment during treatment (Fig. 1). In patients treated with HIPEC, single cell (sc)RNA-sequencing demonstrated a robust increase in heat shock response which was most significant in select populations of CD8+ T cells, B cells, and dendritic cells with limited response in tumor cells. We identified rapid increases in MHCI and MHCII levels post treatment, supporting priming of antigen presentation. Using a mouse model to study hyperthermic chemotherapy treatment, we determined that hyperthermic cisplatin leads to suppression of tumor growth compared to normothermic cisplatin treatment and importantly requires an intact immune system. Using this model, we analyzed the impact of hyperthermic chemotherapy on immune infiltration. At 24 hours, CD8+ and CD4+ T cells were increased post hyperthermic chemotherapy treatment compared to normothermic chemotherapy. After 2 weeks, CD8+ and CD4+ T cells remained elevated as well as elevated regulatory T (Treg) cells in hyperthermic chemotherapy treatment compared to normothermic treated mice. The mouse studies complement the (sc)RNA-sequencing findings that heat activation targets immune cells during HIPEC (Fig 2). Our findings provide the foundation for mechanistic studies focused on the immune system in HIPEC and yield insights on how HIPEC orchestrates the ovarian cancer tissue response to improve patient survival.
Fig. 1

Process for HIPEC Specimen Collection and Analysis

Epithelial ovarian cancer
Patient consented for cytoreductive surgery and HIPEC

Tissue Collection
Single Cell Suspension
Single Cell RNA-seq
Data Analysis and Visualization

Fig. 2

Hyperthermia Activates the Immune System to Enhance Chemotherapeutic Response
Photothermal therapy using immunostimulatory Prussian blue nanoparticles generate potent antigen-specific T cells for solid tumors

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Fig. 1

Contralateral transient contrast enhancement in a patient with IDH1wt MGMT promoter-methylated GBM responding to TMZ and individualized multimodal immunotherapy

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Question. Immunotherapy-induced MRI changes remain challenging when treating GBM patients with immunotherapy as part of a combined treatment. The iRANO criteria provide a decision-tree in order to avoid over- and under-treatment reactions when contrast-enhancing lesions become visible and should be interpreted. Given the challenges for making clinical decisions for patients, reporting novel observations remains important. Case report. We report a 34-year female, 34 weeks pregnant, who presented with epilepsy, and was diagnosed with inoperable IDH1wt MGMT promoter-methylated GBM after biopsy. On MRI, the left occipital lesion was mostly cystic-necrotic with peripheral contrast enhancement, and crossed over the corpus callosum to the right. The volume was calculated as 64 cm³ (abc/2 formula). She was treated with radiochemotherapy and 12 TMZm cycles. Within each TMZ cycle 5 days of immunogenic cell death (ICD) therapy (5 injections with Newcastle Disease Virus and 5 sessions of modulated electrohyperthermia (Oncotherm 50 min 40-60 Watt) was added at days 8 to 12. After all chemo-/ICD-therapy we continued with active specific immunotherapy: two autologous mature monocyte-derived dendritic cell vaccines loaded with ICD therapy-induced serum-derived antigenic extracellular microvesicles and apoptotic bodies (IO-Vac®).
One month after the second IO-Vac®, 17 months after diagnosis, a transient right FLAIR-visible region showed expansion, and three months later also diffuse contrast enhancement, which was confirmed in a control scan one month later. The original tumor was meanwhile reduced to 16 cm³. However, in the last available scan, two months after the former, the contrast enhancement was disappeared, and the pathologic area on FLAIR was diminished. The original tumor size was reduced to 2 cm³, two year after first diagnosis. She showed allergic skin reactions to TMZ, which was covered with systemic histamine intake. There were no side effects related to individualized multimodal immunotherapy. Conclusion. Transient MRI changes can be observed even in distance from the original tumor and still can be interpreted as immune-mediated effects, rather than relapse, when the original tumor is responding.

L26
Hyperthermia system development in the perspective of the new European medical devices regulation

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³Introducing.

1. Introduction

The European Medical Devices Regulation (MDR) 2017/745 is a new set of directives that governs the production and distribution of medical devices in Europe, with the purpose to set high standards of quality and safety. Implementing these directives when developing a hyperthermia system is a complex task which requires understanding of safety standards, regulations as well as demands on the performance of the heating device.

2. Objectives

The aim of this contribution is to provide an overview of the main aspects which shall be considered while developing a system intended to deliver hyperthermia. We focus on external RF/MW devices, that operate at frequencies between 50 MHz and 1GHz.

3. Materials & methods

The V-Model for product development was adopted. In this model, the left arm represents the requirements on the system at different phase of development, first on a general level, and then for each subsystem and single components. The right arm then describes the validation against these requirements, thus defining the relationships between each phase of the development life cycle and its associated phase of testing.

4. Results

We defined the Intended use of the device, classified it as class IIB device and identified all the relevant ISO and IEC standards. Our research resulted in thirty different applicable standards regarding the electrical and biological safety, as well as the suitable guidelines developed by various societies. We divided the HT system into four subsystems (signal amplification, applicator, temperature monitoring, treatment planning) and proposed testing strategy for each of them, and later for the entire system. We recognize the eventual EM interference between different components as one of the major concerns associated with inaccuracies at heat delivery at almost all system levels. A final risk analysis, performed according to standard IEC 60812, suggests the strategies to mitigate the risks associated with use of the device.

5. Conclusion

The proposed procedure can help the researchers and technicians involved in the clinical implementation of the hyperthermia technology to assure an appropriate development process, that is in full compliance with the above-mentioned regulation.
Comparison of the clinical performance of the Alba 4D and AMC-4 locoregional hyperthermia systems

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Objective: The 70 MHz AMC-4 locoregional hyperthermia system developed at the AMC (Amsterdam, The Netherlands), has been in clinical use from 1984 until 2019. Recently, this system was commercialized as the Alba 4D (Medlogix\textsuperscript{®}, Rome, Italy), utilizing the same geometrical 4-waveguide design. Electric field measurements in tissue-mimicking phantoms showed similar heating patterns and reliable phase control. This study evaluated the clinical performance of the Alba 4D compared to the AMC-4.

Methods: During one year after clinical acceptance of the Alba 4D at AMC, locoregional hyperthermia was applied in patients using both the Alba 4D and AMC-4 systems. Consecutive patients scheduled for locoregional hyperthermia treatment without simultaneous chemotherapy were included. The first treatment was with the AMC-4, next treatments were allocated to either device. Differences in treatment characteristics power, achieved temperature and treatment time per treatment were evaluated between Alba 4D and AMC-4 treatments and tested using linear mixed models for repeated measures with patient as random effect. Furthermore, we evaluated incidence of patient complaints during treatment.

Results: From March 2018 until April 2019, 11 patients with cervical, vaginal, pancreas carcinoma or leiomyosarcoma received 32 treatments with the Alba 4D and 34 treatments with the AMC-4. Hyperthermia was applied within one hour after radiotherapy (n=9) or the day after chemotherapy (n=2). Number of treatments per patient varied from 3-13 (median 5). None of the treatment characteristics was significantly different between the two systems (Table 1, Figure 1). Per treatment, a median of one treatment complaint occurred, with no significant difference between the systems. Most complaints could be solved with phase-amplitude steering (n=31) or with medication (n=2). Fourteen treatments were stopped prematurely; 13 treatments of patient 1 (27±7 min) and the final treatment of patient 5 (4 min).

Conclusion: Clinical performance of the Alba 4D and AMC-4 locoregional hyperthermia systems did not differ. Therefore, clinical results using the Alba 4D are expected to be similar to results achieved with the AMC-4 system.

Figure 1. The achieved T50 per patient for each hyperthermia treatment with the Alba 4D (blue) and the AMC-4 (grey) locoregional hyperthermia systems.

Table 1. Treatment characteristics (mean±SD or median (range)).
Fig. 1

Fig. 2

<table>
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<th>Parameter</th>
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<td>T90 (°C)</td>
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L28
Thermal dose effect relationships: the importance of heating and thermometry quality

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Purpose: The challenge to explain the diffuse and unconvincing message reported by hyperthermia (HT) studies investigating a thermal dose parameter is still to unravel. In the present systematic review of thermal dose effect relationships studies, we investigated a wide range of technical and clinical parameters characterising the HT treatment to better understand the probability of detecting a thermal dose effect relationship in clinical studies.

Methods: Included studies fulfilled the criteria of (1) treatment of cancer with HT and radiotherapy and (2) report on associations of temperature/thermal dose parameters with treatment outcome or toxicity. Treatment related categories included total treatment duration, number of sessions per week and per patient, sequence (i.e., before or after radiation-, chemotherapy) and the used heating technique. Thermometry related categories comprised used temperature measurement technology, thermometry placement, acquisition rate, number of invasive probes and number of invasive sensors. Influence of each of these categories on relation of temperature/thermal dose parameters with treatment outcome or toxicity was tested and trends evaluated.

Results: Forty-seven articles were included, reporting a total number of 4098 patients with different tumour pathologies. Treatment outcome was investigated in 90% of the studies, while toxicity was investigated in 51% of the studies. Significant associations between temperature related parameters and these two endpoints were reported in 62% and 15%, for outcome and toxicity, respectively. The distribution of these associations over time showed opposite trends for superficial and deep HT: decreasing trend for superficial HT and increasing trend for deep HT. Most of the current thermal dose effect relationships is based on microwave and radiofrequency systems (radiative technology). Temperature acquisition (i.e., non-continuous versus continuous and acquisition rate) was found to be close to significant for the detection of temperature/thermal dose parameters predicting both outcome and toxicity.

Conclusions: The reliability of thermal dose parameters as treatment descriptors is highly dependent on the thermometry procedures. One evident difficulty hindering further understanding of the reported temperature/thermal dose parameters is the fact that thermometry is not or not uniformly reported. Standardised reporting is needed to better investigate thermal dose effect relationships.

L29
Quality assurance for locoregional hyperthermia devices using the ESHO phantom

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Introduction

Regular quality assurance (QA) is important to ensure adequate performance of clinical hyperthermia devices. Reliable phase steering is an important aspect in this procedure. Cylindrical phantoms with the larger recommended 315 mm diameter are proposed to validate the focusing capability for phased-array radiative locoregional hyperthermia systems.

Methods

Adequate characterization of focus shift requires a phantom with a relatively large diameter for locoregional systems operating at 60-150 MHz. A 315 mm diameter PVC tube with a length of 640 mm and a 3 mm wall is used to build a wallpaper paste (WPP) phantom, mimicking 2/3 of muscle tissue properties (Figure 1). Horizontal catheters are placed...
in the central transverse plane, 40 mm apart to accommodate thermocouple probes with sensor distance between 15 and 25 mm. The sensors in the midline catheter are used to measure the focus size.

A similar liquid tissue-equivalent phantom, 1070 mm in length is used to scan the E-field with 10 mm resolution using a diode dipole sensor. This phantom can also be used to visualize the E-field strength using a LED matrix at the transverse plane.

All phantoms are heated using an ALBA 4D, using 4×300 W for the WPP phantom and 4×50 W for the E-field phantom. Phase settings are: 4×0° and 0°, 0°, 30°, -30° for top, bottom, left and right antenna. The WPP phantom is heated for 10 min and temperature rise recorded. The focus size is determined by the infliction points of a 4th degree polynomial fit over the horizontal axis through the center of the phantom.

Results

Figure 2 shows the measurements in the transverse plane with central and shifted focus. Both E-field scan and LED matrix images show a similar focus shift. Compared to the temperature rise, the E-field scan shows a more pronounced focus. The focus size is 79 mm for central focus using temperature rise data and 100 mm using E-field data.

Conclusions

The focus shift caused by phase steering with phased-array systems can be validated with presented phantoms. Most accurate results are achieved by scanning the E-field, though this also requires a robot. Measuring temperature rise in the WPP phantom or using a LED matrix in the liquid phantom can also be used to validate the performance of a phased-array system, and is suitable for fast QA procedures.

Figure 1 An open 315 mm phantom with catheters and an E-field phantom with LED matrix

Figure 2 Focus shift for temperature rise, E-field and LED matrix in transverse plane

Fig. 1
A modular phantom with sweating, circulation and metabolic heat production capabilities for personalized thermal treatment planning

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Introduction: Personalized thermal treatment planning constitutes the key towards precision medicine. Patient variability in body weight, sweating rate and metabolic heat production limit the accuracy of current passive phantom models [1].

Objectives: The goal of this work is the fabrication and characterisation of an active modular phantom with a circulatory system, tuneable sweating rate and active heat production.

Materials & methods: The phantom consists of interconnectable identical units to obtain any weight or dimension. Each unit consists of two agar-based blocks, an active heat source and an embedded water circulation. The latter was constructed using an aluminium serpentine on multiple levels. Agar gel was produced, modifying the recipe in [2] to mimic the average thermal properties of the human tissues (thermal conductivity 0.37 W/m°C, density 1080 Kg/m3, heat capacity 3980 J/Kg°C). Each block was wrapped with PVC foil to prevent water evaporation. A heating pad between two blocks simulated metabolic heat generation. A phantom of 30 kg with a heat production of 30 W was assembled. A pump ensured a 200 l/h water circulation. A HFP01 heat flux plate was used to record heat exchange with the environment. Thermal gradients were quantified for different environmental temperatures. The cooling effect of sweating was investigated by creating openings in the foil.

Results: The maximum temperature gradient within the phantom was 2°C when conditioned at 36°C for more than 2 h. This increased to 2.7°C at an environmental temperature of 25°C. Temperature uniformity can be improved by increasing the water flow rate. The phantom cooling rate averaged at 0.5°C/h for an intact foil. Exposing 50% of the gel surface by removing the foil increased the cooling rate significantly.

Conclusions: This versatile modular phantom models heat exchange by convection, conduction, radiation and evaporation. The latter has the most significant impact on the thermal balance of the human body. Thermal properties, dimensions, water flow, metabolic heat production and sweating rate can be easily tuned to match those of specific patients, enabling personalized treatment planning.
References


Fig. 1

![Image 1](image1.png)

Fig. 2

![Image 2](image2.png)
L31
Thermal characterisation of QA phantoms for deep and superficial hyperthermia

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³Chalmers University of Technology, Department of Electrical Engineering, Göteborg, Sweden

Introduction: Tissue mimicking phantoms have been developed, used, and recommended in the design, optimization and quality assurance (QA) of electromagnetic-based hyperthermia medical devices. Specifically, such phantoms are used for deep or superficial clinical hyperthermia systems, to guarantee their correct performance during treatments [1–4]. Hyperthermia therapy aims to deliver a controlled temperature increase in a target tissue or area, thus such phantoms should approximate the tissue’s electrical and thermal properties. While the electrical properties have been extensively evaluated, the thermal properties of those phantoms are generally not available. Thermal properties, such as thermal conductivity and volumetric heat capacity contribute to the thermal process occurring in the tissue during exposure to an electromagnetic field, and they define the final temperature increase and the extension of the heat distribution. Both the European electromagnetic hyperthermia community (https://www.cost.eu/actions/CA17115/#tabs|Name:overview) and the American Society of Mechanical Engineers (ASME) have recognised the relevance of such properties and are working to provide standardized guidelines and approaches.

Method: The three type of phantoms (high-viscosity, semi-solid and solid) usually employed in QA of deep hyperthermia were characterised at room temperature by this group in [5]. The transient hot-wire technique was employed to conduct such measurements. The same measurement set up is proposed in this work to characterise QA phantoms recommended for superficial hyperthermia systems at room temperature: muscle and fat mimicking phantoms were considered [1]. Moreover, both deep and superficial hyperthermia phantoms thermal properties have been investigated over the hyperthermia temperature range (i.e. up to 45°C).

Results: An increase up to 5% was observed during heating for the deep hyperthermia phantoms, and up to 6% for the superficial hyperthermia phantoms. Observed variations were within the accuracy of the measurement device.

Conclusion: The measurements showed that that thermal properties of the phantoms are stable and appropriated to mimic the thermal properties of the tissues over the heating experiments.


L32
Evolution of treatment planning for multi-catheter interstitial hyperthermia therapy in patients undergoing gynecologic interstitial HDR brachytherapy

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Introduction: Radiosensitization with hyperthermia therapy (HT) has demonstrated improvement in oncologic outcomes for gynecologic (GYN) malignancies. Data for interstitial HT (IHT) with interstitial high-dose rate (IHDR)
brachytherapy is limited, with the majority of current data utilizing a limited number of catheters and outdated IHT planning techniques. **Objectives:** To analyze impact of evolving IHT planning techniques on oncologic outcomes in patients treated with concurrent IHDR and IHT (IHDR-IHT). **Patients & Methods:** Between 2015-2021, 34 consecutive patients with bulky/recurrent GYN malignancies were treated with Ir-192 IHDR via Syed-Neblett template and concurrent IHT. IHT was performed after IHDR treatment using 915Mhz antennas inserted in the IHDR catheters to generate 40-44°C within the tumor. IHT planning techniques evolved during the study period with a transition point in late 2019 when we initiated 3D IHT planning (3D-IHT) of thermal dosimetry with respect to high-risk clinical target volume (HRCTV). We also adjusted thermistor placement within the interstitial catheter for improved temperature monitoring, used more centrally located catheters, and developed a systematic planning process for antenna and thermistor placement. We compared patients treated before and after adopting 3D-IHT. Chi-square and Mann-Whitney tests were done to compare variables between the two groups and Kaplan-Meier method was used to estimate survival outcomes. **Results:** Based on the transition point, patients were grouped into pre-3DIHT (n=12) and post-3DIHT cohorts. Median follow up was shorter for pre-3DIHT cohort compared to post-3DIHT cohort: 27.5 vs 11 months, p=0.02. The majority of patients had cervical cancer (n=22, 65%), de-novo disease (n=27, 79%), and EBRT prior to IHDR (n=33, 97%). Median IHDR dose in the two cohorts were comparable (22.5Gy and 23.9Gy, p=0.84), respectively. Median HRCTV D90 EQD2 was higher for the post-3DIHT cohort (79.8Gy vs 75.4Gy, p<0.001). 1yr local control trended towards significance in the post-3DIHT cohort (52% vs 81%, p=0.09). 1yr overall survival was comparable (82% vs 88%, p=0.55). **Conclusion:** We have demonstrated successful incorporation of 3D-IHT planning for patients receiving IHDR-IHT. Initial evaluation of outcomes suggest a signal for improvement though limited by small sample size. Future efforts will involve expansion of this experience and knowledge dissemination for adoption at other institutions.

**Fig. 1**

<table>
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<th>Patient, tumor, treatment characteristics</th>
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<th>Post-3DIHT n=22</th>
<th>p-value</th>
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</thead>
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<tr>
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<tr>
<td>Disease Site</td>
<td></td>
<td></td>
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<tr>
<td>Cervix</td>
<td>5 (41%)</td>
<td>17 (77%)</td>
<td></td>
</tr>
<tr>
<td>Endometrial</td>
<td>3 (25%)</td>
<td>1 (5%)</td>
<td></td>
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<tr>
<td>Vaginal</td>
<td>2 (17%)</td>
<td>3 (14%)</td>
<td></td>
</tr>
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<td>Urothelial</td>
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</tr>
<tr>
<td>Recurrent Disease</td>
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<td>19 (86%)</td>
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<td>4 (33%)</td>
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<tr>
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<td>3 (25%)</td>
<td>1 (5%)</td>
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<tr>
<td>Brachytherapy Dose</td>
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<td></td>
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<tr>
<td>HRCTV D90 EQD2 (Gy, range)</td>
<td>75.4 (14.1-79.2)</td>
<td>79.8 (72.9-105.1)</td>
<td>&lt;0.001</td>
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<td>HRCTV volume (cc, range)</td>
<td>61.25 (24.9-376.28)</td>
<td>64.02 (30.31-128.89)</td>
<td>0.557</td>
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</table>
A randomized phase-II study of reirradiation and hyperthermia versus reirradiation and hyperthermia plus chemotherapy for locally recurrent breast cancer in previously irradiated area

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Background: In patients with inoperable local regional recurrences of breast cancer in previously irradiated areas, local control is difficult to maintain and treatment options are limited. The Dutch standard treatment for such recurrences is reirradiation combined with hyperthermia. Apart from enhancing the effect of reirradiation, hyperthermia is also known to improve local effects of chemotherapy like cisplatin. This randomized phase-II trial compares reirradiation and hyperthermia versus the same treatment combined with cisplatin.

Patients and methods: From December 2010 up to January 2019, 49 patients were randomized, 27 in the standard arm and 22 in the combined arm. A total of 32 Gy was given in eight fractions of 4Gy in 4 weeks, two fractions per week. After January 2015, the radiation schedule was changed to 46 Gy in 23 fractions of 2Gy in 4 1/2 weeks, five fractions per week. Hyperthermia was added once a week given within one hour after radiotherapy. Superficial thermometry at the skin surface was used and in almost all patients invasive catheters were used for thermometry as well. The combined arm was treated with four cycles of weekly cisplatin 40 mg/m² given concurrent with the hyperthermia session.

Results: Complete response rate was 60.9% in the standard arm and 61.1% in the combined arm (p=0.87). Partial response rate was 30.4% in the standard arm and 33.3% in the combined arm (p=0.79). One-year overall survival was 63.4% in the standard arm and 57.4% in the combined arm. One-year local progression-free interval was 81.5% in the standard arm and 88.1% in the combined arm (p=0.95). Twenty-five percentage of patients in the standard arm experienced grade 3 or 4 acute toxicity (during treatment: 6 with radiation dermatitis, 1 with skin burn due to hyperthermia) and 29% of patients in the combined arm (during treatment: 3 with radiation dermatitis, 3 with catheter related infection) (p=0.79).
Conclusion: No potential benefit could be detected of adding cisplatin to reirradiation and hyperthermia in patients with recurrent breast cancer in a previously irradiated area. In both arms most patients had subsequent local control until last follow-up or death. However the number of patients in this study is too small for definitive conclusions.

L34

**Combination of wIRA-hyperthermia and radiotherapy for non-resectable skin malignancies**

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1. **Introduction**: Skin cancers (e.g., malignant melanoma, squamous cell carcinoma, basal cell carcinoma) have shown growing incidences over the last decades. While surgery is the standard of care in most cases, a certain fraction of patients presents with lesions that are non-resectable, either because of tumour extension or due to co-morbidities. This is particularly true in elderly patients, who require individual approaches. In such situations, radiotherapy (RT) is a useful treatment modality. However, both toxicity and the large number of treatment sessions may challenge treatment adherence and successful completion of therapy.

2. **Objectives**: We hypothesized that contactless superficial hyperthermia using water-filtered infrared-A (wIRA-HT) can reduce fraction numbers and may improve treatment efficiency of skin cancers through HT-induced radiosensitization.

3. **Patients & Methods**: Histology, staging and the therapy parameters of all patients presenting with malignant skin tumours who received a combined treatment with wIRA-HT, immediately followed by RT, between 2019 and 2021 have been analyzed. Treatment responses and toxicities are assessed and compared to published data.

4. **Results**: At the University Medical Centers Freiburg and Magdeburg and at the Lindenhofspital Bern, 18 patients presenting with 22 regions with squamous cell carcinoma (n = 8), basal cell carcinoma (n = 7), malignant melanoma (n=5), and Merkel cell carcinoma (n=2) received combined superficial wIRA-HT and RT. Seventeen out of 22 regions were located at the face and scalp. Seventeen regions received hypofractionated treatment with single doses of 4 Gy up to a total dose of 20-24 Gy, analogous to an established HT/re-RT regimen for recurrent breast cancers [Notter at al., Int. J. Hyperthermia, 2017]. Another 5 regions were irradiated following standard fraction schedules up to 44-56 Gy total dose. The wIRA-HT was performed 1-2x weekly directly before RT. All patients received photo-documentation to quantify response. Complete remission (CR) occurred in 12 out of 22 treated regions. No toxicities > grade II have been observed with the wIRA-HT+RT combination used.

5. **Conclusion**: wIRA-HT is a tolerable modality for radiosensitization of skin tumours. The optimization of RT dose and fractionation is subject of ongoing research.
L35
Repurposing and modifying a 27.1 MHz capacitive shortwave diathermy unit for locoregional hyperthermia: Feasibility and initial clinical results of an ongoing registry trial at Mahatma Gandhi Institute of Medical Sciences, India

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Question: Patients in low- and low-middle income countries (LMICs) often present with advanced cancers where radiotherapy (RT) ± chemotherapy (CT) have limited success. Adding hyperthermia (HT) to RT±CT could be expected to improve outcomes as reported in recent meta-analysis. Unfortunately the costs of the commercially available HT and lack of technical expertise have not allowed HT to be routinely adapted in LMICs along with RT±CT. The study aims to evaluate the safety and efficacy of easily available shortwave diathermy unit in LMICs for loco-regional HT.

Methods: A 27.12 MHz capacitive unit was technically modified to deliver uninterrupted heating for at least 120 minutes. Following the modifications, a registry trial, RESHMA (NCT05099809) was initiated at MGIMS, India to evaluate the safety and efficacy of this unit in locally advanced cancers of head neck, breast, cervix, anorectum and other common sites. HT for 60-90 minutes, 1-2/week was added to the standard departmental treatment protocols of RT±CT for each of these sites. Before launching, approval of the Institutional Ethical Committee was obtained. All patients signed an informed consent. The endpoint of this study was assessed using RECIST criteria while acute and late morbidities were scored according to CTCAE v5.0.

Results: HT was delivered pre-RT or concurrently with CT. The median number of HT sessions were 4 (range 2-10) and mostly once/week (67.7%). In house custom made circulatory water bolus was used. A mean power of 80-300W for 60-90 mins was applied respecting patient tolerance. This resulted in minimum, average and maximum surface skin temperatures of 36.1± 0.9ºC, 38.2± 0.8ºC and 40.2± 1.4ºC respectively. Of the 33 patients treated to date, 25 were treated with definitive intent (5 with HTRT and 20 with HTCTRT). Complete response was evident in 19/25 (76%) and partial in 6 (24%). Neoadjuvant HTCT was used in 8 patients with primarily inoperable locally advanced breast cancers. Significant tumor downstaging was achieved in all, enabling them to undergo definitive surgery. None of the patients experienced any additional acute of late skin morbidity due to HT, nor did they report any discomfort during treatment. Patient tolerance and compliance were excellent.

Conclusions: Promising treatment outcomes and patient compliance evident with the repurposed 27.12 MHz capacitive system could allow a cost-effective method for HT delivery, especially in resource constraint countries.

L36
Adjuvant re-irradiation with hyperthermia following surgery of radiation-associated angiosarcoma of the breast: Current status and feasibility of a randomized trial

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2Oedensklinikum Linz, Radiation Oncology, Linz, Austria
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Radiation-associated angiosarcoma of the breast (RAASB) is a rare late severe side effect of adjuvant radiotherapy (RT) after breast surgery. Nonetheless, the incidence of RAASB and the number of related publications have distinctly increased in recent years. Currently, the generally accepted therapeutic approach is surgery. The high risk of local recurrence can significantly be lowered by extended surgery. However this is often mutilating and may not be suitable for all patients. Since RAASB always occurs in previously irradiated area, re-RT using a reduced total RT dose, combined with hyperthermia (HT) may be a promising approach.
In published data on combined HT/re-RT this has preferentially been applied in advanced, localized disease, such as locally recurrent and/or non-resectable RAASB leading to good local control in spite of poor prognosis. A systematic review showed that surgery and adjuvant radiotherapy increased 5-year locoregional control compared to surgery alone. Retrospective data on patients of the affiliated institutes who received (neo-)adjuvant re-RT/HT directly before or after surgery are encouraging.

Since local control of surgery alone is poor, the efficacy of re-RT/HT should be evaluated in a randomized trial of surgery alone versus surgery with adjuvant HT/re-RT. A positive therapy outcome may help to establish HT/re-RT in RAASB as a treatment standard and may increase the interest in adjuvant HT/re-RT even for other, more frequent indications. Due to the low number of the RAASBs, patients would have to be recruited worldwide by surgeons and radiation oncologists. The only prerequisite is the provision of devices capable of delivering superficial hyperthermia according to the standards of the ESHO guidelines for superficial hyperthermia clinical trials. A close cooperation with surgeons is mandatory.

The need, relevance and feasibility of a RAASB clinical study will be discussed during the ESHO Meeting. As will be the radiation schedule and the optimal timing of the re-irradiation and hyperthermia (adjuvant or neo-adjuvant).

L37
A mono-centric, first in-human (FIH), safety and pre- liminary efficacy study of (neo)adjuvant, model-based, whole- body hyperthermia (WBHT) treatment in advanced solid cancer patients or stage IV (TxNxM1) metastatic pancreatic adenocarcinoma patients

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2University of Antwerp, Antwerp, Belgium
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Background: Hyperthermia is applied alone or as an adjunctive treatment to various established cancer treatment modalities such as radiotherapy and chemotherapy.(Hegyi et al., 2014) Whole-Body Hyperthermia (WBHT) represents the only hyperthermia modality available for patients with disseminated malignancies.(Behrouzkia et al., 2016) The biological rationale for the treatment of malignant disease by heat is based on a direct cell-killing effect at temperatures in the range of 41–42°C and driven by a number of reasons: 1) the survival of cells depends on the temperature and duration of heating. (Jung et al., 2019) 2) the tumor cell environment that negatively influences the tumor cell killing by ionizing radiation and some chemotherapy regimens, is beneficially influenced by heat therapy.(Elming et al., 2019) 3) the differential sensitivity of normal and tumor cells to heat is dependent on cell type and environmental conditions. (Elming et al., 2019) 4) heat treatment enhances the biological effect of both radiation and chemotherapy agents. (Jordan et al., 2012; Habash et al., 2011) The range percentage of viability and proliferation cell index of different pancreatic cancer cell lines (e.g. BxPC-3, PanC-1, Capan-1) is 50% at 41.5°C whereas the range percentage in healthy cell line (PWR-1E) is 100% at 41.5°C. Cellular and tissue level studies indicate that tumor protein denaturation is the most likely thermal effect causing permanent irreversible damage whereas the healthy cells undergo reversible process of damage. (Goldstein et al., 2003) Phase-I minipig study design proved the safety of WBHT.(Carneiro et al., 2021) In addition, our phase-I veterinary (dog) clinical study proved the safety of WBHT treatment alone and in combination with standard of care therapy in dogs with cancer. (Wylleman et al., 2022)

Method: This is a ongoing first in-human, mono-centric, non-randomized trial, designed to establish the safety and preliminary efficacy of WBHT with a medical device alone in patients with advanced solid cancer (cohort A) or adjunctive to SOC chemotherapy according to the NCCN guidelines in patients with stage IV (TxNxM1) metastatic pancreatic adenocarcinoma (cohort B,C,D).
**Trial design:** The treatment is applied in the operating room at the University Hospital Antwerp (UZA); all the patients will undergo the treatment under deep anesthesia; the patient’s body temperature will be monitored by specific sensors (liver, oesophageal, rectal and cutaneous).

**Fig. 1**

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**L38**

Patient positioning robust microwave hyperthermia treatment planning: A proof of concept study

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²Eindhoven University of Technology (TU/e), Department of Electrical Engineering, Eindhoven, Netherlands

**Introduction:** HTP is the process of modeling the treatment to find the optimum settings of an hyperthermia applicator to maximize the target heating while minimizing the healthy tissue heating. While there has been a great research focus on finding the optimum antenna settings, translating these settings into the clinic requires a high accuracy in patient positioning and even small variations can create large deviations. Here, we introduce the patient positioning robust HTP concept to minimize the loss of treatment quality in case of treatment positioning errors.

**Theory:** At Erasmus MC, HTP aims at maximizing the target SAR, while minimizing the hotspot SAR (i.e. the average SAR in 50ml of healthy tissue that is exposed to the highest SAR).

\[
\text{Maximize (THQ)} = \frac{\text{avg}(\text{SAR}_{\text{target}})}{\text{avg}(\text{SAR}_{\text{HS}})}
\]

To minimize the effects of positioning errors, we modified the optimization parameter such that

\[
\text{Maximize } (\text{THQ}_{\text{avg}}) = w_1 \times \text{THQ}_1 + w_2 \times \text{THQ}_2 + w_3 \times \text{THQ}_3
\]

where \(\text{THQ}_1\) represents the original planned position, \(\text{THQ}_2\) and \(\text{THQ}_3\) represents two misaligned patient positions in the applicator.

**Methods:** We have prepared HTP for a head and neck hyperthermia patient (Murphy from EVPR (Bellizzi et al. 2020)) in the Hypercollar3D applicator. First, we optimized the treatment for the planned position and showed the effects
when the patient is mispositioned 1cm in X and Y direction. Then, we reoptimized the settings with the weights $w(n)=[0.6, 0.25, 0.15]$. The choice of the weights were done to ensure planned position still has the highest priority, while the shift in the X direction given higher priority than Y since it has shown greater deviations.

**Results:** HTP for intended position and the effect of mispositioning is given in Table 1. 1cm shift in X direction reduced the treatment quality by 31% while, 1cm shift in Y direction reduced treatment quality by 1.7%. The reoptimized HTP for positioning robust settings are given in Table 2. While this reduced the original treatment quality by 3.6%, it also improved the quality of possible mispositioning in X direction by 18% compared to the THQ achieved in the original settings.

**Conclusion:** We have shown that positioning errors can greatly reduce the planned treatment quality. By including the possible misalignment in HTP step, these deviations can be greatly reduced with a small trade-off to original treatment quality. This can potentially improve hyperthermia treatments when positioning cannot be monitored during the treatments, i.e. non-MRI guided treatments.

**Fig. 1**

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<th>$\Delta Y$</th>
<th>THQ</th>
<th>$\Delta$THQ (%)</th>
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**L39**

Sensitivity analysis of the thermal and physiological properties of human breast tissue

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Electromagnetic (EM) hyperthermia (HT) studies rely on computational modelling to simulate the temperature increase within biological tissue due to EM exposure. Thermal calculations using the Pennes’ bioheat equation require knowledge of the density, specific heat capacity, thermal conductivity, metabolic heat generation rate and blood perfusion rates of the tissue under test. When modelling the breast for HT applications, the three main tissues involved are fibroglandular, fatty and breast tumour. Recently, we conducted a thorough review and found that accurate data on the thermophysical properties of these breast tissues is lacking, which stems from limited resources of measured data. This has led to significant variations in reported data on the thermophysical properties of breast tissues, with little conformity in the literature.

This study follows from the review with a sensitivity analysis of these thermal and physiological properties. The analysis investigates the influence of the properties of healthy and cancerous breast tissue on the simulated thermal results. The Sim4Life model Luna [1], together with the implemented theoretical HT applicator are used to keep the breast model and EM calculations consistent throughout the analysis while considering thermal variations. Polynomial chaos expansions [2] are used to generate combinations of the input data, i.e. the thermophysical properties of fibroglandular, fatty and tumour breast tissues, depending on their population distribution as determined from the

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review. For each input combination, the simulation in Sim4Life determines the CEM43 within the tumour. The simulation output is used to determine which properties have the greatest influence on the thermal calculations within the breast model. This also serves as a foundation on which to base future measurement campaigns, indicating the thermophysical properties which require the most urgent attention.


L40
The effect of a temperature-dependent calibration on the dielectric measurements of standard liquids

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The knowledge of the dielectric properties of biological tissues is fundamental for the development of medical applications which are based on the material’s interaction with electromagnetic fields. To date, various studies have been carried out characterising the permittivity of various biological tissues at body temperature. However, few have investigated the variation of the permittivity with both temperature and frequency and the published studies focus mostly on the characterisation of liver tissues.

When reviewing published dielectric studies, it can be noted that the majority of these were conducted at room/body temperature and in most of the cases the calibration temperature is not reported. For dielectric studies characterising biological tissues at temperatures higher than body temperature, very often the reported calibration temperature is done at room temperature. Only a few papers mention the calibration temperature as a possible cause of uncertainties in the dielectric measurement (DM) data [1].

In this study we investigate the calibration process for DM at high temperatures. In particular, the effects of a temperature-dependent calibration are studied to establish whether a constant temperature calibration conducted at room temperature would introduce an additional measurement uncertainty when conducting DMs on the material under test at higher temperatures.

To address this, a set of experiments were devised with the setup calibrated at three temperatures: 23 °C, 55 °C and 80 °C, following which complex permittivity measurements on 0.1 M NaCl, Ethanol, TX-100 and Oil were considered. These standard liquids were selected as they represent a wide range of permittivity over the frequency considered. Effects become more significant when a calibration at room temperature is used for DMs with the MUT set at 80 °C. As an example, the comparison between the DM of Ethanol at 80 °C done with two calibration temperatures, 23 °C and 80 °C for both real and imaginary part is shown in Fig.1. A difference between the dielectric data measured with the two setup calibration temperatures is visible.

Fig 1. Dielectric permittivity of ethanol at 80 °C measured with a setup calibrated with deionized water at 23 °C and at 80 °C

L41
Effects of dielectric expansion due to heating for an uncooled microwave ablation antenna

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Introduction: Microwave thermal ablation is a percutaneous surgical procedure for treating tumours. A needle-like applicator incorporating an antenna deposits microwave energy into a target region, and the interaction of microwaves with tissues causes an increase in temperature to above 100°C, causing necrosis in the targeted area. Most currently available applicators include an outer chamber where chilled saline water or CO2 is circulated to cool the antenna [1]. Uncooled coaxial-fed antennas benefit from reduced manufacturing complexity, but significant antenna degradation occurs during ablation due to dielectric expansion.

Objective: Investigation of the effects due to structural changes in an uncooled coaxial monopole antenna during ablation.

Method: Ablation was performed in porcine liver with coaxial antennas at pre-set power levels of 30, 40 and 50 W for 1, 2 and 3 minutes, each time replacing the antenna. Each antenna was immersed in tap water before the ablation procedure and the S₁₁ was measured. Following the ablation procedure, the antenna was cleaned and the S₁₁ was re-measured in the same liquid.

Results: Pre- and post-ablation S₁₁ comparison indicates that degradation was present in all experiments, more prominently at 50 W. Antenna inspection under a microscope revealed dielectric expansion persisting after cooling.

Conclusion: Dielectric expansion is possible due to two different mechanisms, the power induced in the cable and/or the temperature of the surroundings. This hypothesis is currently being investigated by immersing the antenna, powered and non-powered, in heated liquids to characterise the antenna's degradation. This may suggest an optimal temperature to avoid excessive degradation and a feedback protocol to control the power input that minimises this effect.

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Dielectric spectroscopy using a microwave ablation antenna operating at 5.8 GHz

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Introduction: The number of cancer diseases diagnosed yearly is continuously rising, with liver cancer being one of the main death causes in this category according to statistics from 2020. One of the least invasive therapeutic techniques for treating this condition is microwave thermal ablation (MTA) technique.

Antenna design, treatment planning and treatment success greatly rely on the available knowledge of dielectric properties of biological tissues and monitoring techniques. Although, liver is one of the most researched tissues, further advancements are needed. Furthermore, the currently used monitoring techniques include ultrasound, contrast enhanced computed tomography, and magnetic resonance imaging. All of these techniques are reliable to a certain extent, are expensive and in some cases pose a further health risk for the patient. Therefore, having a real-time monitoring technique operating in situ is very important. One of the emerging examples of such system is dual-mode MTA antenna able to both ablate and measure dielectric properties at 5.8 GHz in liver tissue.

In this work, study on the sensing ability of this antenna in a broad frequency range and in respect to the transversal dimension of the material under test is performed.

Methods: The open-ended coaxial slot antenna design was both modelled in CST Studio Suite® 2019 (Dassault Systèmes, Vélizy-Villacoublay, France) and physically constructed. The simulations were performed with the antenna immersed in 100x100 mm blocks of liver; different materials were used for calibration (different NaCl solutions, distilled water and open circuit). The transversal dimension of the block was scaled down up to 50 mm for the analysis of the transversal dimension influence.

Dielectric properties were re-constructed from measured reflected coefficients using the Stuchly & Stuchly de-embedding model. The measurement accuracy was estimated as a relative deviation of the results from the reference properties of the measured materials.

Results: Good accuracy of the reconstruction of the dielectric properties of the material is achieved in a frequency range 5-6 GHz if the antenna is relatively matched in the calibration liquid at the operating frequency of the antenna. Furthermore, the transversal dimension of the MUT does not influence the ability of the antenna to measure.

Conclusions: The open-ended coaxial slot MTA antenna can be used to measure dielectric properties with good accuracy in a 1 GHz band (5-6 GHz) around the operating frequency. This analysis may be extended and applied to other MTA antenna types.
Study of a system for stable microwave image reconstruction applied to muscle rupture detection

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1. Introduction

Muscle Rupture is a common injury in sports, particularly in the front and back of the thigh. Small injuries can be difficult to diagnose with only a clinical examination, and often MRI examination is needed. Patients with smaller ruptures need to rest from sports until the injury is completely healed. MRI is a scarce and costly resource and therefore many patients are undiagnosed. Consequently, patients with ruptures risk returning too early to sports and thereby worsening the injury. To improve the diagnostics of these patients a more accessible and low-cost alternative to MRI is needed. A system based on the microwave technique could fulfil these requirements and be used to detect bleedings in the muscles following the rupture.

2. Objectives

Investigate a microwave system and assess the accuracy and stability of microwave measurements. Reconstruct images in a stable, repeatable, and robust manner.

3. Materials & methods

To represent the examination of a patient during lab experiments and simulations, a simplified scenario is used with only two tissues: muscle and blood. The muscle represents the leg of the patient and the blood represent the bleeding accompanying a muscle rupture. The antennas used are monopole antennas in containers filled with lossy gel mounted in a semi-circular array with 16 cm diameter and equal spacing between the individual antennas. The Delay Multiply and Sum algorithm (DMAS) beamforming algorithm was used to reconstruct the images. A numerical simulation study of the measurement system and phantom was also made using dielectric properties taken from experiments.

4. Results

Based on experimental data, the differential signals are calculated, i.e., input signals to the DMAS algorithm. The differential signals are stable and repeatable, although the level of noise increases with the frequency. Using stable differential signals we get stable reconstructed images with the correct position of the blood phantom.

5. Conclusions

The results were obtained in good agreement between simulated and experimental data. In a repeated image reconstruction experiments using the DMAS algorithm, the lossy antenna proved to create stable results. The results are promising, and we conclude that the microwave technology is interesting for this application. Yet, fine tuning and optimization of the antenna and system characteristics is needed to further enhance the image reconstruction.
L46
Safety and feasibility clinical trial of expedited laser interstitial thermal therapy and chemoradiation for patients with high-grade gliomas

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Objective: This clinical trial evaluates the safety and feasibility of expedited Laser Interstitial Thermal Therapy (LITT) and chemoradiation initiation in patients presenting with new high-grade gliomas (HGG). Our objective is to maximize the clinical benefits of LITT when used in conjunction with chemoradiation while mitigating risks.

Background: HGGs are incurable primary brain tumors. Glioma stem cells (GSC) are a major contributing factor to treatment resistance and represent important targets for therapy. Hyperthermia can radiosensitize GSCs and extend survival in preclinical models of HGG. LITT is a minimally invasive surgery that administers hyperthermia to treat HGGs. Our preclinical evidence suggest that a decrease in the time interval between LITT and chemoradiation can improve tumor control. We hypothesize that decreasing the standard time interval from 3-4 weeks to ≤ 7 days in clinical protocols would improve tumor control without escalating procedural adverse events.

Methods: Adults with suspected HGG on MRI and KPS ≥ 60 with pathologic diagnosis of HGG were enrolled and evaluated. All patients received biopsy at the time of LITT. Patients received concurrent radiation (60 Gy) and TMZ within 7 days of LITT. Occurrence of wound dehiscence, new treatment-refractory seizures, cerebral edema, failure to complete radiation from the completion of LITT to the end of radiation therapy was the primary endpoint.

Results: 10 patients, median age 66 years, with median KPS of 85 were enrolled. The median time post-LITT for initiation of chemoradiation was 7 days. There were no occurrences of protocol-related adverse events. The median overall survival was 9.9 months (IQR: 1.6-16.5).

Conclusions: Accelerated initiation of chemoradiation after LITT is safe and feasible for patients with HGG.

L47
The use of qualitative and quantitative hyperthermic effects as discrimination criteria in radiobiological models

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Purpose: The inhibition of DNA repair is one of the mechanisms by which moderate hyperthermia (HT) acts as a radiosensitizing adjuvant to radiation therapy (RT). To evaluate the impact of timing, thermal dose and radiation dose-rate on combined HT-RT treatments, a profound understanding of the DNA repair kinetics is pivotal. Mathematical models and computer simulations may provide insights into the underlying dynamic processes but, due to the complexity of the cell, model validation and calibration are challenging. Previous research revealed difficulties in the combined use of clonogenic survival and time-resolved comet assay data for model calibration. Therefore, we propose a model-based analysis approach to derive additional criteria for model calibration: DNA repair dynamics are encoded in the dose-rate dependence of the surviving fraction in clonogenic assays. This study demonstrates that the use of experimental data gained at different dose-rates in combination with HT can help to identify the appropriate parameters for modelling the cell survival after the treatments combination.

Materials & methods: The Multi-Hit Repair (MHR) model is used because of its dynamical nature and its capability to incorporate data from diverse biological experiments, such as clonogenic and comet assays. After reviewing the
literature data, diverse theoretical discriminators, based on common qualitative effects of HT+RT, were defined and used to exclude parameters sets which result in unrealistic repair kinetics. Finally, survival experiments at different dose-rates combined with HT were performed for HeLa and SiHa cell lines to validate and adjust the proposed methods.

**Results:** After incorporating the obtained experimental data, the model fitting was improved by reducing the parameters search ranges, i.e. the ambiguity on these parameters fitting. Moreover, a large number of parameters sets leading to non-realistic repair kinetics were discarded by the derived theoretical discriminators.

**Conclusions:** The results encourage the use of indirect methods to improve the radiobiological models fitting and, consequently, to obtain a better understanding of cell repair dynamics and the combined effects of HT and RT. Moreover, even when experimental data are not available, it is possible to define qualitative theoretical discriminators to exclude non-realistic scenarios. This knowledge helps us to optimize the combined treatment planning for HT+RT.

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**L48**

**Combining immunotherapy with treatments, such as radiation, drugs, or hyperthermia, that both directly and indirectly kill tumor cells**

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**Introduction:** Checkpoint inhibitors are now being combined with more conventional therapies. Our plan will be to investigate the combination of one such inhibitor, anti cytotoxic T-Lymphocyte associated protein 4 (anti-CTLA-4) with treatments that have a bi-functional cell killing action. Such treatments include high dose proton radiation, the vascular disrupting drug OXi4503, and hyperthermia, that have induce both direct cytotoxicity as well as indirect effects mediated through the induction of vascular damage.

**Objectives:** To investigate the critical factors influencing the tumor growth inhibition seen when we combine anti-CTLA-4 with radiation, OXi4503, or hyperthermia.

**Materials & Methods:** All experiments used a C3H mammary carcinoma grown in the right rear foot of CDF1 mice. Treatments started when tumors were at specific sizes of 50, 100, 200, or 400 mm³. These included proton radiation (local tumor irradiation with 20 Gy on day 0), OXi4503 (50 mg/kg, injected i.p. on days 0, 3, 7, and 10), hyperthermia (tumors heated at 42.5°C for 60 minutes on day 0, achieved by immersing the tumor bearing leg in a water-bath), and anti-CTLA-4 (injected i.p. on days 1, 4, 8, and 11). The endpoint was tumor growth delay (time to grow to 1000 mm³).
Results: The tumor growth delay results are summarized in Table 1, and show the median time in days taken for tumors to reach 1000 mm³.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tumor Size at Start of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 mm³</td>
</tr>
<tr>
<td>Controls</td>
<td>13</td>
</tr>
<tr>
<td>Anti-CTLA-4</td>
<td>18</td>
</tr>
<tr>
<td>Proton Radiation</td>
<td>43</td>
</tr>
<tr>
<td>Proton Radiation + Anti-CTLA-4</td>
<td>90</td>
</tr>
<tr>
<td>OXi4503</td>
<td>26</td>
</tr>
<tr>
<td>OXi4503 + Anti-CTLA-4</td>
<td>90</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>17</td>
</tr>
<tr>
<td>Hyperthermia + Anti-CTLA-4</td>
<td>17</td>
</tr>
</tbody>
</table>

Conclusions: Experiments were done using both male and female animals and this had no influence on the results (data not shown). Anti-CTLA-4 alone only had a small effect in the smallest tumors. An enhanced response was obtained when anti-CTLA-4 was combined with radiation or OXi4503, but not heat. Tumor size at treatment clearly played a significant role, with smaller tumors showing the greatest enhancement. It is possible that the degree of enhancement is dependent on the initial level of damage.

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L49
Investigation of the Importance of Antenna Elements above the head for Thermal MR of Brain Tumors at 297.0 MHz

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Purpose: Ultrahigh field (UHF) MRI is ideally suited for an integrated thermal intervention within a Thermal MR setup as it operates at shorter wavelengths compared to conventional MRI scanners. This work examines the feasibility of multi-channel RF applicators using broadband Self-Grounded Bow-Tie (SGBT) antenna building blocks. The report focuses on two RF applicator configurations: (i) a 10-channel annular RF array (AA, Figure 1) with the elements equally positioned around the head and (ii) a 10-channel Helmet RF array (HA, Figure 1) with 8 elements being equally arranged around the head plus two elements covering the top of the head.

Figure 1. Design of the Helmet RF applicator and of the 10-element annular RF applicator and their SAR10g distributions inside the phantom and Duke voxel model. Mean target SAR10g and B1+ mean values and target coverage percentages are annotated in the figure.

Figure 2. Comparing SAR-based indicators results for TV and healthy tissues in three different planes.

Discussion: Enhancing targeted localized RF power deposition requires high-density RF antenna arrays. This constitutes a challenge for Thermal MR of the head due to the small surface area. To address this challenge the
Helmet RF applicator takes advantage of two SGBT antennae placed in a direction that provides a contribution to MRI and which allows for ample contribution to RF-induced heating. Previous Thermal MR applicators have considered only annular configurations since brain applicator antennas could be placed in a vertical direction to contribute to imaging too.

**Conclusion:** Our phantom studies demonstrate that the Helmet RF applicator affords a ~10% improvement of maximum SAR10g in the TV over the conventional annular RF array. Our findings obtained for the human head voxel model Duke show higher maximum MTS and an improved target coverage of high SAR10g for the helmet RF applicator. Based on the results shown in table 1, in the superior plane, all the factors show improvement. For main and inferior planes of the head, there are improvements or comparable values in HC, SAF, and THF for the HA vs AA. To conclude, the 10-channel Helmet RF applicator is better suited for Thermal MR than the 10-channel annular RF applicator.

Fig. 1
Meta-analysis of the effect of acute heat shock on gene expression in mammalian cells

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Introduction

Hyperthermia (HT) is a clinically applied cancer treatment in which the tumor volume is heated to supraphysiological temperatures during a certain period of time. HT has mostly been used as a sensitising agent in conjunction with radiotherapy and/or chemotherapy. These effects are believed to be caused, at least partly, by hyperthermia-induced reduction of DNA damage repair.

Objectives

Use publicly available gene expression and proteomic datasets to identify the genes regulated during acute heat shock response in mammalian cells.

Materials & method

A systematic literature review was performed using Embase and PubMed databases. As a first step, keywords related to the topic were selected and used to extract articles from both databases. The articles were then filtered for inclusion based on the following: publication date between 2002 and 2022, English or Spanish language, study type (preclinical study), and inclusion of gene expression or proteomic analysis. As a second step, articles that were not accompanied by data sets that were either available online or provided by the authors were excluded from further analysis. The available datasets were then processed and analysed with R using the R Bioconductor package. A gene was classified as upregulated or downregulated depending on how its expression was affected by hyperthermia treatment in each dataset. Individual genes were considered if their regulation was consistent across at least 75% of the datasets in which they appeared.
Results

The initial screening resulted in 683 potentially relevant references, of which 505 were subsequently excluded after reviewing abstracts and titles. Following the review of all 178 manuscripts, a total of 12 manuscripts were selected for final analysis. The omics techniques used in the studies were cDNA microarray, Real-time qPCR, and ChIP-seq. In total, 12 genes were found to be consistently regulated by hyperthermia treatment: 2 were downregulated and 10 were upregulated. The biological functions related to these genes were mostly related to protein synthesis.

Conclusions

The identified genes are closely associated with hyperthermia-induced cellular responses and may prove to be valuable clinical targets. Biological validation of these results is ongoing. Further studies related to the interaction between gene expression and hyperthermia are warranted to provide insights into the molecular mechanisms driving cellular responses to hyperthermia.

L51

Radiobiological modeling in treatment planning for locoregional thermoradiotherapy

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Introduction: Mild locoregional hyperthermia (increasing the tumor temperature to 40-45° C) is routinely used in combination with radiotherapy to improve treatment outcome. Clinical evidence shows a thermal dose-effect relationship. Locoregional hyperthermia is given using phased arrays of RF antennas capable of focusing power onto the tumor. Treatment planning for hyperthermia consists of simulating the effect of the electromagnetic fields emitted by the heating device in normal and tumor tissue. Treatment parameters can then be optimized in order to achieve a high thermal dose, while avoiding normal tissue hot spots. Taking into account the combined effect with radiotherapy is attractive but challenging because of the additive and synergistic effects that are involved.

Aim: an overview of state of the art approaches to radiobiological modeling in locoregional hyperthermia in combination with radiotherapy. Clinical applications for treatment planning are included, but also models that add a certain level of complexity that could be useful in the future for treatment planning.

Summary: Effects of mild hyperthermia include direct cell killing and enhancement of radiotherapy. Several mechanisms happen at different scales and time frames. For example, for DNA repair inhibition, there is an exponential dependency with temperature, and an exponential decay with the time interval between modalities. Some of the reviewed models incorporate this dependence as a modification of the radiosensitivity, quantified by the parameters of the Linear Quadratic Model, α, β or α/β. This allows for modeling at a voxel level when the temperature distribution is available.

For other effects, such as oxygenation and blood flow changes, modeling is much more complicated, not only because of the anatomical complexity, but also because of the large intra and inter patient variation, where some of the data can be obtained from imaging. Some of the reviewed models incorporate these effects in more or less complex ways.

Conclusion: Treatment planning of locoregional hyperthermia in combination with radiotherapy incorporates radiobiological models to account for the radiosensitizing effect of hyperthermia. Accounting for these and additional effects requires a deep understanding of the underlying mechanisms. Models for use in the clinic also need to be practical enough for implementation.
L52
The influence of temperature and time interval between radiotherapy and hyperthermia on the predicted enhanced equivalent radiation dose

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Introduction: The radiosensitization effect of hyperthermia can be considered as an enhanced equivalent radiation dose (EQD_{RT}), i.e. the dose needed to achieve the same effect without hyperthermia. EQD_{RT} can be predicted using biological modeling based on an extended LQ-model, with temperature-dependent parameters. Clinical data show that both the achieved temperature and time interval between radiotherapy and hyperthermia correlate with clinical outcome, but their impact on expected EQD_{RT} is unknown.

Objectives: To provide more insight in the influence of achieved temperatures and time interval between radiotherapy and hyperthermia on the predicted EQD_{RT}.

Materials & Methods: Biological modeling was performed using our in-house developed software X-Term, considering an external beam radiation scheme of 23×2Gy, as applied for locally advanced cervical cancer. First, the EQD_{RT} was calculated for homogeneous temperatures, evaluating time intervals between 0h and 4h. Next, real radiotherapy and hyperthermia treatment plans were combined and the EQD_{RT} was calculated for 10 locally advanced cervical cancer patients. The impact of achieving 0.5-1°C lower or higher T50 temperatures (in case of occurrence or absence of treatment limiting hot spots, respectively) was evaluated.

Results: EQD_{RT} increases substantially with both increasing temperature and decreasing time interval (Fig. 1). At higher temperatures (>41°C) the influence of time interval is most pronounced. At a typical hyperthermic temperature level of 41°C an enhancement of more than 8Gy can be realized with a 0h time interval; which is halved for 4h. Most enhancement is already lost within 1 hour.

For heterogeneous temperature distributions in patients, also a strong effect of both temperature and time interval on predicted EQD_{RT} is observed (Fig. 2). Mean T90, T50, and T10 were 40.4, 41.4 and 42.5°C, respectively. For a 4h and 0h time interval the average additional EQD_{RT}(D95%) was 2.2Gy and 6.3Gy, respectively. The impact of 0.5-1°C lower or higher temperatures is most pronounced at high temperature levels and short time intervals. The additional EQD_{RT}(D95%) ranged between 1.5 and 3.3Gy and between 4.5 and 8.5Gy extra for a 4h and 0h time interval, respectively.

Conclusion: Biological modeling provides relevant insight in the relation between treatment parameters and expected EQD_{RT}. The combination of high temperatures and short time intervals is shown to be very important to maximize EQD_{RT}.
Figure 1: Equivalent radiation dose for radiotherapy plus hyperthermia as a function of time interval between radiotherapy and hyperthermia for different homogeneous temperatures. An external beam radiation scheme of 23 × 2 Gy was considered, as applied for locally advanced cervical patients.

Figure 2: Predicted effect of achieving 0.5-1°C lower or higher T50 temperatures (compared to the planned situation) on the equivalent radiation dose for 10 cervical cancer patients, for 4h and 0h time intervals.
Numerical feasibility of balloon implant for simultaneous magnetic nanoparticle hyperthermia and HDR brachytherapy of tumor resection cavities in brain

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Introduction: The radiosensitization effect of hyperthermia (HT) is dramatically enhanced if HT and radiation are delivered simultaneously. We are developing a thermobrachytherapy balloon implant for treating at-risk tissue around a tumor resection cavity (tumorbed) using magnetic nanoparticle (MNP) HT combined with high-dose rate brachytherapy.

Objectives: To validate in silico the ability of MNP-balloon implants to heat a brain tumorbed using realistic anatomical models.

Methods: The CAD model consisted of spherical balloons with a diameter (d) of 2, 3, 4 and 5 cm incorporated in a human head model truncated from the full-body Static VHP-Female model v2.2 (NEVA BioElectromagnetics, USA). A 5-mm spherical shell was added around the balloon to model the tumorbed. Balloons were analyzed in the frontal, parietal, and occipital lobes for a total of 12 simulation scenarios. Temperature was computed using the bioheat transfer model using COMSOL, IT’IS tissue properties database v4.0, and a heat source (P_{mnp}) in the balloon to mimic the MNP heating. A dynamic blood perfusion model was used to account for 2.5-fold increase in brain perfusion at 45°C. P_{mnp} was optimized so that the maximum temperature at the balloon surface was 50°C. The MNPs planned for clinic use have an iron oxide concentration of 4.5% v/v and will be activated by a 132 kHz external magnetic field (H₀) induced by a dedicated coil. The MNP solution was tested in this coil to determine the power density (PD, W/mL) vs H₀ relationship.

Results: 30 min was required to establish steady state temperature conditions surrounding the MNP implants. For the 3 different lobes, the minimum temperature in the 5-mm tumorbed was 39.7-39.8°C (d=2cm), 40.0°C (d=3cm), 39.6-40.1°C (d=4cm), and 39.4-40.2°C (d=5cm). To achieve these temperatures, the heat sources used were: 8.2±0.1W (d=2 cm), 16.3W (d=3cm), 26.1W (d=4cm), and 37.0±8.2W (d=5cm). Based on the simulated temperature profiles, the first mm is expected to result in ablated tissue. The measured power density profile was PD = 0.0763H₀² - 0.0843H₀. We can then estimate the H₀ requirements to heat the tumorbed to be within 3.2-5.7 kA/m, which are well below the maximum safe field capabilities of the system (8.1 kA/m).

Conclusions: Numerical simulations demonstrate the ability to heat highly perfused brain to hyperthermic levels ≥5 mm from an implanted balloon surface, paving the way for future brain tumor treatments using surgery, HT and radiation.
L54
Liposomal drug delivery of cisplatin using MR-HIFU Hyperthermia in a large animal model

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Question

Hyperthermia-induced local release of cytotoxic drugs from thermosensitive liposomes (TSLs) is an effective way to increase their therapeutic window. For clinical translation of this concept, we performed a series of swine studies using a novel formulation of cisplatin (CisPt) in phosphatidyldiglycerol (DPPG2)-TSLs in combination with magnetic resonance guided high intensity focused ultrasound (MR-HIFU)-mediated hyperthermia.

Methods

German landrace pigs (35 to 39 kg) received a 30-min infusion of CisPt containing TSLs (20 mg CisPt/m²). The pigs' biceps femoris was treated locally in two separate target areas with 30 min of mild hyperthermia using MR-HIFU, starting 10 min and 60 min after initiation of the infusion, respectively. The pharmacokinetics and biodistribution of CisPt were determined and the influence of the CisPt plasma concentration on drug accumulation in the target region was analyzed. Additionally, the pharmacokinetics of CisPt were determined in one pig (54 kg) thus far.

Results

Compared to untreated tissue, we found an approximately 2-fold increase in CisPt concentration in the muscle volumes that had undergone hyperthermia. The pharmacokinetic analysis showed a much higher concentration of CisPt of the liposomal formulation in all timepoints.

Conclusions

We have demonstrated a workflow for MR-HIFU hyperthermia drug delivery that can be adapted to a clinical setting, showing that HIFU-hyperthermia is a suitable method for local drug release of CisPt using DPPG2 based thermosensitive liposomes in stationary targets. Preliminary data also shows markedly higher drug concentrations achieved with the liposomal formulation. Further experiments are planned to determine the governing rate constants and the impact of hyperthermia on drug accumulation.

Figure 1:

Pharmacokinetics of DPPG2, liposomal CisPt and free CisPt, both total amount and unbound form (CisPt dose: 20 mg/m²).
First results on improving the efficacy of new magnetic and optical particle mediated treatments for glioblastoma multiforme and melanoma uveal: Hyperthermia using non conventional energy delivery magnetic and optical systems and magnetomechanical linearly induced damage (nanorobotics)

J. Serrano-Olmedo, M. Ramos, R. Martinez, M. Zeinoun, J. Domingo, L. Souiade, C. Alcaide, O. Casanova

Recent results are presented showing that it is possible to improve the efficiency of the anticancer hyperthermia treatment mediated by magnetic and optical micro and nanoparticles by optimizing the way in which the energy is released to the particles to cause the cell death. A new device [1] for research in magnetic hyperthermia is presented that can produce alternating magnetic fields with unconventional trapezoidal as well as conventional sinusoidal waveforms (Fig. 1). The comparison between both forms of excitation of magnetic nanoparticles demonstrates a superior efficiency of the trapezoidal in terms of the thermal power dissipated in calorimetry tests (Fig. 2) [2], although more research is still needed to optimize this result and reach a deeper understanding on the mechanism of energy release. In optical hyperthermia, gold nanorods (GNR) are used that are capable of targeting cancer cells when biofunctionalized against molecules specifically overexpressed in cancer cells. Studies with different particle sizes, as well as the combination with other non-absorbent biocompatible silica particles, but scatterers of the infrared light used, allow establishing treatment parameters that optimize cell death, allowing the reduction of tissue exposure to energy and particles then reducing further toxicity risks. Finally, promising results are also presented on the design of a new device that implements a magnetomechanical damage technique based on the linear movement of magnetic microparticles and nanoparticles aggregates. It is possible to cause cell death, without neither exposure to high temperatures nor to high frequency or intensity alternating magnetic fields, which dramatically minimizes the secondary effects induced on the tissues. This work focuses on the elimination of tumor cells using murine glioblastoma multiforme (CT2A) and melanoma (B16F10) cell lines as models, with the aim of determining the best performance of each technique. Mainly in vitro and also in vivo results are presented [3].


Fig. 1

Fig. 2

38.6mgFe/ml nanoparticles at 100, 200, 500kHz and 1 MHz
3D in vitro evaluation of iron oxide nanoparticle for application of hyperthermia

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INTRODUCTION: Magnetic nanoparticle (MNP) hyperthermia is a rising star in clinical hyperthermia[1], with the advantage of selective heating of only the tumor tissues containing the MNP. For clinical application and accurate treatment planning, it is crucial to determine the toxicity and diffusion speed of MNPs as well as the thermal dose effect of MNP hyperthermia. We have evaluated these properties using 3D cell spheroids and both iron-oxide MNPs (FeMNP) and palladium-iron-oxide MNPs (PdFeMNP).

MATERIALS & METHODS: U87 MG human tumor cell line derived from human malignant glioblastoma was used in vitro study. U87 3D spheroids were prepared using the liquid-overlay method at 2000 cells per 200 µl medium in U-shaped 96-well plates. Before MH application using Magnetherm Digital device, spheroids (n=6) were transferred in a 1.5 ml Eppendorf tube and incubated with 1 mg/mL or 5 mg/mL of MNPs at 37˚C. Glo3D assay was performed to confirm the cell viability, and Prussian blue staining was used to evaluate the diffusion of MNPs within spheroids.

RESULTS & DISCUSSION: FeMNP reduce spheroid viability to 66% in the range of 100-200 µg/ml whereas PdFeMNP reduce viability to 83% at 100 µg/ml and 63% at 200 µg/ml. The MNP diffusion within U87 spheroids increased with increasing concentration from 25 µg/ml to 200 µg/ml. At concentration below 100 µg/ml, the MNPs uptake was above 80%, while the uptake percentage reduced to 56% at 200 µg/ml, confirming MNP saturation within the spheroids. Increasing the hyperthermia dose leads to decreased spheroids' viability and growth. However, the effect was not apparent for the lowest hyperthermia doses (30 CEM43). For FeMNPs, at 120 CEM43 (45˚C for 30 min), the U87 spheroid viability was reduced to 88% at 1 mg/ml MNP, while the viability reduced drastically to 10% at 5 mg/ml. On the other hand, PdFeMNPs reduced U87 spheroid viability to 75% at 1 mg/ml, while the viability reduced further to 58% at 5 mg/ml.

CONCLUSION: The results show that at higher concentrations, FeMNPs caused greater toxicity than PdFeMNPs. On observation, the FeMNPs were more aggregated in the cell culture medium than PdFeMNPs. Moreover, the FeMNPs and PdFeMNPs had similar Fe concentrations and their SAR values were 130 W/g and 225 W/g, respectively. Thus, indicating the possible occurrence of mechanical and nanoscale heating effects due to aggregation of FeMNPs at 5 mg/ml leading to the breakdown of the U87 spheroids post-MH.

[1]https://magforcestudy.com/

Liver cancer treatment through intrahepatic triggered drug release from thermosensitive liposomes using local mild hyperthermia

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INTRODUCTION The introduction of smart drug delivery systems has the potential to improve the treatment outcome in cancer patients. By combining thermosensitive liposomes (TSLs) with application of mild hyperthermia (HT), local tumor drug concentrations could be increased in comparison to administration of free drug. However, thus far clinical
trials showed marginal improvements. To obtain optimal results hyperthermia treatment planning, including parameters such as onset, localization, duration, and set temperature, should be optimally matched with the type of TSL, tumor type and localization, and tumor pathophysiology.

OBJECTIVES As liver cancer is a potential target for TSL-based therapy, the goal is to establish a heating system in combination with intravital microscopy to evaluate TSL performance in hepatic tumors.

MATERIALS & METHODS Localized mild hyperthermia was established in hepatic tissue using a 2.45 GHz directional microwave antenna. Optical monitoring of the hepatic tissue was performed before, during, and after hyperthermia application with the use of confocal intravital microscopy. For this purpose, Rhodamine-labelled stable liposomes and TSLs containing the mock drug carboxyfluorescein were systemically introduced to visualize vasculature, intratumoral pharmacokinetics, and heat-triggered drug release and -diffusion. The efficacy of local hyperthermia was determined through real-time visualization of intrahepatic drug release from TSLs.

RESULTS Preliminary studies have elucidated that the developed HT system is able to adequately heat a distinct volume to the threshold temperature. Modulation of the input power is ensured by a closed-loop feedback system to avoid overshoot of the target temperature. Thermal evaluation via infrared images and thermocouples showed the establishment of mild hyperthermic temperatures in hepatic tissue. Intravital imaging confirmed hyperthermia-mediated content release from TSLs as increased extravascular intensity was visible compared to baseline images.

CONCLUSION The set-up design allows for precise hyperthermic control and complex evaluation of TSL-based therapy. Current ongoing studies are focused on further optimization of the hyperthermia set-up and investigation of the therapeutic response of TSL-based therapies in an intrahepatic xenograft tumor model.

L58 Fluorescent, semi-conducting photothermal nanoparticles for the detection and treatment of oxaliplatin-resistant colorectal cancer

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Heated Intraperitoneal Chemoperfusion (HIPEC) is often employed for regional hyperthermia to enhance chemotherapy for treatment of disseminated colorectal cancer. To improve the precision of hyperthermia specifically to a tumor location, near infra-red (NIR) light activatable donor-acceptor, semi-conducting polymer nanoparticles are emerging as excellent photothermal materials owing to their excellent light harvesting nature, biocompatibility and tunable optical absorption. Here, we describe the development of variable molecular weight nanoparticles (VMWNPs) composed of poly[4,4-bis(2-ethylhexyl)-cyclopenta[2,1-b;3,4-b”]dithiophene-2,6-diyl-alt-2,1,3-benzoselenadiazole-4,7-diyli] (PCPDTBSe), which generate heat and exhibit NIR fluorescence. VMWP are stable, inert, and can be heated and imaged repeatedly without loss of their fluorescence or heat generating capacity. The nanoparticles were used against luminescent colorectal cancer cells that were either sensitive or resistant to the chemotherapy drug, oxaliplatin. Rapid (60 s) hyperthermia (42 °C), generated by near-infrared stimulation of variable molecular weight nanoparticles (VMWNPs), increases the effectiveness of oxaliplatin in the oxaliplatin-resistant CRC cells. Fluorescence from VMWNPs was observed inside cells, which allows for the detection. VMWP-induced hyperthermia can induce cell death in a few minutes, compared to classical bulk heating. Changes in the luminescence of the cancer cells can be used to determine the thermal dose induced by the nanoparticles, which may be correlated with the cell viability and therapeutic response. CT26 murine colorectal cancer cells were used to develop micro-metastasis in the abdomen of Balb/C mice. Peritoneal delivery identified that DAPPs localized to tumors to identify where NIR stimulation needed to be applied in an open abdomen. Photothermal ablation was not possible for widespread treatment of disseminated colorectal cancer, due to the optical absorption of the abdominal vasculature. However, the nanoparticles may be useful for fluorescently detecting tumors for resection during surgical procedures. The results demonstrate that VMWNPs can be used for augmenting chemotherapy in drug-resistant colorectal cancer cells, and may be beneficial for identification of colorectal metastasis, where they could be supply mild hyperthermia to facilitate improved chemotherapeutic response in a Nano-HIPEC model.
Patterns of care analysis of hyperthermia in combination with radio(chemo)therapy or chemotherapy in European clinical centers


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Background The combination of hyperthermia (HT) with radio(chemo)therapy (RCT) or chemotherapy (CT) is an established treatment strategy for specific clinical indications. However, its application in routine clinical practice in Europe depends on regulatory and local conditions.

Objective We conducted a survey among European clinical centers to determine the current practice of HT.

Methods A questionnaire with 22 questions was sent to 24 European HT centers. The questions were divided into two main categories. The first category assessed how many patients are treated with HT in combination with RCT or CT for specific clinical indications per year. The second category addressed sequence and time interval between modalities, and which thermometric parameters are recorded. The answers were evaluated using descriptive analysis methods.

Results The response rate was 71% (17/24) and 16 centers were included in this analysis. Annually the 16 centers treat approximately 637 and 205 patients using HT in combination with RCT or CT, respectively. The most common tumors treated with HT in combination with RCT, in decreasing frequency, are recurrent breast cancer (37%), cervical cancer (16%), sarcoma (13%), rectal and bladder cancer (6%), anal cancer (5%), head & neck cancer (3%) and one pediatric cancer patient (Fig. 1a). Clinical indications treated with HT in combination with CT alone are sarcoma (73%), followed by bladder cancer (7%), recurrent breast cancer (5%), pancreatic cancer (3%), cervical cancer (2%), rectal cancer (2%) and 2 pediatric cancer patients (Fig. 1b). On average, 34% of all patients are treated in clinical study protocols. Temperature readings and the time interval between HT and RCT or CT are recorded by 13 (81%) and 9 (56%) centers, respectively. The thermal dose quality parameter "cumulative equivalent minutes at 43 °C (CEM43°C) is evaluated in 5 (31%) centers for each HT session. With regard to treatment sequence, 8 (50%) centers administer HT before RCT, and the other 8 in the reverse order. Furthermore, patients are treated with HT in combination with simultaneous CT in 9 centers (75%) and sequential CT in three centers (25%).
**Conclusion** There is significant heterogeneity among European HT centers as to the indications treated, treatment sequence and the level of recording of thermometric parameters. More evidence from clinical studies is necessary to achieve standardization of HT practice.

Fig. 1

Fig. 2

**Fig. 1.** Approximate number of patients (N) treated per year with HT in combination with (a) RCT and (b) CT.
First commissioning tests of the BSD2000-3D Universal Arch MR-compatible hyperthermia device

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Introduction: Characterisation of the performance of hyperthermia applicators by phantom experiments is an essential aspect of quality assurance. This aspect gains further relevance when new state-of-the-art devices are installed. The aim of the present study is to describe first commissioning tests for a Magnetic resonance (MR) guided hyperthermia system, the BSD2000-3D Universal Arch MR-compatible system operating with the GE MR450w 1.5T MR scanner (Fig 1a).

Materials and Methods: All tests were conducted using a cylindrical phantom. To evaluate the influence of the MR-compatible device on MR image quality (Fig 1b, experiment A), the signal to noise ratio (SNR) was calculated in two different setups: (i) phantom only and (ii) phantom heated with the device, using the clinical MR thermometry (MRT) sequence (Curto et al, 2020). Heating performance (Fig 1b, experiment B) was evaluated in terms of ability and stability using MRT with the proton resonance frequency shift method. Six experiments were performed and temperature increase in a region of interest (ROI) of 3cm diameter in the target was obtained. For stability, temperature precision was calculated in the same ROI between the same measurements. The Gamma method was applied to compare the reproducibility of the six repeated measurements. Criterion of 5%/5mm was used, given resolution and required treatment accuracy. Table 1 details these tests.

Results: Concerning image quality, the SNR of the phantom only setup was 248 and decreased to 106 under the influence of the device. Yet, this shows a drastic improvement over the previous generation of this device, which had an SNR of 15 due to the requirement of off-center phantom placement. Regarding heating ability, temperature increase in the target ROI was on average 6°C in 10 minutes. Temperature standard deviation was 0.32°C, showing the heating stability of the MR-compatible device. Comparison of all central target measurements yielded a median gamma index of 95%, for a criterion of 5%/5mm.

Conclusion: This study showed that image quality with the new device increased by a factor of seven compared to the older generation. Ability of heating in terms of temperature increase followed quality assurance guidelines. Since no specific commissioning tests are defined in the literature, these tests and results may be used as a first assessment to standardize the commissioning of MR-compatible devices.
Fig. 1

Figure 1: BSD2000-3D Universal Arch device integrated in the MR scanner with the cylindrical phantom inside (a). The phantom is filled with a mixture of deionized water and premixed perfusor wallpaper paste (Mulder et al, 2018). Summary of the experiments performed (b): experiment A image quality and experiment B for heating ability and stability.

Fig. 2

Table 1: Summary of the performed tests.]

<table>
<thead>
<tr>
<th>Test</th>
<th>Evaluated parameter</th>
<th>MR method and sequence</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Image quality</td>
<td>SNR</td>
<td>double echo gradient recalled echo</td>
<td>$SNR = \frac{P_{signal}}{P_{noise}}$</td>
</tr>
<tr>
<td>- Heating ability</td>
<td>Temperature increase in a ROI in target</td>
<td>PRFS: double echo gradient recalled echo</td>
<td>$T_{ROI} = \frac{1}{\text{card}(J)} \sum_{j=1}^{j} T_j$</td>
</tr>
<tr>
<td>- Heating stability</td>
<td>Temporal temperature precision</td>
<td>Gamma evaluation (5%/5mm)</td>
<td>$SD_{ROI}^2 = \frac{1}{n} \sum_{n=1}^{n} (T_{ROI})^2$</td>
</tr>
</tbody>
</table>


$T_{ROI}$ gives the average temperature within the ROI, where $T$ is the temperature, $j$ is the index of voxels, and $\text{card}(J)$ is the number of voxels within the ROI.

$SD_{ROI}^2$ is the spatial temperature standard deviation of the ROI evaluated, where $n$ is the total number of measurements.

$\gamma$ from Low et al, 1998.
The Amsterdam UMC clinical protocols and experience with intratarget temperature monitoring during superficial hyperthermia treatment

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In 2010, we have standardized the use of intratarget catheters for temperature monitoring during superficial hyperthermia (HT) treatment at the Amsterdam UMC, location AMC. Here we describe our clinical protocol and experience.

We aim to measure the temperature in the target area in every patient with a target depth ≥1 cm. In our institute, patients are treated with superficial HT in combination with (re-)irradiation for locoregional recurrent (LRR) breast cancer (i.e. post-operative and inoperable), melanoma, sarcoma, or other recurrences in previously irradiated area. Superficial HT is administered with either 434 MHz microwave radiation (Alba 4000, Medlogix®, Rome, Italy) or water-filtered infrared-A (wIRA, Hydrosun® TWH1500, Müllheim, Germany). On the first day of HT, directly before the (re-)irradiation fraction the catheter is placed by a radiation-oncologist, physician assistant, technical physician, or interventional radiologist, followed by CT images to verify the catheter position. A 7-sensor thermocouple probe with a measurement trajectory of 3-6 cm is inserted in the catheter to monitor temperature.

According to our protocol, patients received at least one intratarget catheter to monitor temperature (Fig 1). Patients with reconstructions or silicon prosthesis were eligible for 1-3 catheters. In seroma a new catheter was inserted before each HT treatment, which was removed directly afterwards to minimize the risk of infection. The catheter was removed when the site of insertion shows signs of infection or when the patient experiences pain. In several datasets, e.g. patients with post-operative treatment for LRR breast cancer (n=121), seroma (n=18), silicon prosthesis (n=7), we found no association between skin and intratarget temperatures. In a cohort of 112 patients with LRR breast cancer treated post-operatively in the Amsterdam UMC, only 1.8% of the patients developed a catheter related infection. In 74.1% of the patients intratarget temperatures were monitored during all HT treatment sessions.

Intratarget temperature monitoring during superficial HT is feasible and safe. Since there is a clear HT dose-effect relationship with complete response and locoregional control, we will continue to monitor intratarget temperature during superficial HT to ensure reaching optimal target temperatures and thus enhance the radiosensitizing effect of HT.

Fig 1. Intratarget catheter to monitor temperature during superficial hyperthermia treatment.
The effect of thermal dose in patients with non-muscle-invasive bladder cancer treated with chemohyperthermia

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Incidence of recurrences remain high for patients with non-muscle-invasive bladder cancer (NMIBC) despite different adjuvant intravesical therapies. Previous studies showed a clear advantage of hyperthermia (HT) combined with mitomycin C (MMC) compared to MMC alone. Thermal dose-effect relationships on clinical outcomes have not yet been investigated.

We aimed to investigate the effect of HT thermal dose (TD) on recurrence-free survival (RFS) and in relation to toxicity in patients with non-muscle-invasive bladder cancer (NMIBC) treated with chemohyperthermia.

In this retrospective study, 60 patients with high-risk NMIBC treated with six weekly sessions of loco-regional chemohyperthermia with MMC followed by four maintenance sessions between 2009-2020 were included. Temperature was monitored in the bladder and bladder region (i.e. urethra, rectum and, if applicable, vagina). Groups were divided using an outcome-related cut-off point into "low" (n=30; <16.6 min) and "high" (n=30; ≥16.6 min) TD groups by the total CEM43T50 (=median cumulative equivalent minutes at 43°C) from the bladder region. Actuarial RFS, and toxicity were analyzed. Multivariate Cox regression and inverse probability weighting (IPW) analysis were performed.

Median follow-up period was 21 months (range 3-123). RFS rates at one-, two- and three-year were 76.5%, 57.2% and 46.4%, respectively. Actuarial RFS was significantly higher in the high TD group than in the low group (p=0.028, Figure 1). For the low and high TD groups, the RFS rates at one-, two- and three-year were 72.9% vs. 80.0%, 48.7% vs. 65.7% and 27.0% vs. 65.7%, respectively. These RFS rates remain stable at four and five years. After adjusting for pre-specified potential confounders, the effect of high TD remained significant on RFS (low vs. high; adj. HR 2.5; 95% CI 1.1–5.7; p=0.031). IPW analysis (low vs. high; HR 2.5; 95% CI 1.9–3.1, p=0.031) confirmed this result. Toxicity was not significantly different between low and high TD groups (p=1.00). Grade 1 and grade 2 toxicity was observed in 63.3% (n=38) and 31.7% (n=19) of the patients, respectively. No grade ≥3 toxicity was reported. Besides discomfort, the most frequently reported toxicities were urinary urgency (n=25, 41.7%), bladder spasms (n=23, 38.3%) and urinary tract pain (n=19, 31.7%, Table 1).
High TD (total CEM43T50 ≥16.6 min) was associated with significantly higher RFS in patients with NMIBC treated with chemohyperthermia.

Fig. 1

![Graph showing recurrence-free survival (RFS) for patients in high TD and low TD strata.]

**Log-rank p = 0.028**

<table>
<thead>
<tr>
<th>Strata</th>
<th>Time (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High TD</td>
<td>30 24 18 16 14 12 10 8 4 4 1</td>
</tr>
<tr>
<td>Low TD</td>
<td>30 19 9 4 2 2 2 1 1 1 0</td>
</tr>
</tbody>
</table>

Fig. 2

**Table 1.** Frequency and type of toxicities during chemohyperthermia treatment.

<table>
<thead>
<tr>
<th>CTC-AE score</th>
<th>Low TD (n=30)</th>
<th>High TD (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discomfort due to treatment</td>
<td>24 (80.0%)</td>
<td>Discomfort due to treatment</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>12 (40.0%)</td>
<td>Urinary urgency</td>
</tr>
<tr>
<td>Urinary tract pain</td>
<td>7 (23.3%)</td>
<td>Urinary tract pain</td>
</tr>
<tr>
<td>Bladder spasm</td>
<td>3 (10.0%)</td>
<td>Bladder spasm</td>
</tr>
<tr>
<td>Fat necrosis</td>
<td>3 (10.0%)</td>
<td>Fat necrosis</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>3 (10.0%)</td>
<td>Urinary frequency</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>2 (6.7%)</td>
<td>Cystitis noninfective</td>
</tr>
<tr>
<td>Hematuria</td>
<td>1 (3.3%)</td>
<td>Hematuria</td>
</tr>
<tr>
<td>Dysuria</td>
<td>1 (3.3%)</td>
<td>Dysuria</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1 (3.3%)</td>
<td>Allergic reaction</td>
</tr>
</tbody>
</table>

Grade 2

| Discomfort due to treatment | 24 (80.0%) | Discomfort due to treatment | 26 (86.7%) |
| Urinary urgency | 12 (40.0%) | Urinary urgency | 13 (43.3%) |
| Urinary tract pain | 7 (23.3%) | Urinary tract pain | 12 (40.0%) |
| Bladder spasm | 3 (10.0%) | Bladder spasm | 7 (23.3%) |
| Fat necrosis | 3 (10.0%) | Fat necrosis | 6 (20.0%) |
| Urinary frequency | 3 (10.0%) | Urinary frequency | 3 (10.0%) |
| Urinary incontinence | 2 (6.7%) | Cystitis noninfective | 3 (10.0%) |
| Hematuria | 1 (3.3%) | Hematuria | 2 (6.7%) |
| Dysuria | 1 (3.3%) | Dysuria | 1 (3.3%) |
| Allergic reaction | 1 (3.3%) | Allergic reaction | 1 (3.3%) |

*During the treatment sessions 75% of the patients (n=45) developed more than one type toxicity.*

**Abbreviations:** TD = thermal dose.
**L63**

**Rationale for combining stereotactic radiation and hyperthermia**

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**Introduction:** Stereotactic radiation treatments (SRT) can kill cells directly, and indirectly via the induction of vascular damage. The latter effect will also increase the poor microenvironment conditions within tumors and cells under such conditions are more sensitive to treatment with hyperthermia, thus combining heat with SRT should have greater anti-tumor effects.

**Objectives:** To investigate the potential of combining various SRT schedules with hyperthermia in our C3H mammary carcinoma, which responds to both high radiation doses and heat treatment.

**Materials & methods:** A C3H mammary carcinoma grown in the right rear foot of CDF1 mice was used when at 200 mm³. SRT (X-rays), involve 1-5 fractions of 5-25 Gy administered in a one-week period. Hyperthermia entails immersing the tumour-bearing leg in a water bath and heating at 40.5-42.5°C for 60 minutes starting 30-240 minutes after the final irradiation. Endpoints include tumor growth delay (time to 5x treatment volume; TGT5) or local tumor control at 90 days; 3-days after the final radiation a clamped top-up dose was given to produce a dose response curve from which the TCD50 value (radiation dose controlling 50% of tumors) was determined. Vascular mediated effects estimated using dynamic contrast-enhanced magnetic resonance imaging; the endpoint being the initial area under the uptake curve (IAUC). Statistical analysis involved a Student’s T-test or Chi-squared test (p<0.05 for both).

**Results:** The mean (+ 1 S.E.) TGT5 for control tumors was 5 days (+ 0.2) and this significantly increased to 22 days (+ 0.7) following irradiation with 20 Gy. This radiation dose resulted in a small, yet non-significant, 18% (+ 6) decrease in IAUC, Preliminary studies with a SRT treatment of 3 x 15 Gy resulted in a TCD50 value (+ 95% CI) of 30 Gy (+ 8). Heating tumors at 41.5°C 4-hours after the last irradiation significantly decreased this value to 10 Gy (+ 4).

**Conclusions:** Our preliminary results with high radiation doses are consistent with some degree of vascular damage and that applying heat after SRT significantly enhanced local tumor control. Additional studies are ongoing to determine the optimal SRT schedule and heat treatment for the greatest anti-tumour response.

*This project has received funding from the European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 955625 (Hyperboost; www.Fyperboost-h2020.eu) and a grant from the Danish Cancer Society.*

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**L64**

**Combined thermal ablation and high dose radiotherapy: Optimizing for dose reduction and tumor control**

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The field of radiation oncology continues to advance in the application of high dose, low fraction number regimens, with many noted improvements in response rates. At the same time, the field of thermal medicine has advanced with the advent of image-guided (MRI or Ultrasound) thermal ablation (HIFU, RF etc.) as well as various interventional oncology approaches. As technologies advance, the use of MRI or ultrasound to assist in radiotherapy or thermal therapy treatment planning suggests that a single treatment room may be possible for image guided high dose radiation and thermal ablation. Thus, there is unmet need to better understand the biology and physiology so that the basic science involved is exploited and a deep knowledge of possible normal tissue effects is used in treatment planning. Our work has been focused on using new tools to understand tumor and stromal cell sensitivity/resistance mechanisms more clearly PMID: 26308944, PMID: 28822765. In addition, development of an innovative non-invasive
monitoring method for these treatments by detecting the gradient of hypoxic cells released via tissue damage and death (a measure of the effect of these therapies on the most difficult areas to control in the tumor) will create opportunities for more tailored treatment approaches in the future. Dose reduction strategies could optimize effectiveness and application of stereotactic radiotherapy in large fractions for patients presenting with tumor sites previously untreatable due to risk of complications. We have demonstrated that thermal ablation and vascular damaging tumor necrosis factor (TNF)-coated gold nanoparticles can significantly improve the response of solid tumors to 20 Gy single dose by reducing the hypoxic tumor burden and destroying tumor vasculature PMID: 22335229. Thermal ablation can destroy the hypoxic core of the tumor but by itself suffers from notable recurrence rates and incomplete coverage in larger tumors, thus combining with hypofractionated radiotherapy to create clear margins may be highly effective. Importantly, establishing the dose modification, or reduction, factor (DMF) obtainable by the combination of high dose radiotherapy, thermal ablation and/or anti-vascular drugs has yet to be defined and this knowledge may open significant new avenues combined treatment success.

L65
Fractionated MR-HIFU Hyperthermia in the pancreas of a large animal model

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Question: Several clinical studies using ultrasound-guided high-intensity focused ultrasound (HIFU) for thermal ablation of pancreatic cancer have shown to improve local control and alleviate pain. Preclinical studies showed that hyperthermia-mediated drug delivery with temperature sensitive liposomes prior to ablation allows treatment of the tumor rim adding additional therapeutic efficacy. As a step towards this combination therapy, we investigate the application of hyperthermia in the pancreas of landrace pigs using MR-guided HIFU.

Methods: Two German landrace pigs (49 and 45.5 kg) were anesthetized and positioned on a commercially available MR-HIFU System (3T Achieva®, Philips Healthcare, Best, The Netherlands & Sonalleve® V2, Profound Medical, Toronto, Canada), equipped with an abdominal compression device. Preparations involved bowel cleansing, digestive tract filling, application of an anti-foaming agent, suspension of bowel movement, and belly shaving. Before treatment, a suitable apnea protocol was determined for each animal. To reduce field drift, gradient warm-up was performed. Then, phases of apnea and hyperventilation were alternated. During the apnea phases, MR-HIFU hyperthermia was applied in the pancreas.

Results: In the first animal, several challenges were identified, including mobile air pockets near the target region leading to severe susceptibility artifacts. These led to unstable thermometry, which prompted automatic abortion of the treatment. In the second animal, these challenges were addressed by a refined bowel preparation, an enhanced masking of low-quality thermometry voxels and the suspension of automatic treatment abortion in the MR-HIFU software. This allowed the application of fractionated hyperthermia for ~14.5 minutes (Fig. 1 and Fig. 2).

Conclusions: We have demonstrated the feasibility of MR-HIFU fractionated hyperthermia in the pancreas of landrace pigs. While several challenges relating to temperature monitoring remain to be addressed, this is a step towards clinical translation of highly effective therapies combining Hyperthermia-mediated drug delivery and tumor ablation. Upcoming experiments target refinement of the technique and are expected to demonstrate reproducibility and feasibility over longer timespans.

Fig. 1: T curves in ROI over time showing alternating apnea/hyperthermia and breathing/pause phases

Fig. 2: Thermometry during final apnea/hyperthermia phase. Left: coronal view; Right: sagittal view
L66
Clinical application of laser interstitial thermal therapy in Neuro-oncology

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Laser interstitial thermal therapy (LITT) is a treatment modality to kill tumor cells using hyperthermia via a stereotactic guided surgery and under real time control with intra-operative MR thermometry. There are several indications for LITT in for intracranial applications including epilepsy surgery and brain tumors.

We will review the current application of LITT for intra-axial tumors like glioma or brain metastasis including review of current literature for high quality evidence as well as our personal experience with over 250 cases of LITT along with future directions.

Recent literature shows that in difficult to access gliomas, LITT plus concurrent chemo/radiation has a better outcome compared with biopsy only patients. In addition for brain metastasis in the setting of failure after radiosurgery, LITT has durable response in cases of radiation necrosis and in combination with radiosurgery has better outcome compared with other modalities.

There are also some benefit of LITT in opening blood brain barrier and sensitizing to radiation that needs more exploration.

L67
Peripheral immune changes in patients with newly diagnosed glioblastoma receiving expedited chemoradiation after laser interstitial thermal therapy

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Introduction

Glioblastoma (GBM) is the most aggressive and common primary adult brain cancer. Despite the effectiveness of gross total resection (GTR) to prolong survival, approximately 20% of patients with newly diagnosed GBM are poor candidates due to co-morbidities or deep-seated and large tumors. Focal hyperthermia, as delivered using laser interstitial thermal therapy (LITT), has been shown to deliver an accurate thermal ablation of GBM leading to >9months of progression-free survival in patients with adequate thermometry and is an exciting potential treatment option for these patients. Preclinical models show that focal hyperthermia can increase radiosensitivity, blood-brain barrier permeability, and consequently tumor control by optimizing the effects of chemoradiation after surgery. Thermal damage can recruit immune cells to the tumor bed via chemokines stimulating both innate and acquired immune cells. Clinically, GBMs have high concentrations of infiltrating myeloid-derived suppressor cells (MDSC) and tumor-infiltrating lymphocytes that may also result in the accumulation of these cell types in the periphery.

Objective

Characterize the peripheral immune landscape of patients with newly diagnosed GBM both before and after undergoing LITT with expedited chemoradiation.
Materials & Methods

Ten patients were enrolled in the clinical trial (NCT02970448) and circulating blood cells were assessed for counts and immune cell markers ("LITT" group). Furthermore, blood samples were collected from patients undergoing either gross total resection or biopsy alone without LITT to serve as control subjects ("No LITT" group). Samples were collected from all patients in the trial at timepoints included under standard care for trial patients to minimize needle sticks.

Results

The "LITT group" patients showed increased uncommitted MDSC (UC-MDSC) populations highly expressing VISTA within 48 hours after LITT, compared to the "No LITT" group which showed little to no relative increase in UC-MDSC or VISTA expression. Furthermore, the number of peripheral mononuclear MDSCs (PMN-MDSCs) did not increase 48 hours after LITT as they did in the "No LITT" group, but they demonstrated increased relative expression of PD1 and VISTA which was not seen in the No LITT group.

Conclusion

These data suggest that LITT may modulate myeloid cell function and suggest the use of anti-PD1 therapy within 48 hours after LITT.

L68

Personalized image-guided transbronchial microwave ablation treatment of lung tumors

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Advances in virtual bronchoscopy and navigation systems, cone beam CT (CBCT) imaging, and robotic bronchoscopy platforms, integrated with flexible ablation systems, offer potential to enable minimally invasive diagnosis, staging, and treatment of lung nodules in a single session for the large population of patients who are not surgical candidates. We have developed a 2.45 GHz microwave ablation system, including a custom flexible water-cooled microwave ablation (MWA) catheter, suitable for bronchoscopic ablation of lung tumors. Computational and experimental characterization of the MWA catheter on the benchtop and in an in vivo non-survival porcine model demonstrate the ability to create 1–3 cm diameter ablation zones in 5–10 min. A survival study was conducted to assess safety of the procedure and radiologic–pathologic correlation in normal porcine lung, with animals survived for up to 13 days following 90 W, 5 min transbronchial MWA (n=4 pigs). No pneumothorax, major bleeding, or fistula were observed during and after ablation procedures. On day 13, extents of the ablation zone on CT imaging (16–21 mm) were well aligned with gross pathologic assessment (14–20 mm) following viability staining. Progress is underway towards technical feasibility and safety assessment of the transbronchial MWA system in a first-in-human ablate and resect study.

Our pre-clinical experience highlighted the significance of comprehensive treatment planning, accurate and consistent device positioning, and monitoring of MWA progress in achieving successful outcomes. To guide patient-specific selection of MWA treatment delivery parameters, we are developing a personalized simulation-based modeling framework informed by tumor radiomics analysis. In a retrospective study of percutaneous lung MWA in 60 patients, the personalized modeling framework demonstrated a 29% improvement in average absolute error and 20% improvement in Dice similarity coefficient over manufacturer estimates of the ablation zone, when compared to post-ablation CT. We participated in pilot in vivo porcine studies demonstrating the feasibility of delivering transbronchial MWA with robotic bronchoscopy under CBCT guidance and intra-operative monitoring. Together, the transbronchial microwave ablation system integrated with the predictive planning platform delivered through a robotic
bronchoscopy system under CBCT guidance and monitoring offers potential for effective and consistent MWA treatment of lung nodules.

L69
An in vitro system for focused ultrasound hyperthermia (and radiotherapy) studies using spheroids

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Introduction

Ultrasound can be used for clinical hyperthermia. \textit{In vitro} studies are challenging as acoustic interactions in 2D cell suspensions are not representative of those \textit{in vivo}. The lack of absorption in culture medium means acoustically induced thermal effects are absent. A system for ultrasound (US) hyperthermia studies (+/- radiotherapy (RT)) of 3D \textit{in vitro} models, with thermal dosimetric control has been built with the aim of improving prediction of \textit{in vivo} outcomes.

Material and methods

Acoustic holography was used to design a lens that widened and shortened the focal region of a 64 mm diameter (F-no=1) 1.66 MHz ultrasound transducer (H148MR Sonic Concepts, USA) from 2 mm diameter by 12 mm to 6 mm x 8 mm wide by 8 mm on axis.

For exposure, U87MG glioma spheroids were held in a two-part ultrasound-absorbing biocompatible gel (IEC standard tissue mimic + 1\% phenol red). The lower half had 25 or 100\mu m diameter T-type thermocouples (TCs) mounted with their junctions within 0.5 mm of the bottom of each of three 1 mm diameter, 0.7 mm deep dimples spaced 2 mm apart. The top, flat, 4 mm thick, gel fitted within the 3D printed frame holding the first part.

One spheroid was pipetted into each dimple before sealing with Matrigel. Medium was used to couple the gel lid to its base and the ensemble placed in a 38oC water tank. After equilibrating, real-time temperature and thermal dose monitored US was delivered until the central spheroid received 119.5 CEM43. The thermal dose in the other wells was ~30 and 75 CEM43. Controls were sham-exposed simultaneously in the same water bath. Spheroids were exposed to 0, 2 or 6 Gy RT (Xstrahl Cell irradiator) 0 to 6h later. Spheroid size (Celigo Imaging cytometer) and viability (Cell Titer Glo 3D assay) were measured on day 12.

Results

Of 117 US exposed spheroids, 110 were successfully harvested. 121 (n=39), 75 (n=35) and 31 (n=36) CEM43 were delivered (standard deviations 1, 11 & 23\% respectively). RT alone had little effect. US alone (>= 31 CEM43) resulted in <50\% viability but with less effect on spheroid size, while US+RT enhanced viability loss to <10\%.

Conclusion: The exposure system works well, with 94\% spheroid harvest possible, and clinically relevant thermal doses being achievable. Comparison of viability and size data suggests the latter to be a poor indicator of cellular response. 75 & 121 CEM43 had similar effects. The combination of HT+RT resulted in greater loss of viability than either alone.
L70
Heating power of dual-material radioactive magnetic nanoparticles for thermo-brachytherapy

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INTRODUCTION: Magnetic nanoparticles (MNP) are known to generate heat in alternating magnetic fields of a frequency that does not interact with tissue. With this method, it is possible to selectively heat tumor tissue loaded with MNP, while the surrounding healthy tissue remains at body temperature. When the MNP have sufficient heating power, i.e. have strong interaction with the magnetic field, it is possible to reach thermal ablation temperatures within the tumor. By combining these magnetic properties with radioactivity, thermo-brachytherapy can be delivered in one treatment. As a first step, dual-material radioactive magnetic nanoparticles were developed and their heating power measured.

MATERIALS & METHODS: The specific loss power (SLP), i.e. heating power, of a series of the novel, hybrid MNP was measured using Magnetherm Digital device with frequencies ranging from 50 kHz to 750 kHz and field strengths of 15 to 30 mT. Magnetic properties of the hybrid MNP were evaluated using superconducting quantum interference device (SQUID) magnetometer measuring saturation magnetization (Ms) as a function of magnetic field (H).

RESULTS & DISCUSSION: Hybrid nanoparticles with a core of palladium, which will serve as the radioactive source using 103Pd, and with a magnetic shell of iron-oxide were synthesized. By varying the synthetic conditions, hybrid MNP in different sizes, shapes, and magnetic properties are obtained. As reference the SLP of the hybrid MNP are compared to the SLP of commercial iron-oxide MNP using the same experimental setups. The obtained SLP values for the hybrid MNP’s ranged from 0 to 225 W/g. Some samples were not stable in suspension and aggregated, which resulted in reduced or even no heating power. Samples with high saturation magnetization, normally showed larger SLP, however SLP values of such samples were significantly reduced upon aggregation. The stability is mostly dependent on the surface functionalization of the nanoparticles. When stable in solution, the MNP with a higher Fe/Pd ratio showed larger SLP.

CONCLUSION: Hybrid MNP with a non-magnetic core can be synthesized reaching SLP values up to 225 W/g, with SLP values increasing with larger Fe/Pd ratio and larger Ms. This SLP is expected to be sufficient for thermal ablation of tumors as small as 15 mL with 1mg/mL MNPs in the tumor and as small as 1mL tumor volumes using 5mg/mL dose.

Acknowledgment: Research funded by NWO-TTW, Project 16238 NP-thermobrachy
Multi-Echo Gradient Echo Sequences: Which is best for MR thermometry?

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During hyperthermia therapy (HT), tissue temperature is increased towards 43°C to stimulate radio-, chemo- or immunotherapy. The HT effect is strongly temperature dependent so real-time monitoring is crucial for treatment quality. MR thermometry (MRT) is a promising tool to measure the temperature distribution during treatment non-invasively, but it’s not yet established in clinical routine. This study compares the PRFS-MRT performance of different multi-echo gradient echo sequences in order to make acquisitions more reliable and robust.

We investigated Double-Echo Gradient Echo (DEGRE: 2D, 2 echoes), Multi-Echo Fast Gradient Echo (ME-FGRE: 2D, 11 echoes), and a three point Dixon multi echo sequence (IDEAL IQ: 3D, 11 echoes). All acquisitions were made using a 22-channel head&neck coil on a 1.5T MR scanner. In-plane motion was compensated by rigid body image registration. For each ME-FGRE and IDEAL IQ scan the off-resonance frequency and proton density water/fat maps were calculated by a multi-peak fitting tool. An automatic method to select the internal body fat was developed to correct for the B0 drift in the volunteer scans. An important advantage of this method is that it needs no user input, as it uses the proton density maps from the multi-peak fitting tool. The temperature change from baseline was computed from the change in off-resonance frequency. Accuracy was calculated in phantom as the average absolute difference between the probe measurement and MRT temperature. In-vivo stability was calculated as the mean absolute deviation from zero of the temperature change.

IDEAL IQ outperformed all other sequences with an accuracy of 0.32°C (Fig 1) and a stability of 0.75°C (Fig 2). The IDEAL IQ data was also most robust concerning the fat mask selection, with only 5% of slices having to be excluded, compared to up 30% for other sequences.

IDEAL IQ is 83% more accurate and 62% more stable than the standard in use today and thus is deemed the most promising candidate from the sequences investigated here. Its superior accuracy and stability in vivo enable reliable detection of small temperature increases during the relatively long treatment times. Beyond its convincing MRT performance, the multi-echo nature enables the automatic selection of internal body fat for B0 drift correction, as an important feature for clinical application.
Fig. 1

![Graph showing MRT temperature vs BSD temperature with different markers for DEGRE TR620, DEGRE TR200, ME-FGRE, and IDEAL IQ.]  

<table>
<thead>
<tr>
<th></th>
<th>Including all</th>
<th>Excluding motion + too little fat</th>
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<tr>
<td></td>
<td>stability (°C)</td>
<td>SD (°C)</td>
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<tr>
<td>DEGRE TR620</td>
<td>6.74</td>
<td>3.17</td>
</tr>
<tr>
<td>DEGRE TR200</td>
<td>6.95</td>
<td>3.33</td>
</tr>
<tr>
<td>ME-FGRE</td>
<td>9.72</td>
<td>5.72</td>
</tr>
<tr>
<td>IDEAL IQ</td>
<td>3.09</td>
<td>3.04</td>
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Improvement of Magnetic Resonance (MR) Imaging-based temperature-controlled hyperthermia by reconstructing highly undersampled MR acquisitions

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* R. Khatun and S. Chatterjee have equal contributions

Hyperthermia (HT) in combination with radio- and/or chemotherapy has become an accepted cancer treatment for distinct solid tumour entities. In HT, the tumour tissue is exogenously heated to minimal temperatures of 40 to 41°C for 60 minutes. Temperature monitoring can be performed non-invasively using dynamic Magnetic Resonance Imaging (MRI). However, a big challenge is that the MRI is an inherently slow process. Consequently, the scan time for high-resolution imaging is long compromising with the temporal resolution. Longer scan times can also lead to an increase motion artefact due to the movements of the patient during the image acquisition time. The speed of the image acquisition can be reduced by discarding parts of the data, known as undersampling. But that leads to loss of resolution and can also produce artefacts, due to the invalidation of the Nyquist criterion.

Hereby, MRI image reconstruction or reduce of motion artefacts is in high demand. This work aims to reconstruct highly undersampled MR acquisitions, with better resolution and with less artefacts compared to conventional techniques like compressed sensing. Using the Fourier-PDUNet and Fourier-PDNet models as the network backbone, the NCC1701 pipeline has been seen to be capable of removing artefacts from highly undersampled images. However, hereby, the focus is on the magnitude images only, while the phase images are ignored which are fundamental requirements for MR thermometry. This work extends the previous to reconstruct magnitude as well as phase images, or simply, trying to reconstruct complex images, as a Complex-Valued Convolutional Neural Network.

For evaluating this approach, image sets of 48 different patients with different types of sarcoma cancer, mainly originated in the leg of the patients, has been used. This 48 cancer patient data has been randomly segregated training set, validation set and test set: 26 subjects has been used for training set, 7 subjects has been used for validation set and 11 subjects has been used for testing the model.

The Structural Similarity Index or SSIM is used as a metric to measure the similarity between two given images. The SSIM value have is shown in violin plot where the similarity of reconstructed magnitude images by Fourier-PDUNet and Fourier-PDNet with ground truth is 90% and 91%, respectively. Regarding the undersampled images, 64% was achieved (Fig. 1(a)). In Fig. 1(b), the SSIM value is shown in violin plot where the similarity of reconstructed phase images by Fourier-PDUNet and Fourier-PDNet with ground truth is 43% and 44%, %, respectively, and that of the undersampled image is 31%. In Table 1, the mean value root mean square error (RMSE) of reconstructed temperature map is shown. Here the temperature difference between ground truth and undersampled images is 1.508±0.059 which is 1.5°C more than ground truth. But the mean value of RMSE of Fourier-PDUNet 1.079±0.039 and Fourier-PDNet is 1.079±0.036, respectively, which has 1°C difference with ground truth. So, the models are giving 40% better accuracy to reconstruct the temperature map.

Figure 1: (a) SSIM value of magnitude images of different models. (b) SSIM value of phase images based on the indicated models used.

Conclusions: The results show that deep learning-based methods were able to alleviate the undersampling problem and managed to bring the temperature difference close to the ground-truth. Still, a 1°C temperature difference can...
be seen in the deep learning results. This can be attributed to the performance difference of the models between the magnitude and phase images. Future work will focus on improving the networks’ performance on the phase images, which should also reduce the temperature difference.

**Acknowledgement:** This work has been supported by the European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 955625, Hyperboost.

Fig. 1

![Graph 1](image1)

Fig. 2

![Graph 2](image2)

**Table 1: Mean Value of RMSE of Reconstructed of Temperature Map from different models**

<table>
<thead>
<tr>
<th>Undesample</th>
<th>Fourier-PDU Net</th>
<th>Fourier-PDNet</th>
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<tr>
<td>1.508±0.059</td>
<td>1.079±0.039</td>
<td>1.079±0.036</td>
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Silent PRFS MR thermometry based on looping star sequence

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Mild hyperthermia (HT) aims at heating tumour tissue to 39-43°C and is a powerful tool to enhance chemo- radio- or immunotherapy. Different tissue effects at different temperatures and the narrow temperature range aim, makes real-time feedback as well as retrospective validation of temperature reached particularly important. MR thermometry (MRT) can supply 3D real-time temperature maps during treatment. Proton resonance frequency shift (PRFS) is popular for MRT, due to its near tissue independence and linear behaviour with temperature. But MR acquisitions are loud and run throughout treatment. With patient comfort in mind, we investigated the quiet Looping Star sequence, a 3D multi-echo gradient echo sequence, with radial acquisition for its in-vivo stability – trialling for the feasibility of silent MRT.

Two volunteers were imaged with a head coil on a 1.5T MR scanner (GE Healthcare). The scan protocol consisted of: 1) echoes=8, echo spacing ES=3.4ms; 2) echoes=10, ES=2.2ms. These parameters were chosen so that they roughly cover the same total echo train length and the ES will provide good fat/water contrast. For comparison, a double-echo gradient-echo (DEGRE) scan was also taken of the same volunteers, being the standard sequence used at our institution for HT treatments. All post processing was done in MATLAB. Rigid image registration was performed to the complex valued data at the two acquired time points. The ROI evaluated for all slices, scans and volunteers is shown in Fig. 1 in green, superimposed on magnitude image (purple). Stability was calculated as the mean absolute deviation from zero of the temperature change in the ROI in 3 slices.

The stability achieved with the 8-echo and 10-echo Looping Star acquisition was 0.28°C and 0.30°C respectively. Fig. 2 shows an example of the change in temperature maps for all slices. A signal drop out in the frontal areas of the brain can be observed here, as well as a temperature gradient across the image most likely due to scanner drift. The stabilities achieved by the same volunteers in the same scanning session using DEGRE (2-echo, 2D) were 3.33°C (0.88°C after drift correction).

With the prospect of further improvements, our study already shows the benefits of Looping star for PRFS MRT. Looping Star promises more accurate temperature mapping compared to DEGRE, while at the same time greatly increasing patient comfort during HT treatments, due to its silent nature.
L74
Evaluation of Magnetic Resonance Thermometry reproducibility during MR hyperthermia treatment of Soft Tissue Sarcoma

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Introduction: Magnetic Resonance Thermometry (MRT) is the only known method for real-time 3D monitoring of the tissue temperature during deep regional hyperthermia treatments. The proton resonance frequency shift (PRFS)-based MRT method uses differential phase maps and hence is sensitive to tissue motion affecting MRT reproducibility and accuracy in regions such as the pelvis or the lower extremities (1).

Objectives: The aim of this study was to evaluate the reproducibility of MRT in patients with Soft Tissue Sarcoma (STS) at two anatomical sites (pelvis and lower extremities), before and during treatment. Covariance filtering as a means to exclude MRT voxels with low Signal to Noise (SNR) suggested in (2) was also studied.

Patients and methods: 27 Hyperthermia treatments (HT) were performed on 9 patients with STS of the pelvis and lower extremities in the Pyrexar BSD2000-3D/MR hybrid system (Pyrexar Medical Corp., Salt Lake City, USA), integrated in a 1.5T Philips Ingenia MRI (Philips, Netherlands), according the clinical routine protocol at LMU Klinikum (Munich, Germany). Two consecutive standard DEGRE sequences were applied before treatment and every 10 minutes during HT. The temperature increase during HT was calculated via the PRFS method using the phase information of the second echo, and temperature error maps (TEM) were calculated from each two consecutive scans. Reproducibility was quantified by the standard deviation (σ) of the TEM prior to treatment ("baseline") and during treatment ("treatment"). A covariance filtering was implemented in order to exclude noisy MRT data and the reproducibility was re-evaluated (Figure 1).

Results: Before covariance thresholding, the mean temperature difference (μ) and σ of TEM are (0.0±4.7)°C, (0.1±3.5)°C and (0.1±2.5)°C, (0.0±2.6)°C for pelvic and extremities, during treatment and in baseline condition, respectively. Results after covariance masking are shown in Table 1.

Conclusions: In this study, we quantified MRT reproducibility in patients with STS at two representative anatomical sites. Similar results were obtained for both sites during treatment after covariance masking. Specifically for the pelvic region, our results indicate that future non-heating volunteer studies enable to analyse new pulse sequences and post-processing correction methods.

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Figure 1: (A) un-masked TEM on top of the intensity image of the PRF scan of the extremities (up) and of the pelvis (bottom); (B) covariance mask; (C) masked TEM on top of the PRF scan intensity distribution of the extremities (up) and of the pelvis (bottom).

Table 1: The mean temperature difference (μ) and standard deviation of the differences (σ) from masked TEM for all patients at each anatomical location.
The benefit of recursive temperature estimation in MR-guided hyperthermia for cervical cancer


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Introduction: Hyperthermia elevates the tumor region’s temperature to 40-44°C. Since the success of this treatment depends on well-controlled heat delivery, accurate temperature monitoring is essential to ensure an effective hyperthermia treatment. Magnetic Resonance thermometry (MRT) is the only clinical option to monitor temperature non-invasively. However, the accuracy of MRT in cervical regions is not always sufficient for thermal dosimetry due to the susceptibility artifacts caused by gas motion. Model-based temperature estimation has the potential to correct and supplement real-time temperature monitoring. Since simulations for the pelvic region are too complex to be conducted in real-time, reduced models are needed. This study proposes combining reduced thermal models with Kalman filtering to improve the temperature estimation using MRT.

Patients and methods: This study includes data from three patients diagnosed with cervical cancer, chosen based on the acquired MRT accuracy. All treatments were conducted in the MR compatible system. During treatment, the temperature was monitored by intraluminal probes and MRT. Thermal simulations created the library as input for proper orthogonal decomposition (POD), which was used for model reduction to make the model tractable for estimation algorithms. Kalman filter was used to estimate temperature by combining POD predictions (reduced thermal model) and MRT. In this way, the reliable part of the MRT is combined with simulation-based interpolation in space. Note that Kalman filter reduces noise and enables estimating temperature throughout the whole treatment for better dose assessment. We evaluated the temperature near the location of the probes and we calculated the mean absolute error (MAE) and standard deviation of the error (SDE) for MRT and POD-Kalman filtered temperatures. We considered an MAE ≤ 1°C and SDE ≤ 0.5°C acceptable.

Results: Table 1 shows the MAE and SDE. The POD-Kalman filtering reduced MAE by 29% and SDE by 47%. Although the POD-Kalman filter improved both parameters, these were still above the acceptable thresholds for patient C. This method might enable reaching the acceptance limits if the thermal simulations are improved. Fig. 1 shows the temperature distributions of 3 patients. The intestinal gas motion was low, medium, and high in patient A, patient B, and patient C, respectively.

Conclusions: The results suggest that the POD-Kalman filter improves the temperature estimation in patients in which MRT is unreliable.

Fig. 1
L76
The impact of Sequence-Dependent drift characteristics on PRFS thermometry

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Introduction: MR thermometry allows for non-invasive temperature feedback of hyperthermia treatments, using e.g. MR-HIFU. The widely used PRFS thermometry is phase-based and therefore sensitive to phase errors. A known source of such artifacts lies in the MR scanners' magnetic field drifting over time. Especially MRI sequences with high gradient duty cycles, such as echo-planar imaging (EPI), used in rapid thermometry, are strongly affected. This phase drift evolves spatially heterogeneous over time and is dependent on gradient utilization, therefore also on slicing direction.

Objectives: The objective of this project was to characterize scanner-specific magnetic field drift produced by a gradient-demanding MRI sequence, especially observing scanning parameters like slice orientation.

Methods: Experiments were conducted on a 3T clinical MRI (Philips Healthcare, Best, The Netherlands). A standard saline-based phantom was positioned near the scanner isocentre. Blocks of five minutes with continuous EPI-based PRFS thermometry imaging were used for hardware heat up. A 3D B0 map was derived from a 3D low-resolution double-echo gradient echo acquisition (TA=34s) before the first and after each block. Experiments were repeated for sagittal-, transverse-, coronal-only and combined slicing direction. Each was started after substantial hardware cool-down time. In addition, reproducibility and general warm-up and cool-down periods were characterized. Post-processing was performed in Python 3.7.6.

Results: Analysis suggested that spatio-temporal drift characteristics express a reproducible behavior when using same sequence type and device. Strong influences on drift arise in pre-scan warm-up and cool-down periods. Another important factor are the sequence-specific scan factors, e.g. slice orientation, since phase drift is tied to gradient utilization. As shown in Figure 1, e.g. scanning only sagittal slices, led to a drift substantially different from transversal-only acquisitions.

Conclusions: Characterization and understanding of magnetic field drift plays a vital role in being able to correct for it. Current drift compensation relies mainly on scanner warm-up and in-place 0-,1st-or 2nd-order drift correction. Analysis of our datasets suggests that a customized higher-order compensation may be required. Spatial drift behavior over time is reproducible and would allow for even more robust drift compensation in 3D.

Fig. 1: Temperature drift in phantom (15min)
Hyperthermia holds great promise to advance immunotherapy in the treatment of cancer. Pre-clinical studies have demonstrated the ability of hyperthermia to enhance each of the 8 steps in the cancer-immunotherapy cycle including stimulation of tumor-specific immunity. The study of hyperthermia with immunotherapy is particularly compelling when considered in the context of new treatment paradigms for application of heat with immunotherapy. Novel concepts include elicitation of a tumor-specific immune response not requiring whole tumor heating, potentially shorter treatment times, better treatment tolerance as opposed to other multi-agent approaches to immunotherapy and the ability to apply heat repeatedly over extended periods of time with immunotherapies, unlike ionizing radiation. Several questions remain with regard to clinical integration which are being addressed in our laboratory at New York Medical College. Our strategy and preliminary results will be discussed. Our ultimate goal is thoughtful clinical trial design building upon lessons learned at the bench and from clinical trials combining radiation and immunotherapy.
Challenges and opportunities in tissue thermoregulation modelling – a plea for temperature measurement standardization, collaboration and inference

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Introduction:

Hyperthermia treatment planning (HTP) relies on joined electromagnetic and thermal modelling. While electromagnetic modelling can achieve good accuracy, thermal modelling accuracy is not at that same level.

Methods and Results:

Key hurdles include gaps in the knowledge on thermal and thermoregulation tissue properties. In humans, the optimum core temperature is within a small band of temperatures around 37°C, which is maintained by thermoregulation processes. Metabolism in cells, up-regulated during heavy exercise, can cause tissue temperature to exceed 38°C. Tissue temperature can also rise due to the absorption of electromagnetic energy. The temperature in these conditions is regulated through tissue cooling by blood perfusion combined with thermal conduction processes. Blood perfusion, the process of delivering blood to a volume of tissue, plays a major role in extracting excessive heat according to metabolic demands. The extent, timing, and impact on the tissue cooling depend strongly on heating duration and intensity, i.e., they depend on a quantity that could be expressed through a thermal dose concept. This thermoregulatory response also depends on the average skin temperature and is strongly dependent on the temperature of the hypothalamus. Temperature-dependent perfusion is also very inhomogeneous within and between tissues: upregulation is smaller in tumour tissue compared to upregulation in muscle and skin. Note that this knowledge is mostly from studies in small rodents, and must be validated in humans.

Since the direct application of perfusion measurements in thermal modelling is currently impossible, thermal and thermoregulation tissue property determination requires inference from thermal data. Therefore, accurate temperature measurement methods, like magnetic resonance thermometry, are imperative to obtain quantitative and reliable thermal and thermoregulation tissue properties.

Conclusions:

Accurate tissue properties for a wide range of normal and tumor tissues can be obtained by combining standardization of temperature measurements and reporting, data sharing and large scale data inference. Such collaboration in the hyperthermia community is crucial for supporting the application of thermal modelling in the entire hyperthermia community: for treatment guidance and the development of new devices and approaches.
The impact of uncertainties in individual tissue and perfusion properties on predicted temperature distributions in loco-regional hyperthermia

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Hyperthermia treatment planning (HTP) tools provide qualitative insights that can guide treatment delivery. However, the lack of quantitative predictability precludes accurate heating and leads to sub-optimal treatment. Uncertainties in tissue and perfusion property values significantly contribute to the quantitative inaccuracy of HTP. Assessment of these uncertainties allows better judgement of reliability of treatment plans and improve its value for treatment guidance. However, the quantitative impact of individual tissue and perfusion property uncertainties have not been systematically investigated.

In this study we set out to quantify the impact of uncertainties in individual tissue properties on the predicted temperature distributions.

A novel Polynomial Chaos Expansion (PCE)-based uncertainty quantification was performed for locoregional hyperthermia of a modelled tumour in the pancreatic head. The patient model was based on the Duke digital human model version 1 (IT’IS Foundation, Zurich, Switzerland) (figure 1). Using Plan2Heat, treatment plans were created and optimised for treatment using the Alba 4D heating system (figure 1). For all 34 tissues in the model, the impact of tissue property uncertainties electrical conductivity and permittivity, density, thermal conductivity, specific heat capacity, and perfusion was analysed individually. Next, combined analysis was performed on the uncertainties with the largest impact (top 15 electrical conductivity and all perfusion uncertainties).

Uncertainties in thermal conductivity and heat capacity were found to have negligible impact on the predicted temperature (<1*10⁻¹⁰°C), density and permittivity uncertainties had a small impact (<0.33°C), uncertainties in electrical conductance and perfusion can lead to large variations in predicted temperature (figure 2). Uncertainty of muscle properties result in the largest variations at locations that could limit treatment quality, with an ADmax of 3.8 and 1.6°C for perfusion and electrical conductivity respectively (ADmax is the average deviation at the location of maximum impact). The combined influence of all significant uncertainties leads to a ADmax of 6°C.

To conclude, uncertainties in tissue and perfusion property values can have a large impact (up to 6°C) on predicted temperatures from hyperthermia treatment planning as shown in our overview of all major uncertainties and their impact, this PCE-based analysis helps judging reliability of treatment plans.
Fig. 1

Fig. 1 | Hyperthermia treatment plan with phase-amplitude settings optimised for heating a target in the pancreas head of the Duke digital human model version 1.0 (TS Foundation, Zurich, Switzerland). Non-tissues (intestine and stomach filling) were excluded from the analysis (grey).

Fig. 2

Fig. 2 | Impact of uncertainties in perfusion values (blue) and electrical conductivity values (orange) on the predicted temperature distribution per tissue type. ADmax is the average deviation at the location of maximum impact.
Experimental validation of thermal predictions in recently developed HIPEC treatment planning software

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Introduction: Patients diagnosed with peritoneal metastases are treated with cytoreductive surgery to remove all visible lesions from the peritoneal cavity, followed by hyperthermic intraperitoneal chemotherapy (HIPEC) to treat residual microscopic disease. Thermal distributions should be optimized towards homogeneity to increase cytotoxicity of the chemotherapy, and thus treatment efficacy. Treatment planning software could provide a unique tool in locating and preventing possible heterogeneities. It is key to validate the treatment planning software rigorously to ensure its validity. In a previous study we successfully validated the drug module and here we aim to validate the thermal module.

Objectives: Validation of the thermal module of our HIPEC treatment planning software and the investigation of a robust thermal measurement procedure for use during clinical HIPEC treatments.

Methods: We developed treatment planning software based on the computational fluid dynamics software OpenFoam. We extended the rodent software presented in Löke et al., 2020 towards human applications. We used the 4D eXtended Cardiac Torso (XCAT) models, provided by Duke University, to develop a 3D-printed phantom (Fig. 1a). This phantom was used in an experimental HIPEC setup (Fig. 2) using extensive thermometry. We measured temperatures for a duration of 30-minutes using 9-point thermal probes in 9 different regions (Fig. 1b), based on the clinically used peritoneal cancer index. Catheter position and flow rates were varied and experimental values were compared to simulated values.

Results: Predicted temperatures compared well to measured values to within 0.5 °C. Results showed that the use of 9-point probes is necessary to obtain a correct representation of the temperature within each of the 9 regions. Optimizing catheter positions significantly increased the overall homogeneity as well as the average treatment temperature. Also, higher flow rates increased the overall treatment temperature.

Conclusions: The treatment planning software was able to predict the temperature in the 3D-printed phantom accurately. Furthermore, the thermal measurement procedure provides thermal data per region which could be used for patient specific optimization of HIPEC. Our next step will be clinical validation in patients.

Figure 1: A) 3D-printed phantom. B) Division of peritoneal surface into 9 regions.

Figure 2: Experimental setup using the 3D-printed phantom.
Fig. 1

Fig. 2
Feasibility of intact breast hyperthermia with a phased array applicator: a theoretical study on 22 patient models

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Introduction

Microwave (MW) hyperthermia (HT) with phased array applicators has been effectively developed and clinically applied for deep seated tumors in the lower body and head and neck area. In the area of the breast, MW hyperthermia is currently applied with superficial hyperthermia applicators, with a serious restriction to only target superficial tumors. Phased array applicators could play a role in breast HT, by extending to deep seated tumors as well, and better targeting the heat towards the tumor.

Objectives

The objective of this work is to investigate the feasibility of performing HT for patients with cancer in the intact breast with a wide variation of breast and tumor characteristics.

Materials & methods

Anatomical MRI images of 22 breast cancer patients with different anatomical and tumor characteristics and locations were segmented to bone, fat, fibroglandular, muscle, skin, and tumor tissues (Figure 1.b). The 3D breast models were created and tissue properties were assigned according to the ESHO benchmarking guidelines [1]. A generic 434 MHz dipole antenna phased array applicator, as proposed by the ESHO benchmarking guidelines [1], was positioned around the breast models (Figure 1.a) and a SAR based treatment plan was created using VEDO (Figure 1.c) [2]. Steady state temperature simulations were used to predict the thermal behavior, based on the resulting treatment plan, with the maximum overall tissue temperature restricted to 44°C (Figure 1.d). The treatment plans were evaluated using the target-to-hotspot quotient (THQ), and the T10, T50, and T90 values.

Results

The generated breast models had large variations in breast volume (154.1-1336.5 ml), fat content (30.5-62.6 %), tumor volume (1.44 – 39.26 ml), and tumor center to skin distance (12 – 43 mm). The resulting median THQ was 0.83 (0.50 – 1.20) and the median T90, T50, and T10, were 41.3°C (38.9 – 42.7), 42.3°C (39.8 – 43.3), and 43.2°C (40.9 – 43.8), respectively. From all the evaluated patients, only two patients had T90 values bellow 40°C, and one patient had a T50 value bellow 40°C.

Conclusion

Intact breast hyperthermia with a generic phased array applicator is feasible for the vast majority of patients.

References

[1] M. Paulides et al., IJH, 2021
INTRODUCTION

The identification of the optimal operating frequency for phased array deep hyperthermia systems has been the subject of numerous design studies. To date, clinical applicators are narrow band, and their design frequency is chosen as a compromise between focal size and penetration depth. In some patients, however, the power deposition pattern at a single fixed frequency might prove inadequate to achieve therapeutic temperatures or target coverage. UWB systems can theoretically convey an additional degree of freedom to the treatment planning stage and allow for wavelength adaptation. Alternatively, the addition of a second operating frequency can exploit complementary power deposition patterns to improve the temperature distribution. Yet, no systematic study exists to quantitatively evaluate the potential clinical benefit of these solutions.

OBJECTIVES

This contribution investigates the improvement in heat delivery when the operating frequency can be selected across a defined UWB range. We further assess the benefits of including a second operating frequency to the treatment plan.

MATERIALS & METHODS

We prepare single and multi-frequency treatment plans for a standardized set of six patients (ESHO Grand Challenge repository) with targets in the neck, breast, and pelvis. The single frequency plans are obtained for frequencies in the...
100 – 1000 MHz range, while the multi-frequency plans are obtained for binary combinations of frequencies in the range. We compare the SAR and temperature distributions in terms of clinical indicators TC50, TC75 and T50, T90, respectively.

RESULTS

The analysis confirms a strong dependence of all clinical indicators on the operating frequency. The optimal frequency for single-frequency treatment varies less than 20% among different patients in a specific body region. Nevertheless, the drop in T50 and T90 can become substantial (up to 0.5 °C) in this interval. In many cases, the best single-frequency solution achieves the same temperatures as the best multi-frequency one. However, in one neck model (Alex), the multi-frequency plan improves T90 by 0.5 °C.

CONCLUSION

Current applicators are designed for frequencies close to the optimal for their target region. However, UWB hyperthermia systems can be beneficial for certain patients as they can provide better target coverage for irregular tumor shapes.

L85
Deep learning for abdominal blood vessel segmentation to improve hyperthermia planning

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Introduction: Thermal simulations in deep hyperthermia treatment planning are more accurate when large blood vessels are taken into account. However, manual segmentation of these vessels is too time-consuming, hence currently not being used in clinical practice. Automatic segmentation could offer a solution.

Objectives: To develop a deep learning method for automatically segmenting the large blood vessels in the abdomen for hyperthermia treatment planning.

Materials & methods: The training set contained 126 retrospective post-contrast MRI scans of 91 patients with pancreatic cancer. The aorta, vena cava, and vena portae with their corresponding branches were manually segmented using ITK-SNAP. 3D U-Nets were implemented and trained with leave-one-out cross-validation in ensembles, and probability distributions were averaged over five runs. The test set consisted of 21 scans of 13 patients. Blood vessel segmentations were evaluated on sensitivity, specificity, accuracy, precision, and Dice similarity coefficient.

To evaluate whether the automatic segmentations were sufficient for treatment planning, we generated hyperthermia treatment plans in the two worst-performing segmentations (lowest sensitivity) using Plan2Heat, for the four waveguide 70 MHz ALBA-4D system. For this, blood vessel segmentations were registered onto corresponding CT scans with Elastix, and centerlines were obtained with 3D Slicer. The T90 of the tumor segmentation was maximized, with hard constraints of 45°C to normal tissue. Optimization was performed for three situations: with cooling based on manual (1) and automatic (2) segmentations, and ignoring cooling from vessels (3). All approaches were re-evaluated with cooling based on the manual blood vessel segmentations, which is the gold standard for the delivered plan.

Results: The evaluation metrics for the automatic segmentations were superior for the arteries compared to the veins (Figure 1). When evaluating optimized plans on the ground truth vessel cooling, for patient 1, all plans were almost identical (Figure 2). For patient 2, optimization with automatic blood vessel segmentations resulted in an equivalent
treatment plan to optimization with manual segmentations, and outperformed (higher overall delivered temperature) the plan that ignored cooling.

Conclusion: The results indicate that with automatic segmentation of abdominal blood vessels, plans of higher quality than in current clinical practice may be achieved.

Fig. 1

![Figure 1](image1.png)

Figure 1. The evaluation metrics for the blood vessel segmentations. The two patients selected for deep hyperthermia simulations are highlighted. Patient 1 has the tumor in the tail of the pancreas, and the minimum of the sensitivity results over all blood vessels is 0.383. Patient 2 has the tumor in the head of the pancreas, and the minimum of the sensitivity results over all blood vessels is 0.584.

Fig. 2

![Figure 2](image2.png)

Figure 2. The results of the hyperthermia simulations for patient 1 with the tumor in the tail of the pancreas (left), and patient 2 with the tumor in the head of the pancreas (right). All results have been re-evaluated with the manually segmented blood vessels. For patient 1, all graphs are almost identical, with T90 = 40.2°C, T50 = 41.0°C, T10 = 41.4°C. For patient 2, both graphs with automatic and manual blood vessel segmentations are almost identical, with T90 = 42.3°C, T50 = 43.5°C, T10 = 44.3°C. The graph without blood vessels has T90 = 41.5°C, T50 = 42.8°C, T10 = 43.5°C.
Approaches to improve abdominal hyperthermia using the annular-phased-array technique and time-multiplexed optimization

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Advanced abdominal tumors are common oncological diseases with a poor prognosis. There is a strong rationale to combine chemotherapy and abdominal hyperthermia for a primary or (neo-)adjuvant treatment of abdominal tumors [1], targeting the most involved organs (peritoneum and liver) [2,3]. That this extended coverage is a non-trivial task was already outlined previously [4,5].

A platform for hyperthermia treatment planning (HTP) based on Sim4Life (ZurichMedTech, Switzerland), Matlab (Mathworks, USA) and a guaranteed globally optimal multiplexed optimization algorithm [6] for test cases (phantom, patients) was used to perform simulation studies. We evaluated easy modifications of the multi-antenna Sigma-Eye applicator (Pyrexar, USA) to determine whether these can already lead to substantial improvements in abdominal hyperthermia and thus open up an innovative treatment approach for abdominal tumors. We investigated three upgrades to the current Sigma-Eye applicator design to increase longitudinal coverage of the abdomen and liver by iteratively prolonging the water bolus from 47 to 70 cm, shifting the antenna rings apart and stretching the dipole antennas for increased longitudinal coverage (Fig.1a-d). We analyzed the SAR distribution achieved after manual HTP and time-multiplexed optimization in a muscle-equivalent phantom and two pancreatic cancer patient models (1f/1m, Fig.1e+f).

We found that the original Sigma-Eye applicator is already suitable for abdominal hyperthermia in selected patients when applying algorithm-based HTP. The exemplary results for patient 1 are summarized in Fig.2. With peak $\text{SAR}_{50} > 50 \text{ W/kg}$ in the peritoneum, the required temperatures above 42 °C in abdomen and liver can be safely ($\text{SAR}_{\text{healthy}} \leq 100 \text{ W/kg}$) achieved, if a programmable switching option over time between specified power deposition patterns were available for time-multiplexed optimized HTP. Generally, the bolus contact length in the Sigma-Eye applicator should be extended to 70 cm.

References:

Fig. 1

Figure 1: Left: schematic view of the virtual models of the original applicator design (a) and the three iterations longer bolus (b), shifted antennas (c) and stretched antennas (d). The applicators are shown without the external PVC cover (very light blue frame in e-f) to ensure visibility of the dipole antennas. Right: View of the female (e) and male (f) patient model centered in the original applicator in an exemplary slice through the pancreatic CTV, the peritoneal cavity, liver, spleen and lung. Except for the kidneys (not visible in this slice), the rest of the body is automatically segmented into fat, muscle and bone.

Fig. 2

Figure 2: 2D SAR distribution in the central slice of the target volume for the voxel model of patient 1 (female) with the applicator centered on the navel for various phase settings and applicator design upgrade. An increase in target exposure and coverage is clear when moving from the original applicator design (left, manual and optimized SAR distributions) to the applicator design updates. Including liver and spleen in the extended target volume for optimization further enhances target exposure.
Simultaneous ThermoBrachyTherapy: fast and accurate multi-applicator temperature-based treatment planning

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Introduction

For the implementation of high quality Simultaneous ThermoBrachyTherapy (STBT), fast and accurate treatment planning of the thermal dose is necessary (Androulakis et al. 2021). This is a challenging task, since the electromagnetic (EM) and temperature calculations are computationally demanding. First, the thin structures of the applicator make it difficult to model. Second, finite-difference time-domain (FDTD) full wave EM simulations are computationally expensive. Third, superpositioning of the temperature distribution is theoretically not allowed. This makes the required temperature precomputations for the treatment planning optimization process seriously dependent on the number of applicators. This number is typically around 20 for prostate cancer treatments.

Objective

In this study we simplified the pre-optimization calculations that are necessary for temperature based optimization of the STBT treatment, while maintaining the resulting calculation quality.

Materials and Methods

First we simplified the applicator geometry, by replacing the original geometry by a set of coaxial parallelepipeds (Fig.1). In addition, we utilized a quasistatic approximation, replacing the FDTD full wave EM simulations. Moreover, we applied a simplified temperature superpositioning principle, to reduce the amount of required temperature precomputations. We evaluated the accuracy of both EM and temperature simulation results, using gamma index analysis.

Results

The EM simulations resulting from the simplified model (Fig.2.a) and quasistatic approximation calculations (Fig.2.b) were benchmarked with the FDTD results. They showed a >99% passing rate on a gamma index analysis with DD=1% and DTA=0.5 mm. The superpositioned temperature simulations (Fig.2.c) were benchmarked to a single temperature simulation. They showed a >95% passing rate on a gamma index analysis with DD=5% and DTA=0.5 mm. Calculation speed increased ~3000 fold (from >11h to 13 s) for a single EM simulation. The amount of necessary precomputed temperature simulations for n applicators reduced from n² to n.

Conclusion

We significantly reduced computation time for EM simulations and reduced the amount of temperature simulations that are necessary for the optimization process. This ensures that the hyperthermia part of the treatment planning can be performed in parallel to the brachytherapy part of the treatment planning, hereby making fast and accurate treatment planning for STBT possible.
Fig. 1 – 3D view of the ThermoBrachyTherapy applicator (upper left) and the simplified equivalent geometry (lower right). Dielectric materials are visible in grey, while the copper parts are visible in dark yellow color.

Fig. 2 – Treatment planning results resulting from increased speed calculations implemented in this work. (a) side view of the three dimensional model of the patient, with the simplified ThermoBrachyTherapy applicators visible; (b) the point SAR distribution on a central slice in the prostate, overlaid on the patient CT scan; (c) the temperature distribution on the same slice in the prostate, overlaid on the patient CT scan after 20 min of heating.
P01
Systematic review supports the safety and efficacy of modulated electrohyperthermia in the treatment of high grade gliomas

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BACKGROUND. Glioblastoma is an aggressive type of cancer which can be very difficult to treat, and a cure is often not possible. Modulated electro-hyperthermia (mEHT) emerged in its treatment, which combines the advantages of hyperthermia and tumor treating electromagnetic fields.

METHODS. We performed a systematic review to assess the effect of mEHT on gliomas. The literature search was performed following the recommendations of PRISMA and CHSRI and in accordance with the recommendations for optimization of search strategies. Publications identified were screened with a two-stage process. Databases were searched from 1981-SEP-01 to 2021-SEP-01: Cochrane, PubMed, BMC, MedLine, EUDRACT, UMIN, ClinicalTrials.gov, Embase and Wiley. The search terms were set in advance. Focus was the EHY-2030 or equivalent device.

RESULTS. A library of peer-reviewed publications was built; duplicate hits were excluded. All searches regarding glioma and glioblastoma were then restricted to clinical practice guidelines, systematic reviews, and meta-analyses. We hand searched clinical trial registries and neuro-oncology conference proceedings. A total of 188 references were identified which were manually reviewed based on titles and abstracts. Ninety-one entries were then screened for full-text content. Twenty-three studies were extracted, in the final summary 17 papers were analyzed for data on clinical safety and performance.

mEHT is a safe form of hyperthermia which has shown to effectively sensitize deep tumors. The technology has demonstrated equal benefits compared to other forms of hyperthermia. mEHT also improves local control and survival rates and induces an abscopal response. Glioblastoma participants in the mEHT treatment group across studies had a significantly higher overall positive response. These results provide strong motivation for further investigations into the inclusion of mEHT in the palliative management of GBM patients. LEVEL OF EVIDENCE 2 (II) is reached based on small, randomized trials with a suspicion of bias or trials with demonstrated heterogeneity.

CONCLUSION. The clinical data retrieved in the systematic review support the acceptability of the benefit-risk ratio of mEHT in the treatment of glioblastoma/glioma indication. New risk factors, i.e., statistical increase in the frequency or severity of known side-effects was not identifiable, previously unknown side-effects or serious adverse events have not emerged in association with the delivery of mEHT.

P02
Hyperthermia in the treatment of superficial tumors or lymph node metastases in head and neck cancer – clinical experiences from 2011 to 2022 of the institute of radiation oncology in Prague, Czech Republic

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Introduction: Superficial hyperthermia in combination with radiotherapy represents very effective local treatment of locally recurrent head and neck cancer. We present a group of patients treated in our institution from 2011 to 2022. The aim of this work is the evaluation of local response to the treatment in our group of patients.

Material and methods: From 2011 to 2022 we treated group of patients with locally recurrent head and neck cancer. 89 patients were treated for locally advanced tumor, local recurrence or for lymph node metastasis. Hyperthermia was combined with 6 MV radiotherapy, usually using IMRT or VMAT radiotherapy technics. Max dose of radiotherapy...
was from 74 Gy to 69.9 Gy. Hyperthermia was done using microwave ALBA Hyperthermia System for superficial hyperthermia working on 434 MHz and was applied once a week, 1 to 7 applications during the course of radiotherapy, mainly immediately after radiotherapy, for 60 min. The temperature was measured using thermistor probes superficially, minimally in the six points. We tried to achieve temperatures in the range from 42 to 43, 5 °C, but the actually measured temperatures were limited by the tolerance of patients. 11 of the patients did not tolerate the application and the application was terminated after the first fraction. The anesthetics were not used.

Results: A local response was observed in 95% of patients, and although predominantly patients with locally advanced tumors are included in this group, several patients survived for more than 5 and 7 years, respectively.

Conclusion: Superficial hyperthermia is a useful tool for enhancing the effects of radiation in the treatment of locally recurrent head and neck tumors. In most treated patients, a complete response is achievable without further side effects. This combined topical treatment significantly reduced tumor quality, especially in devastating locally progressive tumors, and improved patients' quality of life.

P03
Development of an electro-magnetic heat simulation for planning preclinical hyperthermia treatments of mice

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Introduction: Successful study of the effects of microwave-mediated hyperthermia in mice requires careful control over the deposited power as well as in depth knowledge of the temperature changes in treated tumour tissue. Direct measurement of these temperatures is with the exception of the skin, difficult without invasive implantation of sensors.

Objective: The goal is then to infer the temperature gradient via surface measurements and an electromagnetic and subsequent thermal simulation.

Materials & Methods: Treatments are carried out with a BSD microwave-based hyperthermia device and then simulated via the software Sim4Life. Successful simulating requires knowledge of the interstitial MA-251 applicator's properties as well as of the material properties of the treated tissue. Initial validation of the simulation is carried out by means of muscle tissue mimicking agar phantoms. The phantom's thermal properties where measured with a differential scanning calorimeter and the dielectric properties were determined via the reflection of electromagnetic-waves at the end of a coaxial probe.

Results: The specific heat capacity of the agar phantom was found to be 2.73 ± 0.2 J/g*K and in good accordance to the numerically predicted value of 2.9 J/g*K. Furthermore, the value was almost temperature independent (0.069 J/g*K) over a range from 35 to 52.5°C. At a frequency of 915 MHz, the dielectric properties of the material were measured to being \( \varepsilon = 56.0 \pm 0.6 \) and \( \sigma = 1.04 \pm 0.04 \) S/m and therefore of similar value as those of actual muscle tissue with 55 and 0.95 S/m, respectively. Input of the material properties and simulating the interstitial applicator as a monopole yields heating-distributions in good qualitative accordance to the manufacturer specifications. Consequently, the Antenna heats an area of approximately 3.85 cm² whereas the tumour is usually only 0.25 cm² large.
Conclusion: The phantom's close mimicking of the dielectric properties of muscle tissue and the stability of the heat capacity justify its use as a first material substitute for simulation validation. However, these experiments show the need for techniques to reduce the heated area; perhaps through the use of a cooling water bath. Lastly direct contact between antenna and tissue risk surface burns from heat development in the antenna and should be avoided.

The work is being supported by the Bayerische Forschungsstiftung (MikroHyperTumImmun; AZ-1495-20).

P04
Safety of long-term whole body hyperthermal treatment for cancer in a chicken embryo model

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Introduction

Whole body hyperthermal treatment (WBHT) is gaining popularity as an add-on treatment modality for several cancer types. However, there is still concern about its safety in general and about a potential risk for increased incidence of metastases following WBHT.

Objectives

In this study, the safety of different durations of WBHT (41.5 °C) was evaluated in a chicken chorioallantois membrane (CAM) model of human pancreatic ductal adenocarcinoma.

Materials & Methods

First, chicken embryos (White Leghorn) were grafted at ED9 with 1 x 10^6 BxPC-3 tumour cells. At ED11, these xenografted embryos were subjected either to one session of a 24h WBHT, or up to four sessions of six hours each at a temperature of 41.5 °C in a custom heating device (HyperThermEGG, Elmedix). Xenografted embryos, kept at 37 °C served as controls. The primary end-point was embryo survival in function of varying HT duration. Liver and brain were also evaluated for histological abnormalities via H&E staining as secondary end-points.

Results

For all HT-treated embryos, the WBHT sessions did not result in increased embryonic mortality compared to control embryos at 37 °C. For the latter group, a mortality of 16% (3/19 embryos) was observed. On average, 2 embryos (11%) died prematurely (prior to ED18) in the hyperthermia (HT) groups. Embryonic mortality did not significantly rise with increasing HT duration. Furthermore, histological analysis of liver and brain samples showed no morphological differences between control and HT-treated embryonal liver or brain tissues, indicative of the absence of neuro-or hepatotoxicity induced by the WBHT. Importantly, no obvious signs of metastasis were observed in the livers of both control and of HT-treated embryos either.

Conclusion

The present study confirms the validity of the CAM model in this type of research. We believe that these data may further support the increased implementation of CAM models in pre-clinical research, especially considering their low-cost and fast turnover. In conclusion, our results suggest that WBHT at a temperature of 41.5°C at distinct durations up to 24h in this xenografted model does not lead to increased mortality or to increased incidence of metastasis.

Figure 1. Comparison of embryo survival at ED18 between the various hyperthermia (HT) exposures showed no significant differences in mortality.
Introduction: The survival rates of patients suffering from pancreatic ductal adenocarcinoma (PDAC) remain low. One of the main reasons for common therapy failure is the hypoxic tumor microenvironment, as it acts as a barrier. The multi-faceted effects of hyperthermia on such tumors have been proven preclinically. By investigating combination treatment modalities, an innovative neo(-adjuvant) therapy may arise which improves both treatment efficacy and/or quality of life for patients.

Objectives: We aimed to investigate a possible synergism of irradiation and hyperthermia in an in vivo chicken embryo model.

Materials & methods: Eggs at EDD6 were inoculated with $3 \times 10^6$ BxPC-3 cells and incubated at 37.5°C. On D10, the eggs were randomized into six groups ($n=8$) and started their respective treatment. For administration of heat treatment (HT, 41.5°C for 6 h), a custom heating device (ElmediX) was used. Two groups received only irradiation (RT) at a dose of 2 Gy on D12 and D14. Two other groups received an identical RT schedule, preceded by HT on D10 and immediately followed by the same HT on D12 and D14. Control groups included a normothermic condition (37.5°C) and a hyperthermic condition (41.5°C) without RT. Before and after treatment, tumor volume was estimated from microscope surface measurements. On D15, the tumors were harvested and prepared for further analysis.

Results: After normalization and homogenization of the data, a trend emerged. The combination of RT and HT slows the tumor growth at all timepoints compared to normothermic or single treatment controls.

Conclusion: Although the results are not statistically significant due to small sample size, there is an observable trend over all timepoints which indicates a beneficial effect of HT in combination with RT, over RT or HT treatment alone. To confirm this, more experiments with larger sample size are warranted. The result leads us to believe that there is a synergic effect between RT and HT that can be exploited towards creating more effective treatment modalities in PDAC. Further histological and molecular analysis are ongoing at the time of writing, but preliminary results show to be promising and corroborate our synergism hypothesis.
A short time interval between radiotherapy and hyperthermia leads to better tumor control in cervical cancer models

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Abstract: Combined hyperthermia and radiotherapy is an effective treatment for locally advanced cervical cancer, especially for patients with a contraindication for chemotherapy. Radiotherapy induced DNA damage will be repaired within a short time interval, but hyperthermia can temporarily inactivate homologous recombination (HR). Therefore, combined hyperthermia with radiotherapy induces an increased radiosensitizing effect for shorter time intervals. Our previous data demonstrated that a short time interval between hyperthermia and radiotherapy induced a lower cell survival, in particular with a higher temperature of hyperthermia and higher dose of radiation. However, in vivo data are scarce. The purpose of this study is to determine the effect of time interval between hyperthermia and radiotherapy on tumor tissue and normal tissue in an in vivo model. In this study, SiHa cells were injected on the hind leg of Athymic nude mice. Tumors on mice were treated with different time intervals between hyperthermia and radiotherapy (0, 2, 4 and 8 hours), and in opposite sequence. Our results demonstrated that shorter time intervals between hyperthermia and radiotherapy resulted in a better tumor control. Moreover, in cervical cancer cells lines (SiHa, HeLa, Caski) and patient-derived cervical cancer organoids, we also found that a short time interval between radiotherapy and hyperthermia resulted in lower cell survival.

Keywords: human papillomavirus; ionizing radiation; hyperthermia; time interval; in vivo
Microwave monitoring of the temperature change during hyperthermia

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Introduction

Non-invasive temperature monitoring of hyperthermia cancer treatment is one of the crucial points for its successful clinical applications. MRI is often discussed to be a prospective solution of this problem. But it is very expensive way. Because of that cheaper solutions, based e.g. on microwave technology, could be convenient alternative to MRI temperature monitoring.

Methods

Our theoretical and experimental research work is focused now on two following methods:

A. Microwave differential tomography (MDT)

Microwave differential tomography is at the Czech Technical University (CTU) developed by people from Dept. of Biomedical Technique in cooperation with Prof. Andrea Massa from Eledia Research Center (Trento, Italy). It seems to be realistic that the MDT methods can be used for 3D non-invasive temperature monitoring of the treated volume during thermotherapy in oncology.

B. UWB radar

Microwave UWB radar technology for noninvasive microwave imaging and/or noninvasive temperature monitoring is developed in cooperation of TU Ilmenau (team of Dr. Marko Helbig) and CTU. The detection principle of temperature change via UWB radar signal is based on a fact that the complex permittivity is changing with temperature (like it was stated for microwave differential tomography) and with the distance.

Results:

Existing suitable reconstruction algorithms, which allow quasi-real-time monitoring of changes of dielectric properties due to change of temperature, were implemented. The obtained results using Distorted Born Algorithm (DBA) and Born Algorithm (BA) were compared in terms of algorithms ability to reconstruct shape and position of the target and flatness of the obtained object function in regions without change in dielectric properties. We have demonstrated that it is possible to detect these changes by either MDT or UWB microwave radar.

Conclusion

It seems to be realistic that the MDT and UWB Radar methods can be used for 3D non-invasive temperature monitoring of the treated volume during thermotherapy in oncology.
P08

Frequency and the magnetic field dependence of magnetothermal properties of ZnMn ferrite nanoparticles

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Magnetic hyperthermia is the advanced method that permit to kill tumor cells due to heat generated by magnetic nanoparticles (MNPs) delivered to the target lesion area in an alternating magnetic field. The method has shown high potential in the clinical treatment of deep tumors due to its non-invasiveness and no limitations on the depth of treatment. However, the thermal conversion efficiency of MNPs used in present clinical practice is very low. The specific absorption rate (SAR) is the most important parameter to characterize the efficiency of the heating process. The SAR values of MNPs depend on many different parameters, such as size, size distribution, shape, chemical composition, frequency and amplitude of the external magnetic field, etc. Therefore, the aim of this work was to investigate the character of the dependence of the SAR value of ZnMn ferrite MNPs on the magnetic field amplitude and frequency and to fix most appropriated its value. These studies were performed at field amplitudes and frequencies close to Brezovich’s limit (the product of the field frequency and its amplitude should not exceed a level of about $10^7$ Oe × Hz). ZnMn ferrite MNPs were selected for their nontoxicity and good thermal properties, and were obtained by chemical co-precipitation method. The results show that the ZnMn ferrite MNPs with less zinc content have higher SAR values at low frequencies. The ZnMn ferrite MNPs with more zinc content have higher SAR value at high frequency. It has been demonstrated the SAR values of some MNPs have a super-quadratic dependence on the magnetic field amplitude. We therefore propose the new strategy: to select MNPs of Zn content ranging from 10%–20% according to frequency, and to exploit the full potential of the magnitude dependence of the super-quadratic law on thermal output.

P09

Nanoparticle spatial distribution in tumor tissues: numerical modeling for a more precise evaluation of thermal and radiation dose in magnetically mediated hyperthermia coupled with radiotherapy

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Question

In the last decade, thanks to the advances in nanotechnology, magnetically mediated hyperthermia (MMH) has become a promising candidate for hyperthermia based therapies, because of a more selective heating [1]. Moreover, by using nanoparticles (NPs) with a radioactive core and a magnetic shell, one could deliver the radiation dose directly to the tissues to be treated and contemporarily release heat. Histological examinations, however, showed a tendency of NPs to create clusters inside tissues [2]; the non-homogeneous distribution of NPs in the target tissue may lead to differences in the delivered radiation dose as well as to a non-uniform temperature distribution within the tumour, causing potential under-treatment of some regions or damage to healthy tissues [3]. Therefore, in in vivo applications of NPs their accurate delivery and release into target tissues are crucial aspects to achieve effective treatments.

Methods

To address this problem and support the development of optimal infusion strategies and treatment planning we propose a numerical tool to simulate the administration process of NPs in the tumour and to reconstruct their spatial-
temporal distribution in cancer tissues. The model uses a Transport-Diffusion-Reaction partial differential equation to evaluate the NP concentration inside a 3D anatomical reconstruction of the tissue. Moreover, the model takes in account the binding of the NPs to cell membrane, as well as the internalization phenomena.

Results

With our model we evaluated the influence of administered dose of NPs and delivery strategy on the local concentration of NPs in the tissue, in order to achieve an adequate spatial distribution for hyperthermia and radiotherapy treatments.

Conclusions

The obtained data will be used to provide a better local estimate of the temperature changes during MMH application and of the local radiation dose in the tumour volume in in silico modelling, correlating the effects to the NPs concentration.


P10
Surface coating as a mean to improve hyperthermia properties of iron oxide nanoparticles

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Question Magnetic hyperthermia is a tumour therapy that exploits magnetic nanomaterials, typically iron oxide nanoparticles (NPs), and AC magnetic fields, to increase the temperature of diseased tissues [1,2]. Local temperatures in the range of 42–45°C can be exploited to induce alterations in tumour cells and thus improve radiotherapy or chemotherapy efficacy, enabling a reduction in radiation or drug dose. Iron oxide NPs have demonstrated to be optimal heat mediators when excited by AC magnetic fields in the range of 50-500 kHz [3]. Large research efforts have been devoted to the engineering of NPs with high specific loss power (SLP), analysing the role of size, shape, material composition and surface coating. The latter can also improve dispersion in solution, colloidal stability and biocompatibility.

Methods To study the influence of coating, we prepare and characterize Fe3O4 NPs with different surface functionalization, i.e. trisodium citrate or carboxymethyl cellulose (CMC). The NPs, synthetized via co-precipitation method, are characterized in terms of dimensional, morphological, magnetic and hyperthermia properties, by using different techniques, i.e. TEM, X-ray diffractometry, thermogravimetric analysis, Dynamic Light Scattering (DLS), static and dynamic hysteresis loop measurements, and thermometric measurements for SLP evaluation.

Results As shown by TEM images (Fig. 1a), the produced NPs have a quasi-spherical shape and exhibit a narrow size distribution around 10 nm. Dynamic hysteresis loop (Fig. 1b) and thermometric measurements (Fig. 1c) demonstrate the improved hyperthermia properties of citrate-coated NPs with respect to uncoated and CMC-coated NPs.

Conclusion The surface coating of Fe3O4 NPs with trisodium citrate has proved to be an efficient solution to increase the SLP as well as to improve dispersion in solution and colloidal stability.
Question. A synergistic activity between maintenance temozolomide (TMZm) and individualized multimodal immunotherapy (IMI) during/after first-line treatment has been described for improving the overall survival (OS) of adults with IDH1 wild-type MGMT promoter-unmethylated (unmeth) GBM (Genes&Immunity 2022). IMI includes 1/ immunogenic cell death (ICD) therapy (injection of Newcastle Disease Virus and sessions of modulated electrohyperthermia), 2/ active specific immunotherapy with loaded mature dendritic cell (DC) vaccines, 3/ modulatory immunotherapy, and 4/ complementary medicines. We aimed to expand the data and include the OS of MGMT promoter-methylated (meth) adults with documented IDH1 wild-type GBM.

Methods. Unmeth (10 f, 18 m) and meth (11 f, 10 m) GBM patients treated between 27/05/2015 and 01/01/2022 were retrospectively analysed.

Results. There were no differences in age (median 48y, range 18-72y) or Karnofsky performance index (median 70, range 50-100). There were no differences in number of vaccines (median 2; range 0-6), total number of DCs (median 25.6x10^6; range 0-120.58x10^6), number of NDV injections (median 31; range 6-133) and number of mEHT sessions (median 28; range 0-174) between both groups. The median OS of 29 unmeth patients was 22m (2y-OS: 39%, CI95%: +19, -19) confirming previous results. OS of 21 meth patients was significantly better (logrank: p=0.0414) with OS of 33m (2y-OS: 82%, CI95%: +12, -29). The combined treatment was well tolerated without major IMI-related toxicity.

Conclusions. The OS in both unmeth and meth patients strongly exceeded reported (Lancet Oncol 2009) data with radiochemotherapy and TMZm alone (median OS 12.6 resp.23.4m; 2y-OS 14.8% resp. 48.9%). The hyperthermia community should join efforts together to improve immediately the prognosis for IDH1 wild-type GBM patients based on these reported observations, and should initiate common data collection. Ultimately, the addition of IMI during/after standard of care should be prospectively explored in a phase II trial using an external control arm.

Please be aware that all abstracts are printed as submitted. Editorial deadline: 5 September 2022
P12
A joint Phagelysate and mNP hyperthermia approach for cancer treatment

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Magnetic nanoparticle (MNP) hyperthermia is a treatment technique which can be used alone or as an adjunct to chemotherapy, radiation therapy, or immunotherapy for the treatment of cancer. During treatment, MNPs are administered to the cancerous tissue, locally or systemically. If the MNP are of sufficient quantity and configuration they generate heat when subjected to an appropriate alternating magnetic field (AMF). However, like all nanoparticle therapies, the tumor microenvironment presents a significant challenge in delivering therapeutic levels of NP to the tumor. The tumor microenvironment (TME), which has an integral role in cancer development, progression, and metastasis, maintains an immunosuppressive state in many tumors, greatly reducing drug (and nanoparticle) delivery. It is now known that this situation can significantly affect the differentiation of precursor monocytes into M1 and M2 polarized macrophages. Recently, bacteriophages and phage induced lysed bacteria (bacterial phage lysates - BPL) have been shown to be capable of modifying the tumor environment. Phage/BPL coated proteins tend to elicit strong antitumor responses from the innate immune system, prompting phagocytosis and cytokine release. It has also been reported that the microenvironment of bacteriophage and BPL-treated tumors facilitate the conversion of M2-polarized (tumor associated macrophages) to a more M1-polarized (tumoricidal) environment post phage treatment.

The primary objective of this research is to demonstrate the feasibility and enhanced efficacy of combining E.coli phagelysate (EcPHL) and MNP hyperthermia in a rodent cancer model. Specifically, we propose to demonstrate the EcPHL vaccination effect on the tumor microenvironment and on MNP distribution in Ehrlich adenocarcinoma tumors. We will use daily tumor measurements to assess the anti-tumor immunomodulation effect and histology (H&E and Prussian Blue) and ICP-MS to assess the levels and distribution of MNP in tumor and normal tissue.

P13
Hyperthermia activated intravenous Liposomal-Vitamin C plus microbubbles sonoporation in bulky tumors. Proof of concept study

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Question: Deep Local Hyperthermia (DLH) is a procedure useful at obtaining cancer control with a synergistic approach. It has proven efficacy activating liposomes as strategy to better concentrate compounds inside tumors. Microbubbles Sonoporation (MS) increases vascular and cellular membrane permeability. Intravenous Liposomal Vitamin C (LVC) has antitumor effects as an adjuvant cancer treatment. Effects on vasculature, tumor stroma and immune response can be seen in the following table:
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Vasculature</th>
<th>Tumor Stroma</th>
<th>Immune Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbubbles Sonoporation</td>
<td>Increased blood perfusion and micro-vascular permeability.</td>
<td>Disruption of the collagen matrix.</td>
<td>Released DAMPs. T cell activation. Increase intracellular signaling.</td>
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We are planning a proof-of-concept study in palliative setting with bulky tumors not candidates for curative approaches. We will describe the experience with the first cases of the Interventional Oncology Institute Khuab, Comprehensive Tumor Center Barcelona.

**Methods**: Study was initiated in April 2022 including patients with bulky tumors. The device employed to perform Hyperthermia treatments is a Andromedic® HY-DEEP 600 from Rome, Italy. All patients receive simultaneous IV infusion of LVC at 1 gr/kg. MS with Sonovue® ultrasonic contrast is used in half of the patients to compare effects. All patients signed informed consent.

**Results**: The distribution of the cases, stage of the disease, complications, toxicities are recorded. Clinical and pathology responses are presented.

**Conclusions**: DLH plus LVC plus/minus MS is a synergistic oncologic treatment in the advanced tumor setting. Expected toxicities are low. Results will encourage further studies.
Establishing a general protocol for microwave hyperthermia antenna excitation regulation with Deep Learning

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Introduction: Determining the proper excitations of the antennas used in a microwave hyperthermia (MH) system is of critical importance. Focusing the electromagnetic (EM) energy to the desired target, while avoiding energy deposition in the healthy tissue (hotspots), is the main purpose of MH. The available techniques are mostly system-specific preventing large-scale applicability. For instance, in [1], the phase difference is defined as a function of distance between antenna elements, requiring a new excitation optimization algorithm for a different antenna system. Therefore, there is a need to define a robust optimization approach.

Objectives: Towards this end, in this study, our goal is to demonstrate Convolutional Neural Network (CNN)-based methods to define a general-purpose protocol of antenna excitation regulation.

Methods: A realistic digital breast model [2] is used. Linearly placed wideband Vivaldi antennas are used [3]. One antenna per simulation is excited at 2.45GHz with unitary excitation and the electric fields are recorded. Employing superposition, a database of heating potentials (HP) is created with varying excitation power and phase (full). The database is employed for training CNN models where HPs are inputs and excitation parameters are assigned as the outputs.

Results: The trained CNN models achieve high target-to-breast HP ratio (TBR) with a low hotspot-to-target HP ratio (HSTR). In Fig.1a-b, CNN results of phase only (PO) and fully optimized HPs are presented for a tumor at (26,12,0) mm position. Created database is used as a lookup table and the parameters giving the highest TBR are recorded. Resulting HPs are given in Fig.1c-d. CNN provides 4.64 % lower HSTR in PO, and 0.4 % higher TBR and 0.22 % lower HSTR in full application. Input powers are scaled such that the total input power is 6W. CNN provides 1.64- and 1.30-times higher target power for the same amount of total input power, respectively for PO and full applications.

Conclusion: The proposed method is independent of system or antenna of choice, the medium or the operation frequency. It can be used as a protocol for determining the antenna excitations for any MH system.

Figure1: Heating potentials from the CNN: (a)Phase only, (b)full; from the Lookup table:(c) Phase only, (d)full.


[2] UWCEM-Phantom Repository

Microwave detection of the shunt malfunction in hydrocephalus children

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\textbf{1. Introduction}

Each year, in Sweden, around 70 children are diagnosed with a malignant brain tumor. After surgery this type of tumor can lead to a condition named Hydrocephalus where an accumulation of cerebrospinal fluid occurs within the brain. Hydrocephalus can be treated using a shunt catheter in the brain which drains away the CSF from the brain. The problem is 4 out of 10 shunts malfunction in the first year of the surgery. Therefore, the performance of the shunt needs to be monitored continuously. There are various ways to detect this malfunction and among them, Computed Tomography (CT) using X-rays is dominant which is ionizing radiation.

\textbf{2. Objectives}

In this project, the MD100 system from Medfield Diagnostics AB is used as the detection system (Shown in Figure 1). As this system is designed to be used on adults, placing that on children"s heads might create air gaps between the antennas and the head. These gaps can create wave reflection that in turn deteriorates the detection. Therefore, it is crucial to avoid them. Another objective is to develop a signal processing algorithm to detect the changes in the brain size in repetitive measurements.

\textbf{3. Materials & methods}

A dielectric layer with electrical properties close to the head called a matching medium is designed to overcome this challenge. This medium is placed between the antennas and the head (Dark blue parts shown in Figure 1). Matching mediums are placed in plastic covers that are replaceable before each measurement (light blue parts in Figure 1).

Previously, machine learning algorithms had been developed to be used in this project. The main challenge with these methods is that they need large amount of training data to be able to provide reliable results. An unsupervised signal processing method is developed based on calculating the distance correlation between each pair of antennas to detect anomalies in the brain.
4. Results

By using the matching layers designed to deliver the maximum power to the brain, and applying the distance correlation algorithm to the data, the change in the brain size in phantom models was detected correctly.

5. Conclusions

The results are promising and showing Microwave diagnostic method as a potential alternative for CT in this application to reduce the child’s exposure to harmful radiation.

Fig. 1

P17
An alternating magnetic field focusing device for MNP hyperthermia treatment of brain cancer

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Despite considerable progress in the field of cancer treatment over the last two decades, glioblastoma (GBM) remains incurable. In 2022, an estimated 25 thousand people will be diagnosed with one of the over 100 types of brain cancer, with a mere 33% 5-year survival rate. GBM treatment involves surgical resection when possible, followed by some combination of radiation, chemotherapy, immunotherapy and hyperthermia treatments. Magnetic nanoparticle hyperthermia (MNPH) therapy, a localized form of hyperthermia therapy, has been evaluated in clinical trials in combination with radiation therapy and chemotherapy and has demonstrated significant survival benefits of the combined treatment. However, one of the shortcomings reported included the necessary removal of metal implants within 40 cm of the treatment area. During treatment, MNPs are administered to the cancerous tissue and generate heat when subjected to an alternating magnetic field (AMF). This treatment method can, however, be limited by eddy current heating in normal tissue, which is an unavoidable phenomenon directly resulting from the presence of an AMF. This phenomenon is exacerbated in the case of deep-seated tumors, such as in some brain cancers, where, relative to the treatment of more superficial tumors, larger coils carrying higher currents are required to provide sufficient AMF at the tumor exposing larger volumes of tissue to this unwanted heating. In this work, we explore the applications of an alternative AMF delivery device for the treatment of some brain cancers with MNPH, by presenting a novel device for guiding and focusing the AMF within the body. The AMF and eddy current heat distributions are demonstrated for a high-resolution human model within each tissue type using full EM and bio-heat equation solvers.

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Uncovering the relationship between extracellular drug dose, hyperthermia time and the resulting intracellular dose and cell kill

M. Newsome, L. Baù, S. Payne, R. Carlisle, C. Coussios

1. Questions

The recent clinical translation of ultrasound-mediated hyperthermia to trigger drug delivery from liposomal doxorubicin enabled quantification of the tissue concentrations of drug, ranging from 1-4 ug/ml without hyperthermia to 5-22 ug/ml with hyperthermia (Lyon et al., Lancet Oncology 2018). This new information now poses the challenge of identifying the optimal combination of local extracellular drug concentration and hyperthermia time required to maximize the intracellular drug uptake and associated cell kill.

The aim of the present work is to explore the relationship between hyperthermia, extracellular drug concentration and exposure time, intracellular drug concentration, and cell kill through a combination of experimental in vitro work and mathematical modelling, in order to further our understanding of the mechanisms associated with cellular uptake and to improve therapeutic outcomes.

2. Methods

For both viability and uptake, CT26 cells were treated with doxorubicin-spiked media (or a negative control) for a range of short exposure times (15 to 120 minutes) and doxorubicin concentrations (0.25, 1, 4, 16 and 64 µg/ml) at 37°C or 42°C.

Percentage survival was quantified using a clonogenic assay. Cellular uptake of doxorubicin was quantified separately by lysing treated cells in dH2O, estimating the number of cells using a BCA assay, and using HPLC fluorescence detection to approximate the amount of drug per cell.

3. Results

As shown in Table 1, at all clinically relevant drug concentrations (1-16 ug/ml) and hyperthermia durations (15-120 minutes), the combination of hyperthermia with doxorubicin reduces cell survival compared to doxorubicin alone.

At the clinically achievable extracellular drug concentration of 16ug/ml, complete cell kill (defined as <1% of cells surviving in culture) is not achieved without hyperthermia, but is achieved with 30 minutes of hyperthermia.

Based on these results, a compartment-style model was implemented relating the extracellular and intracellular concentrations of doxorubicin to the associated cell kill.

4. Conclusions

These experimental results and associated model demonstrate that maintenance of elevated extracellular doxorubicin concentrations in the tissue is challenging, with the concentration halving within half an hour of reaching its peak (Figure 1). This evidences the key role that hyperthermia plays in mediating cell kill given the clinically achievable tissue concentrations and hyperthermia times.
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<td>( % survival)</td>
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<td>60 minutes</td>
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<td>120 minutes</td>
<td>63.6 +/- 11.6</td>
<td>27.4 +/- 3.4</td>
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|                | HYPERTHERMIA   |                      |                      |                      |                      |
|                | ( % survival)  | 0.25µg/ml            | 1µg/ml               | 4µg/ml               | 16µg/ml              | 64µg/ml              |
| 15 minutes     |                |                      |                      |                      | 0.49 +/- 0.16        |
| 30 minutes     |                |                      |                      | 10.1 +/- 2.7         |                      | 0.55 +/- 0.04        |
| 60 minutes     | 91.1 +/- 16.3  |                      | 41.1 +/- 2.6         | 1.38 +/- 0.46        |                      |
| 120 minutes    | 86.0 +/- 5.5   | 11.6 +/- 0.5         | 1.18 +/- 0.39        |                      |

Fig. 1

Fig. 2

**Compartment model prediction of extracellular doxorubicin concentration, based on treatment parameters in the TARDOX Phase I Clinical Trial (Lyon et al, Lancet Oncology, 2018)**
The potential of time-multiplexed steering by temperature optimization in microwave hyperthermia

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Introduction: In clinical practice at Erasmus MC, the target-to-hotspot-quotient (THQ) of the specific absorption rate (SAR) is used to optimize phases and amplitudes of the signals to be applied to the hyperthermia applicator [1]. Recent research showed that the ratio between tumor and healthy tissue temperatures can be increased when amplitudes and phases are time-multiplexed when applying SAR optimization [2]. However, direct temperature optimization achieves higher tumor temperatures when considering time-multiplexed antenna steering [3]. In this work, we investigated the benefit of time-multiplexed steering when applying temperature optimization in models of patients with tumors on the head and neck region.

Methods: For five patients with a tumor in the head and neck region, a Sim4Life model was created and treatment planning was applied for the HyperCollar3D. A single distribution SAR based THQ optimization was performed for reference. A novel temperature optimization scheme was developed, which optimizes the tumor temperature for the first 15 minutes of the treatment. This results in higher tumor temperatures throughout the treatment by explicitly including the transient effects in the optimization. The evaluation was based on simulations of the full treatment time of 75 minutes, with the total power scaled to reach maximum 43°C in the tumor. Performance was evaluated by comparing T50 for both healthy and tumor tissue during treatment.

Results: The ratio between T50 in the healthy and tumor tissue was improved when using the novel temperature-based optimization for time-multiplexed distributions (Figure 1C). The SAR THQ showed a lower ratio for the time-multiplexed solution, this is resolved in the temperature simulations (Figure 2).

Discussion: The resulting T50 values, show that the temperatures during treatment might benefit from the temperature optimized with the multiplexed steering approach: either the temperature in the tumor tissue can be higher or the temperature in healthy tissue could remain lower. Although the approach seems beneficial, assessment of the impact of uncertainties in thermal parameters and inclusion of a larger dataset is still required to assess the significance of the improvement and the expected clinical benefit [4].

References

P20
Increasing the quality of life in NSCLC patients by opdivo and taxotere with hyperthermia

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Topicality: Treatment of oncological patients and getting clinical remission is an unfortunate topic even for the 21st century; despite the correctly selected therapy, which gives minimal risks of complications because of the chemosensitive tests, there are important problems connected with the quality of life of patients and naturally we ask questions to ourselves: How can we manage to increase the quality of life in oncological patients on the 3rd and 4th levels and decrease the number of the side effects that accompany Ch/therapy and R/therapy procedures.

Aim: The aim of the study was the patient with a 55-year diagnosis: NSCLC Thigh bone MTS, 3rd stage; R/therapy and 4 Courses CH/therapy; ECOG-2. Clinical remission was not achieved; Symptoms of progression of the hip fracture were strengthened, and the institution was addressed with the aforementioned history.

Methods and Materials: For the patient was selected CH/courses with hyperthermia and target therapy, we use Docetaxel 80 mg/m2 and obpivo recommended to strengthen the course effectiveness, weaken toxicity and to
improve the quality of life recommended for the treatment CH/therapy + target therapy with hyperthermia and hypoglycemia; For this procedure, a hyperthermic camera was installed, where the procedure is carried out at 43-48 degrees Celsius, and we have a sugar content of 25-30000 per one 40-45 mm / l in the bloodstream.

Results: Only 2 courses were conducted with the patient with a CH/therapy and target therapy with hyperthermia.

Conclusion: So, we managed to get maximal results through high-tech hyperthermic chemotherapy, patient’s clinical remission and this was without any side effects. Increasing the quality of life, We recommend giving a hyperthermic chemotherapy and target therapy oncolgical patients at 3rd and 4th stage, which is a firm guarantee of increasing their quality of life.

P21

Effect of hyperthermia when combined with radio(chemo)therapy for treatment of pelvic tumors

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Purpose A retrospective analysis was performed to evaluate the effect of deep regional hyperthermia (HT) when combined with radio(chemo)therapy (RCT) in patients with pelvic tumors.

Methods In total 31 patients (n) with pelvic tumors were treated with curative (subgroup I, n=20) or palliative intent (subgroup II, n=11) between 2017-2021. The overall survival (OS) and progression free survival (PFS) rates were analyzed. The complete response (CR) rate was also assessed for subgroup I. Tumor-temperature achieved at x% (Tx) and cumulative equivalent minutes at T90 (CEM43°CT90) and the net integrated power (NIP) for each HT session were calculated using Rhythym [1].

Results Patients in subgroup I and subgroup II received total radiation doses of 30-61.2 Gy and 26-54 Gy with median of 5 HT sessions, respectively. One patient from subgroup II received a brachytherapy boost. Chemotherapy was administered in 45% of patients. In total, 20% of treated tumors were recurrent in subgroup I and 64% in subgroup II. The 1-year and 2-year OS rates were 85% and 75% for group I and 72% and 54% for group II, respectively. The 1-year PFS rates were 63% for subgroup I and 66% for subgroup II. Patients from subgroup I had a 1-year CR rate of 83% (95% CI: 55-95%). Significant differences of T50, Tmin and T90 computed with mean of 14 and 7 measurement points in 11 patients with nonrecurrent and recurrent tumors, respectively, were detected (Tab.1). However, no such differences were found for CEM43°CT90 and NIP.

Conclusion The use of HT in combination with RCT is associated with good clinical outcome. Further analysis are required to assess the effect of temperature parameters per each HT session on treatment outcome for specific clinical indications.

Tab 1. Analysis of temperature parameters for 11 patients with recurrent and nonrecurrent tumors based on t-test (two-sided p-values at a significance level of α=0.05).

P22
DIELECTRIC CHARACTERIZATION OF MATERIALS AT HYPERETHERMIA FREQUENCIES

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Introduction. The open-ended probe technique is commonly used to measure the dielectric properties of materials in a wide frequency range and with an easy preparation of the sample. The use of commercial probes is usually recommended at frequencies higher than 500 MHz because the accuracy of these cables decreases under this limit. However, an exact dielectric characterization of biological tissues under 500 MHz is essential for those medical techniques, like hyperthermia, that work in this frequency range. For this reason, it is necessary to improve the accuracy of this measurement technique.

Objectives. The experimental measurements conducted in this work want to show that the accuracy of the open-ended probe technique, in the frequency range of interest, can be increased choosing the optimal dimensions of the coaxial cable.

Materials and methods. Through a theoretical and a numerical analysis it has been already shown that the accuracy of the open-ended probe technique can improve, at low frequencies, using probes which are bigger than the commercial ones. Experimental measurements have been conducted to measure the permittivity of ethanol with two different cables: the slim form which is a commercial one of small dimensions (inner radius $a = 0.35$ mm and outer radius $b = 0.9$ mm) and the SM250 which is not a commercial one and has bigger dimensions ($a = 0.835$ mm and $b = 3.15$ mm). The considered frequency range goes from 10 MHz to 2 GHz and for both cables the calibration has been done with open, short and isopropanol.

Results. The real and the imaginary part of ethanol’s permittivity have been reconstructed both with the slim form and with the SM250 cable. The results obtained in the two cases have been compared with the reference model finding that, especially at low frequencies, the bigger cable (SM250) gives the best reconstruction.

Conclusion. Experimental results have validated what has been already stated by a theoretical and a numerical analysis. The dielectric characterization of materials at hyperthermia frequencies (< 500 MHz) can improve using coaxial cables of dimensions that are bigger than the commercial ones.