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ABSTRACTS

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Nanotechnology

OP 01

A numerical analysis of magnetic nanoparticle induced hyperthermia using the finite volume method

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Introduction: Hyperthermia induced by magnetic nanoparticles (MNPs) under the action of an alternating magnetic field (AMF) can today be seen as a propitious treatment technique. The technique being new still requires further research for effective treatment planning. Computational simulation of this treatment will help to optimize the treatment parameters.
Objective: Effects of treatment parameters (frequency, amplitude, of the AMF, and the volume fraction of MNPs) on temperature distribution in tumor, as well as the healthy tissues surrounding it, are analyzed in this work.
Method: MNP based hyperthermia is simulated by numerically solving the Pennes bio-heat equation [1] using the Finite Volume Method (FVM). Both, two-dimensional, and three-dimensional models, are used. The two-dimensional model constitutes a rectangular healthy tissue of length 2 L, width L, and a square tumor having sides of span L/4 at its center (Fig. 1). Similarly, the three-dimensional model constitutes a cuboidal healthy tissue, with a cubical tumor at its center. L is taken as 0.05 m. Magnetite and fcc FePt MNPs [2] with uniform distribution in the tumor are considered in this analysis.
Results: On application of an AMF with frequency 300 kHz, and magnetic induction 50 mT, on tumor with MNP volume fraction of 2×10^{-5}, the temperature at tumor center increases and becomes constant after 600 seconds (Fig. 2 (a)). Highest temperature is observed at tumor center and decreases with distance from it. After a distance of about 0.025 m from tumor center along x-axis, the temperature becomes constant, and attains a value of 37.1 °C (Fig. 2 (b)). In two-dimensional model, the maximum temperature reaches 46.9 °C with fcc FePt MNPs, and 41.6 °C with Magnetite MNPs. With increase in amplitude and frequency of magnetic field, as well as volume fraction of MNPs, the temperature at tumor center, and its vicinity, increases. Due to loss of heat through the additional dimension, the maximum temperature attained in the three-dimensional model is less than the two-dimensional model.

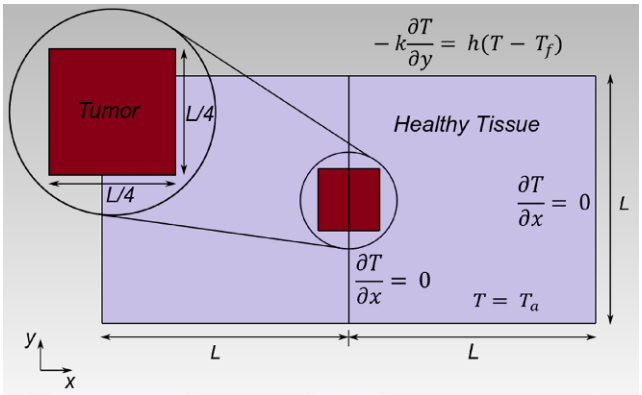

Fig. 1 OP 01. Two-Dimensional Model

Conclusion: Temperature distribution in tumor and its surrounding tissues, has a strong dependency on the treatment parameters.

References

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OP 04

Neoadjuvant treatment of locally advanced soft tissue sarcoma with doxorubicin-containing thermosensitive liposomes – Results from a proof of concept study in spontaneous feline fibrosarcoma

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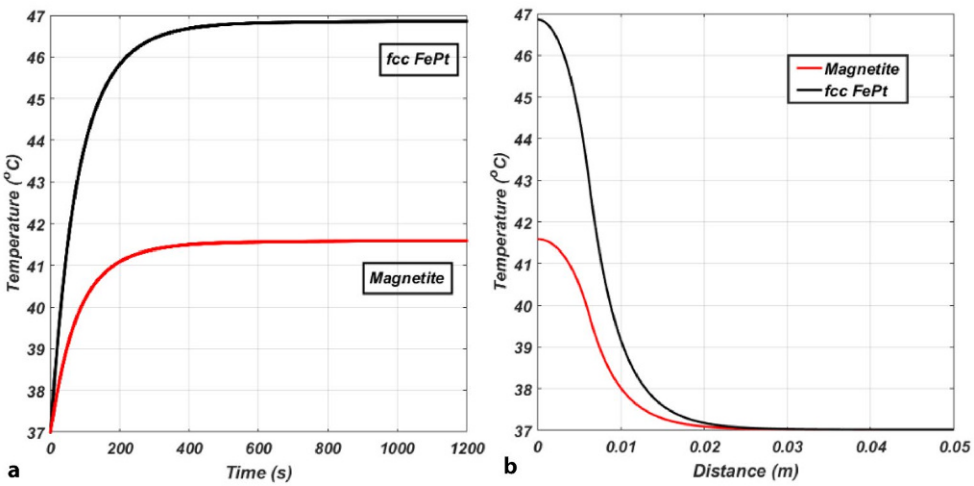

Fig. 2 OP 01. a Evolution of temperature with time, at tumor center; **b** Temperature distribution along x-axis, from tumore center, at 600 s

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Objective: Neoadjuvant anthracycline and IFO based Ctx in pts with high-risk STS has shown to improve survival. However, response to DOX and IFO combination chemotherapy is limited to less than 30% for most STS subtypes. Increasing the dose is hindered by systemic side effects and DOX tumor penetration is usually limited to the first cell layers. This can be overcome with intravascular release of DOX from thermosensitve liposomes (TSL) based on phosphatidyldiglycerol (DPPG2) showing an improved PK profile.
Methods: Twenty-two client-owned cats with advanced STS were enrolled. Intraindividual dose escalation was allowed in the first group receiving DPPG2-TSL-DOX ($N=5$, 0.1–0.4 mg/kg DOX). Constant dose levels of DPPG2-TSL-DOX were applied in the other groups with DOX 0.4 ($N=3$), 0.6 ($N=3$), 0.8 ($N=3$) and 1.0 ($N=4$) mg/kg, respectively. The control group received free DOX at 1.0 mg/kg ($N=4$). Regional hyperthermia (RHT) with a target temperature of 41.5 °C was started 15 min before i. v. drug application and continued for a total of 60 min. Six RHT treatments were applied q2wk. Tumor growth was monitored by MRI and for dose levels ≥ 0.6 mg/kg DOX also with 18 F-FDG PET. Histopathologic response was assessed in resected tumors. Blood analysis, echocardiography and clinical investigations have been routinely performed.
Results: Dose escalation of DPPG2-DOX-TSL + RHT up to 1.0 mg/kg DOX q 14 days for 6 cycles was feasible without reaching dose-limiting toxicity. Tumor responses were dose dependent and most pronounced in the highest dose level. Here, all cats treated with DPPG2-DOX-TSL + RHT (4/4) showed a metabolic partial response whereas for cats treated with free DOX+RHT, only one cat showed a MPR (1/4). The pattern of response was also different with a continuing metabolic response for the DPPG2-DOX-TSL group whereas for the free DOX group an initial response was seen after 2 cycles with further progression after 6 cycles. The metabolic response was also confirmed by the histopathologic response (vital tumor cells: 2 x < 5%, 5–10%, 10–20% vs 50%, 80%, > 95%, one missing due to progression).
Conclusion: Neoadjuvant treatment with DPPG2-DOX-TSL in feline fibrosarcoma leads to a significantly improved metabolic and histopathologic response rate. The change in response pattern suggests overcoming drug resistance mechanism by a more effective drug delivery. This offers a new treatment option for the neoadjuvant treatment of high-risk STS in humans.

Whole body hyperthermia

OP 07

Prospective evaluation observation of systemic cancer multistep therapies (sCMT)

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Introduction: The sCMT is a special form of therapy consisting of the steps extreme whole-body hyperthermia (WBH) ≥ 41.5 ° C + induced hyperglycemia + relative hyperoxemia. In the past, in therapy-refractory and palliative situations, this treatment method has shown promising results. A first step towards further investigation could be found in the fact that the therapy can be carried out safely and in comparable quality, with simultaneously low rates of side effects.
Objectives: The aim of the study was therefore to investigate whether the treatment is safe, has few side effects and is comparable in quality. At the same time, it should be investigated whether the frequency of side effects changes with and without chemotherapy.
Patients and methods: The evaluation was prospective and includes the data from 1998 to August 2016. The 613 sKMT treatments were performed in 306 patients with 311 entities. All data was recorded in appropriate quality assurance forms and additionally recorded automatically by computer. Patients were treated according to the sCMT protocol. For extreme WBH, the IRATHERM® 2000 technique was used. The adverse reaction classification was according to WHO criteria.
Results: Of 655 sCMT treatments, 94.59% reached at least 41.5 °C. The minutes per temperature level averaged 74 minutes at 41.5–< 42.0 C (range 5–130 min). For the level ≥ 42.0 °C, an average of 39 minutes was observed (range 5–95 min). A thermal dose average (EM43) of 21.57 min was determined. 60% achieved EM43 of more than 20 minutes. Assuming 13 minutes as EM43: over 80% of the therapies reached this value. There were less than 10% adverse reactions in 595 treatments.
Conclusion: The sCMT is reproducible in comparable quality. The treatment is certainly feasible and associated with few side effects. Most side effects are very short term. With the addition of chemotherapeutic drugs (thermo-chemo-therapy), the intensity of side effects is slightly higher and the overall number of possible side effects is higher. Previous studies also showed that patients were able to benefit, and despite palliative and refractory situations, response was seen in most cases. It is therefore strongly recommended to investigate this form of extreme WBH more closely.

OP 08

Use of whole-body hyperthermia in treatment of metastatic renal cell carcinoma

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Introduction: Before "target therapy era" metastatic renal cell carcinoma (mRCC) was considered as a fatal disease with very few options for treatment. Whole-body hyperthermia (WBH) is one of the methods of therapy for mRCC after cytoreductive nephrectomy for patients with intermediate risk.
Material and method: In our study heating up to basal temperature 41,5–42°C was provided by high-frequency (13,56 MHz) electromagnetic irradiation. During heating induced hyperglycemia was 22–33 mmol/l, and for chemotherapy doxorubicine 45 mg/m2 was used. The procedure is fulfilled under general anesthesia and takes 3–4 hours. First course of the treatment was performed during 45-days period of time after cytoreductive nephrectomy and the courses were repeated every three weeks. Landmark Analysis (LA) point was 90 days after diagnosis.
Results: Three and more courses were performed to 33 patients with mRCC. Control group included 153 patients, who did not take WBH. Both of groups were comparable according to age, sex, and tumor characteristics. Follow up median in the group of patients, who took three and more courses of WBH, was 75 months and in control group 74 months, median overall survival was 50 months versus 16 months in control group (odds ratio (OR) 0,55; 95% CI 0,34–0,9) ($p=0,011$).
Conclusion: The case-control study demonstrates significant benefit of three and more courses of WBH combined with induced hyperglycemia and chemotherapy in treatment of patients with mRCC with intermediate risk after nephrectomy.

Clinical hyperthermia session

OP 10

Is the classification of local extensions an appropriate tool in the treatment of pre-irradiated locally recurrent breast cancers using re-RT and HT?

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Introduction: Superficial hyperthermia (sHT) combined with radiotherapy (RT) has proven efficacy in the management of locally recurrent breast cancer (LRBC). Response rates and local control are considerably influenced by the extension of LRBC. Tumor extensions should be classified to allow for well-designed studies and a better comparison between studies. We therefore suggest a classification using 5 stages and present our results according to these stages.
Methods: This retrospective analysis includes a total of 140 patients with pre-irradiated LRBC, all subsequently treated with combined hypo-fractionated re-RT of 20 Gy total dose (5×4 Gy, 1x/week), delivered 1–4 min after contact-free, thermography-controlled water-filtered infrared A hyperthermia (wIRA-HT). 29 patients had microscopic disease, 111 presented macroscopic disease. The 5 stages of LRBC were defined as follows:

Stage 0: microscopic disease (after resection).

Stage I: limited to homolateral chest wall, extension smaller 12×12 cm.

Stage II: limited to homolateral chest wall, not passing mid line or median axillar line, infraclaviculär and superior rib bow, extension larger 12×12 cm.

Stage III: homolateral chest wall and supraclavicular fossa and/or contralateral chest wall and/or abdominal wall.

Stage IV: stage III + extension on the back (cancer en cuirasse).

Results: Response rates of macroscopic disease according to these stages:

Stage I (28 patients): 82% CR and 18% PR.
Stage II (34 patients): 56% CR, 41% PR and 3% NC.
Stage III (28 patients): 50% CR, 46% PR and 4% PD.
Stage IV (21 patients): 5% CR, 76% PR, 14% NC and 5% PD.
Stage I—IV (111 patients): 51% CR, 43% PR, 4% NC and 2% PD.

Updated information on duration of local control data and progression free survival as well as re-RT-related toxicity data of these patients (including stage 0) will be presented. No thermal skin damage (TSD) ≥ grade 2 was observed.
Conclusions: Response rates are greatly dependent on the extension of LRBC. Our suggestion aims at initiating a discussion in ESHO, STM, and ASHO to agree on a classification of LRBC-extensions. Our data show a "cut off" of local control at stage IV with only one patient achieving a CR. Compared to literature data, many of our patients presented with locally very advanced stages, e. g., 44% (49/111) had stage III/IV. Especially these patients can benefit from reRT immediately followed by sHT.

OP 11

Feasibility of re-irradiation plus hyperthermia for recurrent pediatric sarcoma – an *In Silico* study

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Introduction: Recurrent tumors are a challenge in pediatric oncology since treatment options can be limited, particularly in previously irra-

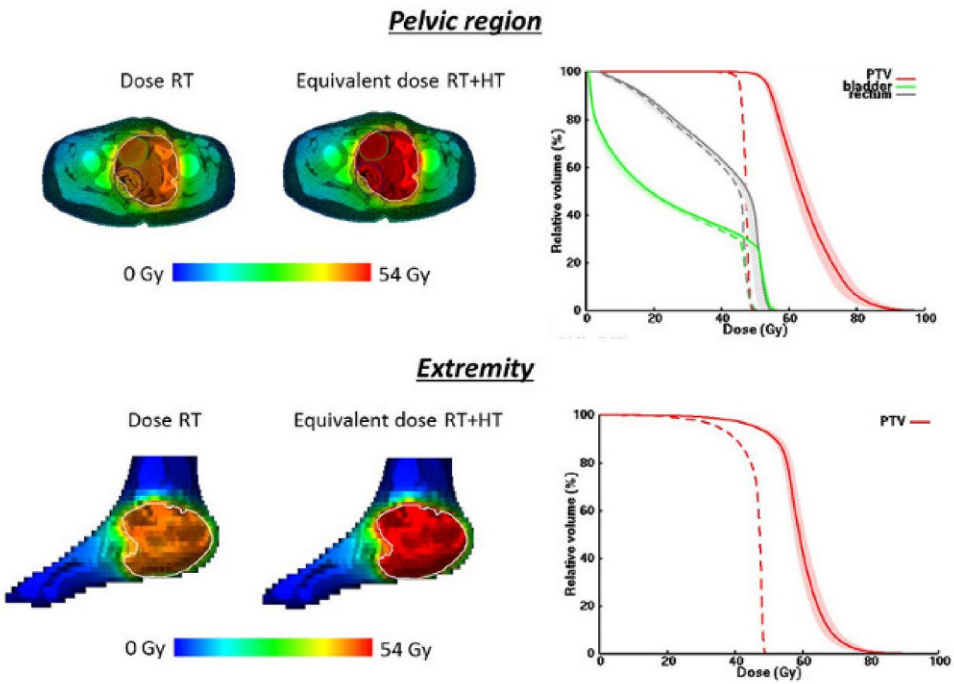

Fig. 1 **OP 11.** Radiotherapy (RT) dose distributions and predicted equivalent dose distritutions for radriotherapy + hyperthermia (RT + HT) in the pelvic region (*top*) and in a foot (*bottom*). *Dotted lines* in the dose volume histogtam represent RT alone, *solid lines* RT + HT

diated patients. Positive results have been reported for chemotherapy and hyperthermia (HT), but re-irradiation combined with HT has not been investigated so far, although it is a proven treatment strategy for indications in adults.
Objectives: We investigated the theoretical feasibility of re-irradiation+HT for recurrent pediatric sarcoma in the pelvic region and extremities.
Methods: All 47 recurrent pediatric sarcoma diagnosed at the AMC since 2002 were evaluated. Patients not previously irradiated and locations other than the pelvis and extremities were excluded. Two patients with a previously irradiated sarcoma in the pelvis and two in an extremity were eligible. HT and re-irradiation treatment plans were simulated for realistic low dose 23×2 Gy treatment schedules and weekly HT. The radiosensitizing effect of HT was quantified using biological modelling with a temperature-dependent change in the α and ß parameters of the Linear Quadratic model. The possible effectiveness of re-irradiation+HT was estimated by calculating the equivalent radiotherapy dose distribution.
Results: Treatment planning showed that pelvic locations and extremities can be heated effectively in children. Evaluation of the equivalent dose distributions indicated that hyperthermic radiosensitization can be quantified as a target-selective additional D95% of typically 10 Gy in the PTV, thereby realizing a possibly curative dose of 54 Gy, without substantially increasing the equivalent dose to organs at risk (e. g. bladder, rectum). Fig. 1 shows example treatments of a pelvic and an extremity tumor.
Conclusion: This planning study showed that re-irradiation+HT is a theoretically feasible and effective treatment for recurrent pediatric sarcoma in the pelvic region and extremities. Based on these positive results, evaluation of the clinical feasibility is worthwhile.
Acknowledgement: This research was supported by Kika (grant 253)

OP 12

Re-irradiation combined with Capacitive Hyperthermia in the treatment of irresectable recurrent breast cancer. Report from the first center in Portugal implementing this treatment association in their clinical Radiotherapy practice

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Introduction: Loco regional breast cancer recurrences may be the cause of severe suffering when uncontrolled, without being life-threatening at short time. The therapeutic effect of Hyperthermia (HT) in association with Radiotherapy (RT) has been extensively demonstrated in a wide variety of oncological settings, playing an important role in the treatment of recurrent disease, previously irradiated.

The Celsius TCS 42 System is a non-invasive medical equipment of local capacitive hyperthermia that, through its 2 active electrodes, emits a radiofrequency of 13,56 MHz, which allows to raise the temperature of the tumour in a selective and focused way.
Objectives: To describe the initial Portuguese experience in treating locoregional breast cancer recurrences with radiotherapy—reirradiation—combined with local capacitive hyperthermia.
Patients and methods: We retrospectively analysed the data of 12 patients, who underwent RT and HT, between May 2016 and August 2017. All patients were treated with IMRT technique and the same radiation schedule of 4 Gy twice weekly, to a total of 32 Gy, with an interval of 3 days between fractions, and one hour of HT, once a week. The time interval between RT and HT session was 30 minutes.
Results: The treatments were well tolerated with acceptable toxicity. The median follow-up period was 9 months. The skin reaction was moderate to marked erythema in all cases, treated with conservative measures. The complete response rate was 83%, which confers a valuable local palliation and may be an option for patients for whom there are no longer valid therapeutic proposals to offer.
Conclusion: The combination of RT with capacitive HT results in a complementary tumoricidal effect and has been used in the treatment of such lesions, with a high rate of response and acceptable toxicity.

A longer follow-up period is necessary to evaluate late reactions and duration of remission.

Capacitive hyperthermia

OP 13

Survival of cervical cancer patients with or without associated HIV infection and treated with modulated electro-hyperthermia combined with chemo-radiotherapy

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Introduction: Survival rates of cervical cancer patients treated in low resource settings have been estimated to be up to 50% lower than in developed countries.
Objectives: We report on preliminary 2-year survival results for the ongoing Phase III trial investigating the effects of the addition of modulated electro-hyperthermia (mEHT) to chemoradiotherapy protocols for HIV positive and negative cervical cancer patients in Johannesburg, South Africa.
Patients and methods: Patients classified as FIGO stage IIb to IIIb were randomised to either Intervention or Control group (CG). HIV positive patients on antiretroviral medication and with a CD4 count <200 cells/μL were eligible to enter the trial. All participants were prescribed chemo-radiotherapy (CRT). Participants in the Intervention group (IG) were prescribed, in addition to CRT, two mEHT treatments per week (130 W). Absolute survival at 6 months is reported (Chi2). Two-year survival analysis was estimated using Kaplan-Meier method. The study was approved by the local Human Research and Ethics Committee.
Results: 51% of participants are HIV positive and two-thirds (66.6%) are in Stage III of disease. 160 participants have data available for analysis at 6 months: Survival is 91% ($n=70$) in the IG vs 81% ($n=90$) in the CG. Complete response rate is better (47%;$n=33$) in the IG versus the CG (32%;$n=27$). 70 participants have data available for 2-year survival analysis. In a pre-specified per-protocol analysis of participants who completed treatment, 2-year survival was more likely in the IG (78% vs 65%; Prob>chi2 = 0.0334; adjusted for age). Progression free survival, adjusted for age, is also more likely in the IG (76% vs 61%; Prob>chi = 0.0317). There is no significant difference in survival in the HIV negative compared to the HIV positive participants (Prob>chi2 = 0.8657). We expect more data to be available at the time of the presentation and this will be included in the report in order to expand the data set.
Conclusion: Early results show 6 month and 2-year survival, as well as 2-year disease free survival, are more likely to be achieved in the group treated with mEHT combined with CRT, regardless of their HIV status. Further follow up of participants is required to confirm these results.
Declaration: The device being used is supplied by Oncotherm GmbH. Study is funded by the National Research Foundation of South Africa.

OP 14

Hyperthermia combined with radiotherapy and chemotherapy in the locally advanced, recurrent or metastatic disease

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Introduction: From 2013 to 2017 63 evaluable patients affected by diffuse tumors were treated by using chemotherapy and/or radiotherapy combined with hyperthermia, in the most of case with palliative intent.
Patients and method: Patients were affected by locally advanced, recurrences and/or metastatic disease and they were treated by following the ESHO guidelines. Indications were distinguished between EBM level -1 (breast recurrence, sarcoma, head and neck, cervix and bladder cancer) and EBM level-2 and 3 (primary and metastatic liver cancer, lung, kidney, prostate, esophagus and rectal cancer). We used two different equipments for superficial (microwaves of 434 MHz, max output 200 watt) and deep hyperthermia (radiofrequency of 13.56 MHz, max output 600 watt). Usually a session per week was delivered, monitoring temperature and kilocalories (until a max of 43 °C and 305 kilocalories in 60 min). Both system have an integrated cooling system.
Results: Primary end points were clinical response and side effects and results were evaluated by using RECIST Criteria. Sixty % of patients reached a good response (23.8 CR, 36.5% PR), whereas 23.8% obtained SD and 15.8% PD. Better response were reported in breast cancer recurrences and in head & neck cancer with superficial hyperthermia.
Conclusions: booth superficial and capacitive hyperthermia combined with radio and/or chemotherapy are effective treatments, especially if indications are supported by EBM I level.

SBRT and brachytherapy combined with hyperthermia

OP 15

Salvage HDR/PDR brachytherapy combined with interstitial hyperthermia in locally recurrent prostate adenocarcinoma after previous irradiation – actual status of multicenter phase II study

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Objectives: The aim of this work is to present actual status of ongoing clinical trial. The primary endpoint of the study is to estimate the rate of late Grade ≥3 gastrointestinal (GI) and genitourinary (GU) toxicities related to salvage treatment for locally recurrent prostate cancer after previous external beam radiation therapy.
Material and methods: The patients are recruited in Center of Oncology in Krakow and Center of Oncology in Warsaw (Poland) and in University Hospital in Erlangen (Germany). In this trial, the dose prescribed to the PTV will be 30 Gy in three 10 Gy fractions spaced 21 days apart for HDRBT (the most common fractionation scheme in Poland) and 60 Gy in 2 fractions spaced 28 days apart for PDRBT (scheme from Erlangen). In both protocols, the brachytherapy will follow interstitial hyperthermia treatment. Interstitial hyperthermia (IHT) treatment is scheduled before every brachytherapy fraction and it should end no more than one hour before the start of irradiation. Hyperthermia will be carried out in accordance with the QA guidelines published by the RTOG for interstitial hyperthermia. The objective of treatment is to achieve a tumor/prostate temperature of 40–47 °C.
Results: To date, there are 74 patients recruited out of 77 planned, of which 13 patients in Krakow, 20 in Warsaw and 41 in Erlangen.
Conclusions: The standard dose prescription and schedule are not established yet for salvage brachytherapy re-irradiation of locally recurrent prostate cancer. The literature presents a wide range of treatment protocols. Consequently, a prospective trial is urgently needed to attain clear structured prospective data. The purpose of this report is to introduce a new prospective phase 2 trial combining Iridium-192 brachytherapy with interstitial hyperthermia (IHT). The primary aim of this trial is to analyze toxicity of the combined treatment, and the secondary aim is to define the efficacy (bNED, DFS, OS) of salvage brachytherapy and heat.

OP 16

Treatment of advanced cervical cancer with radiotherapy and local hyperthermia – preliminary results

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Objectives: To report institutional outcomes for the use of local hyperthermia (HT) in treatment of advanced cervical cancer
Material and methods: To determine clinical benefit of local HT overall survival (OS), disease free survival (DFS) and response rate (RR) were assessed in randomized trial. All patients ($n=83$) received external beam radiation and low-dose-rate interstitial brachytherapy. Forty patients from them during radiotherapy (RT) additionally received 10 sessions of local hyperthermia (HT). Heating of tumor site was provided by Celsius TCS device. Sessions of local HT with gradually increasing of thermal dose were performed three times per week.
Results: Two-year overall survival in group of patients after RT without HT ($n=43$) was 70 ± 1,0%, in group of patients who received RT with HT ($n=40$)—86 ± 7%, ($p=0,5790$), DFS in group without HT was 44,8 ± 1%, with HT—70,4 ± 9% ($p=0,4157$). Complete response in former was 65,1% ($n=28$), in latter 82,5% ($n=33$).
Conclusion: The preliminary results of randomized trial demonstrate some clinical benefit of local HT for patients with advanced cervical cancer in two-year OS, DFS and RR, but there was no statistically significance. The trial and patients recruiting is going on.

Cinical trials session

OP 18

Does hyperthermia with radiotherapy/chemoradiotherapy offer a therapeutic advantage in inoperable locally advanced cancer cervix? – a systematic review and network meta-analysis

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Introduction: Therapeutic options in locally advanced cervix cancer (LACC), (stages IIB-IVA) have primarily evolved around radiotherapy (RT) and/or chemotherapy (CT). However a number of options, like neoadjuvant (NACT), adjuvant (ACT), concurrent (CTRT) and other modalities like hypoxic cell sensitizers including hyperbaric oxygen

(HypCS), immunotherapy (Imm) and hyperthermia (HT) have been tried either with RT alone or in combinations.
Objectives: To generate and synthesize clinical evidence for the most appropriate treatment option by systematic review and network meta-analysis (NMA) for each of the four endpoints—long-term loco-regional control (LRC), overall survival (OS), grade III+ acute (AE) and late effects (LE) in LACC.
Material and methods: A detailed search of 5 major databases was conducted as per the PRISMA guidelines. 6,284 articles were mined. Only randomized trials in untreated LACC, without surgical interventions were selected. Each article was assessed for risk of bias using Cochrane collaboration tool. Outcomes of therapeutic interventions for each of the four endpoints were compared with NMA using random effects model. Network diagrams, league tables, pair-wise forest plots and inconsistency plots were generated. The treatment options were ranked according to their surface under the cumulative ranking curve (SUCRA) values, that provides quantitative evidence of ranking treatments in order of their most pronounced impact on outcomes.
Results: 60 articles were finally shortlisted. Based on their individual control or study groups, interventions were classified into 13 groups—RT alone, CTRT (weekly CDDP), CTRT (3 weekly CDDP), CTRT (non-CDDP), CTRT (combination CDDP), CTRT+ACT, RT+ACT, HTRT, HTCTRT, RT+HypCS, RT+Imm, NACT+RT and NACT+RT+ACT. A total of 9,094 patients were included (LACC: 97.4%; squamous cell cancer: 93.9%). SUCRA values varied for each endpoint, the highest being HTRT for LRC (0.83), CTRT (3 weekly CDDP) for OS (0.89), RT+ACT for AE (0.98) and NACT+RT+ACT for LE (0.80). The best overall SUCRA values were for HTRT followed by HTCTRT and CTRT (3 weekly CDDP).
Conclusions: Based on the NMA and overall SUCRA values, HT with RT/CTRT has the most pronounced comprehensive impact on key clinical endpoints in LACC. These evidences should encourage launching of multi-centric well designed phase III randomized trial (HTRT vs. HTCTRT vs. 3 weekly CDDP based CTRT) along with synchronous cost effective analysis in LACC.

OP 19

Gemcitabine and cisplatin combined with regional hyperthermia as salvage therapy for patients with recurrent pancreatic cancer after adjuvant gemcitabine chemotherapy

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Objectives: The prognosis for patients with pancreatic cancer after curative resection is improved by adjuvant chemotherapy in terms of survival. We aimed to determine the efficacy and safety of gemcitabine and cisplatin combined with regional hyperthermia (RHT) as salvage treatment for patients with pancreatic cancer who failed adjuvant gemcitabine chemotherapy.
Material and methods: Patients with recurrent disease who had undergone curative resection of pancreatic cancer followed by standard adjuvant gemcitabine chemotherapy were eligible. Patients were to receive salvage chemotherapy consisting of gemcitabine (1000 mg/sqm) and cisplatin (50 mg/sqm) combined with RHT every two weeks for eight cycles. Toxicity was assessed according to CTC criteria and ESHO guidelines. TTR was defined as time from start of adjuvant gemcitabine therapy to first relapse. TTP was defined as time from start of salvage gemcitabine-cisplatin plus RHT until second progression. Relapse-free survival (RFS) was defined from start of adjuvant chemotherapy until progression or death with first relapse not considered as an event. Overall survival (OS) was defined from first diagnosis until death. Endpoints were analyzed according to Kaplan-Meier.
Results: Ten patients who had undergone initial curative resection and who had received gemcitabine adjuvant chemotherapy developed local or distant failure after a median TTR of 8.9 months. After salvage treatment (median 6.5 cycles) median TTP was 5.4 months. Median relapse-free survival was 14.3 months and median OS was 23.7 months. One patient developed grade 3 toxicity and no grade 4 toxicity was observed. Side effects due to hyperthermia were rare and moderate.
Conclusions: For patients with resected pancreatic cancer who failed adjuvant standard chemotherapy, the use of second-line gemcitabine plus cisplatin combined with RHT showed clinical results comparable with the published results of first-line adjuvant gemcitabine. Within the multicenter HEAT phase 3 study, this salvage regimen is currently tested as first line treatment compared with standard adjuvant chemotherapy for patients with resected pancreatic cancer (clin.trialsgov. NCT 01077427). An overview of the most recent status of the HEAT study will be given.

OP 20

Combination treatment with transarterial chemoembolisation, radiotherapy, and hyperthermia (Capacitative Hyperthermia with 13,56 Mhz) (CERT) for hepatocellular carcinoma with portal vein tumor thrombosis – final results of a prospective phase II trial

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Objectives: This study was designed to evaluate the efficacy and safety of combination transarterial chemoembolization (TACE) followed by radiotherapy (RT) and hyperthermia (Capacitative Hyperthermia with 13,56 Mhz), (CERT) in hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT).
Methods: This single-institution, single-arm, prospective phase II study was performed from October 2013 to February 2016. The objective response rate (ORR) was evaluated at 3 months after CERT completion, and overall ORR was the primary end point.
Results: During the study period, 69 of 77 patients who consented to participate underwent at least one session of hyperthermia and RT. More than half of the patients (39, 56.5%) complained of severe hyperthermia-related pain. The overall ORR was 43.5% (30/69), and the

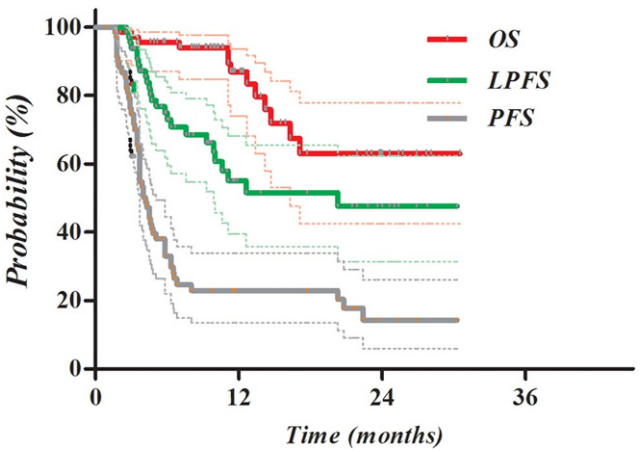

Fig. 1 OP 20. Kaplan-Meier survival curves after CERT. Local progression-free survival (LPFD), progression-free survival (PFS), and overall survival (OS) of all enrolled patients at 2 years were 62.9%, 47.6% and 14.3%, respectively

ORR of the RT target area was 69.6% (48/69). Liver function status was not significantly affected by CERT. Overall survival, local progression-free survival, and progression-free survival of all enrolled patients at 2 years was 62.9%, 47.6%, and 14.3%, respectively.
Conclusions: An overall ORR of 43.5% was observed after CERT, but a promising ORR of 69.6% was achieved in the RT target area. Toxicities related to CERT were manageable, and pain intolerance to hyperthermia was the main obstacle to treatment maintenance.

OP 21

The role of regional hyperthermia in the treatment of soft tissue sarcoma

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Introduction: Neoadjuvant chemotherapy is considered to improve overall survival for patients with locally advanced high-risk soft tissue sarcoma (HR-STS). Thereby standard anthracyclines and IFO outperform the newer, histology tailored approaches with GEM/TAX for undifferentiated pleomorphic sarcoma (UPS), high-dose ifosfamide for synovialsarcoma, ETO/IFO for malignant peripheral nerve sheath tumors (MPNST), GEM/DTIC for leiomyosarcoma. Only trabectedin for myxoid leiomyosarcoma was not inferior.
Objective: To summarize recent result and activities for the use of RHT in soft tissue sarcoma.
Results: Regional hyperthermia (RHT) combined with DOX/IFO/ETO as neoadjuvant therapy for HR-STS has shown to improve survival after 11-years follow up of the EORTC-62961 ESHO-RHT-95 trial (Issels et al. JAMA Oncology 2018). As the patients in the control arm have been treated also with the same chemotherapy regimen and as all patients have received the best available local therapy consisting of surgery and radiotherapy, RHT combined with anthracycline/ifosfamide containing therapy should be considered as the most effective treatment modality in this setting. ETO is not considered to be a first line drug for conventional STS and is associated with the risk of secondary leukemia. Therefore it was omitted for the current treatment protocol of our Sarcoma Center (SarKUM). Subsequent analyses have shown equal effectivity of both regimens (Schuebbe et al. DKK 2016).

RHT plays also a role in second-line chemotherapy regimens. For the combination with IFO/CARBO/ETO (mini-ICE) in 110 anthracycline pretreated patients a progression-free rate >40% had been observed (Bücklein et al. MS submitted). For patients not suitable for ifosfamide treatment, RHT has been successfully combined with anthracycline/DTIC also in the neoadjuvant setting. In patients where surgery is not amenable the combination of RHT with radiotherapy can provide long term tumor control. The rationale of inhibiting DNA-repair by RHT and thereby increasing cytotoxicity of DNA double strand breaks causing agents like trabectedin is currently investigated in a randomized phase II trial (Hyper-TET). Novel doxorubicin-containing thermosensitive liposomes have shown significantly improved tumor responses in feline sarcoma. This technology bears the potential to overcome standard anthracyclines for the neoadjuvant therapy of locally advanced HR-STS.
Conclusion: An overview of the most recent achievements and developments of RHT for the treatment of STS will be given.

Thermoablative therapy

OP 23

A clinically-oriented computer model for radiofrequency hepatic ablation with internally cooled wet electrode

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Introduction: Various computational modeling studies analyzed the electrical and thermal performance of radiofrequency ablation (RFA) with internally cooled wet (ICW) electrodes with the aim of enhancing the hepatic tumor management in clinics. Still, the results could not yet be extrapolated to the clinical practice due to the lack of a detailed physical description needed to optimize the treatment.
Objectives: To improve the existing computational models by building a clinically-oriented, three-compartment FEM model of RFA with an ICW electrode considering a more precise geometry of saline infusion and tumor embedded in a healthy tissue.
Materials and methods: RFA with an ICW electrode was simulated on a three-compartment computational model including liver tissue, tumor (<2 cm) and saline irrigated tumor. Saline spatial distribution was determined by means of an *in vivo* study on pigs using X-ray mapping. The results of the three-compartment computational model were compared with single and two-compartment computational models and a clinical trial. Saline spatial distribution and tumor domain inclusion were correlated to impedance evolution, roll-off occurrence and coagulation zone size.
Results: Tumor domain inclusion resulted in a roll-off delay by >20 s whereas there was no roll-off in cases considering saline hydration domain. Both domains separately had an effect on an initial impedance decrease of 15–17% (tumor) and 10–12% (saline hydration). Inversely, saline hydration imposed greater coagulation zone size increase (22–36%) than tumor domain (18–31%). It was also seen that the spatial distribution of volumetrically identical saline affected coagulation zone size. A three-compartment model most matched the clinical results.
Conclusion: To obtain a clinically validated FEM model with ICW electrode, a precise saline spatial distribution and a three-compartment computational model are required.
Declaration of interest: EB, FB and RQ declare stock ownership in Apeiron Medical, a company that has a license for the patent on which the device tested in the clinical trial is based. The other authors report no conflict of interests or financial ties to disclose.

OP 24

Systematic review of computational models of irreversible electroporation

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Objectives: Irreversible electroporation (IRE) is a new ablation technique that uses short high-pulsed electric fields between electrode pairs to create nanopores in cell membranes that cause (apoptotic) cell death. As a result, IRE is proposed as a non-thermal ablation technique and is supposedly less prone to the cooling effect by large vascular structures. However, several studies have reported a significant temperature increase during IRE treatment, with histological signs of thermal damage in the ablation zone.
Aim: A systematic review was performed to give an overview of the available computational models used to calculate the voltage and the thermal distributions of IRE, and to assess the thermal damage caused by IRE.
Materials and methods: Multiple medical and technical databases and search engines (Cochrane Library, Embase, IEEE Xplore Digital Library, PubMed, ScienceDirect, Scopus, and Web of Science) were searched for original articles describing mathematical/in-silico models regarding irreversible electroporation. These articles were included based on predetermined criteria. Most important inclusion criterion was the use of multiple mathematical equations.
Results: Out of 2987 articles, 60 met the inclusion criteria. In the majority of these 60 articles the authors initiate their study with the calculation of voltage distribution in tissue using Laplace equation. After calculation of the electric field distribution using negative gradient of the voltage, Joule heating was obtained and used in Pennes' Bioheat Equation to calculate temperature distributions. Dirichlet and/or Neumann boundary conditions were used to perform numerical calculations. Finally, the thermal damage assessment was presented by using the calculated temperature in an Arrhenius type equation and/or by calculating the equivalent amount of time at 43ºC (CEM43), which can be correlated to thermal damage.
Conclusion: The majority of the articles that calculated voltage and temperature distributions of IRE used quasi-static Maxwell's equations and Pennes' Bioheat equation, and minority used Arrhenius type equation and CEM43 to assess the thermal damage caused by IRE. In conclusion, these equations are useful tools to predict the thermal effects of IRE.

OP 25

Hyperthermic Ablation with Focused Ultrasound (FUS-HIFU) in liver and pancreatic cancer. Results of a seven-year observational comparative study of retrospective cohorts in pancreatic tumors

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Introduction: FUS-HIFU is an Hyperthermic Interventional Oncology procedure that is usefull at obtaining local disease control with a non-invasive approach. We describe the experience of the HIFU Oncology Ablation Unit of Hospital University Mutua Terrassa (Barcelona, Spain), and the Interventional Oncology Unit of Institute Khuab Barcelona, treating malignant advanced liver and pancreatic tumors.
Objectives: To describe our experience treating liver tumors with FUS-HIFU and to compare our experience of treating pancreatic cancer with FUS-HIFU plus standard chemotherapy regimens versus a cohort of patients treated at the same institution at the same period of time with standard chemotherapy regimens only. This is a seven years observational comparative study of retrospective cohorts in pancreatic tumors.
Materials and methods: From February 2008 to May 2016 we have treated 180 malignant cases. Of those, 40 cases of primary and metastatic liver tumors are studied. We include patients that were not candidates for surgery or standard ablation. All the patients continued their systemic chemotherapy treatments after the ablation procedure was performed.

We also included a total of 57 patients with non resectable pancreatic tumors, stage III and IV. These patients were treated with FUS-HIFU plus standard combinations of chemotherapy with gemcitabine. We only included stage IV patients that responded previously to chemotherapy. As a control group, we have a cohort of 58 patients treated at the same institution at the same time. We present the results of the 115 group of pancreatic patients.
Results: We first analyze the 40 liver tumors. Total treatment timings are between 60 and 180 minutes. Difficulties related to pacient positioning, access to segments VII and VIII, and real-time response evaluation prolonged the procedures. Access to deep lesions its feasible (segment I, Inferior Vena Cava). Clinical responses (ablation obtained) were 92% in all cases. Major complications included skin burning grade III that required plastic surgery (1), and costal osteonecrosis (1). Overall Percent Survival is 28.5% at 5 years follow up.

The distribution of the 115 pancreatic cases treated reflects no relevant differences in descriptive data. We specially analyze the 57 patients in the FUS-HIFU plus chemotherapy group. Clinical responses (ablation obtained) were 82% in all cases. We obtained 12 complete responses (21%) at the end of the combined treatment. Major complications included severe pancreatitis (2), skin burning grade III that required plastic surgery (2), duodenal perforation (1). One patient died from a delayed duodenal perforation. Median Survival is 23 months (6 mo–4.3 year) and Overall Percent Survival is 18% at 5 years follow up. Survival analysis between the two cohorts of patients shows a statistically significant benefit for the group of patients treated with FUS-HIFU plus chemotherapy ($p = 0.0025$). Hazard ratio is 0.45
Conclusions: FUS-HIFU is an effective and safe ablation of malignant liver and pancreatic tumors. In liver lesions, difficulties related to available devices makes it too cumbersome for accessible lesions at present compared with other ablations available. Access to deep lesions shows an opportunity for this system to increases its possibilities of use. In pancreatic tumors, compared with a similar cohort of patients treated a same hospital, it shows a clear survival advantage in non resectable stage III and IV cancer. These results encourage us to engage our efforts towards a Randomized Multicenter Study. Hyperthermic tumor ablation needs to be considered as group of oncological therapies along with Medical, Radiation and Surgical Oncology and re-considered at the light of this experience.
Keywords: Interventional oncology, High-intensity focused ultrasound ablation, FUS, HIFU, Cancer, Liver cancer, Primary hepatic cancer, Hepatocellular carcinoma, HCC, Hepatic metastases, Pancreatic cancer, Chemotherapy, Hyperthermic tumor ablation

Biology session

OP 26

In vitro testing of antitumor efficacy of modulated electro-hyperthermia in C26 colorectal adenocarcinoma model

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Objectives: Modulated electro-hyperthermia (mEHT) can induce heat shock at ~42ºC, leading to selective damage of malignant tumors. We

set up and optimized an *in vitro* model for assessing the efficiency and molecular background of this process.
Methods: Confluent C26 mouse colorectal adenocarcinoma cell cultures were treated at 42°C using mEHT for 2×30 min or 2×60 min, respectively leaving 120 min intervals between interventions. After 1, 3, 9 and 24 hrs, stress response, apoptosis and growth signaling related markers were detected compared to untreated control cultures, furthermore indication for stem-cell survival was performed with clonogenic assay. The effect of combined 2×30 min mEHT and 1 μM doxorubicin treatment was also tested.
Result: Tumor damage rate of ~50% (LD50) was achieved after 2×30 min mEHT treatment, while 2×60 min killed the majority of tumor cells. After 1 and 3hrs pro-apoptotic mRNA levels were increased and anti-apoptotic rates were decreased. At 24 hrs significant translocation of phosphatidyl-serine to the outer cell surface detected with annexin V flow cytometry indicated massive apoptosis. Elevated levels of heat stress induced Hsp70 and calreticulin, as well as cleaved caspase-3 and cytoplasmic phospho-ERK1/2 proteins were also revealed *in situ*. Stem-cell predictive colonies were also significantly reduced after mEHT treatment using colony forming assays. Combination of mEHT and doxorubicin treatments caused major reduction in cell viability compared to each monotherapy.
Conclusion: Our results indicate that mEHT can induce irreversible cell stress leading to apoptosis even in tumor stem cells and cause deregulated cell growth in C26 colorectal carcinoma cultures. Synergistic effect of mEHT and chemotherapy support feasibility of using electro-hyperthermia for complementing cytotoxic tumor therapy.

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OP 27

Malign cell survival – comparing hyperthermia via incubator with hyperthermia via EM fields – exciting at first – disappointing at last

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Introduction: All commercial loco regional hyperthermia devices use electromagnetic power (be it radiation or capacitative) to generate the heat. Thus we may not be able to differentiate between pure temperature effects and effects due to influences of the electro-magnetic field.
Objectives: Repeatingly there exists rumor that EM effects may be an as influential cause or account even more than the pure temperature effect. This thesis was to be tested.
Material and methods: A series of different malign cell lines were taken to three identical samples and put to the incubator at 370 C. The first sample was taken once a day for consecutive four days and been put in another incubator at 420 C for 30 min. The second sample was taken in a capacitative hyperthermia devices and as well exposed to max 420 C for a period of 30 min. The third sample was left untreated. All samples were taken once a day to measure cell survival via ATP-luminescence acc.to Andreotti.
Results: The first series of cell lines showed least cell survival in the first samples (put in the incubator), however after four days a pattern could be observed that the second sample (electro hyperthermia) suddenly dropped in cell survival significantly below the sample of the incubator and the control sample. However what in the beginning looked as interesting results could not be consistently reproduced in the repetition of the experiments.
Conclusion: One ought to be very cautious in setting claims of therapeutic benefits due to electro-magnetic effects on malign cells. Still it remains an unproven speculation and it would be wise to associate hyperthermia only with claims that can be proven and reproduced. Otherwise the doubtless potential of hyperthermia will be harmed again in the eyes of the majority of oncological clinicians.

OP 28

Temperature dependent effectiveness of chemotherapeutic agents in colorectal cancer cell lines

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Introduction: Peritoneal metastases of colorectal cancer origin (PMCRC) are found in 30% of patients with recurrent CRC. The only curative option for these patients is cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) with 5-year survival of 30%. During HIPEC, a chemotherapy solution heat-

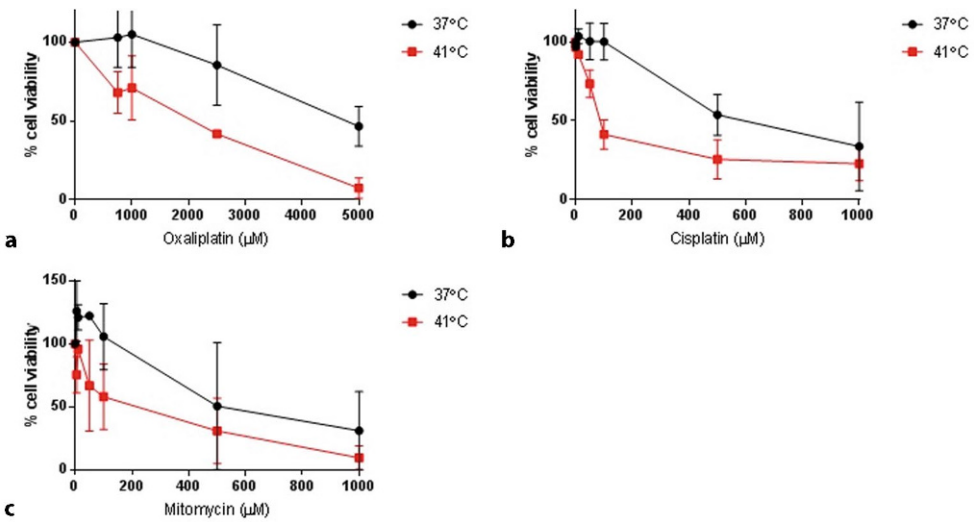

Fig. 1 **OP 28.** The effects of hyperthermia in comination with serveral chemotherapeutic agents on human colorectal carcinoma cell line RKO

ed to 42 °C is circulated through the peritoneum for 30–90 minutes. During HIPEC temperature inhomogeneities will occur, which have a negative impact on the effectiveness of chemotherapy. The clinical effectiveness of HIPEC can be enhanced by developing patient specific HIPEC planning software to predict, control and optimize the flow, temperature and chemo distribution.

Objectives: Biological data on the temperature dependent effectiveness of the chemotherapeutic agents are required to develop patient specific HIPEC planning software. Our aim is to determine the temperature dependent Thermal Enhancement Ratio (TER) of oxaliplatin and other drugs by using *in vitro* experiments in colorectal cancer cells.

Methods: Two human colorectal carcinoma cell lines RKO (p53 wild-type) were used. To derive TER as a function of temperature we determined cell survival curves as a function of treatment time at different temperatures relevant during HIPEC: 37 °C, 38 °C, 39 °C, 40 °C, 41 °C, 42 °C, 43 °C.

Results: The first *in vitro* experiments show more reduction in cell viability after RKO cells were incubated with oxaliplatin during 1 hour at 41 °C compared to 37 °C (Fig 1 A). RKO cells incubated with cisplatin or mitomycin C also showed more reduction in cell viability when treatment is combined with hyperthermia, although the cell viability was less decreased compared to the results with oxaliplatin (Fig 1B, 1 C). Other chemotherapeutics agents, 5-FU and gemcitabine, did not significantly reduce the cell viability in RKO cells when combined with hyperthermia treatment.

Conclusions: Results show clearly enhanced TER values for oxaliplatin, cisplatin and mitomycin C in the *in vitro* experiments. Next step is to confirm these in in vivo experiments, which will be performed in a PMCRC rat model by transplanting tumor fragments into the abdomen of rats to develop carcinomatosis in the abdomen. HIPEC will then be performed at different temperature levels with clinically relevant doses, after which animals will be sacrificed to determine the tissue penetration depth of oxaliplatin and the other agents.

OP 29

Analysis and simulation of the response of 3D tumour spheroids to combination treatments of radiation and hyperthermia

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Introduction: Thermo-radiosensitisation offers the possibility of successful treatment of radio-resistant tumours. However, tumour response heterogeneity, due to intrinsic, or microenvironmental factors, may influence treatment outcome. 3D tumour spheroids allow the study of these effects in a more physiological environment than 2D cultures.

Objective: We present a systems oncology framework, based on experimental data, to study the response of 3D cultures to radiotherapy (RT) and hyperthermia (HT), and point out important differences with 2D models.

Materials and methods: A cellular automaton model for RT and HT treatments [1] was extended to spheroid simulation. This included

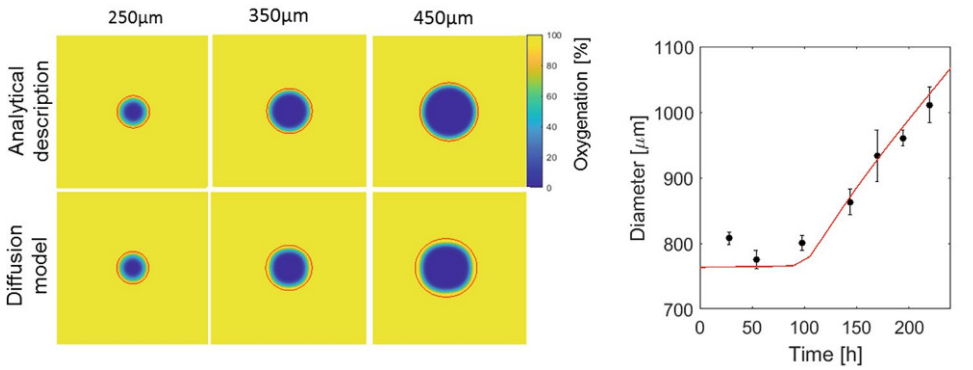

Fig. 1 OP 29. *Left*: Oxygenation levels within spheroids of different radii calculated using the analytical description of Grimes et al. (*top*), or obtained by iterative solution of the oxygen reaction-diffusion equation in the cellular automation model (*bottom*). *Right:* Simulated (*solid line*) and experimentally measured (data points, mean and std. of 6 spheroids) diameter of an HCT116 spheroid formed from 10.000 cells seeded on day

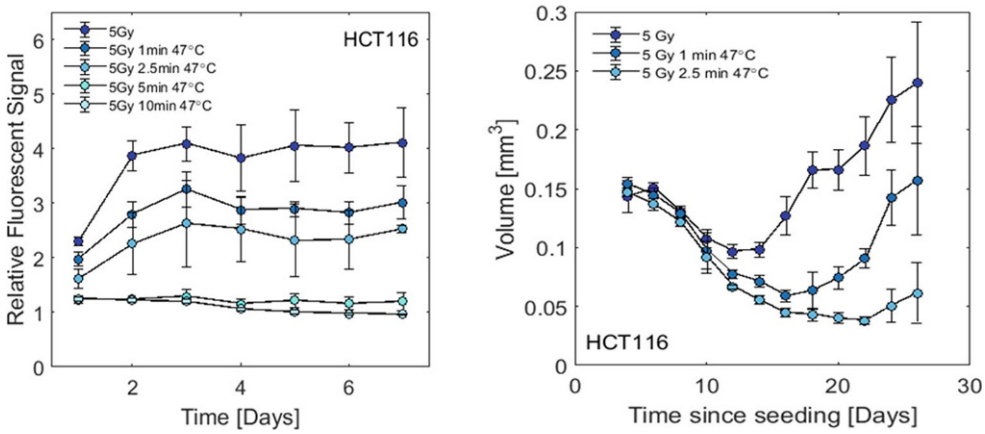

Fig. 2 OP 29. *Left:* Growth curves of 2000 treated HCT116 cells seeded in 96 well plated evaluated by the resazurin assay. The relative fluorescent signal of the sample and control wells containing only culture medium and assay reagent are assumted to be directly proportional to the number of viable cells present. Average data and standard errors of the mean of three independent experiments are shown. *Right:* Experimental spheroid growth curves of HCT116 spheroids formed after seeding of 4000 cells on day 0. Mean values and standard errors of the mean of the least three independent measurements are shown

modelling of 3D geometries, oxygen diffusion, treatment specific cell death mechanisms and cell clearance.

For simulation calibration and validation, three human cancer cell spheroids were tested for their response to RT (0–20 Gy), HT (0–240 CEM), and combinations thereof. Growth was monitored for 25 days using a cytometer. Immunohistochemical staining allowed analysis of distributions of viable (KI67), hypoxic (pimonidazole), and necrotic (haematoxylin and eosin) sub regions. For comparison, 2D clonogenic and resazurin assays were performed.

Results: The framework was first calibrated by modelling untreated spheroids while accounting for the influence of hypoxia induced necrosis at their core. Simulations were matched with experimental growth curves and histological sections, as well as with an analytical oxygenation model [2] (figure 1). For treatment response modelling it was essential to consider the influence of the underlying cellular response mechanisms, such as necrosis, mitotic catastrophe, or cellular senescence. In contrast to 2D cultures, the clearance of dead cells was an important additional step in order to fully capture the dynamic response of 3D populations. This may explain response differences observed in growth delay between 2D and 3D cultures (figure 2).

Conclusions: It was found that cellular treatment response may differ with culture systems, i. e. 2D or 3D. The proposed framework provides an important step towards *in vivo* modelling of RT and HT and allows for optimization of treatment combinations and scheduling under physiological conditions.

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OP 30

Hyperthermia and low LET radiation has equivalent in vivo anti-tumor activity as high LET radiation

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Objectives: It has been suggested that combining hyperthermia with intermediate linear energy transfer (LET) radiation (i. e., protons) would have anti-tumor activity equivalent to that seen with high LET radiation (i. e., carbon ions). This is based primarily on in vitro observations. We now present in vivo results showing that even low LET (i. e., photons) combined with hyperthermia is as good as, if not better than, high LET radiation.

Methods: Non-anaesthetised female CDF1 mice with a 200 mm^3 C3H mammary carcinoma growing in the right rear foot were used in all experiments. Treatments were performed with the tumor bearing leg immersed in a water bath maintained either at 25°C for radiation (240 kV X-rays) alone or with heating at 41–43°C for 30 or 60 minutes. For the simultaneous combination of radiation with heat, the radiation was administered in the middle of the heating period. The percentage of mice showing local tumor control 90 days after treatment with graded radiation doses was recorded and following logit analysis of the radiation dose response curve, the TCD50 value (radiation dose causing tumor control in 50% of mice) was estimated.

Results: The TCD50 value following irradiation with photons alone was found to be 54 Gy. This was decreased by heating, such that the therapeutic enhancement ratios (TER, ratio of TCD50 values for radiation alone to radiation and heat) increased with heating time and temperature; the TER values following heating for 30 minutes at temperatures of 41.0, 41.5, 42.0, 42.5 and 43°C were 1.0, 1.2, 1.5, 1.8 and 2.3, respectively. These values were respectively increased to 1.1, 1.6, 1.9, 2.4 and 3.5 with a 60-minute heating period. Our previous published results with carbon ions in the same tumor model (Sørensen et al., Acta Oncol., 2015;54:1623–30) found that carbon ions resulted in a TCD50 value that was 1.5 times lower than that seen with photons.

Conclusions*:* In this C3H mammary carcinoma model, carbon ions had a greater anti-tumor effect than photon irradiation. However, the same anti-tumor effect could be obtained by simultaneously combining photons with hyperthermia at a temperature of only 42°C for 30 minutes or 41.5°C for 60 minutes.

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Immune effects of hyperthermia and novel drug combinations

OP 31

Regional hyperthermia and immuno-oncology

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Objectives: In the EORTC 62961-ESHO 95 randomized clinical trial (329 high-risk soft tissue sarcoma (STS) patients) survival was significantly improved by adding regional hyperthermia (RHT) to neoadjuvant chemotherapy (Issels et al. JAMA Oncol 2018). We made two observations; first, survival was equally pronounced in patients with extremity or non-extremity tumors; second, survival curves separated late. Distant metastases are the leading cause of death of extremity tumors and delay in survival benefit is observed in immunotherapy trials. Hyperthermia effects are pleiotropic including immune modulation (Issels et al. Int J Hyperthermia 2016). Here, we review preclinical findings and clinical post-hoc results to support the use of RHT in the context of immune therapy.

Methods: Tumor cell death triggered by chemo- or radiotherapy initiates an immune-adjuvant pathway that contributes to the success of cytotoxic treatments. Adding RHT to chemotherapy can increase tumor response significantly. The heat shock response includes the expression of stress proteins. In preclinical models, we demonstrated that HSP70 enabled cross-presentation of tumor antigens triggering T cell responses (Noessner et al. J Immunol 2002; Bendz et al. J Biol Chem 2007) Membrane expression of HSP70 on tumor cells (Multhoff et al., Int J Cancer 1995; Stangl et al. PNAS 2011) was recognized by NK cells (Multhoff et al. J Immunol 1997). HSP70 peptide/IL-2-activated NK cells killed membrane Hsp70 positive tumor cells in vitro and re-infusion of extracorporeal HSP70-treated NK cells was feasible under clinical conditions (Krause et al. Clin Cancer Res 2004). In chemo-naive STS patients, NK cell function was found to be a priori impaired (Bücklein et al. Oncoimmunol 2016). Assessing 137 core biopsies from 109 patients (EORTC-ESHO 95) we found evidence that high TILs were predictive for local control and disease-free survival (Issels et al. ESMO 2015). In case reports of chemo-refractory STS, RHT combined with low-dose chemotherapy induced long-term survival (>25y) or an abscopal effect on distant metastases (Issels et al. in prep).

Conclusion: We postulate that RHT targeting the tumor area is a therapeutic modality exploiting antitumor immunity. “Cold” tumors might be turned to be inflamed by RHT. The findings open a new window for

the use of hyperthermia in the context of current immune anticancer therapy and should be confirmed prospectively in the context of controlled clinical studies.

OP 32

From cold to hot – increasing tumor immunogenicity by combining checkpoint inhibitors with hyperthermia

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Objectives: Despite the success of checkpoint inhibitors (CI) many patients do not respond. Since hyperthermia can influence immune response we have investigated the effect of combining it with a monoclonal antibody (ab) that targets CTLA-4 (anti-CTLA-4 ab) in a non-immunogenic "cold" tumor.
Methods: Male CDF1 mice with a 200mm3 C3H mammary carcinoma in the right rear foot were given either sham treatment (controls); local heat treatment (42.5 °C for 1 hour) on day 0; intra peritoneal injection with anti-CTLA-4 ab (10 mg/kg) on day 1, days 1 and 3, or days 1–4; or a combination of heat treatment with anti-CTLA-4 ab. Tumor size was measured daily, and time to reach five times treatment volume (TGT5) recorded. Results are listed as mean (± standard error, SE). One-way ANOVA comparison of group means was performed, and a $P < 0.05$ was considered significant.
Results: The TGT5 for the control group was 6.6 days (± 0.2). For the groups treated with anti-CTLA4 ab on day 1, days 1 and 3, or days 1–4, the TGT5 was 5.8 days (± 0.4), 5.8 days (± 0.4) and 6.8 days (±0.3). There were no significant differences between treated animals and controls. In the heat group, the TGT5 was significantly increased to 11.1 days (± 0.9). This was further increased when heat was combined with anti-CTLA-4 ab to 11.6 days (± 1.2) for treatment on day 1, 12.9 days (± 2.7) for days 1 and 3, and 15.4 days (± 0.8) for days 1–4. The values for day 1 and 1 and 3 were not significantly different from heat alone, but the heat and anti-CTLA-4 ab on days 1–4 was significantly increased ($p = 0.004$). One mouse remained without signs of recurrence after 3 months, and is not included in the statistics.
Conclusion: As the C3H mammary carcinoma is insensitive to treatment with CIs, it is to be considered as a non-immunogenic "cold" tumor. However, when treated with heat, the tumor becomes "hot"; it gets CI sensitive to anti-CTLA-4 ab administered on days 1–4. Our data thus clearly show the potential benefit of combining hyperthermia and specific CIs to improve tumor immunogenicity. A novel study is currently investigating T cell up-regulation and tumor infiltration based on histology.

OP 33

Hyperthermia as part of multimodal immunotherapy for children with DIPG

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Introduction: The most deadly pediatric malignancy is Diffuse Intrinsic Pontine Glioma (DIPG), in spite of radiotherapy, chemotherapy and/or biopsy-driven targeted therapy.
Objectives: To analyze retrospectively the treatment results of DIPG children with multimodal immunotherapy (Newcastle Disease Virus, modulated electrohyperthermia, DC vaccines loaded with NDV+-mEHT-induced serum-derived antigenic extracellular vesicles) as individualized treatment approach.
Patients and methods: 38 DIPG children with median age 5.5y (range 2–19y) were treated, 26 of them as part of primary treatment (DIPGprim), before or after radiotherapy, and 12 at time of progressive disease after first line treatment (DIPGprog). 83% of DIPGprim children had a Lansky score >70.
Results: At start of immunotherapy, 31% of patients had deficient IFN-g expression in the CD4+ T cells. Diminished NK function was observed in 77%. The repetitive NDV infusions, the mEHT and the production and administration of the DCs all were feasible. No major toxicity was observed. We detected the increase of GBM antigen cross-reacting IFN-g-producing T cells in those patients that could be immunomonitored. Median PFS of DIPGprim children was 8.26 m. Rescue after progression was mainly re-irradiation. Median OS was 14.23 months. 18 m OS was estimated as 28% (asymmetrical 95%CI: +21.34, –18.15). Median OS of the 12 DIPGprog children calculated from last event prior to immunotherapy was 3.14 m.
Conclusion: Multimodal immunotherapy is feasible for children with DIPG without major toxicity and with potential efficacy when placed early as part of consecutive treatment strategies.

OP 34

Hyperthermia induced synthetic lethality in cervical cancer

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Introduction: Cervical cancer is the 4th most common cause of cancer death in women worldwide. Chemoradiation is the standard treatment of cervical cancer. However, some patients are resistant to chemotherapy (CH), possibly caused by repair of DNA damage. Research showed that adding hyperthermia (HT) to radiotherapy (RT) also improves tu-

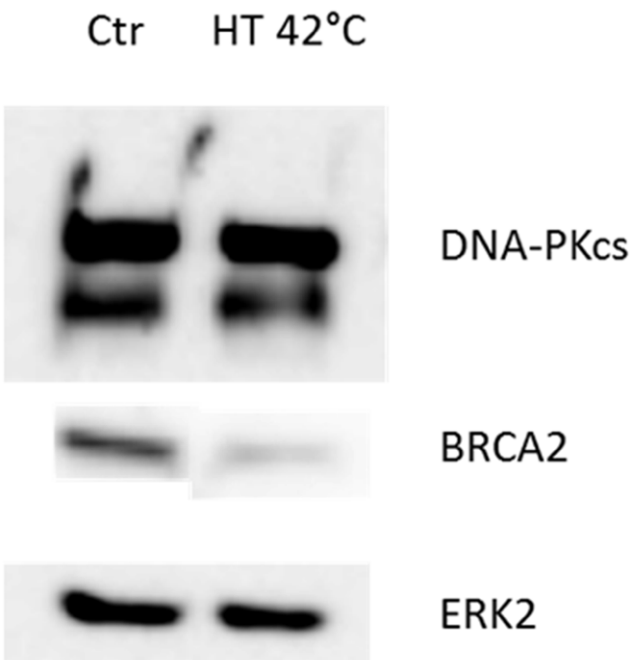

Fig. 1 OP 34. Western Blot demonstration that BRCA2 is downregulated after HT, whilte DNA-PKcs is not altered in SiHa cells

mor control. Combining HT with CH and RT is thought to target all DNA repair mechanisms, leading to apoptosis. Knowledge is growing about the exact mechanisms with which HT affects the DNA damage response.Ionizing radiation induces DNA double strand breaks (DSBs) as well as single strand breaks (SSBs). HT inhibits DNA repair while PARP1 is responsible for repair of SSBs. We hypothesize that combining HT and PARP1-inhibition with RT induces synthetic lethality by acting upon both the SSB and DSB Repair.

Objectives: To unravel the underlying mechanisms through which HT sensitizes current treatment options.

Methods: Combinational treatment was given to cervical cancer cell lines with RT at 2 Gy and HT at 42 °C. Apoptosis was measured by clonogenic assays. DNA DSBs were analyzed by the γH2AX staining. To study the role of HT signaling in DSB repair, transfections with commonly used reporter systems for Homologous Recombination (HR), a key pathway in this repair was tested in cervical cancer cells and analyzed by flow cytometry. Western blotting was performed to interpret the expression levels of different DNA repair proteins.

Results: When SiHa cells were heated at 42 °C for 70 min, DNA-PKcs levels were unchanged compared to SiHa cells kept at 37 °C. BRCA2 protein expression was decreased after heating at 42 °C (Fig 1). Cellular survival was decreased when adding HT to RT treatment in SiHa and HeLa cells. Combining PARP1-i showed an even larger decrease in cell survival.

Conclusion*:* Results show that combining HT and PARP1-inhibition with RT and/or CH induces synthetic lethality, since both SSBR and DSBR will be inhibited. BRCA2 protein expression was downregulated after hyperthermia treatment, indicating its effect on HR. DNA-PKcs expression, involved in DSB repair pathway Non-Homologous End Joining (NHEJ) was not altered after hyperthermia treatment. The effects of HT on other proteins involved in both pathways are still under investigation.

Medical physics in hyperthermia

OP 35

Analysis of the required number of sensors for adequate monitoring of skin temperature distribution during superficial microwave hyperthermia treatment

A. Bakker[1], R. Holman[2], D. B. Rodrigues[3], H. Dobšíček Trefná[4], P. R. Stauffer[3], G. van Tienhoven[1], C. R. N. Rasch[1], **H. Crezee**[1]

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Objectives: Minimum and maximum tissue temperatures during hyperthermia are related to tumor response and treatment toxicity, respectively. We analyzed the required number of sensors to adequately monitor the skin temperature distribution during superficial hyperthermia treatment of breast cancer patients.

Patients and methods: From a database of patients with recurrent breast cancer treated with reirradiation (23 × 2 Gy) and hyperthermia using single 434 MHz applicators (effective field size 351–396 cm2) hyperthermia treatments monitored with ≥60 stationary temperature sensors were selected. Reduced temperature monitoring schemes involved randomly selected subsets of stationary sensors, and another subset to simulate thermal mapping. Temperature differences (ΔT) be-

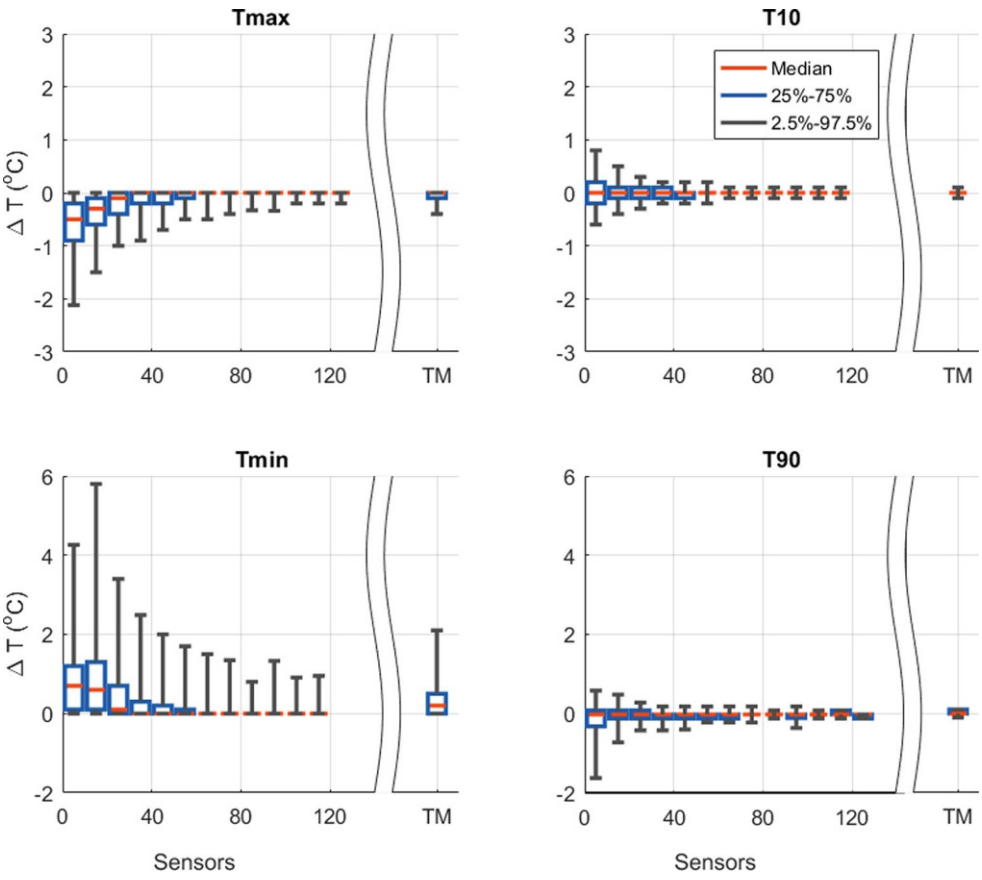

Fig. 1 OP35. Tukey boxplots of the temperature difference (ΔT) between randomly selected subsets (5000 simulations) and the complete set of sensors during a hyperthermia session. Thermal mapping (TM) is displayed separately (400 simulations)

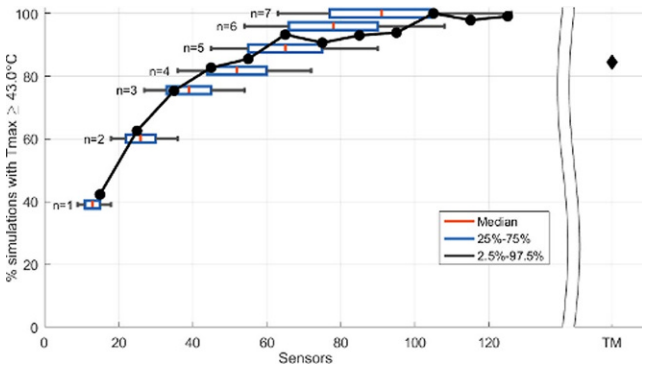

Fig. 2 OP 35. Normalized percentage of simulations that identify a maximum temperature (Tmax) ≥43.0 °C (2524 simulations) as a function of randomly selected sensors. Thermal mapping (TM) is displayed separately (85 %; 200 simulations)

tween subsets and complete sets of sensors were evaluated in terms of overall minimum (Tmin) and maximum (Tmax) temperature, as well as T90 and T10, which are the 90th and 10th percentile of the temperature measurements, respectively.
Results: 80 patients were included, yielding a total of 400 hyperthermia sessions. Median ΔT between subsets (8–126 sensors/session) and complete sensor sets (60–147 sensors/session) was <0.01 °C for T90 with a 95% confidence interval (CI) ≤0.5 °C, when >50 sensors were used. (Fig. 1). Subsets of <10 sensors result in underestimation of Tmax up to –2.1 °C (ΔT 95% CI), which decreased to –0.5 °C when >50 sensors were used. Thermal mapping (8–21 probes with 60–147 temperature points) yielded a median ΔT < 0.01 °C for both T90 and Tmax, with an ΔT 95% CI of –0.2 °C and 0.4 °C, respectively. The detection rate of Tmax ≥43 °C is ≥85% while using >50 stationary sensors or thermal mapping (Fig. 2).
Conclusion: Adequate monitoring of the skin temperature distribution during superficial hyperthermia, (e. g. identification of local hotspots and T10 and T90 temperature distribution descriptors within ± 0.5 °C), requires the use of >50 stationary sensors or thermal mapping points per 400 cm2 applicator.

OP 36

On the experimental validation of deep hyperthermia devices – study of representative phantoms

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Introduction: Simple phantoms are often used both in experimental and numerical studies devoted to the validation and optimization of hyperthermia devices [1–3]. These phantoms help in the settlement of the devices excitation to reach a definite goal, i. e., to focalize the electromagnetic power absorption in definite positions within the body without inducing hot spot in other positions. Their simplicity allows experimental verification by measuring the electric field or the temperature increase and performing simple comparisons with numerical results. The question is how representative are simple phantoms with respect to the electromagnetic and temperature distribution achievable by hyperthermia devices in the human body. Additionally, what are the tissues and organs that should be considered to make these phantoms representatives and, at the same time, keep them as simple as possible for easiness of use.
Methods: Simulations were performed considering a radiative deep hyperthermia system and several phantoms. In particular, the model of a 26-year-old woman was considered [4] both as non-homogeneous and with increasing simplifications of the considered tissues. A phantom with anthropomorphic shape and composed by uterus, bladder, bone of the ileum, muscle and sub-cutaneous fat was considered also. Comparison was made on the percentage electromagnetic power absorbed by the different tissues in all considered cases
Results: The obtained results show that the geometry and dimension of the body models and of their internal organs don't change the absorbed power distribution. On the contrary, body composition, i. e. the tissues and organs which are considered into the body, influence the absorbed power distribution. In particular, the presence of fat, including both the subcutaneous one and the visceral fat that surrounds the most internal organs, proved to change the percentage electromagnetic power absorbed by the different organs.
Conclusions: Phantoms to be used in validation studies as well as in quality assurance procedures for deep hyperthermia systems should include both subcutaneous and visceral fat to correctly evaluate power absorption into deep body organs.

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OP 37

Application in the clinical practice of hyperthermia of 3 quality indicators – the experience of candiolo cancer institute

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Introduction: The development of Quality Indicators in the field of quality benchmarking is evolving. The aim of this study was to analyze the practical feasibility and efficacy of the Quality Indicators elaborated by Candiolo Cancer Institute group.
Methods: A preliminary set of 11 indicators was selected on the basis of evidenced critical issues. Three structure, six process and two outcome quality indicators were obtained. Numerical values for the standard were selected from the international literature and from guidelines on hyperthermia/radiotherapy, or empirically on the basis of the experience of the Italian Institutes. (ESHO Congress, Athens, 2017). To date, in our Institute, we analyzed 3 of the 11 indicators proposed. (temperature measurement, treatment outcome/toxicity and patient compliance, Table 1). For this purpose, 43 consecutive patients treated in our Department were analyzed and the results are reported according to the appropriate indicators.
Results: Considering the analyzed indicators, we obtained that the number of treatments in which temperature measurements is performed during patient treatment is 100% and a minimum of five different locations to measure skin temperature every minute during superficial hyperthermia are used according to the European Society for Hyperthermic Oncology technical committee; the number of complete response (CR)/> G2 toxicity was 31% in mean from 6 to 36 months; the percentage of number of patients that complete the total hyperthermia treatment is 86% and patient satisfaction with the staff obtained a

Fig. 1 OP 37. The three Quality Indicators and relative results

Indicator	Topic	Type of indicator	Numerator	Denominator	Standard	Results
1. Temperature measurement	Hyperthermia treatment accuracy	Process	Number of treatments in which temperature measurement is performed (yes/no)	Total number of hyperthermia treatment	100%: each plan should be checked during treatment	100%
2. Treatment outcome and toxicity	Quality improvement of patient management	Outcome	Number of complete response (CR)/ No patients showed toxicity ≥ G2 at 12 months after the treatment	Total number of treated patients	CR=40% (late response); Toxicity G2 (12 months after the treatment): 0%	31%
3. Patient compliance/ satisfaction	Treatment compliance	Outcome	Number of the patients that complete total hyperthermia treatment	Total number of treated patients	100%: total number of patients complete hyperthermia treatment	86%/ 89%

very high compliance (89%). Conclusion: Our purpose of Quality Indicators need the monitoring of the activities of the Institute in order to assess critical factors and it could be the starting point to improve the quality and to compare national and international quality assurance results. In our daily practice it can be a valid help in choosing the indication of hyperthermia and in the selection of patients who can benefit from it.

Reference

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OP 38

Multicenter quality assurance evaluation of MR-guided deep hyperthermia systems

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Introduction: The Pyrexar BSD2000-3D-MRI is the most clinically used system for magnetic resonance (MR)-guided hyperthermia treatment of deep-seated tumours. The applicator operates inside a GE 450 W 1.5 T MR scanner at Erasmus MC and inside a Siemens Magnetom Symphony 1.5 T at the Heinrich-Heine-University Düsseldorf, University Hospital Erlangen and University Hospital Tübingen. The new Pyrexar Universal Applicator has been recently installed at the Ludwig-Maximilians University Munich to operate inside a Philips Ingenia 1.5 T. Applicator quality assurance (QA) measurements are usually implemented independently at each institution.
Objectives: This work presents the results of a systematic QA measurement procedure performed at the different institutions using the same set of phantoms.
Materials and methods: Phantoms of different complexity have been specifically developed to evaluate the performance of the applicators. The first set of phantoms are 25 cm inner-diameter cylindrical homogeneous phantoms. The second set are anthropomorphic and contain plastic pelvic bones and spine. Catheters are positioned in the phantoms for temperature measurements using Bowman sensor probes. Measurements were performed aiming to have a centric and eccentric heating focus at 3 cm from the center.
Results: Steering accuracy was 1.5 ± 0.5 cm (mean ± sd) for cylindrical phantoms. For anthropomorphic phantoms, a variation of ±10% among institutions was found in the uniformity of the temperature increase for centrically located probes and a central target. More detailed analyses are ongoing.
Conclusion: This work provides pioneering results on the performance of different MR-guided deep hyperthermia systems operating in MR scanners of different vendors. The relevant variations obtained confirm the necessity of standardized QA guidelines.
Acknowledgements: COST BM1309 EMF-MED, KWF-DDHK 2013-6072, Dr Sennewald Medizintechnik GmbH.

SAR pattern control by multi-antenna systems, potentials and limitations

OP 39

SAR distribution created by combination of external and interstitial applicator

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Introduction: Our paper deals with SAR distribution created by a superposition of EM expositions done contemporary by external and interstitial applicator. Three different cases are numerically and experimentally studied and compared in this paper. In the first case we will describe the shape of SAR distribution created only by monopole antenna, which represents interstitial applicator. In the second case we will discuss the SAR distribution created only by external microwave stripline type applicator with TEM mode. In the last case we will describe a superposition of SAR distribution created by EM expositions done contemporary by external and interstitial applicator. Both ap-

plicators are excited at the same frequency (f=434 MHz), power and phase.

Methods: In all these three cases homogeneous agar phantom representing a muscle tissue (εr=54, σ=0.8S/m) with dimensions 140×140×74 mm was used. In here described studies the microwave stripline applicator was located on the surface of this agar phantom instead the monopole antenna was situated 4 cm deep under the surface of the agar phantom. Both applicators were powered coherently, which allow us to take advantage of their mutual interference. Simulations of the shape of SAR distribution have been done by the FDTD method, in our case it was done by a id of SEMCAD XEM Field simulator.

Results: Both numerical and experimental evaluations of superposition made by exposition by both applicators were compared. In presentation it will be demonstrated a very good homogeneity in temperature increase between aperture of the external applicator and position of interstitial applicator.

Acknowledgment: This study was supported by by a grant from the Czech Science Foundation, number 17-20498 J: "Non-invasive temperature estimation inside of human body based on physical aspects of ultra-wideband microwave channel".

OP 40

Verification of self-calibration algorithms for phased array applicator

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Chalmers University of Technology, Electrical Engineering, Göteborg, Sweden

Introduction: In microwave hyperthermia (MW-HT), treatment planning determines the steering parameters for a phased array to yield appropriate tumor coverage and hot-spot suppression. In real HT systems, however, such arrays are subjected to mismatches, which might not be considered in the models used in treatment planning. While certain mismatches can be addressed via channel calibration, those occurring inside the array are more difficult to predict as they can vary during the treatment session itself. The effect of such mismatches can be as relevant as to disrupt the interference pattern.

Objectives: This contribution proposes self-calibration (SC) as a solution for real-time compensation of various types of mismatches, such as different cable lengths, manufacturing tolerances, patient misplacement and air bubbles in the water bolus. Two SC algorithms have been designed for use with applicator arrays of arbitrary shapes.

Materials and methods: The algorithms are based on comparison of simulated and measured S-matrices of the phased array. The extra time delays caused by various mismatches at each channel are then compensated accordingly. The verification of both algorithms includes virtual and experimental models of our neck applicator used in a setup with a patient model and a muscle phantom. The accuracy has been evaluated numerically by comparing the ideal E-field distributions with those obtained by introducing a set of randomly distributed mismatches to the applicator model. The proof-of-principle has then been demonstrated experimentally by means of temperature measurements.

Results: Results indicate that at least one of the tested SC algorithms converge to the correct compensation solution with performances largely comparable and sometimes even exceeding those typical of an external calibration. Antenna offsets of ±5 mm and air bubbles about 1 cm big are well handled. Improvements can be done with respect to patient misplacement, which is compensated by the algorithm up to ±1 mm. Experimental results confirm the ability of the algorithm to restore focus shape.

Conclusion: Self-calibration can be a valid solution for mismatch compensation in MW-HT. The potential real-time application of SC makes it a desirable candidate for use in clinical settings.

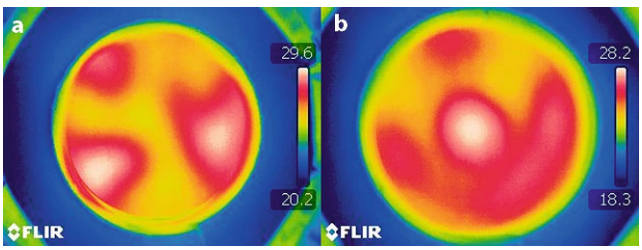

Fig. 2 OP 40. Thermal image of phantom section after heating test @ 490 MHz, comparison of uncalibrated **(a)** vs self-calibrated **(b)**

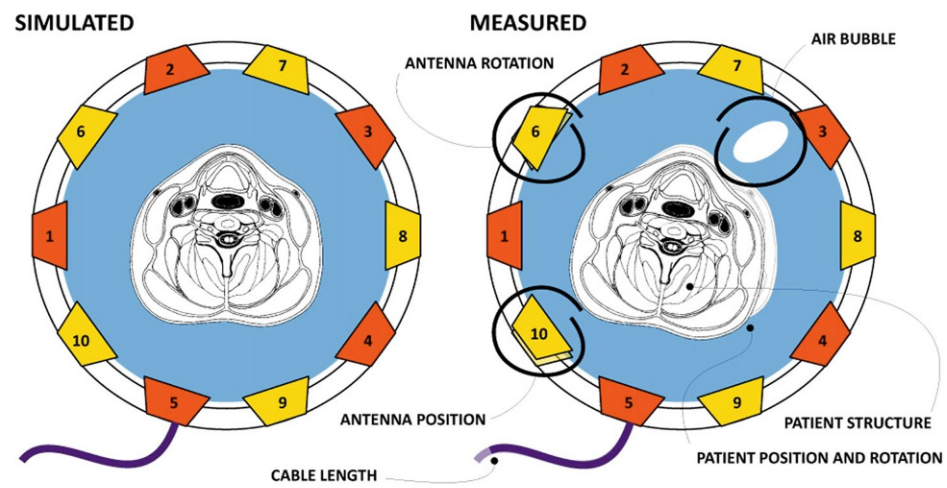

Fig. 1 OP 40. Illustration of considered possible mismatches

Abstracts of ePoster presentations

Best poster „Flash“ presentation

P 02

CHIPOR (Hyperthermic Intraperitoneal Chemotherapy [HIPEC]) – A promising treatment for relapsed intraperitoneal ovarian cancer. Chipor an ongoing phase III, European multicentric randomized trial. Unicancer – FEDEGYN 02

J.-M. Classe[1], **I. Jaffré**[1], C. Ioic[1], P. Meeus[2], E. Leblanc[3], G. Houvenaeghel[4], S. Gouy[5], F. Marchal[6], F. Lecuru[7], M. Pocard[8], F. Guyon[9], S. Durand Fontainer[10], J. J. Torrent[11], C. Jouffroy[12], G. Ferron[13], O. Glehen[14]

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This prospective multicentric international randomized phase III trial compares SCS with or without HIPEC (cisplatinum, 75 mg/m², 42 °C for 1 h), after at least 6 cycles of second-line platinum based chemotherapy. Patients are randomized during surgery, if the resection is complete. The primary objective is to improve OS by one year, which requires 222 patients be included in each group (with and without HIPEC). A pharmacokinetic study will evaluate the absorption of cisplatin from the peritoneal cavity to the systemic compartment, as well as, the cisplatin plasma exposure, allowing the first comparison of open to closed HIPEC techniques.
Main objective: To assess overall survival of patients treated with HIPEC. The study is based on the hypothesis that HIPEC provides an improvement of OS of 12 months.
Secondary objectives: Relapse-free survival, quality of life (QLQ-C30 and FACT-O) and pain, treatment related toxicities, including renal toxicities and morbidity.

Medico-economic study: collection of socio-demographic data and patient-related management costs.

Pharmaco-kinetics study
Main inclusion criteria: • Previous treatment for epithelial ovarian cancer • Patient with intraperitoneal relapse (more than 6 months after the end of the initial treatment), resectable without distant metastasis (except pleura effusion, sensitive to platine-based second line chemotherapy and resectable lymph-nodes in the groin or retro peritoneal) • Second-line platinum-based pre-operatory chemotherapy: carboplatin-paclitaxel or carboplatin-caelix (pegylated liposomal doxorubicine: with gemcitabine, trabectidine, hycamtin authorized) • Complete cytoreductive surgery • Delay between the last cycle of second-line chemotherapy and surgery must be between 5 and 12 weeks •P erformance Status WHO < 2
Main non-inclusion criteria: • Previous cancer in the last 5 years • Known hypersensitivity to cisplatin, • Metastasis, • Use of anti-angiogenic treatment (within the 8 weeks before surgery), • More than 2 segmental digestive resections concomitant to HIPEC is foreseen, • Any progressive disease during the second-line chemotherapy (platinum-based), • Relapse occurring less than 6 months after the end of the initial treatment, •N on-epithelial ovarian tumor, •Patient who has already been treated by HIPEC for ovarian cancer
Initiated sites: France (26 sites), Spain (1 site) Belgium (1 site), Canada to be initiated in 2018
Inclusions: 292 (January 2018)

P 03

Ultrasound-induced hyperthermia – radiosensitization in glioblastoma, prostate and head and neck cancer – preliminary studies

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Introduction: Hyperthermia treatment (HT) has been reported to sensitize cancer cells to chemotherapy and radiation therapy (RT), both *in vitro* and *in vivo*. Ultrasound (US) is able to generate HT in tissue precisely and noninvasively while temperature is controlled via MR imaging methods. In this study, we investigated the effects of US-HT *in vitro* to increase radio-sensitivity of human glioblastoma (T98G), prostate (PC-3), and head and neck cancer cell lines (FaDu and UTSCC-5).
Methods: We have developed a high throughput *in vitro* US therapy system for sonication of 96 well µ-clear plates (Greiner Bio-One GmbH) possessing 96 individual piezoelectric transducers delivering acoustic energy to the individual wells by means of acoustic dry coupling (frequency: 1 MHz; intensity: 0.75 W/cm2). US-HT (40–45 °C) was generated for 20 min. As a control, thermoblock HT was performed. Real-time temperature was monitored by an infrared thermal camera (PI450, Optris GmbH). Cells were irradiated 15 or 60 min post HT treatment with a 150 kV X-Ray device (DARPAC 150-MC) for RT at dose of 10 Gy. Cellular metabolism (WST-1 assay), newly synthesized DNA (BrdU assay) and DNA double-strand breaks (gH2A.X assay) were evaluated post treatment.
Results: Metabolic activity (NAD(P)H) decreased in US-HT group for all investigated cell lines (T98G: 72%, FaDu: 10%, UTSCC-5: 12.5%), revealing a higher efficiency of US-HT, compared to control HT group (T98G: 80%, FaDu: 79%, UTSCC-5: 96.5%). There was a greater reduction in NAD(P)H levels in T98G cells when RT was performed 15 min post HT(47% viable cells) compared to 60 min post HT (58% viable cells).
Conclusion: Our preliminary data suggest that US-HT-RT had a greater treatment effect in all tested cell lines compared to thermoblock-HT-RT. This may be due to the additional biomechanical effects of US. The shorter time interval between HT and RT was also the most effective. Future studies will investigate the mechanisms of the combined treatment.

P 04

U-251 human glioblastoma cell line model to study hyperthermia as radiosensitizer

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Introduction: The Glioblastoma multiforme (GBM) is the most aggressive brain tumor with poor survival despite the many therapeutic strategies explored.

Conventional radiotherapy remains the main treatment for GBM, but several clinical trials performed in the last decade suggest that hadrontherapy, especially with carbon ions, could be particularly promising.

Hyperthermia (HT) has been considered to be the most powerful way of sensitizing ionizing radiation, and the hypothesis that hyperthermia coupled with proton (PT) irradiation could mimic 12 C-ion therapy is currently investigated.

Objectives: To evaluate the *in vitro* combined effects of HT coupled with different qualities of ionizing radiation (X-rays and protons) on the tumourigenic U-251MG human GBM cell line. Purpose is to define the determinants of radiosensitivity and to assess the optimal thermal dose and treatment sequence for planning the ensuing *in vivo* investigations in a xenogenic mouse model.

Materials and methods: U-251 MG cells are being investigated for their radiosensitivity to X-rays and PT (in the range 1–8 Gy) and thermosensitivity (in the range 42–45 °C, 15–60 minutes) by means of clonogenic assay (either survival or delayed survival assay), cell-viability assay (MTT), apoptosis induction, cell-cycle analysis, micronucleus assay. A digital thermostatic bath was used for HT exposure; temperature was strictly monitored in dummy samples throughout the experiments.

Results: U-251 MG cells displayed radioresistance, as demonstrated by the large shoulder on the survival curves, while they showed a good HT response (45.5% ± 2.1% surviving fraction after HT at 42.8 ± 0.1 °C for 60 min). The combined treatment X-rays and HT showed a large thermal radiosensitization in the shoulder region not dependent on the treatment sequence. Experiments with PT combined with HT are in progress.

Conclusion: The achieved results are encouraging and show that HT could represent a promising approach to improve the response of GBM to radiation treatment.

Ultimate goal is to define the optimal treatment protocol for HT-PT combination to be used with the *in vivo* U-251 MG mouse model.

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P 05

Contraindication for radiative deep regional hyperthermia for patients with large carbon implants

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Introduction: Hyperthermia with radiative heating to temperatures of 41–43 °C has shown to be a valuable sensitizer for radiation- and chemo-therapy in cancer treatment. In this study the influence on specific absorption rate (SAR) and temperature by carbon fiber reinforced polyether-ether-ketone (CFR-PEEK) implants which are used to replace titanium (TI) implants was investigated.

Methods: The influence on SAR and temperature was investigated in three rods with identical diameter of 5.5 mm and length of 140 mm. The rods were made of a TI, CFR-PEEK and PEEK of which the TI and the CFR-PEEK are commercially available products for trauma and reconstructive surgery provided by icotec AG, Altstätten, Switzerland. For the SAR measurements the samples were placed inside an elliptic phantom filled with saline inserted in the SigmaEye applicator of the BSD-2000 3D deep hyperthermia equipment (Pyrexar Medical, Salt Lake City, USA). Inside the tube, a SAR probe (EASY4/MRI, SPEAG, Zürich, Switzerland) was moved along the samples and the relative SAR strength was recorded. For the temperature measurements, the samples were placed in a tissue equivalent gel phantom inside the SigmaEye applicator. The temperature rise following a power pulse of 1000 W for 5 minutes (pulse#1) was measured.

Results: The SAR measurements parallel to the axis of the rods showed a clear increase of maximum relative SAR strength for both TI and CFR-PEEK but no increase for the PP and PEEK material. Relative SAR increased by 329% for TI and 297% for CFR-PEEK at the tips of the rod. Temperature measurements in the gel phantom showed a similar behavior with a maximum temperature rise at the tips of the rod up to 27 °C for both TI and CFR-PEEK and 3 °C for PEEK after pulse#1 (Fig. 1).

Conclusion: TI and CFR-PEEK show a similar influence on SAR and temperature in a deep hyperthermia treatment set-up. Thus CFR-PEEK implants, like metal implants, must be a contraindication for radiative deep hyperthermia treatment.

P 06

Dual mode microwave ablation applicator

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Objectives: Microwave ablation (MWA) gains interest in the last decades as alternative treatment option for cancer patients with unresectable hepatic tumors. A further enhancement of this technology is proposed by a dual mode applicator for thermal ablation treatment with sensing capabilities designed to operate under MRI guidance with an operational frequency of 10 GHz.

Methods: The additional sensing mode provides additional information for the interventional radiologist to achieve a more accurate localization of the targeted tumor and reduced number of insertions. It

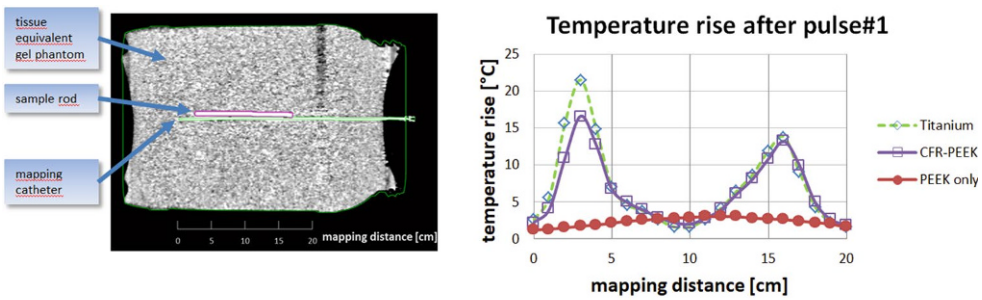

Fig. 1 **P 05.** CT image of the gel phantom with mapping catheter (*green*) and sample (*red*) inside

is realized by analyzing the reflection coefficient of the applicator that reveals information about the surrounding tissue around the tip of the applicator. Hence, an accurate positioning becomes possible by evaluating local permittivity changes of 15%–30% indicating the presence of tumors. Once a tumor is detected, the applicator can be switched from low power operation for diagnostics to the high power treatment mode and the input power is increased to perform thermal ablation.
Results: Measurements of the dual-mode device with phantoms mimicking a dieletric contrast between healthy and malignant tissue reveal a minimum relative resolution of 3.4% that exceeds the required resolution in order to detect tumorous tissue. Moreover, temperature measurements of the applicator inserted into ex-vivo bovine liver tissue show a rapid temperature increase of the tissue close to the applicator of 130 °C after 4 minutes with a continuous wave input power of 20 W. The resulting lesion zone size is 2 cm^2.
Conclusion: The dual mode concept presents an advanced technology for MWA tools with the advantage of providing information of the tissue state at the applicator that can be combined with MRI guidance to improve the positioning procedure during the intervention. Moreover, less power and treatment time is needed to achieve therapeutic temperatures due to the high frequency of operation.

P 07

Fast clinically feasible MR sequences to map electrical tissue conductivity for improved accuracy in hyperthermia treatment planning (HTP)

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Objectives: Patient-specific electrical properties can be measured by MR-Electrical Property Tomography (EPT) [1,2]. EPT-based conductivity σ values are essential for hyperthermia treatment planning (HTP)[1]. A transceive phase ($\Phi^{\pm}$) map must be acquired to reconstruct σ. Normally, a spin-echo (SE) is used. We evaluated faster alternatives for $\Phi^{\pm}$ and σ mapping: bSSFP [3] and PLANET [4].
Methods: MR measurements (3 T, Philips Ingenia, NL) were performed on a phantom and on a healthy volunteer's brain with the body coil for transmission, and a 15-channel receive head coil. Each technique was run with 5 different resolutions. *Table 1* summarizes phantom properties and imaging parameters of SE, PLANET and bSSFP.

The precision of the measured $\Phi^{\pm}$ was assessed by fitting a 2D parabola to the inner compartment [5]. The RMSE was associated with $\Phi^{\pm}$ uncertainty, $\Delta\Phi^{\pm}$. This uncertainty was multiplied by the measurement time to derive the sequence efficiency. Finally, σ was reconstructed based on each technique by using *phase-only EPT* and transceive phase assumption [3].
Results: With respect to $\Phi^{\pm}$, bSSFP was the most precise (*Fig. 1a*) and efficient technique (*Fig. 1b*). Its efficiency out-performed PLANET with factor 8, and SE with factor 20–34 at 1.5–3.75 mm, respectively. The σ-standard deviations in *Fig. 1c* confirmed the $\Delta\Phi^{\pm}$-trends shown in *Fig. 1a*.

The brain MRI was done at 2.5 mm resolution, where all techniques have comparable $\Delta\Phi^{\pm}$. The bSSFP $\Phi^{\pm}$-map was mildly corrupted by local field variations, that were amplified during σ reconstruction. PLANET and SE had similar σ-maps, but PLANET was faster.
Conclusion: PLANET intrinsically corrects for local field variations corrupting bSSFP, is precise and has clinically feasible scan times. Thus, PLANET seems a good candidate for brain σ_{EPT} and could replace SE in the HTP imaging protocol.

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Sequence / Parameters	SE					PLANET					bSSFP				
FOV (mm)	240 x 240 x 60					240 x 240 x 60					240 x 240 x 60				
Imaging mode	2D Multi-slice					3D					3D				
Phase-cycling scheme	N.A.					bSSFP with 8 cycles, phase increment = 45°					N.A.				
Imaging flip angle (°)	90					25					25				
Resolution (mm)	**1.5**	**1.88**	**2.5**	**3**	**3.75**	**1.5**	**1.88**	**2.5**	**3**	**3.75**	**1.5**	**1.88**	**2.5**	**3**	**3.75**
TE (ms)	5.2	5.2	5.2	5.2	5.2	2.7	2.4	2.33	2.33	2.33	2.7	2.4	2.33	2.33	2.33
TR (ms)	1200	1200	1200	1200	1200	5.4	4.8	4.7	4.7	4.7	5.4	4.8	4.7	4.7	4.7
BW (Hz/pixel)	1100.4	1097.2	1094.1	1096.5	1094.1	287.2	359	340	337.1	339.7	287.2	359	340	337.1	339.7
Scan duration (min:sec)	13:02	10:28	7:56	6:38	5:22	8:58	5:00	2:04	2:04	1:16	1:07	00:38	00:22	00:16	00:10

PHANTOM	*NaCl (g/L)*	*ε (a.u.)*	*σ (S/m)*	*T_1 (ms)*	*T_2 (ms)*
Inner compartment	6.22	80	1	2490.5	88.9
Outer compartment	12.85	80	2	2759.4	67.4

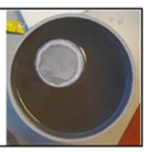

Fig. 1 P 07. Sequence settings and phantom characteristics, „Scan duration" is the time needed to perform both acquistitions (positive/negative readout gradient polarities) to obtain eddy-current-free transceiver phase maps. Regarding phantom composition, the amoung of salt to be diluted in water to get the desired conductivity values was calculated with Stogryn's equation. T1 and T2 values were average values taken from T1 and T2 maps measured with the vendor-specific mix-TSE sequence

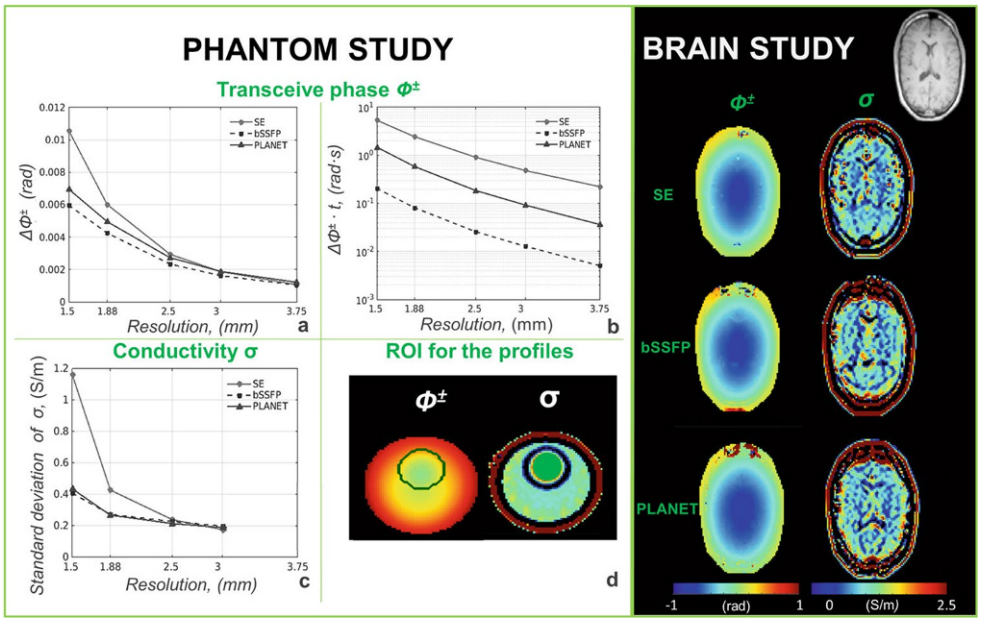

Fig. 2 P07. Phantom and brain studies. For the phantom study each technique was evaluated at 5 different resolutions with respect to: (**a**) its uncertainty in the transceive phase Δϕ±; (**b**) its efficiency factor Δϕ± – t; (**c**) the standard deviation of its conductivity; (**d**) manually-delineated ROI inside the inner compartment (**d**, *green circle*) where Δϕ± and σ-SD were calculated. Note that a sequence performs best when the efficiency factor is low, i.e. fast acquisition time (t) and low Δϕ±. In (**c**) in the number of voxels in the ROI at resolutions>3 mm was insufficient to compute σ-SD values. For brain study, maps for the ϕ± and σ are shown for all the techniques at 2,5 mm resolution

P 08

Fast and efficient generation of patient models for hyperthermia based on radiation therapy contours

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Introduction: Realistic region-based voxelfield models are needed for electromagnetic or thermal simulations. Tumor and organs-at-risk delineation should ideally be performed by experienced physicians. Creation of such models using special voxel-based segmentation editors is time consuming and often inaccurate. On the other hand, accurate and fast contouring state-of-the art platforms are widely-used for radiation therapy. However, the contours are coded by polygonal chains and not as segmented voxelfield data.

Objectives: To create a fast algorithm to convert the standard output based on polygonal chains into a voxelfield data.

Methods: Computed Tomography (CT)-scans were generated and clinical contouring was performed using the standard Varian Treatment Planning System (Eclipse Version 11.0). Open Source platforms "Plastimatch" (www.plastimatch.org) and Octave (www.gnu.org/software/octave/) as well as Matlab 4.2016b were used.

Results: A novel procedure was developed that consists of three main steps (steps → A/B/C marked by *blue/green/purple* colors, resp., in Fig. 1): → A: Contouring in Eclipse; contours (in Fig. 1 *1*, 2, *italic*) coded in a DICOM-RT structure set file. Deciding which overlapping regions can be later overwritten by others ("Ranking info"). If parts of regions cannot be overwritten, non-overlapping sub-regions are created. → B: Plastimatch reads out the DICOM-RT file and writes it in a CTX format, sorting the data as polygonal chains structure by structure. → C. A self-writ-

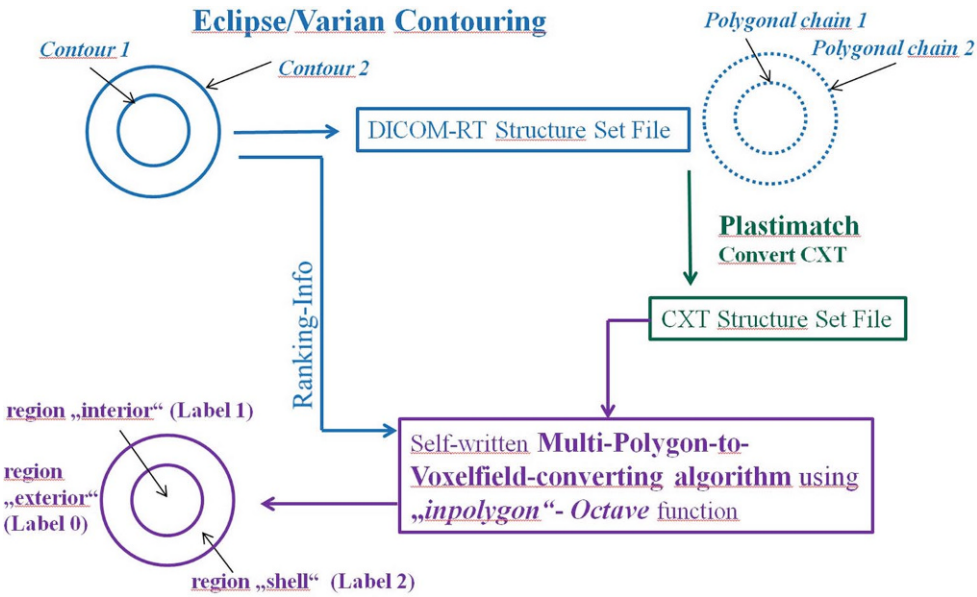

Fig. 1 P08. Multi-Polygon-to-Voxelfield-converting procedure (a simplified example of two structures)

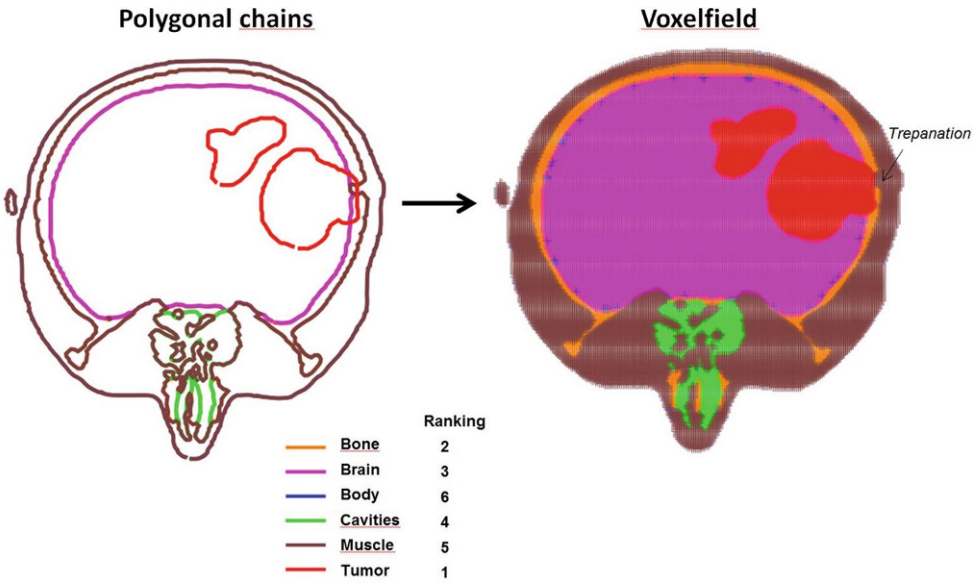

Fig. 2 **P 08**. Multi-Polygon-to-Voxelfield-procedure for a glioblastoma multiforme. Due to ranking, structures may overwrite others if their contours overlap (e. g. at the trepanation tumor structure [rank 1] overwrites bone/skull [rank 2])

ten Octave algorithm reads the CTX file and converts the contours into region-labelled voxelfield data (see also Fig. 2). Especially, it recognizes polygonal chains describing "holes" in regions. A Matlab algorithm performs a sub-region segmentation using Hounsfield unit thresholds, thus making the voxel model an optimal "mixture" of clinically contoured organs/regions and threshold-based segmented subregions.

Conclusion: A procedure for fast and efficient generation of voxel models for a standard radiation therapy contouring platform was developed. No time-consuming additional segmentation in voxel-based editors is needed.

P 09

SAR profiles generated with a capacitive hyperthermia system in a porcine phantom

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Introduction: Capacitive hyperthermia systems are widely used to enhance effects of radiation therapy or chemotherapy, however, less is known regarding their penetration depth in order to assess the effectiveness for superficial and intermediate deep-seated lesions.

Objectives: To measure specific absorption rate (SAR) profiles in homogeneous phantoms using a capacitive system and compare with an analytical solution for an incident transverse plane wave.

Methods: Using two different porcine phantoms with different cross-section thickness (10 cm, 14 cm) we registered SAR-values in various horizontally and vertically distributed points by determination of the temperature rise curves. Heating was applied by use of the Celsius42 TCS system (13,56 MHz) with a forward power of 100 W (diameter of both electrodes 25 cm). SAR-values were compared with calculated SAR profiles (by solving Maxwell'sequations for an ideal transverse plane wave penetrating a homogenous lossy medium for different frequencies) (Fig. 2).

Results: SAR profiles showed a 50% SAR reduction in a depth of 2.8–3.3 cm compared to the SAR measured on the phantoms surface in two different porcine phantoms (Fig. 1). Calculation of the penetration of an ideal transverse plane wave in the frequency range comparable to that used by local microwave applicators (433–200 MHz) results in a 50% SAR depth of only 0.3–0.7 cm. Clearly, for lower frequencies the plane wave solution improves as well (4.5 cm for 30 MHz). However, in this frequency range radiating applicators have unpractical large dimensions (Fig. 2). Therfore, adequate heating of lesions in a depth of several cm (with half SAR in 3 cm and still ¼ of SAR in 6 cm depth) seems to be better accessible by capacitive systems. On the other hand, inhomogeneity might severely disturb the pattern using the capacitive tchnology, possibly more than for microwave or radiowave applicators.

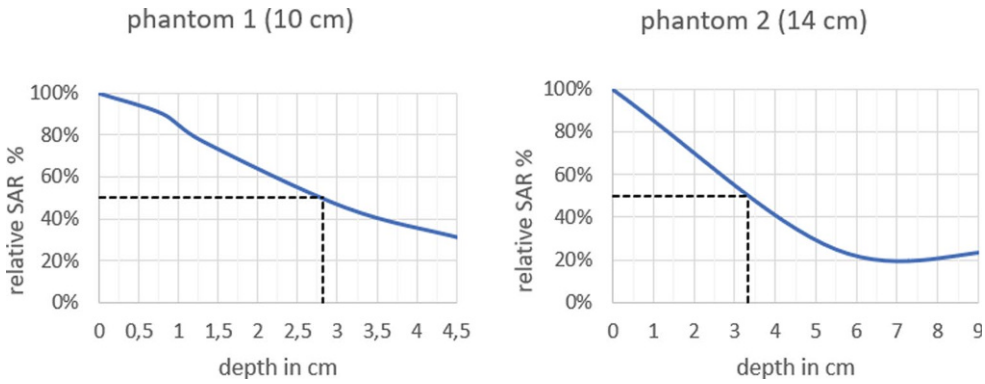

Fig. 1 **P 09.** Measured relative SAR depth profiles in two different porcine phantoms, Celsius42 TCS capacitive applicator, 13,56 MHz, 100 W forward power

Frequency [MHz]	$d_{1/2}$ [cm]	λ [cm]
433	0.3	4.7
200	0.7	10.3
100	1.4	20.3
70	1.9	28.9
50	2.7	40.4
30	4.5	66.1

Fig. 2 P09. Wave length λ and calculated SAR 50 % depth d1/2 (half value of incident power) for a plane wave at a given frequency (MHz) in a medium with σ = 0.55 S/m and εr = 80, d1/2 = 0,346/α, λ = 2π/β

Conclusion: The SAR-distribution in a homogeneous phantom using a capacitive system appears to be suitable for superficial and intermediate deep-seated tumors.

P 10

Temperature shift measurement technique of high-frequency hyperthermia sessions in heterogeneous brain dummy with high grade tumor

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Introduction: Nowadays promising way to improve the survival of patients with brain cancer is to overcome the radio-resistance of high grade tumors. According to the modern point of view, hyperthermia (HT) is the universal and most effective radio- and chemo- modifier [1, 2]. Taking into account firstly the negative consequence of the healthy brain tissue overheating and secondly the positive effect of tumor heating it is necessary to control the temperature distribution in brain during the HT session [1]. The invasive measurement techniques are not applicable in this case because of the high risk of complications. Another approach is magnetic resonance thermometry is time-consuming and very expensive. One of the most promising ways is to use a dummy with a "volume process" including a simulation of high grade tumor and healthy brain tissue.
Objectives: Present work was dedicated to heterogeneous brain dummy creation including healthy tissue, cerebrospinal fluid and viable high grade tumor. This dummy is suitable for thermometric measurements of HT sessions of post-operative brain tumor treatment in combination with radiation therapy.
Materials and methods: The Celsius TCS system for local HT was used for treatment delivery. This system for high-frequency HT uses electromagnetic fields and is based on the principle of capacitative coupling [2]. For the purposes of this research, a heterogeneous dummy simulating the real electrical properties of healthy brain tissues, cerebrospinal fluid and high grade tumor was created. For skull creation a fused deposition method was used. Temperature shift measurements were carried out according to the HT recommendations for brain tumors treatment on Celsius TCS system. The online temperature monitoring was carried out by 4-channel measurement device TempSens (Canada) [2].
Results: Performed experiments show that the maximum temperature increase for the areas corresponding to the healthy brain tissue and cerebrospinal fluid were not significantly different and equal to 8 °C. The temperature increase was 10 °C for the high grade tumor dummy.
Conclusion: The obtained results shows that proposed approach for temperature distribution measurements using developed brain dummy is very promising for estimation of efficiency and safety of the high-frequency HT sessions.

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P 11

3D-electric field and SAR distributions of two hyperthermia applicators – single-spiral antenna (SA-115) and multi-dipole antenna-pairs (Sigma-60)

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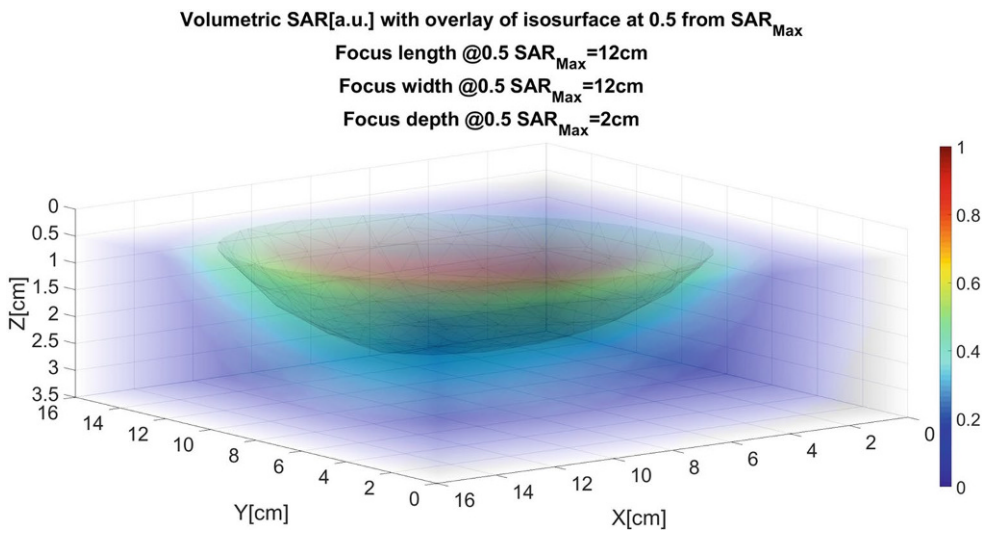

Fig. 1 P11. Volumetric SAR distribution of SA-115

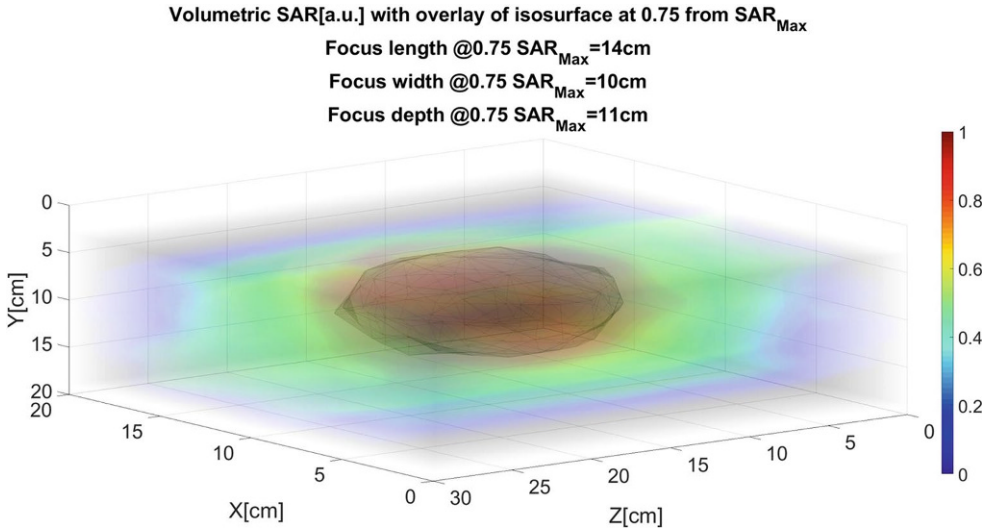

Fig. 2 **P 11.** Volumetric SAR distribution of Sigma-60

Introduction: Loco-regional hyperthermia treatments are applied in our clinic since many years as additional therapeutic modality to radio-chemotherapy. Local hyperthermia is performed with an external applicator, such as spiral antenna SA-115 and regional hyperthermia is performed with a multi-dipole antenna-pairs applicator, such as Sigma-60 (BSD Medical Corp. currently Pyrexar Medical, Salt Lake City USA).
Objectives: As a need of technical aspect of quality assurance in hyperthermia oncology, our objective is to evaluate characteristic parameters of current hyperthermia applicators, predicting possible malfunctions and optimizing a hyperthermia treatment. Knowledge of electric field (E-Field) and specific absorption rate (SAR) distributions in homogeneous phantoms can be used for characterization, improvement and development of hyperthermia applicators.
Materials and methods: A customized electromagnetic field measurement system developed by Kapteos Company (Sainte-Helene du Lac, France) is used to measure the three electric field components (*Ex, Ey, Ez*) of the electric field vector, |E|. The spiral antenna applicator (SA-115) is operated with a power of 100 W at 115 MHz frequency. The Sigma-60 applicator is operated with a power of 300 W at 90 MHz frequency with target [0, 0] without any offset settings of amplitude and/or phase of the dipole-antenna pairs.
Results: Volumetric SAR distribution with an overlay of the isosurface at 0.5 of the SAR max. reveals an effective field size with 12 cm along *x*-axis and 12 cm along *y*-axis, and an effective penetration depth of 3.5 cm below the SA-115 applicator surface.Volumetric SAR distribution of Sigma-60 applicator with an overlay of the isosurface at 0.75 of the SAR max. shows a cylindrical heating volume with 14 cm along *z*-axis, 10 cm along *x*-axis and 11 cm along the *y*-axis.
Conclusion: Both hyperthermia applicators demonstrate the ability to generate heating patterns that are in good agreement with physical reasoning based on the assumed electromagnetic behaviour of the two hyperthermia applicators. The 3D E-field measurements provide important visualization of electric field focus and SAR pattern produced in a phantom similar to patient body geometry and dielectric constants. This work was supported by the AKF-Program from the Medical Faculty of Eberhard-Karls University Tübingen under Grant No. [305-0-0].

Self study ePosters

P 12

14 years fever-range whole body hyperthermia in adjuvant recurrence prophylaxis of breast cancer

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Introduction: In the concept of biological cancer therapy fever range whole body hyperthermia (wbh) plays an important role, but mostly in palliative situation. In the early adjuvant setting, there are only few data.
Objectives: Since 2002 a group of patients is observed, that was treated adjuvant at mostly moderate or high risk constellation after R0 resection with at least two fever range wbh and complementary based therapies. The presentation gives an overview on the immunological importance of fever (e. g. rare in cancer patients, spontaneous remissions after fever), research on hyperthermia-induced tumor perfusion, changes of immunological effector cells (NK cells, dendritic cells, tumor-infiltrating cells) and HSP production. Can tumor patients profit from wbh series in an adjuvant setting concerning tumor survival?
Patients and methods: The largest group are women after breast cancer surgery, $n=50$. With a few exceptions, the patients had moderate to high relapse risk. Some patients had previously rejected conventional adjuvant therapies. In a single arm, prospective monocentric study they recevied a number of 2–20 wbh up to 40 °C after surgery and adjuvant conventional treatments. Every 24 months the study population is evaluated for disease free and overall survival.
Results: A recent (9-2016) evaluation in the recurrence prophylaxis shows a 5-year tumor free survival of >90% (29/32) and an overall survival of >96% (31/32). Only 1/32 patients died 7.7 years after FD of breast cancer. The data are discussed in the context of the risk constellation, frequency of hyperthermia and time after primary diagnosis. Statistically, after complete conventional therapy alone, <70% 5-year tumor free survival and an overall survival of <75% would have been expected.
Conclusion: In the tumor follow up this approach of complementary basic therapy in combination with fever range wbh should be more appreciated and evaluated.

P 13

Secondary and tertiary recurrence prevention with fever range whole-body hyperthermia in (metastatic) malignant melanoma

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Introduction: In the concept of biological cancer therapy fever range whole body hyperthermia (wbh) plays an important role, but mostly in palliative situation. In the early adjuvant setting, there are only few data.
Objectives: Can Malignant Melanoma patients after R0 resection profit from at least two or more wbh series in an adjuvant setting concerning tumor survival? Do they have a second chance after treatment of first metastases (tertiary)?
Patients and methods: I reporte about three patients after primary malignat melanoma surgery with high reccurence risk according to their sentinel lymph node status and/or Clark level (2×Clark Level IV and Sentinel LK pos., 1×Clark Level IV-V, N0). In a single arm, prospective monocentric study the three patients recevied a number of 2–20 wbh up to 40 °C after surgery without other adjuvant conventional treatments. Every 24 months the study population is evaluated for disease free and overall survival. Then I reporte about a now 51-year-old patient who was operated 2/13, tumor formula pT4b, pN2a, stage IV (AJCC 2009). Already 8/13 evidence of a singular brain metastasis on the right parietal and 9/13 1×therapy with radiosurgery (cyber knife 20 Gy). Decision to carry out fever range wbh (9/13-2/15 9x) and other complementary therapies. In questionable evidence of pulmonary metastasis in PET-CT 9/13 only slow progress and in 3/15 lung partial resection with histological confirmation of an MM metastasis. Since then, further fever range wbh (4/15–10/17 9x).
Results: The three patients from the adjuvant group treated with fever range wbh are still alive with NED since FD for already 92, 77 and 61 months. The patient with tertiary recurrence prevention shows actually NED: 11/17 MR brain and 12/17 S-100 (0.028 µg/l), PET-CT and lymph nodes ultrasound, 1/18 clinically. So, he has now a tumor free survival since lung surgery of 34 months!
Conclusion: Adjuvant wbh should be evaluated in MM patients, even after metastases surgery.

P 14

Molecular profiling based metronomic therapy with local hyperthermia in treatment of relapsed refractory infantile fibrosarcoma – case report

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Object: The case report aims to demonstrate clinical benefit of precision medicine approach in situation when standard therapeutic options are exhausted.
Material and methods: To determine potentially effective chemotherapeutic agent for the 3-year-old girl with infantile fibrosarcoma of right mandibular branch after anti-relapse chemotherapy, molecular profiling of progressive/relapsed tumor sample was performed. Biomarkers PGP, ERCC1, TOP2A, TS were assessed. Chemo-, immune- and antiangiogenic therapies were administered in metronomic mode during sessions of local hyperthermia (HT). Heating of tumor site was provided by Celsius TCS device. Sessions of local HT with gradually increasing of thermal dose were performed three times per week. Doxorubicin 10 mg or Carboplatine 150 mg, Bevacizumab 100 mg, IL-2 1 million IU per week were given intravenously.
Results: Course of metronomic therapy included three weeks. Three courses were performed with 2–3 month interruptions. The treatment was well tolerated, grade 1 according CTCAE. Checks up were carried out in 3, 6 and 12 months after start of treatment. CT scan demonstrated stable disease during 1 year.
Conclusion: The case report presents meaningful clinical benefit of chemo-, immune- and antiangiogenic therapies combination with local hyperthermia. Molecular profiling provides reasonable choice of chemotherapeutic agents. Hyperthermia augments cytostatic effect and blocks resistance mechanism. Metronomic mode of therapy allows to avoid adverse event without therapeutic effect loss.

P 15

Clonogenic survival as well as motility of malignant cells is reduced by hyperthermia alone or in combination with irradiation

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Objectives: Reliable experimental data on the efficacy of hyperthermia in cancer therapy are scarce and inconsistent. We have therefore examined the effects of hyperthermia alone and in combination with photon irradiation on the clonogenic survival and motility of cultured breast cancer and glioblastoma cells.
Material and methods: The experiments were performed on MDA-MB 231 (breast cancer) and U251 (glioblastoma) cells. For hyperther-

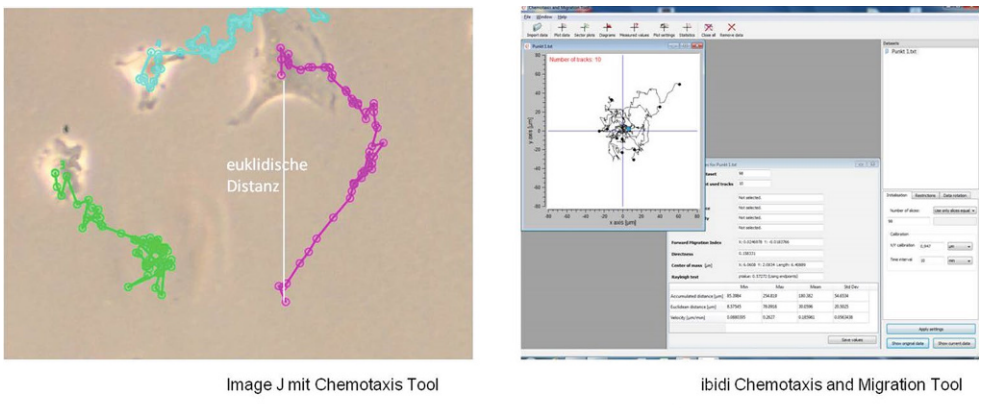

Fig. 1 **P 15.** Motility parameters: total traveled distance, speed, Euclidean distance

mia the cells were incubated for 1 h at 39–42 °C either one time or at five consecutive days. The clonogenic survival was tested in a colony formation assay. The cells were irradiated with photons at 5 Gy/min. The motility of the cells was examined by time-laps videography.
Results: After one-time hyperthermia the clonogenic survival was increasingly reduced with increasing temperature. A maximal reduction for MDA 231 at 40 °C and at 41 °C. The motility of U251 cells was increased significantly after irradiation with 2 Gy. This increase could by totally impeded by hyperthermic treatment following irradiation. After irradiation the accumulated distance was enhanced by 17%, The Euclidean distance by 24%. Additional hyperthermia reduced the values by 13% and by 35% relative to the untreated baseline. With respect to the enhanced value after irradiation the reduction was 48%.
Conclusions: Hyperthermia might counteract recurrences since the hyperthermic treatment decreases the clonogenic survival as well as the motility of malignant cells and is able to suppress the irradiation-induced increase of the cellular migration.

P 16

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

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Objectives: Still capacitative hyperthermia is regarded by some experts as not capable of achieving sufficient temperature rise in the depth of a body. On the other side this heating technology is wide spread in numbers among clinicians. It will be to show that if application is correctly operated sufficient temperatures in the range of effective temperature can and will be reached.
Methods: Temperature measurements by invasive and minimal invasive temperature sensors attached to the tip of a flexible fibre optical cable. Accuracy +/– 0,3 degree Celsius as total system accuracy.
Results: Measured temperature in vivo in depth of the body do range from 39 to 46 degree Celsius. Applied technology and adjusted operating procedures determine the desired effect and are able to overcome the limiting factor of patient tolerance to the impact of higher powers.

Temperature rises/SAR of 1 degree Celsius per 5 minutes/10–12 degree Celsius in 60 minutes can be met.
Conclusion: Capacitative Hyperthermia at 13,56 Mhz as a technology is principally capable of "doing the job". As with all technology it depends in detail on its engineering and on part of the users on its operational handling.

P 17

The Moscow-Berlin hyperthermia treatment planning system

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Introduction: A hyperthermia treatment planning system has been developed that can read a patient model directly from the patient's computed tomography (CT) scans, simulate the treatment on one of several different deep-heating applicators, and then display the results.

Objectives: The purpose of this project is a hyperthermia treatment planning system with the following characteristics:

- The patient model is developed directly from the patient's CT scans.
- The patient"s treatment can be simulated on different applicators, including the Sigma 60, the Sigma 30, and the Sigma Eye.
- The results of the simulations are easily accessible.
- The simulation procedure can be carried out by clinical personnel.

Methods: All of the programs are written in Python, a computer program that has its own graphics and is available free of charge [1]. The EM simulations are carried out using the FDTD method [2].
Results: An example of the model of a patient in a Sigma 60 is shown in Abb. 1. The resulting specific absorption rate (SAR) distribution is shown in Abb. 2. The power focus of the quadrants can be changed and the operator can view different levels in the patient model very easily.
Conclusion: All of the simulations described in this abstract, including the accompanying graphics, were done on a Lenova 71015 laptop computer using the Python programming language.

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1. van Rossum G (1993) An introduction to Python for UNIX/C programers, Proceedings of the NLUUG (Dutch UNIX users group)
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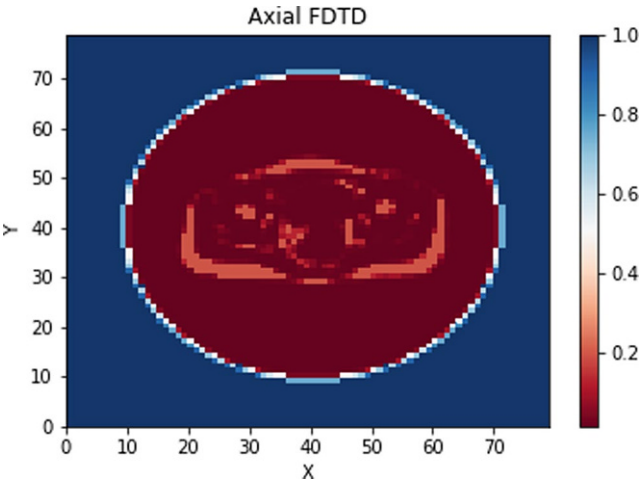

Fig. 1 P 17. Applicator and patient model

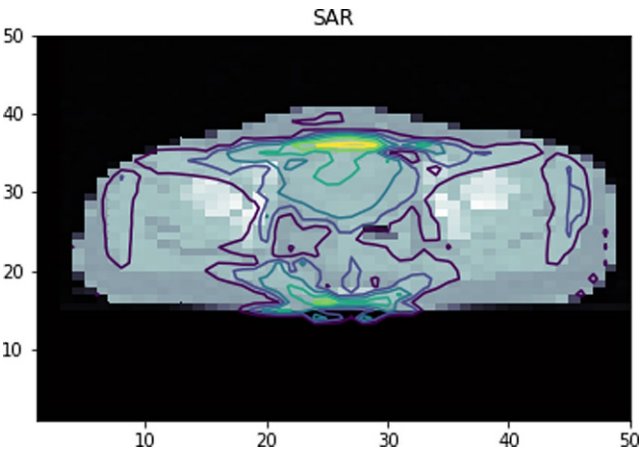

Fig. 2 P 17. The SAR distribution

P 18

The agarose cup – A new tool for *ex vivo* cultivation of skin microbiopsies to assess effects of hyperthermia

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Introduction: In clinical settings the combination of hyperthermia and irradiation is established as a powerful treatment for several tumor entities. Mild hyperthermia in the range of 42 °C has been shown to cause radio-sensitization of cancer cells. Yet the potential damaging effects on normal tissue have rarely been investigated.
Objectives: The skin is affected by hyperthermia and radiotherapy. Experiments designed to study the combinatorial effects of hyperthermia and irradiation are mainly based on the use of cell lines or animal models. The objective of this study was to establish a method for efficient *ex vivo* cultivation of small skin biopsies and to demonstrate their utility in a wound healing assay for treatment with hyperthermia and subsequent irradiation.
Material and methods: Abdominal skin samples of 0.5 × 1 mm were obtained from healthy volunteers by punch biopsies. These were treated with a single dose of hyperthermia +/– irradiation. Subsequently, samples were covered with agarose cups for immobilization. The agarose cup enhances the contact between the tissue specimen and the growth substrate, thus supporting the outgrowth of keratinocytes as a wound healing assay. Moreover, agarose allows visualization and medium supply of the explants. Keratinocyte outgrowth was quantified after histochemical staining and by measurement of the area covered by the cells.
Results: The use of agarose cups for *ex vivo* cultivation of skin microbiopsies resulted in a 100% take rate for untreated samples. The explants were cultivated for two to three weeks and yielded an average keratinocyte layer > 100 mm^2. Hyperthermia at 42 °C for 1 hour did not significantly affect keratinocyte growth. Irradiation with 4 or 6 Gy reduced keratinocyte growth dose-dependently. The combination of hyperthermia and irradiation did not result in enhanced radio-sensitivity of the normal skin explants.
Conclusion: This method represents a wound healing assay for very small tissue samples. Skin specimen are not subjected to additional manipulation and treated immediately after biopsy. This assay allows functional studies of combined treatment modalities.

P 20

Immunogenic cell death during maintenance chemotherapy and subsequent multimodal immunotherapy for GBM

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Introduction: Multimodal immunotherapy is emerging as new treatment modality for patients with GBM.
Objectives: To study the effect of multimodal immunotherapy as part of first line treatment for patients with primary GBM.
Patients and methods: In a retrospective analysis of 56 patients with primary diagnosis of GBM, we detected 20 patients in whom Newcastle Disease Virus (NDV) and modulated electrohyperthermia (mEHT) were added at days 8/9/10 during TMZ maintenance (TMZm) cycles, multimodal NDV/mEHT/DC vaccinations were administered after TMZm, and further NDV/mEHT treatments were given thereafter. Median age was 57.5 years (ranging 17 till 67y, one 7-year old child with gliosarcoma). KPI was >70 (50 for one 17-year old patient). Patients were treated with a median of 27 (14–115) NDV infusions, 24 (4–117) mEHT sessions and 2 (0–13) DC vaccinations.
Results: Median OS was 25 months with a 3-year long-term OS of 50% (CI95% +26%, –32%). There were no major toxicities for this ambulatory treatment. The group was further divided into subgroup 1: 12 patients adding NDV/mEHT immediately after radiochemotherapy; and subgroup 2: 8 patients adding NDV/mEHT later-on during TMZm cycles. Patient characteristics were equal, as were DC vaccinations, while more NDV/mETH were administered in subgroup 1. The median OS was 37 versus 24 months ($p = 0.00119$) for subgroup 1 resp. 2.
Conclusion: The data suggest that addition of immunogeneic cell death (ICD) via NDV/mEHT during TMZm might be beneficial in controlling disease progression. While TMZm only targets dividing tumor cells most when MGMT is methylated, ICD via NDV and mEHT targets both dividing but also non-dividing tumor cells.

P 21

Feasibility of tumor vasculature targeting – comparative study of different cationic and anionic thermosensitive liposomes

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Introduction: Tumor vasculature overexpresses negatively charged proteins and glycoproteins which form a suitable target for localized therapies. Earlier studies demonstrated the possibility to target tumor angiogenic endothelial cells by positively charged nanocarriers, such as cationic liposomes. Cationic thermosensitive liposomes (CTSLs) combine active targeting potential and heat-triggered release capacity of encapsulated compounds from thermosensitive liposomes (TSLs).
Objective: The objective of this study is to design a novel 1,2-dipalmitoyl-sn-glycero-3-phosphodiglycerol ($DPPG_2$)-based cationic TSL formulation ($DPPG_2$-CTSL), which will be used in a comparative study with a previously reported polyethylene glycol (PEG)-based cationic TSL (PEG-CTSL). Nanoparticles binding capability and Doxorubicin (DOX) delivery efficiency were investigated in different cell lines. Furthermore, TSLs were incubated in serum to establish protein adsorption to the surface of these particles. Resulting protein-corona TSLs (P-TSLs) were fully characterized and used in comparative cell binding study against not-serum exposed TSLs.
Methods: Liposomes were prepared by film hydration/extrusion method and DOX encapsulation was performed via active loading. TSLs were characterized by dynamic light scattering, differential scanning calorimetry and thin layer chromatograph. Temperature/time dependent DOX release assays were performed by fluorescence spectroscopy. Interactions of (C)TSL with cells were investigated *in vitro*, by flow cytometry and fluorescence microscopy.
Results: ζ-Potential analysis showed higher overall positive surface charge for $DPPG_2$-CTSL, when compared to other (C)TSLs (5.5 ± 2.3 mV—physiological condition). $DPPG_2$-CTSL had a more performant (2.5 folds) binding potential to all above mentioned cell lines when compared to PEG-CTSL. Furthermore, cells exposed to 50 µM liposomal-DOX showed 1.8 folds higher DOX uptake when treated with $DPPG_2$-CTSL, in comparison to PEG-based CTSL. Protein absorption reduced CTSL binding by ≥60% compared to CTSLs that were not serum exposed.

Conclusions: The lack of a PEG polymer on the TSL surface increased binding efficacy. Nevertheless, protein absorption decreased effective CTSL targeting. This indicates that despite the promising binding kinetics of CTSLs shown *in vitro*, exposure to complex biological environments may prove to be an additional challenge for targeting *in vivo*.

P 22

Identification of suitable electromagnetic and thermal models for patient specific hyperthermia planning for SIGMA30 applicator using direct temperature measurements

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Introduction: The hyperthermia applicator SIGMA 30 is clinically used for small children and extremities in adults. In contrast to SIGMA 60 and SIGMA-Eye applicators, the experimental and numerical data for this applicator is rather sparse.
Objectives: To compare measurements for a therapy in SIGMA 30 and numerical calculations for both SAR and temperature in order to find suitable electromagnetic (EM) and thermal patient models.
Methods: Computed Tomography (CT) data sets were acquired of a 3-year-old child with incompletely resected pelvic rhabdomyosarcoma for hyperthermic chemotherapy under anesthesia using SIGMA 30. For contouring the standard Varian Treatment Planning System (Eclipse Version 11.0) was applied. Voxel models were created from contours by self-written Octave and Matlab algorithms (www.gnu.org/software/octave/, Matlab 4.2016b). An EM model of SIGMA 30 was created, based on FDTD method. An FD procedure was used for solving the Bio-Heat Transfer Equation using temperature-dependent perfusion models [1]. A total of 8 hyperthermia sessions were applied. Temperature sensors were placed in bladder, tumor, and rectum, both last-mentioned were mapped during the therapy and the temperature maximum sensor position was monitored between the mapping intervals. The body core temperature (oral temperature sensor) and vital functions were permanently monitored during therapy.
Results: Channel power and temperature curves were recorded and compared with the calculated ones. For all 8 therapies, the maximal power ranged from 89 to 200 W and maximal temperatures from 40.5 °C to 42.6 °C in tumor, from 40.0 °C to 43.2 in bladder, and from 39 °C to 42.4 in rectum. SAR was derived from temperature decay after power switch off. In order to investigate which model best correlates with the measurements, the patient models were varied with respect to cell size, to preconditioning of regions and interfaces, to temperature-dependent perfusion and to other parameters.
Conclusion: Numerically predicted and measured time-dynamic temperature curves, including the temperature decay period after power switch off for estimation of SAR, were compared using an example pediatric patient treated within SIGMA 30.

Reference

1. Nadobny et al (2007) Evaluation of MR-induced hot spots for different temporal SAR modes using a time-dependent finite difference method with explicit temperature gradient treatment. IEEE Trans Biomed Eng 54(10):1837–1850

P 24

Establishing selected foundations of hyperthermic oncology

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Introduction: Nobel laureate Otto Warburg found that cells usually metabolize glucose in an aerobic way using mitochondria. Cancer cells use an anaerobic process w/o mitochondria. Normal cells reach typical ATP/glucose ratios of 36 (aerobic) on cancer cells the rate is only 2 (anaerobic).
Objectives: This high energy consumption of cancer cells is one of the basic mechanisms of hyperthermic oncology (HTO). Today it is widely assumed, that the maximum body temperature (42.3° C) is a good indicator for the critical temperature for HTO. At this temperature the brain gets critically damaged. To exploit this mechanism a more clear view of the heat sensitivity of cancer and normal cells is required. As a first step we calculated the estimated differential of temperature sensitivity between cancer and normal cells.
Materials and methods: We assumed a 5-fold higher energy turnover depending on glucose and insulin levels and calculated the cell temperature increase versus normal cells using the entropy equation and the cell surface and mass. Then we used heuristic assumptions regarding heat dissipation by conduction (tissue itself), convection (mainly blood) and black-body-radiation and yield a temperature increase cancer vs normal cells in the range of 0.1 K dependent on the thermal conductivity given in W/m/°C of the tissue.
Results: Analyzing the impact of thermal conductivity, we find several groups of tissue (values in W/m/°C)

- Air based tissues like lungs (approx. 0,03)
- Fat based tissues like yellow bone marrow, breast fat (approx. 0.2)
- Bone based tissues like red bone marrow, skull, vertebrae etc. (approx. 0.3)
- Other tissues with a thermal conductivity between 0.31 (breast glands) and 0.6 (water).

In this range the following thermal conductivities are worth mentioning:

- Skin (0.37)
- Pancreas & Prostate (0.51)
- Liver (0.52)

Based on these observations we conclude that a hyperthermic treatment for lung, bone and breast cancers should be more successful than corresponding treatments for pancreas, prostate and liver cancers.
Conclusion: We propose to do the following experimental measurements for lung, breast, bone and skin cancers (LD50 temperature)

- Normal and cancer cells with normal glucose & insulin levels
- Normal and cancer cells with very high glucose & normal insulin levels
- Normal and cancer cells with very high glucose & very high insulin levels

P 25

Modulated electro-hyperthermia in pancreatic cancer patients – initial experience and clinicopathologic evaluation

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Introduction: Modulated electro-hyperthermia (mEHY) as a complementary treatment has gained support in the treatment of cancer patients as supplementary method besides the standard treatment or for those who exhausted conventional treatment. Pancreatic cancer is one of the neoplastic diseases with poor outcome, and we aimed at evaluating this cohort receiving mEHY treatment.
Patients and methods: Twenty-one eligible patients were recruited based on clinical rounds decision since SEP-2, 2016. Primary tumors of patients originated from the pancreas (head and body). Surgical procedure due to advanced stage was not eligible. EHY-2000 and EHY-2030 instrument (Oncothermia Ltd., Budaörs, Hungary) were used and initial power of 50 W was applied. The increments were set to 5–10 W in 5 minute steps until 150 W was reached.
Results: The patients' data was evaluated on JAN-26, 2018. The patients attended mEHY treatment in a range of 8 to 86 occasions (1–14 months). ECOG status: 0–2. Average number of metastases of the tumors were two: 12 lymph node, 8 liver, 7 peritoneal, 1 kidney and 1 pulmonary metastasis was detected. Various chemotherapeutic protocols were administered to the patients as per guideline recommendations, most often Gemcitabine, platinum and 5-FU based regimens. Average treatment time of each mEHY occasion was 59.5 minutes. From the initial power to the final power on average 50 W power increment was reached.

Nine patients (42,8%) had to hold therapy due to neutropenic fever (5), pain (2), rush (1), pneumonia (1) and thrombophlebitis (1). Five of the patients (23,8%) discontinued the therapy due to progression (1), ascites development (2), icterus (1) and severe abdominal pain (1). CEA and CA19-9 levels in pancreatic cancer patients are not predictive for response to mEHY therapy.
Conclusion: Twenty-one pancreatic cancer patients were treated at our mEHY therapy unit. Patients with oligometastatic/inoperable tumors are likely the target population of this treatment approach, especially supplementing systemic therapy. CEA and CA19-9 levels in are not predictive for response to mEHY therapy in our cohort. Identification of better biomarkers is warranted.
Funding: NVKP_16-1-2016-0042 grant. AMS was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences.

P 26

Clinical studies of oncothermia

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Introduction and objectives: Modulated electro-hyperthermia (mEHT), is a particular kind of hyperthermia in oncology. It considers the heterogeneous structure of the tumor and provides selective thermal actions instead of the homogenous heating. Its advantages are the stable safety, extra low toxicity and systemic effect of the local treatment. The systemic effect is made by the development of the immunogenic cell-death and produces an abscopal effect, excluding the relapse of the same tumor in the system. Our presentation intends to show the clinical studies of mEHT in variously advanced primary and metastatic malignancies.
Materials and methods: The collected results are by well-known and widely applied evidence-based medicine. Prospective Phase II and Phase III oncothermia trials exist, together with some retrospective studies. All the retrospective data are compared to large databases and/or historical arms, and many are compared to the multiple clinical practices making statistical evidence of the validity of the data. Multiple clinical studies are in progress at various university research centers including preparation of one FDA controlled trial in the USA.
Results: Such sensitive organs like the brain were successfully treated even with high dose mEHT without extra side effects. The clinical advantages of glioma treatment show important addition to the survival time like it is shown recently in. The small and non-small lung cancer were also successfully treated with mEHT, even in advanced cases.

The gastrointestinal malignancies are also treated successfully with the mEHT method. The liver metastases in colorectal tumors, the primary hepatocellular carcinoma, pancreas carcinoma and unresectable biliary cancer were clinically examined with positive results; in gynecology for ovary, for breast and in cervix. Bone metastases, sarcomas, and even the mEHT treatment of malignant ascites proof the theoretical and experimental results in clinical practice.
Conclusion: mEHT has good clinical achievements in the clinical studies making the stable basis of the clinical applications in various advanced primary and metastatic malignancies.

P 27

Modulated electro-hyperthermia treatment of pancreas ductal adenocarcinoma *in vitro*

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Objective: Modulated electro-hyperthermia (mEHT) is a complementary tumor therapy utilizing capacitive, impedance-coupled radio frequency for inducing cell stress at ~42 °C. It can selectively target malignancies due to their elevated glycolysis, ion concentration and conductivity compared to normal tissues.

Pancreas adenocarcinomas still show very poor survival rates despite of up-to-date chemotherapy. Here we tested the efficiency of mEHT treatment in Panc1, a ductal pancreas adenocarcinoma cell line including the molecular changes induced.
Methods: Panc1 cells were growth on coverslips in Dulbecco Modified Eagle Medium (DMEM). Confluent cell cultures were treated with mEHT for different durations and tested for basic morphology, apoptotic tumor cell death by flow cytometry and cell stress related changes using immunocytochemistry.
Results: Single mEHT treatment for 60 minutes resulted in major ~40% tumor damage showing widespread apoptotic bodies after 24 hours. Flow cytometry using AnnexinV/propidium iodide labeling confirmed significant treatment related apoptosis compared to the untreated control group. Immunocytochemistry revealed elevated number of histone 2Ag positive tumor cells indicating increased DNA double-strand breaks. Also, the treatment caused expression of Alix protein related to apoptosis and exosome formation and of the cell stress indicator calreticulin protein.
Conclusion: Our results showed that mEHT treatment cause efficient tumor cell stress and massive apoptosis involving significant DNA double strand brakes. Further studies are under way to clarify damage mechanisms and apoptotic pathways for translating knowledge for in vivo mEHT therapy.
Supported by NVKP 16-1-2016-0042 research grant

P 29

Definitive outcome of hyperthermia-radiotherapy association for superficial recurrent tumors

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Introduction: Superficial hyperthermia (HT) and radiotherapy (RT) improves the clinical outcome and quality of life in patients (pts) with

Follow-up (months)	CR (%)	PR (%)	SD (%)	PD (%)
1	31	42	16	11
3	34	25	19	22
6	32	4	28	36
12	15	8	31	46
24	44	-	28	28
36	25	-	50	25

Fig. 1 P 29. Response rate in the time (months)

symptomatic lesions. We perform HT to offer another treatment choice to advanced oncological diseases previously (or not) previously irradiated. We want to evaluate the safety, feasibility and toxicity of RT-HT in this cohort of patients.

Methods: 43 pts (mean age 69 years; range: 47–95) were treated: 21 breast carcinoma, 11 H&N cancer, 3 malignant melanoma, 4 sarcomas, 1 uterine adenocarcinoma, 1 hepatocarcinoma, 2 pancreatic carcinoma and 1 small cell cancer of thigh. The treated lesions were 67. 73% of pts received a previous mean RT dose of 50 Gy. RT techniques used were: 3D-CRT (17/42), Arc-Therapy (2/42) or Helical Tomotherapy (23/42). EBRT was delivered in 5–30 fractions of 1.7–5 Gy to a total dose of 20–63 Gy (mean: 40.3 Gy). HT was performed with a double electromagnetic superficial applicators operating at the frequency of 434 MHz by ALBA double unit. HT session was delivered once/twice weekly, 1–2 hours after RT (range: 1–10 sessions, mean: 5). Average, maximum and minimum temperature parameters were recorded during HT treatment. The treatment goal was to reach 40–42 °C in >90% (T90) of measured points for a duration of 60". Acute and late toxicity were evaluated according to the CTCAE criteria, Local control (LC) on the basis of the RECIST Criteria.

Results: The median temperature reached was 40.5 °C (39–42.9 °C). 5 pts interrupted the treatment: 2 pts (5%) for G3 toxicity, 2 (5%) for poor compliance and 1 (2,4%) for clinical progression. 2 pts (5%) had acute cutaneous toxicity ≥ G3 at 1 month, 4 pts had toxicity > G2 at 3 months, 3 pts after 6 months and only 1 at 12 months. The mean follow-up was 13 months (range 1–50). The LC was: 88%, 78%, 68%, 61%, 71% and 75% at 1, 3, 6, 12, 24, 36 months respectively. The mean time to local progression was 8 months (range 1–36). The detailed results are reported in Table 1. 10 patients dead (9 for disease and one for vascular accident). Univariate analysis showed that Tmean, Tmax, Tmin, T90 parameters were not associated with local control rate.

Conclusion: RT-HT showed a good LC and patient compliance. The clinical outcome and the duration of the follow-up is affected by the advanced stage of diseases. A larger pool and a more detailed stratification are needed.

P 30

Pitfalls in acoustic transducer modeling for focused ultrasound (FUS)

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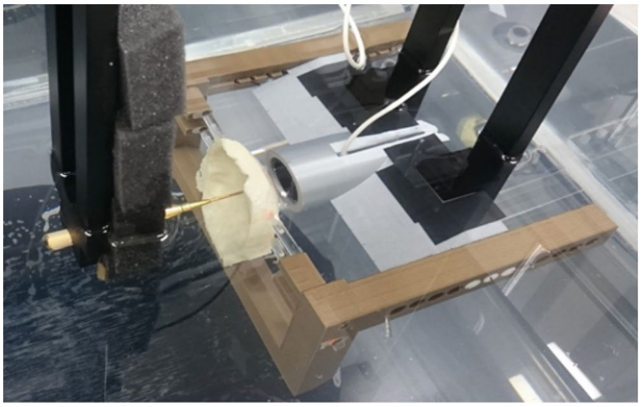
Introduction: When modeling therapeutic applications of FUS, the transducer is typically modelled by modeling the transducer surface geometry and imposing a pressure or velocity boundary condition (depending on the solver type). However, during experimental validation of transcranial FUS modeling, dramatic deviations between simulated and measured pressure distributions were observed that were shown to originate from transducer modeling.



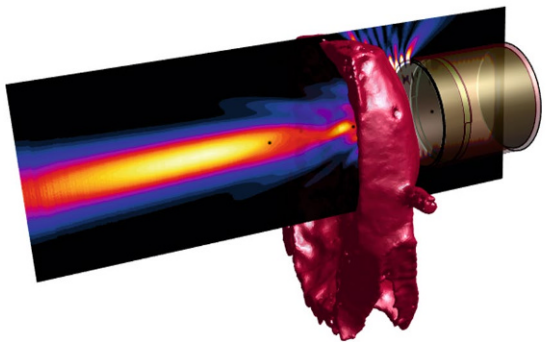


Fig. 1 P 30.

Objectives: A systematic study was performed to investigate the impact of factors to be considered to obtain realistic models of acoustic exposure by US transducers.

Materials and methods: Acoustic pressure fields generated by curved single-element focused transducers (0.5 MHz) in the presence and absence of skull obstacles (pig, sheep, and lamb; characterized by CT and precisely positioned) have been measured using a 3D-scannable, calibrated hydrophone and compared to acoustic simulations of corresponding setup models. Initially the source was modelled as pressure boundary condition imposed on the transducer surface according to the manufacturer specifications. Subsequently, the model was adapted to consider the actually measured geometry, the internal structure of the transducer (planar piezoelectric disk below a shaped matching material), uncertainty about the internal transducer geometry and material properties, and an aperture function accounting for the mechanical impact of, e. g., the transducer wall.

Results: The pressure field sensitivity to the above factors was investigated and after careful model adaptation, good agreement between the simulated and measured fields was obtained in the absence of skulls. Significant deviations are still observed in the presence of skulls and current work focuses on establishing whether they originate from transducer modeling, or from the employed mapping of CT data to acoustic property distributions.

Conclusion: Careful transducer modeling and experimental validation is crucial to reliably simulate FUS fields and common approaches are found to be unsuitable for extended, curved or complex transducers.

P 31

Optimalization of microwave hyperthermia waveguide applicator for head and neck region

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Introduction: The purpose of this contribution is to study the influence of the number of waveguide applicators for the hyperthermia treatment of tumors in the head and neck region. Our team proposed a special applicators system intended for the targeted hyperthermia treatment in the region of head and neck described in [1].
Objectives: The number of applicators was changing from one to five observing the SAR distribution in the target of the simple phantom. The influence of the optimization of the amplitudes and phases for the microwave energy steering was observed. The main idea is to propose an efficient applicator with the possible electromagnetic field steering through amplitude and phase settings of each applicator.
Materials and methods: Our proposed applicator for head and neck hyperthermia treatment is optimized regarding to the highest efficiency of the energy delivery to the various tumors in head and neck region. The single element of the hyperthermia treatment is a waveguide applicator with strip line horn aperture. The working frequency of the applicator is 434 MHz.
Results: In the Fig. 1 there are resulting cumulative SAR volume coverage histograms gained from optimization process of the biggest target and T_1. The black vertical line is indicating the SAR_{25} which is mostly used in hyperthermia as an indicator for the lowest value of successful treatment. The best results were achieved with 4 applicators. The SAR_{25} coverage is in that case about 70%. With more applicators, the SAR coverage is decreasing, but also with the higher absorbed energy in sensitive tissues as a spinal cord.
Conclusion: In this contribution, we observed the influence of optimization (amplitude and phase settings of each applicator) on the SAR coverage of the target and sensitive tissues for different number of applicators. The optimization process is set to increase the absorbed energy in the target of the treatment and thus save the sensitive tissues. This study is used to choose the appropriate number of applicators with the highest efficiency in the relation to the targets in the head and neck region.

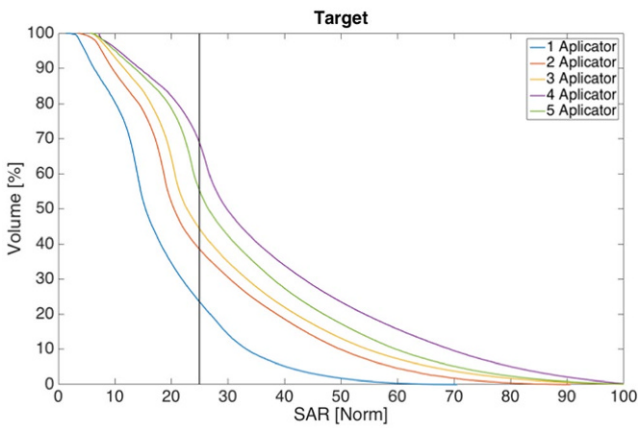

Fig. 1 P 31. The cumulative SAR histogram for the target in the head and neck region

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P 32

Regional deep hyperthermia – comparison of intratumoral invasive thermometry and thermal numeric simulations in patients

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Introduction: The aim of this work was to evaluate the accuracy and reliability of a treatment planning software (SigmaHyperPlan™). The temperatures obtained by the planning software were compared with direct invasively measured temperatures within the tumor volume of patients with high-risk soft-tissue sarcoma (STS) located in the extremity region.
Methods: Five patients underwent CT fluoroscopy-guided closed-tip catheter intratumoral implementation for the invasive thermometry. The invasively measured temperatures were analyzed within the steady-state therapy time by calculating the index temperatures T90, T50 and T20 as well as Tmean, Tmin and Tmax. Furthermore, the thermal dose (CEM43T90) of T90 was determined from the invasive measured temperature. The simulated data from the planning software were evaluated in a similar manner to the measured data by computing index temperatures, except for CEM43T90. Finally, the relative error of the index temperatures between the simulation and the measurement was calculated in order to determine the difference between both approaches.
Results: The invasive thermometry data showed a heterogeneous temperature distribution along all catheters within the tumor volume, while the simulated temperatures were nearly homogeneous. In the temperature range of 38 °C to 47 °C, the five STS patients showed different measured temperature behaviors depending on the tumor characteristic. The CEM43T90 results showed higher values for fast heated tumors and lower values for slow heated ones depending on the tumor blood perfusion. On the other hand, the simulations indicated nearly homogeneous temperature distribution with higher temperatures than invasive thermometry. The global error of the index temperatures between simulation and invasive temperature measurement was found to be ±22%.
Conclusion: No good agreement was found between the invasive thermometry and thermal simulations regarding the temperature distribution in these tumors due to limitations in both methods.

P 33

Implementation of a new MRI-hyperthermia-hybridsystem into clinical routine

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Introduction: The aim of this work was performance evaluation of a new 1.5 T MRI-hyperthermia-hybridsystem to be implemented into clinical routine for regional deep hyperthermia treatment.
Methods: A new design of an MR-compatible multi-antenna applicator of the type SIGMA-Eye (BSD-2000/3D/MR, Pyrexar Medical Corp., Salt Lake City, UT), which can be opened on one side, is integrated in a standard 1.5 T MRI-system (Ingenia, Philips) with an axial coverage of 55 cm and a gantry diameter of 70 cm. The hyperthermia (HT) system has a new water control and temperature calibration system. The high-frequency signals of both systems are filtered two-way to avoid interference. The performance of the hyperthermia system alone was assessed by evaluating reflected power, stability of the HT-amplifier and possible hardware and software errors during the heating process. For these experiments a homogenous gel phantom as well as a lamp phantom was used. The hyperthermia applicator was tested with all channels set to 100%, 700 W, focus (0, 0) and 90 min-heating time. After that the steering accuracy was tested by shifting the heating focus from (0, 0) cm to (0, ±3) cm in all three directions in space applying 300 W. Furthermore, the centering of the temperature distribution of the target was investigated inside and outside the MR-bore. For these experiments a homogeneous phantom was used with 400 W and 20 min heating duration.
Results and conclusion: The overall results indicated that the hyperthermia system is stable und showed a global reflected power on average of less than 10% at all antenna. The heating focus could be shifted from (0,0) cm to (0, ±3) cm in vertical, horizontal and longitudinal directions. Moreover, the heating quality inside the MR-bore was not significantly affected when compared to operation outside the bore. The new system is currently under preparation toward the first clinical hyperthermia patient treatment.

P 34

Extracting information about cellular repair processes after hyperthermia – radiotherapy by model-based data analysis – ambiguities in survival prediction as a challenge?

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Introduction: It has been shown that dynamic models such as the Multi-Hit-Repair- (MHR) model[1] can reproduce many radiobiological effects observed in survival curves. This opens the possibility of extracting knowledge about cell-physiological aspects of combined hyperthermia-radiotherapy (HT-RT) from model parameters if these parameters predict a survival curve observed experimentally. This approach could be used in model-driven treatment planning, but presumes that one survival curve cannot be generated by different sets of parameters.
Objectives: The main objective is to investigate if a set of MHR model parameters yielding a particular survival curve is unique for in-vitro data of various cell lines.
Materials and methods: Cell cultures and clonogenic assays for 8 cell lines (see Tab. 1) were done in triplicates following standard procedures. HT was performed for 60 min. at 42 °C, after a 30 min. ramp-up. Subsequent irradiation at doses between 0 and 6 Gy was performed after a time-gap of 10 ± 4.5 min.

Differential evolution was used for parameter search, minimizing the sum of squared differences (ϵ) between experimental and predicted logarithmic survival fraction for all doses, with and without HT. For each cell lines, two parameter sets with low ϵ from different local minima were selected.
Results: The results (Tab. 1, Fig. 1) reveal that it is possible to generate survival curves with parameters that differ up to one order of magnitude while maintaining a low ϵ.
Conclusion: The ambiguity found was already conjectured in [1]. Due to similarities between the mathematical solutions of different models [2], we suspect that this also holds for other dynamic models. Preliminary results suggest that curves obtained at different dose rates or tracking DNA damage in time can disambiguate these cases.

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Cell Line	α	c_r	c_e	μ_Γ	γ	a	k_2	μ_Λ	ϵ	Parameter Set
A549	1.73	3.01×10^2	4.46×10^1	9.48	8.70×10^2	6.94×10^{-4}	5.60×10^1	1.66×10^1	9.35×10^{-3}	1
	1.87	2.79×10^2	2.76×10^1	6.69	9.93×10^2	5.17×10^{-3}	4.43×10^1	4.93	7.57×10^{-3}	2
Abrams	1.04	4.79×10^2	1.26×10^1	3.86	8.52×10^2	2.42×10^{-3}	6.07×10^1	1.94×10^1	6.20×10^{-5}	1
	9.65×10^{-1}	4.16×10^2	1.46×10^1	3.58	6.31×10^2	2.17×10^{-3}	2.61×10^1	7.77	1.71×10^{-3}	2
D17	1.17	9.00×10^1	4.60	4.43	9.71×10^2	1.35×10^{-3}	7.50×10^1	1.12×10^1	9.84×10^{-3}	1
	1.18	5.37×10^2	3.43	6.34	8.75×10^1	1.73×10^{-4}	4.60×10^1	2.46×10^1	7.44×10^{-3}	2
K9STS	1.27	7.57×10^2	2.34×10^1	2.96	1.19×10^2	3.57×10^{-5}	6.27×10^1	2.31×10^1	5.86×10^{-3}	1
	9.43×10^{-1}	3.98×10^2	5.85×10^1	8.19	9.54×10^2	7.21×10^{-4}	7.30×10^1	1.80	3.00×10^{-3}	2
K9TTC	8.61×10^{-1}	2.51×10^2	2.47×10^1	6.17	8.49×10^2	6.81×10^{-4}	6.50×10^1	2.82×10^1	6.63×10^{-3}	1
	1.14	8.46×10^2	1.40×10^1	3.62	2.82×10^2	1.35×10^{-3}	6.48×10^1	9.50	6.75×10^{-3}	2
MM2	1.73	9.94×10^2	2.27×10^1	9.04	4.42×10^2	1.45×10^{-3}	7.00×10^1	1.13	9.79×10^{-3}	1
	1.73	1.18×10^2	4.79	8.08	8.78×10^1	6.34×10^{-5}	4.49×10^1	2.55×10^1	9.27×10^{-3}	2
OSA17	1.85	9.92×10^2	8.06	8.75	5.64×10^2	1.74×10^{-4}	4.80×10^1	1.52×10^1	7.42×10^{-3}	1
	1.87	1.24×10^2	2.54	3.65	7.35×10^2	9.82×10^{-5}	5.24×10^1	1.11×10^1	7.95×10^{-3}	2
U2OS	1.68	8.38×10^2	2.81×10^1	8.40	1.04×10^2	3.30×10^{-3}	6.28×10^1	1.71×10^1	9.60×10^{-3}	1
	1.65	1.26×10^2	4.18×10^1	3.45	9.56×10^2	1.37×10^{-3}	7.10×10^1	7.50	8.73×10^{-3}	2

Fig. 1 P 34. Model prediction for 3 selected cell lines

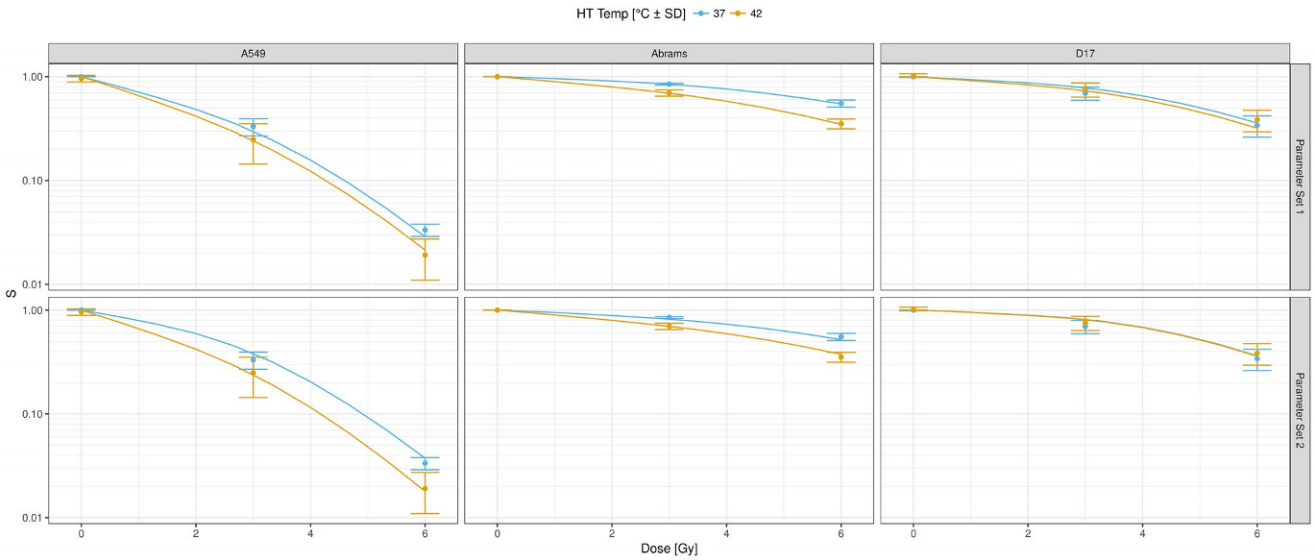

Fig. 2 P 34. Overview of two sets of low-ϵ parameters for 8 cell lines

P 35

Exogenous and endogenous hyperthermia combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range whole body and local regional hyperthermia in stage IV cancer

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Introduction: The breakthrough discovery of immune checkpoint blockade (ICB) has revived cancer immunotherapy but could not change the palliative management of stage IV cancer affecting millions of patients worldwide. ICB is not recommended in "individuals facing imminent death" because of potential serious immune related adverse events (irAE).

In an effort to synergize treatment effects and lowering irAE we combined two ICB with hyperthermia treatments and interleukin-2 (IL-2).

Materials and methods: We previously reported complete remission (CR) of far advanced lung metastasis in triple negative breast cancer at ITOC3 (Munich) 2016, CR of inoperable esophageal Cancer at ITOC4 (Prague) 2017 as well as CR of stage IV breast cancer at ITOC5 (Berlin) 2018. A "Named Patient Use" consisted of an off-label low-dose (LD) ICB treatment (Ipilimumab/Nivolumab) with interleukin-2 (IL-2) under taurolidine protection and loco regional- and whole body hyperthermia (WBH); written informed consent was obtained by the patients. Loco-regional hyperthermia was achieved using 13.56 MHz applicators (Oncotherm and Syncrotherm). WBH was induced using external heating (Heckel and v. Ardenne) followed by systemic fever induction using IL-2. Our concept is following in the footsteps of Coley, father of cancer immunotherapy.

Results: 98 patients (97 stage IV, 1 stage IIIb) underwent this treatment protocol; 79 are currently evaluable. The others were too early to evaluate with follow-up time < 3 months. Response criteria were met with restaging using CT and/or MRI as well as clinical and laboratory evaluation. irAE where greatly diminished compared to published literature on checkpoint inhibitors in cancer therapy.

Overall clinical benefit: 57%: Proportion of patients with reduction in tumor burden of a predefined amount; this includes CR and PR and SD (partial remission of < 50% or stop of tumour growth).

Overall response Rate = objective response rate: 43%. Proportion of patients with reduction in tumor burden of a predefined amount; this includes complete remission (CR) and partial remission (PR); PR must be > 50%.

Conclusion: The unexpected objective response and clinical benefit of advanced metastatic cancer with favorable safety profile following complex immunotherapy treatment including low-dose checkpoint inhibitors, hyperthermia and metronomic chemotherapy warrants further clinical studies.

P 36

Do SAR quality indicators predict temperature? A verification study in head and neck hyperthermia

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Introduction: Despite the demonstrated thermal and thermal-dose-effect relations, it is still unclear whether the SAR or temperature distribution should be optimized in pre-treatment planning. Optimizing the temperature distribution seems optimum and some effectiveness was shown [1], but more extensive study found that the large thermal property uncertainties reduce the inherent benefits [2]. Therefore, we studied if specific absorption rate (SAR)-based treatment quality indicators can predict temperature during clinical decision making. In [3], a literature survey of SAR-based quality indicators distinguished the so-called target to hot-spot quotient (THQ) as most predictive for median target temperature (T50) in loco-regional deep pelvic hyperthermia (DPH). Earlier, a relation was found between the Target Coverage

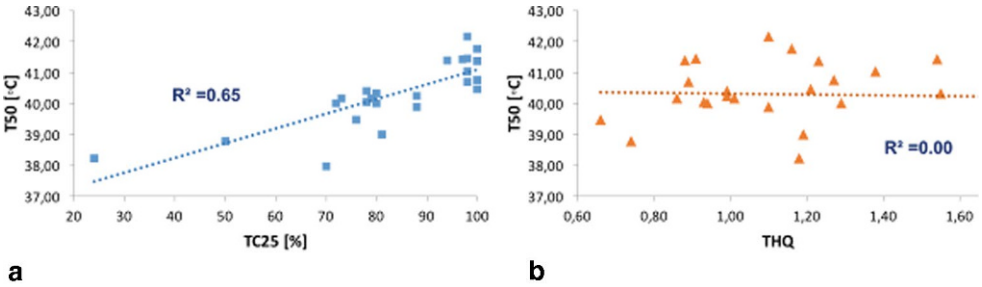

Fig. 1 OP 36. Correlation of TC25 (**a**) and THQ (**b**) with T50

of the 25% iso-SAR volume (TC25) and clinical outcome for superficial hyperthermia (HT) [4].
Objectives: The correlation between THQ and TC25 and predicted T50 was studied for head&neck HT.
Patients and methods: Patient specific treatment planning results of twelve patients for the HYPERcollar3D were selected. Avoiding optimization bias, both the clinical method and focusing via constrained power optimization [5] were used.
Results: Fig. 1 shows a good correlation between TC25 and T50 (R^2=0.65) and no correlation between THQ and T50 (R^2=0.00). Although THQ might still serve as optimization coefficient [3], it might not be predictive for T50. Compared to DPH, the higher THQ values show a more target conformal heating.
Conclusion: These preliminary results indicate a different SAR-temperature relation for target conformal HT devices. Further work aims at revealing the tissue property uncertainties and modelling effect.

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P 37

Thermoresponsive and light-to-heat converting nanogels for biomedical applications

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Introduction: Nanosized hydrogels (nanogels) are soft and highly crosslinked polymer networks that can hold a large amount of water and drugs as cargo. Nanogels can be modified to be sensitive to environmental conditions like pH, temperature changes or magnetic fields, and respond with change in size. We develop different thermoresponsive nanogels as drug delivery systems that collapse upon increased temperature. Moreover, we modify thermoresponsive nanogels with a second, interpenetrated polymer network or nanoparticles which can absorb near infrared (NIR) light and generate heat. This enables a directed heating and thermal treatment of (tumor-)tissue containing accumulated nanogels only at the site of NIR irradiation [1,2].

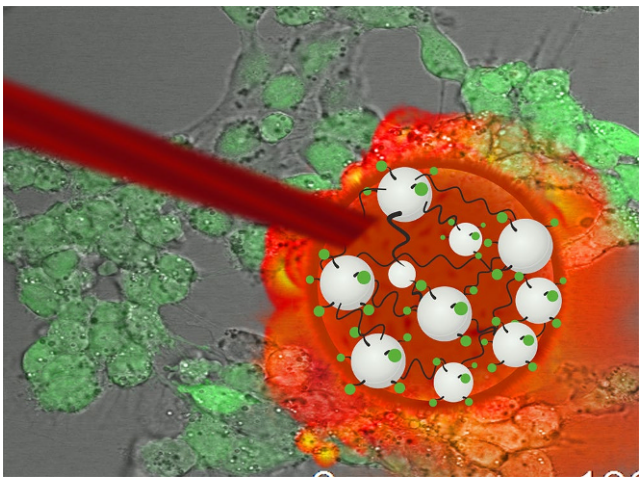

Fig. 1 P 37

Objectives: We develop thermoresponsive nanogel systems and evaluate their applicability for thermal ablation of cells and tissues.
Materials and methods: Different functional nanogels were exposed to cells in culture and their metabolic activity and cellular uptake was studied using MTT Test and confocal microscopy. Nude mice were treated with increasing doses and their weight and blood was monitored. Tumor cells treated with nanogels were irradiated with NIR light and the development of heat was monitored with a thermal camera, as well as their thermal ablation was studied *in vitro* and *in vivo*.
Results: Different thermoresponsive nanogels were synthesized and heat generation upon NIR irradiation was shown. Preparations did not have adverse effects on cell proliferation up to a concentration of 1 mg/ml in vitro and were well tolerated in the nude mouse model in short and long-term application of 100 mg/kg. Tumor cells treated with nanogels semi-interpenetrated with NIR transducers showed a concentration dependent temperature increase up to 20 °C upon irradiation, leading to thermal ablation. In a mouse model, tumor size was reduced to about 50% at 10 days after one-time NIR irradiation as compared to the control.
Conclusion: Thermoresponsive and light-to-heat transforming nanogels show great potential to be used as heat generating agents in biomedical applications.

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P 38

Fever-range whole body hyperthermia with concomitant capecitabine in third line therapy for BRCA mutated metastatic breast cancer

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Introduction: Metastatic breast cancer (MBC) is a heterogeneous disease, with several therapeutic options available, including chemotherapy (ChT). Even so, the response rate after progression to initial first line therapy is not optimal.

Whole body Hyperthermia (WBHT) is a complementary treatment option, already used in several countries concomitant to ChT and radiotherapy (RT), possibly increasing the effects of these treatments in the tumor cells.

Case Report: Female patient, 44 yo, with no co-morbidities.

Right breast carcinoma (ca) diagnosed in 2003 (Hormone receptors (HR) positive, Her2 negative). Treated with mastectomy, lymphadenectomy, adjuvant ChT and hormonal therapy (HT). In 2011 was tested for BRCA mutation, being BRCA2 mutated.

In 2013 left breast ca, HR positive, Her2 negative, ki67 5%, treated with mastectomy with concomitant reconstruction (sentinel lymph node (ln) negative). Started tamoxifen but suspended after 1 year for attempting to get pregnant.

In May 2015 recurrence disease on left breast with skin and ln involvement. She was treated with neoadjuvant ChT (Docetaxel and Carboplatin) for 6 months followed by lesion excision, bilateral oophorectomy, adjuvant RT and HT (Letrozole then Tamoxifen).

After 8 months PET-CT showed disease progression, with ln, bone and liver metastasis. Started 1st line metastatic treatment with Carboplatin and Paclitaxel.

In April 2017 PET-CT scan with new disease progression. Started 2nd line treatment with Palbociclib and Fulvestran.

In July 2017 disease progression on PET-CT scan: cervical, supra-clavicular, infra-carinal, hepatic hilum and para-aortic lymph node involvement; hepatic bilobar lesion, the greatest on segment VII with 35 mm and SUVmax 18; extensive bone involvement—spine, pelvis, femur SUVmax 4 to 13; Lung nodule 1 cm, SUVmax 11.

Patient started Capecitabine with concomitant WBHT on August 2017 (1 session per month, induction to 38.5ºC with 1 to 1 hour and 30 minutes retention, max temperature 39.5ºC).

After 3 sessions of WBHT with concomitant Capecitabine (3rd line metastatic disease), PET-CT scan showed complete response in lymph node, hepatic, spine and femur disease, with reduced SUVmax in pelvic disease from previous 8 to 10 to 5.

Conclusion: WBHT may enhance ChT effects in breast cancer tumors. In this specific patient, response to Capecitabine was better than expected. Prospective randomized trials are needed to validate this therapeutic approach.

P 39

Oncologic deep local hyperthermia in advanced cancer patients – feasibility study

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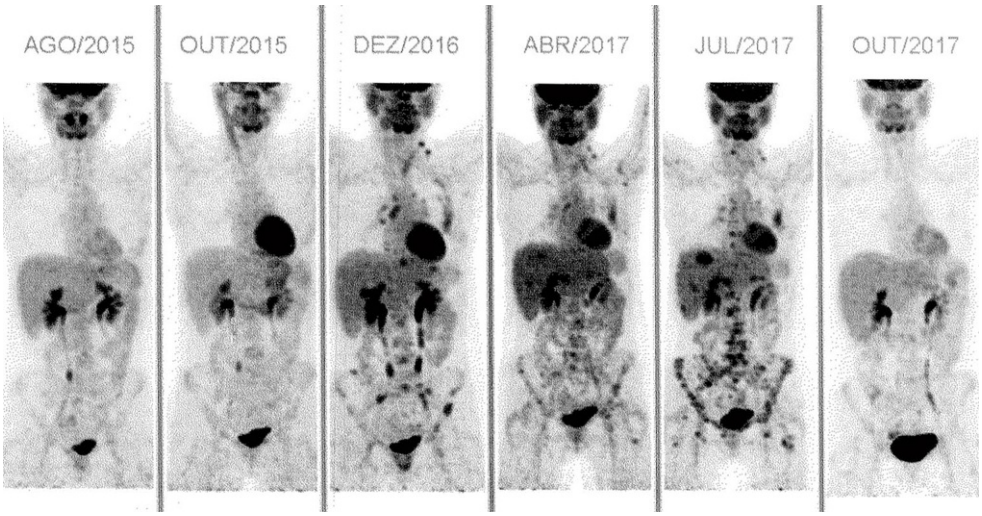
Introduction: Oncologic Deep Local Hyperthermia (ODLH) is a procedure that is usefull at obtaining cancer disease control with a synergistic approach. We describe the experience of the Interventional & Hyperthermic Oncology department, Institute Khuab, Comprehensive Tumor Center Barcelona, treating advanced malignancies. This institution has treated more than 5.000 advanced cancer patients since 2004.

Objectives: To describe our experience from the opening of our Deep Local Hyperthermia treatments in the setting of a comprehensive advanced tumor center.

Materials and methods: From July 2017 to January 2018 we have treated 26 malignant cases. Of those, 5 lung tumors, 4 ovarian, 4 peritoneal carcinomatosis, 3 advanced breast tumors, 2 brain, 2 metastatic liver cancers, 2 cervical, 1 lymphoma, 1 rectal, 1 bone and 1 bladder cancer. The device employed to perform Hyperthermia treatments is a CELSIUS42 from Cologne, Germany. Only 2 patients had ODLH combined with complementary or best supportive care in a palliative setting. Twenty four cases had ODLH combined with other oncologic treatment: 4 patients combined with radiotherapy, 4 with immunotherapy and 16 with chemotherapy. All the patients continued their oncologic treatments after the hyperthermia procedure was performed.

Results: The distribution of the cases treated reflects a miscelaneous group of advanced tumors. We have not recorded any major complication or toxicity. Only two small blisters due to the learning curve of the operative personnel were observed. It is too early to evaluate clinical responses clearly attributable to the hyperthermia itself, but we will describe the relevant cases. Survival is not recorded due to the short follow up.

Fig. 1 P38.



Conclusions: ODLH is a safe synergistic oncologic treatment in the advanced tumor setting. We have not seen any toxicity in our short experience. Acceptance of patients and regional oncology specialists has been a key of success. These results encourage us to engage our efforts towards a broad application of hyperthermic treatments and to initiate clinical studies to determine favorable clinical settings for the use of hyperthermia.
Keywords: Hyperthermia, Oncology, Cancer, Metastases, Combined oncology treatments

P 40

Whole body thermochemotherapy – a treatment passing into silence?

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Introduction: While different techniques of local hyperthermia are intensively researched and used in more and more countries whole-body-hyperthermia is becoming gradually marginalized.
Objective: To provide a literature overview on the evidence for whole body hyperthermia for different cancer entities.
Material and methods: A literature search was performed for publications on whole body hyperthermia and cancer.
Results: Data was identified for breast cancer, ovarian cancer, metastatic colorectal cancer, pancreatic cancer, metastatic prostate cancer and metastatic sarcoma.
Conclusion: Many old studies showing good and promising results for whole body hyperthermia where identified.

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The successful antibiotic augmented thermal eradication of chronic lyme disease

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Introduction: It is scientifically proven that the *Borrelia burgdorferi* bacterium is thermolabile. It is killed at a temperature of 41.6 °C. The thermolability is scientifically proven. Systemic whole-body hyperthermia (SGHT) not only kills the Borrelia, but also activates the body's immune system, especially macrophages and natural killer (NK) cells. This allows the bacteria to be eliminated. In addition, the activity of antibiotics is increased about 16 times by a temperature increase, e. g. per 2 degrees.
Objectives: In my presentation, I explain the effectiveness of the "Antibiotics Augmented Thermoeradication" (AAT) we have developed for the treatment of patients with chronic Borrelia infection and its late sequelae.
Material and methods: We have successfully treated more than 800 chronic Lyme disease patients with AAT and have seen drastic improvements as AAT kills the Borrelia wherever they are in the body, immediately halting the production of neurotoxins. For the elimination of neurotoxins, we have developed our own and individually adapted detoxification programs. The endocrine disorders commonly present in chronic Lyme disease, such as endocrine disorders, hypothyroidism or adrenal insufficiency must be eliminated as well as sexual disorders.
Results: The almost always present intestinal symbiosis (leaky good) can also be recognized and treated.

Because the chronic Lyme disease causes multifunctional disturbances and can imitate almost all clinical patterns, the therapy must also be complex.

Conclusion: The focus is on the elimination of Borrelia by the SGHT in combination with antibiotics, everything else is then a cura posterior, which ensures the success achieved by the whole body hyperthermia and leads the patients back to life after a long history of suffering, to a life without Lyme disease.