24th Annual Meeting of the EUROPEAN SOCIETY for HYPERTHERMIC ONCOLOGY

In conjunction with:
The third ESHO “Educational day”, June 13, 2007

Prague, Czech Republic, June 14 - 16, 2007
The New Generation Designed by BSD
BOOK OF ABSTRACTS

24th Annual Meeting of the EUROPEAN SOCIETY for HYPERTHERMIC ONCOLOGY

In conjunction with:
The third ESHO “Educational day”, June 13, 2007

Prague, Czech Republic, June 14 - 16, 2007
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<th>Time</th>
<th>EDUCA TIONAL DAY</th>
<th>Thursday, June 14, 2007</th>
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<tr>
<td>09:00</td>
<td>Welcome address</td>
<td>08:00 Opening</td>
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<td>09:10</td>
<td>Cellular response to heat</td>
<td>08:15 Plenary lecture</td>
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<td>10:55</td>
<td>Coffee break</td>
<td>09:00 Technological developments</td>
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<td>11:25</td>
<td>Cellular response to heat</td>
<td>10:30 Coffee break</td>
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<td>12:00</td>
<td>&quot;Feel-free-to-ask&quot; lunch break</td>
<td>11:00 Breast cancer and superficial tumors</td>
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<td>12:35</td>
<td>Vascular mediated responses to heat</td>
<td>12:30 Lunch plus poster viewing</td>
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<td>13:45</td>
<td>Vascular mediated responses to heat</td>
<td>14:00 Cervical cancer</td>
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<td>15:30</td>
<td>Coffee break</td>
<td>15:00 Biological developments</td>
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<td>Vascular mediated responses to heat</td>
<td>16:00 Tea break</td>
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<td>17:10</td>
<td>Round table: ask the professors</td>
<td>16:30 Kim awards</td>
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<td>18:00</td>
<td>Welcome drink both for Educational Day and ESHO participants</td>
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Wednesday, June 13, 2007

**EDUCATIONAL DAY**

- Welcome address
- Cellular response to heat
- Coffee break
- Cellular response to heat
- "Feel-free-to-ask" lunch break
- Vascular mediated responses to heat
- Coffee break
- Vascular mediated responses to heat
- Round table: ask the professors
- Welcome drink both for Educational Day and ESHO participants

Thursday, June 14, 2007

- Opening
- Plenary lecture
- Technological developments
- Coffee break
- Breast cancer and superficial tumors
- Coffee break
- Lunch plus poster viewing
- Cervical cancer
- Biological developments
- Tea break
- Kim awards
**Friday, June 15, 2007**

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<tr>
<td>08:00</td>
<td>Plenary lecture</td>
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<td>10:20</td>
<td>Break</td>
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<td>12:05</td>
<td>Discussion &amp; closing remarks</td>
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<td>12:30</td>
<td>Lunch plus poster viewing</td>
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<td>14:00</td>
<td>Sarcomas and paediatric hyperthermia</td>
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<td>14:45</td>
<td>ESHO-BSD Award</td>
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<td>15:15</td>
<td>Tea break</td>
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<td>16:00</td>
<td>Round Table</td>
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<td>Round Table</td>
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<td>18:00</td>
<td>ESHO General Assembly</td>
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<td>20:00</td>
<td>Social dinner at Café Slavia</td>
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**Saturday, June 16, 2007**

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<th>Time</th>
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<tr>
<td>08:00</td>
<td>Plenary lecture</td>
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<td>08:45</td>
<td>Head &amp; neck and brain tumors</td>
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<td>10:15</td>
<td>Gastro-intestinal and prostate cancer</td>
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<td>11:45</td>
<td>Technological developments</td>
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<td>12:30</td>
<td>ESHO Students Awards</td>
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<tr>
<td>12:45</td>
<td>Closing remarks</td>
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June 13th, 2007 - Educational Day

09:00 Welcome address
   Horsman (Aarhus)

Cellular response to heat

09:10 Direct effects: cell killing and molecular event
   Roti Roti (St. Louis)

09:45 Radiosensitization
   Iliakis (Essen)

10:20 Heat shock protein induction
   Calderwood (Boston)

10:55 Coffee break

11:25 A matter of degree: effects of temperature on immune and vascular parameters of the tumor microenvironment
   Repasky (Buffalo)

12:00 Translation into the clinic
   Issels (München)

12:35 “Feel-free-to-ask lunch break”:
   Meet the professors
June 13th, 2007 - Educational Day

Vascular mediated responses to heat

13:45 Angiogenesis and vascular targeting
Horsman (Aarhus)

14:20 Thermosensitive liposomes
Dewhirst (Durham)

14:55 Targeted regulation of lymphocyte-endothelial axis by thermal therapy
Evans (Buffalo)

15:30 Coffee break

16:00 Non-invasive imaging with DCE-MRI
Lüdemann (Berlin)

16:35 Antiangiogenic therapy translated to the clinic: hype, hope or help?
Dahl (Bergen)

17:10 Round Table: ask the professors

18:00 Welcome Drink
(both for Educational Day and ESHO participants)
June 14th, 2007

08:00  Opening

08:15  Plenary Lecture  
Horsman (Aarhus)  
Hyperthermia as a potent radiosensitizer: current status and future prospects  
Chair: Haveman (Amsterdam)

Technological developments: highlights, treatment planning and thermal modeling  
Chair: Bardati (Roma), Crezee (Amsterdam)

09:00  Clinical Imaging of hypoxia with positron emission tomography  
Wong (Durham)

09:15  Thermotherapy using magnetic nanoparticles  
Jordan (Berlin)

09:30  SAR measurements and FDTD calculations in tissue-equivalent phantoms for different types of CFMA-434 applicators for superficial hyperthermia  
Kok (Amsterdam)

09:45  First clinical experience with the AMC-8 locoregional hyperthermia system with 3-D power control  
Crezee (Amsterdam)

10:00  Novel accurate method to treat conformal boundaries within thermal simulations  
Neufeld (Zurich)

10:15  Planning hyperthermia with AMIRAHyperPlan. Clinical experiences  
Cho (Berlin)

10:30  Break

Breast cancer and superficial tumors  
Chair: Hulshof (Amsterdam)

11:00  Progress on conformal microwave array applicators for heating large area chest wall disease  
Stauffer (Durham)
June 14th, 2007

11:15 Prescriptive quantitative SAR dosimetry for chest wall recurrences
Van Rhoon (Rotterdam)

11:30 A phase I study of thermal sensitive liposomes containing Doxorubicin in combination with hyperthermia in breast cancer patients with chest wall recurrence
Jones (Durham)

11:45 Re-irradiation and hyperthermia after microscopic complete resection for locoregional recurrent breast cancer in previously irradiated area: an update
Oldenborg (Amsterdam)

12:00 Local hyperthermia and radiation therapy in the treatment of recurrent pretreated superficial tumors
Gabriele (Torino)

12:15 The palliative effect of radiotherapy and hyperthermia in recurrent superficial melanoma
Hulshof (Amsterdam)

12:30 Lunch plus poster viewing

Cervical cancer
Chair: Dahl (Bergen), Piotrkowicz (Warsaw)

14:00 Temperature and power data analysis of cervical cancer patients treated with hyperthermia during 1991-2005
Fatehi (Rotterdam)

14:15 A radiofrequency hyperthermia with simultaneous interstitial HDR brachytherapy in advanced cervical cancer: interim analysis of a randomized trial
Piotrkowicz (Warsaw)

14:30 The Dutch Deep Hyperthermia Trial: updated results in cervix cancer
Franckena (Rotterdam) (ESHO Student Award winner)

14:45 Hyperthermia in the treatment of gynaecologic cancer: a review of the cervix cancer experience
Jones (Durham)
June 14th, 2007

**Biological developments: biological modifiers of thermal response, liposome delivery systems**
*Chair: Horsman (Aarhus), Vujaskovic (Durham)*

15:00 Hyperthermia enhances anti-angiogenic effect on manganese porphyrin mimetic of superoxide dismutase
*Vujaskovic (Durham)*

15:15 The new vascular disrupting agent - OXI4503 - significantly enhances the anti-cancer effect of radiotherapy combined with mild hyperthermia
*Hokland (Aarhus) (ESHO Student Award winner)*

15:30 Vascular disrupting agents for improving thermoradiotherapy: dependency on drug type and heating temperature
*Horsman (Aarhus)*

15:45 What do we mean by “heating the tumor”?
*Szasz (Godollo - Budapest)*

16:00 **Tea-break**

**Kim awards**
*Chair: Kim (Taegu), Van Rhoon (Rotterdam)*

16:30 Introduction
*Kim (Taegu)*

16:40 Early global gene expression in vivo and in vitro after treatment with hyperthermia
*Borkamo (Bergen)*

16:55 Numerical FEM models for the prediction of temperature during superficial MW hyperthermia treatments
*Candeo (Padova)*

17:10 Hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis. How to establish the appropriate dose of cytostatics?
*Marvan (Prague)*
June 14th, 2007

17:25 In vitro stability and drug release properties of phosphatidyl-glycerol-glycerol containing thermosensitive liposomes with encapsulated doxorubicin
Hossann (Munich)

17:40 The hypercollar: a novel phased array applicator for hyperthermia treatment in the neck
Paulides (Rotterdam)

17:55 Organ preserving quadrimodal treatment of T1-2N0M0 bladder cancer: results after trans-urethral resection and simultaneous radiochemo-therapy (combined with regional deep hyperthermia)
Wittlinger (Erlangen)

18:10 Close
June 15th, 2007

08:00 Plenary Lecture
Hyperthermia in Paediatric Oncology: basic essentials and future directions
Wessalowski (Düsseldorf)
Chair: Osinsky (Kiev)

▶▶ BSD users meeting
Chair: Ott (Erlangen), Dall’Oglio (Verona)

08:45 Introduction
Ott (Erlangen), Dall’Oglio (Verona)

09:00 Recent development and perspectives
Turner (Salt Lake City)

09:20 New developments in Treatment Planning
Eisenhardt (Berlin)

09:35 Hyperthermia treatment planning: real time clinical use of model guided steering
Caners (Rotterdam)

09:50 Superficial hyperthermia
Jones (Durham)

10:05 Interstitial hyperthermia
Skowronek (Poznan)

10:20 Break

10:50 Clinical Deep Regional Hyperthermia: two years experience at Oberstaufen
Rigamonti (Oberstaufen)

11:05 Recent advances in MR-guided hyperthermia
Gellermann (Berlin)

11:20 Active treatment protocols - Hyperthermia and Chemotherapy
Wessalowski (Düsseldorf)

11:35 Active treatment protocols - Hyperthermia and Radiation
Van der Zee (Rotterdam)

11:50 New treatment protocols
Hildebrandt (Berlin)

12:05 Discussion and closing remarks

12:30 Lunch plus poster viewing
June 15th, 2007

**Sarcomas and Paediatric Hyperthermia**
Chair: Wessalowski (Düsseldorf)

14:00 Patient-specific focus steering in anular and bowl-shaped phased arrays used in MR-monitored hyperthermia treatment
Maccarini (Durham)

14:15 Combined LAK-therapy and whole body hyperthermia in paediatric cancer treatment
Ismail-Zade (Minsk)

14:30 Regional hyperthermia combined with systemic chemotherapy in the management of locally advanced, high grade soft tissue sarcomas of the extremities, the body wall and the abdomen. Results of the phase III randomized prospective trial (EORTC-ESHO Intergroup trial)
Issels (Munich)

14:45 **ESHO-BSD Award**
Chair: Maluta (Verona)

15:15 Tea-break

**Round Table: what do we know about thermal dose prescription?**
Chair: Gellermann (Berlin), Ott (Erlangen)

Preordinate contributions

16:00 Thermal dose in patients
Van der Zee (Rotterdam)

16:15 How does one decide on an optimal form for thermal dosimetry?
Dewhirst (Durham)

16:30 Thermal dose in radio-sensitization by hyperthermia
Roti Roti (St. Louis)

16:45 Discussion

17:15 **Round table: how can we perform translation research and clinical trials on EU basis? - The experience of EUROTHERM and the OncTherm application to the EU**
Chair: Issels (München)

18:00 **General ESHO assembly**

20:00 **Social dinner at Café Slavia**
June 16th, 2007

08:00  Plenary lecture
       Online steering control by MR-thermometry
       **Gellermann** (Berlin)
       Chair: **Van Rhooon** (Rotterdam)

▷▷ **Head & Neck and brain tumors**
       Chair: **Vrba** (Prague), **Huilgol** (Mumbai)

08:45  RF capacitive hyperthermia system for brain tumors:
       experimental results and thermal modeling
       **D’Ambrosio** (Padova)

09:00  Experience and results with RF hyperthermia:
       approach in glioblastoma
       **Pigliucci** (Roma)

09:15  Thermoradiotherapy and radiochemotherapy of locally advanced
       larynx cancer with lymph nodes metastases
       **Maslennikova** (Nizhny Novgorod)

09:30  A phased array head and neck applicator: measurements
       of the SAR distributions in a cylindrical muscle phantom
       **Bakker** (Rotterdam)

09:45  **Break**

▷▷ **Gastro-intestinal and prostate cancer**
       Chair: **Issels** (München), **Pigliucci** (Roma)

10:15  Presentation of Hyperthermia European Adjuvant Trial (HEAT) in
       resectable pancreatic cancer
       **Issels** (München)

10:30  Clinical application of intraluminale hot water balloons combined
       with locoregional hyperthermia for treatment of oesophageal
       tumors
       **Van Haaren** (Amsterdam)

10:45  Preliminary experience in the treatment of hepatocellular
       carcinoma residuals after RF ablation using CT-fluoroscopy guide
       **Mangini** (Varese)
June 16th, 2007

11:00 Capacitive hyperthermia plus chemotherapy in inoperable pancreatic tumors
Pigliucci (Roma)

Hurwitz (Boston)

11:30 Quality of life in patients with locally advanced prostate cancer treated with radiotherapy plus hyperthermia
Maluta (Verona)

Technological developments: improved methods for hyperthermia delivery
Chair: Gellermann (Berlin), Stauffer (Durham)

11:45 Transperineal microwave thermoablation in patients with benign prostatic hyperplasia: a phase I study with a new mini-choked microwave applicator
Cai (Firenze)

12:00 Biomedical evaluation of the simultaneous external radiation and hyperthermia induced by a miniature EM applicator
Osinsky (Kiev)

12:15 Slot-line array applicator for superficial hyperthermia treatment
Togni (Prague)

12:30 ESHO Students Awards
Chair: Dall’Oglio (Verona)

12:45 Closing remarks and invitation to ICHO 2008
Issels - ESHO president
Vrba - President of the meeting
**Dr. Joe Roti Roti (USA)**
Department of Radiation Oncology, Washington University School of Medicine, St. Louis, MO

**Dr. Georg Iliakis (Ger)**
Institute of Medical Radiation Biology, University Duisburg-Essen Medical School, Essen

**Dr. Stuart Calderwood (USA)**
Molecular and Cellular Radiation Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

**Dr. Elisabeth Repasky (USA)**
Department of Immunology, Roswell Park Cancer Institute, Buffalo, New York, NY

**Dr. Rolf Issels (Ger)**
Hyperthermia Unit, Department of Internal Medicine III, University Hospital Klinikum Großhadern, München

**Dr. Michael Horsman (DK)**
Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus

**Dr. Mark Dewhirst (USA)**
Department of Biomedical Engineering, Duke University, Durham, NC

**Dr. Sharon Evans (USA)**
Department of Immunology, Roswell Park Cancer Institute, Buffalo, New York, NY

**Dr. Lutz Lüdemann (Ger)**
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Dr. Sharon Evans (USA)
Department of Immunology, Roswell Park Cancer Institute, Buffalo, New York, NY

Dr. Johanna Gellermann (Ger)
Department of Radiation Medicine, Campus Berlin Buch, Charité-Universitätsmedizin, Berlin

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Dr. Georg Iliakis (Ger)
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Dr. Jacoba Van der Zee (NL)
Department of Radiation Oncology, Erasmus MC-Daniel den Hoed Cancer Center, Rotterdam

Dr. Gerard Van Rhoon (NL)
Department of Radiation Oncology, Erasmus MC-Daniel den Hoed Cancer Center, Rotterdam

Dr. Rüdiger Wessalowski (Ger)
Clinic of Pediatric Oncology, University Hospital Düsseldorf, Düsseldorf
**ESHO** Conference site (Betlémská kaple)

1. The Betlem Club Hotel
2. Hotel Cloister-Inn
3. Prague Expres Hotel
4. Penzion Attractive
5. Hotel Two golden keys
6. Hotel Modrá Růže
7. Hotel Elite
8 Hotel Adria Praha
9 Hotel City-Inn
10 Novoměstský hotel
11 Hotel Karlin
12 Hotel Krystal
13 Masarykova kolej
Conference site (Betlémská kaple)

1 The Betlem Club Hotel
2 Hotel Cloister-Inn
3 Prague Expres Hotel
4 Pension Attractive
5 Hotel Two golden Keys
ORAL PRESENTATIONS
by chronological order
and
POSTERS
by alphabetical order
Clinical Imaging of Hypoxia with Positron Emission Tomography

Wong, Terence Z.1; Yuan, Hong1; Koch, Vlahovic, Gordana1; Cameron J.2; Evans, Sydney M.2; Lacy, Jeffrey L.3; Petry, Neil A.1; Bida, Gerald T.1; Dewhirst, Mark W.1
1Duke University Medical Center, Durham, NC, U.S.A.
2University of Pennsylvania, Philadelphia, PA, U.S.A.
3Proportional Technologies, Inc., Houston, TX, U.S.A.

Purpose
Hypoxia has prognostic significance in patients with certain malignancies, and is a critical factor in determining the response of solid tumors to chemotherapy and radiation therapy. Furthermore, reoxygenation following hyperthermia correlates with improved treatment outcome, making hypoxia a highly relevant parameter for monitoring hyperthermia therapy. Imaging techniques using positron emission tomography (PET) can provide non-invasive and semi-quantitative measurement of tumor hypoxia in patients. Several PET radiotracers have been developed which selectively accumulate in hypoxic tissues. However, additional considerations are necessary for a radiotracer to be practical for clinical use. These include factors such as commercial production and availability, and radiation dose to the patient. We present preliminary clinical data on two different PET tracers that show promise for clinical evaluation of hypoxia.

Methods and Results
62Cu-diacetyl-bis(N4-methylthiosemicarbazone) (62Cu-ATSM) is a small molecule which readily diffuses into cells, where it is selectively bioreduced and trapped within viable cells under hypoxic conditions. 62Cu-pyruvaldehyde bis(N4-methylthiosemicarbazone) (62Cu-PTSM) is similar to 62Cu-ATSM, but without the selectivity for hypoxic cells, and has been used as a surrogate marker for perfusion. 62Cu is a short-lived positron emitting radionuclide (t1/2=9.7 min). A 62Zn/62Cu generator has been developed to produce 62Cu from the parent 62Zn (t1/2=9.3 hr), which can be delivered to the PET imaging facility on the day of imaging. This generator, along with a rapid radiosynthesis kit, enables 62Cu-ATSM and 62Cu-PTSM to be produced conveniently on-site. The short half-life of 62Cu allows both 62Cu-ATSM and 62Cu-PTSM imaging to be performed serially in a single session.

Discussion
18F-labeled PET radiotracers have great promise for clinical applications. 18F provides superior spatial resolution due to low initial positron energy. In addition, the 2-hour half-life allows 18F radiotracers to be produced commercially and facilitates widespread distribution to PET centers. Practical methods for the radiosynthesis of 18F-EF5 (2-[2-nitro-1H-imidazol-1-yl]-N-[2,2,3,3,3-pentafluoropropyl] acetamide) have been developed. EF5 has been shown to be an accurate surrogate marker for tissue hypoxia both in animal and human studies, and 18F-EF5 has the potential to become an important PET tracer for imaging hypoxia.

Conclusions
18F-EF5 and generator-produced 62Cu-ATSM and 62Cu-PTSM have potential as PET imaging tracers which could be routinely used in clinical PET studies. EF5 may have greater specificity for hypoxia, but the short-lived 62Cu compounds allow relative measurement of two parameters (hypoxia and blood flow) in a single imaging session. The full clinical utility of these tracers for evaluating hypoxia requires further investigation. Preliminary clinical examples of each tracer are shown.

This work supported in part by NIH NCI P01 CA42745-14.
The biological effectiveness of heat in treating cancer is known for decades and many of the corresponding molecular mechanisms are understood. Elevation of tissue temperature to above 41°C is termed hyperthermia, more than 46°C are called thermoablation. Hyperthermia alters the function of structural and enzymatic proteins within cells as a function of time and temperature, which in turn alters cell growth and differentiation, radiation sensitivity and resistance to certain drugs used in chemotherapy and also can induce apoptosis [1-3]. Thermoablation causes coagulation of cellular proteins, i.e. direct cell destruction.

The major problem of most conventional thermotherapy systems used is to achieve homogeneous heat distribution and deep regional therapeutic temperatures in the treated tumor tissue. A failure may either lead to insufficient temperature rise in parts of the tumor, resulting in further tumor growth, or to negative effects on normal tissue by too high temperatures [4].

The MagForce Nanotherapy also termed “thermotherapy using magnetic nanoparticles” or “Magnetic fluid hyperthermia” is a new cancer therapy, which particularly faces these problems. Herein, a magnetic fluid is directly injected into a tumor and subsequently heated in an alternating magnetic field (100 kHz and variable field strengths of 0-18 kA). The magnetic fluid NanoTherm® MFL AS (MagForce Nanotechnologies AG, Berlin) consists of superparamagnetic iron-oxide nanoparticles in aqueous solution with an iron concentration of 112 mg/ml. The iron-oxide core (diameter 15 nm) is covered by an aminosilane type shell. The particles generate heat in an alternating magnetic field by Brownian and Néel relaxation processes.

This method has been developed by our group in more than 15 years of research at the Charité - University Medicine Berlin and is one of the first applications of nanotechnology in medicine [5].

First Clinical Experience

From August 2003 to July 2004 we performed the first phase-I trial on MagForce Nanotherapy with 14 glioblastoma multiforme patients [6]. All patients of this trial received stereotactic injection of the magnetic fluid into the tumor. Before starting thermotherapy, the position of the instilled nanoparticles was determined by computed tomography (CT). These data were matched to presurgical MR images by a specially designed software (MagForce NanoPlan®), thus allowing the calculation of the expected heat distribution within the treatment area in dependence on the magnetic field strength [7].
Another feasibility study enrolled 35 patients with local relapses of different tumor entities (e.g. cancer of the rectum-, ovarian-, prostate-, cervical- carcinoma and sarcoma). All of these patients received thermotherapy in combination with radio- or chemotherapy [8].

A feasibility study with 10 patients with pre-treated prostate carcinoma, another main focus in the clinical use of the Nanotherapy, was closed in June 2006. The nanoparticles were injected transperineally into the prostate under transrectal ultrasound guidance and fluoroscopy [9, 10]. Another phase I study started in March 2006 on esophageal cancer, which, so far enrolled eight patients. Two phase II trials are in progress to evaluate the efficacy of the new approach on 72 patients with recurrences of glioblastoma multiforme and on 130 patients suffering from prostate carcinoma.

According to the experiences derived from these first clinical trials, the Nanotherapy is effective and can be applied without complications. The heat treatments were tolerated well without or with only minor side effects depending on the tumor location with therapeutically effective thermal doses. The follow-up showed encouraging results for severe oncological diseases.

Acknowledgement

This project was sponsored by The European Regional Development Fund (ERDF) - Project “NanoMed” and the BMBF, Nanobiotechnology, Project “TAN”.
SAR MEASUREMENTS AND FDTD CALCULATIONS IN TISSUE-EQUIVALENT PHANTOMS FOR DIFFERENT TYPES OF CFMA-434 APPLICATORS FOR SUPERFICIAL HYPERTERMIA

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1Dept. Radiation Oncology, Academic Medical Center, University of Amsterdam, The Netherlands. 2Institute of Scientific Research ‘Istok’, Moscow, Russia.

Introduction
Contact Flexible Microstrip Applicators (CFMAs) have an operating frequency of 434 MHz and are applied for superficial hyperthermia in e.g. melanoma and chest wall recurrences. The applied bolus thickness and the effective field size are important parameters for clinical application. Temperature information during clinical hyperthermia is limited, since invasive measurements are limited to avoid implant risks for the patient. Therefore, hyperthermia treatment planning is very useful to analyse the behaviour of CFMAs in different clinical setups (patient anatomies).

Aim: The first step in applying treatment planning is to compare simulated and measured SAR distributions for different types of CFMAs in tissue-equivalent phantoms.

Methods
Measurements: Measurements were performed using a flat rectangular muscle-equivalent phantom (\(\varepsilon_r=77\)) and a rectangular muscle-equivalent phantom with a superficial fat-equivalent layer (\(\varepsilon_r=5.5\)) of 1 cm. A thermocouple sheet at 1 cm depth was used to measure the SAR distribution by applying a power pulse technique. Various applicator sizes were examined, with a bolus thickness varying from 0.5 to 2 cm. The active radiating electrodes of the applicator had a rectangular shape of 7\(\times\)20 cm\(^2\), 16\(\times\)15 cm\(^2\), 29\(\times\)21 cm\(^2\), 21\(\times\)20 cm\(^2\), or 20\(\times\)29 cm\(^2\). The measurement accuracy is approximately 10%.

Simulations: Simulations were performed using our FDTD-based treatment planning system at a resolution of \(x\times y\times z=2\times 2\times 1\ \text{mm}^3\). The \(z\)-axis was modelled perpendicular to the electrode plates of the applicator. The computational domain was truncated using a perfectly matched layer absorbing boundary condition, which absorbs the electromagnetic waves as if the domain was not truncated.

Analysis: Measured and simulated SAR values were normalised. The maximum value was assigned 100%. The measured effective field size at 1 cm depth, i.e. the area contained by the 50% SAR contour, was determined and compared with the simulations. Furthermore, contour plots of the measured and simulated SAR at 1 cm depth were created and compared.

Results
A good correspondence was found between measurements and simulations. The effective field size in the fat-muscle phantom ranges between \~60 cm\(^2\) and \~300 cm\(^2\), depending on the sizes of the antenna. Both measurements and simulations showed a split-up of the SAR focus when a large bolus thickness (~2 cm) was used. Differences between measured and calculated SAR were less than 10%.

Conclusion
CFMA-434 applicators for superficial hyperthermia can be modelled with an acceptable accuracy.
FIRST CLINICAL EXPERIENCE WITH THE AMC-8 LOCOREGIONAL HYPERTHERMIA SYSTEM WITH 3-D POWER CONTROL

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Introduction
The thermal dose achieved in clinical hyperthermia is often suboptimal due to the incidence of treatment limiting hot spots in normal tissue. The AMC-8 loco regional hyperthermia system was designed to cope with this problem by 3D power steering, using two rings of four waveguides (24x30cm) operating at 70 MHz with independent power and phase steering. This system replaces our AMC-4 system with a single ring of four waveguides (24x30cm).

Purpose
Performance and clinical feasibility of the AMC-8 system is tested in the first patients treated, after extensive measurements in phantoms and computer simulations.

Methods
Patients with pelvic malignancies are treated with 5 hyperthermia sessions. The AMC-8 system is clinically introduced in two steps, with 5 patients in each step.

Step (1) compares both systems without 3-D steering. Each patient is treated 3 times using the AMC-4 and twice using the AMC-8 system, using one ring of 4 antennas. This step serves to compare the effective power output of both systems and tests system behavior.

Step (2) compares 2-D with 3-D steering of the AMC-8 system. Each patient is treated 3 times using 4 antennas and twice using 8 antennas of the AMC-8 system.

During each session the steady state temperature expressed as $T_{90}$, $T_{50}$, $T_{10}$, power and SAR (using a $\Delta T$ pulse) are scored. Toxicity is determined by scoring the incidence of treatment limiting hot spots.

Results
Step (1) is complete, five patients have been treated. No significant difference in power (608 and 617 W, respectively) or tumour temperature was found. The tumour temperatures for the AMC-4 and AMC-8 system (4 antennas), expressed as $T_{90}$, $T_{50}$, $T_{10}$, were 40.0°C, 41.2°C, 42.4°C and 40.1°C, 41.5°C, 42.6°C, respectively. Toxicity is acceptable for the AMC-8 and conforms toxicity found for the AMC-4.

Step (2) is not complete yet. The first patients have been treated and the 3D steering works well. Results on tumour temperature and toxicity are analysed when the full number of five patients have been treated.

Conclusion
First clinical experience with the AMC-8 system shows its clinical feasibility, there is no increase in toxicity. After completion of the acceptance test for eight antennas all pelvic tumours will be treated with the AMC-8 system.
The mechanism by which hyperthermia interacts with the body is only partly understood - however, it is clear that the temperature increase causes the effects. Therefore, the goal should be to increasingly use thermal simulations instead of studying only the SAR (specific absorption rate) distribution. When modeling temperature effects, the correct handling of boundary conditions is crucial. Especially superficial hyperthermia can produce temperature distributions that are strongly influenced by surface cooling. Unfortunately, the commonly used finite-difference time-domain (FDTD) technique suffers from staircasing errors due to the rectilinear grid used for the discretization. Therefore any method that reduces these staircasing errors in FDTD is of major importance.

The overestimation of the boundary area is identified as the main source of the problem and increasing the grid resolution does not help. Instead it is proposed, to interpret the FDTD formulas from an energy-flux point of view. The fluxes can then be rescaled using local correction factors. A series of possible factors based on the local surface orientation is proposed and discussed. A simple conformal correction scheme that can easily be integrated into any existing implementation is presented. Some error calculations in 2D are shown; the code as well as the new scheme are validated by simulating two analytically solvable cases. Additionally a number of real world simulations drawn from superficial hyperthermia are presented to illustrate the importance of using a conformal scheme.

The new scheme results in considerably improved, orientation-independent boundary behavior and reduces the inhomogeneities due to staircasing effects. The overall behavior is excellent even for relatively coarse meshes, and local errors can be arbitrarily reduced by reducing the grid step. The conformal correction does not affect the stability of the FDTD scheme. The correction can easily be generalized to graded meshes.

A flexible implementation of the conformal boundary scheme is presented which allows the user to specify different conditions for every interface between two different tissues. A wide range of possible boundary types can be used, which proves valuable for the simulation of bolus cooling, major blood vessels and internal cavities. Furthermore, internal boundary conditions effectively decouple subregions of the computational domain. By restricting the solver to active regions, domains of low density (air) or high thermal conductivity (metal) can be ignored resulting in a considerably increased stable timestep.

Figure 1: Simulation results obtained for a spherically symmetric problem using the standard scheme (left) and the conformal correction at identical (middle) and lower resolution (right).
PLANNING HYPERTHERMIA WITH AMIRAHYPERPLAN®, CLINICAL EXPERIENCES

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Material and Methods
Cases will be presented where planning the hyperthermia with AmiraHyperplan® is implemented. After performing a CT scan and segmentation of the body, the planning is performed. Different parameters of possible hyperthermia are presented. Treatment is performed in the Sigma 60 (BSD, Utah, USA).

Results
Parameter changes in the planning of hyperthermia lead to immediate results with in the patients. The planning can display the side effects of hot spots prior to treatment and can also track the side effects that occur during the treatment. This planning can be well implemented in pelvic as well as in abdominal treatments.

Conclusion
Planning hyperthermia is crucial for optimal treatment. This planning can change the hyperthermia within minutes.
PROGRESS ON CONFORMAL MICROWAVE ARRAY APPLICATORS FOR HEATING LARGE AREA CHEST WALL DISEASE

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Purpose

Previous studies have reported the computer modeling and theoretical performance of single and multiple antenna arrays of Dual Concentric Conductor (DCC) square slot radiators driven at 915 and 433 MHz. Practical CAD designs of microstrip antenna arrays constructed on thin and flexible printed circuit board (PCB) material were reported which evolved into large Conformal Microwave Array (CMA) sheets that can wrap around the human torso for delivering microwave energy to large areas of superficial tissue. Although uniform and adjustable heating patterns have been demonstrated from CMA applicators in simple homogeneous phantom loads, this effort describes additional design efforts required to achieve good coupling and efficient heating from large conformal array applicators treating chestwall recurrent breast cancer patients with an irregular tissue surface overlying contoured anatomy.

Methods

Recent work has extended the theoretical optimization of DCC antennas to improve radiation efficiency of each individual aperture and reduce mismatch reflections, radiation losses, noise, and cross coupling of the feedline distribution network of large array configurations. Design improvements have also been incorporated into the supporting bolus structure to maintain effective coupling of DCC antennas into contoured anatomy and to monitor and control surface temperatures under the entire array. New approaches for non-invasive monitoring of surface and sub-surface tissue temperatures under each independent heat source are described that make use of microwave radiometry and flexible sheet grid arrays of fiberoptic thermal sensors.

Results

Efforts to further improve the CMA applicator radiation pattern and clinical patient interface and move from simple planar rectangular shapes to contoured vest shaped applicators that accommodate entire disease in a larger number of patients are summarized. This includes results in the following areas:

- Changed flexible printed circuit board (PCB) feedline network from open microstrip to buried coplanar waveguide structure to increase efficiency and improve noise immunity of antennas
- Designed and tested new triangular and pentagon shaped DCC antennas that provide smooth SAR contour around the perimeter of vest shape applicators with curving sides
- Integrated non-invasive surface tissue thermometry for more comprehensive monitoring and control using radiometry and fiberoptic array thermal monitoring sheet (TMS) technologies
- Improved bolus design to ensure tight comfortable fit of CMA on convex and concave anatomy
• Measured conformity of CMA to realistic contoured patient anatomy
• Quantified flow balance and temperature uniformity across large coupling bolus surface

**Conclusion**

By applying heat more uniformly to large areas of contoured anatomy, the CMA applicator resulting from the above enhancements should improve the quality of heat treatment and expand the number of patients that can benefit from effective heating of superficial disease in combination with radiation or chemotherapy.

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PRESCRIPTIVE, QUANTITATIVE SAR DOSIMETRY FOR CHEST WALL RECURRENCES

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Purpose

Quality of a hyperthermia treatment is a key factor for treatment outcome. Improvement of hyperthermia treatment quality is severely hampered by the lack of a single prognostic parameter for treatment outcome and our inability to prospectively prescribe the thermal dose. An absolute requirement for future solutions to this problem is that they must be “economically as well as clinically acceptable“. Adequate monitoring of hyperthermia treatment quality is a very difficult task. Neither the patient nor the clinician appreciates extensive interstitial thermometry. Non-invasive thermometry has not been demonstrated to provide the required spatial resolution and temperature sensitivity for superficial hyperthermia. Fortunately, the presently available advanced hyperthermia treatment planning systems provide an excellent opportunity to calculate 3D SAR- or temperature distributions and derive predicted HT-dose parameters from these distributions.

Methods

An FDTD simulation package (SEMCAD, Schmid & Partner Engineering AG, Zürich, Switzerland) is used to predict the SAR distribution for a 2x2 array of Lucite cone waveguide applicators. The 3-D model predictions are validated against 3-D measured SAR distributions using the well-accepted gamma-method. In this manner the relative SAR distributions as predicted by the FDTD model are transferred to quantitative SAR distributions providing the possibility to correct for the different efficacy of the four LCA applicators. The feasibility to quantitatively predict the 3-D SAR distribution in a realistic anatomy is demonstrated for a patient with a tumor located on the chest wall. The HT field involves all macro- and microscopic tumor and should cover the whole RT-field.

Results

A good quantitative agreement was found between the measured and predicted 3-D SAR distribution. The 3-D SAR prediction for the patient shows that the umbrella-style array configuration basically represents a “heating the base” approach: the applicators deposit most their EM power at the tissue below their footprint. The iso-surface of about half the maximum SAR value does not cover the center of the tumor.

Conclusions

The result of this explorative study demonstrates that the SEMCAD model provides reliable predictions of the SAR pattern of the LCA and can be used safely to study the performance of the LCA under clinical conditions. The next step of this project is to apply treatment modelling for SHT in a well-defined group of patients to investigate the potential of predicted 3D SAR distribution as source for a dose parameter that is prognostic for treatment outcome.
A PHASE I STUDY OF THERMALLY SENSITIVE (TS) LIPOSOMES CONTAINING DOXORUBICIN (THERMODOXTM; TDOX) IN COMBINATION WITH HYPERThERMIA (HT) IN BREAST CANCER PATIENTS WITH CHEST WALL (CW) RECURRENCE

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4Celsion Corporation Columbia, MD USA

PURPOSE

Pre-clinically, TS liposomes containing chemotherapy improve drug delivery and tumor control when combined with HT compared to non-liposomal formulations or TS liposomes without HT. As the CW is a common site for breast cancer recurrence, this phase I study utilized TS liposomes containing doxorubicin [TDox, Celsion] in combination with CW HT to define a dose schedule for this multimodality therapy.

METHODS

Patients with bx proven breast adenocarcinoma (>1 cm diameter/<3 cm thick) on the CW and having progressed on chemo and (if ER+) hormonal therapy were eligible. Prior CW radiation therapy was not required and distant mets were allowed. Prior anthracycline dose was limited to < 450mg/m² (Doxorubicin) or 900mg/m² (Epirubicin). Dose escalation of TDox followed a standard 3+3 design (20, 30, 40, 50, 60mg/m² q 21 d for up to 6 cycles). After TDox infusion (30 min), HT was administered for 1 hr using the BSD 500 (Salt Lake City) for a goal of 40–42°C. Response was measured using CT, digital photos, and infrared (IR) imaging prior to cycles 3, 5, and post cycle 6.

RESULTS

To date, 7 pts have accrued (6 pts with prior anthracycline tx) and no dose limiting toxicities have been seen. In the heated areas, 1 CR, 2 PR, 3 SD have been seen. One patient had a PR in the heated area but progressed in the non-heated area after 2 cycles. Infared imaging prior to cycles 3 and 5 correlated with disease response.

CONCLUSION

TDox combined with HT offers a potential treatment option for CW recurrence. Activity to date suggests that the combination of a TS liposome with HT improves anti-tumor effects on the CW compared to non-liposomal chemotherapy alone.

Supported in part by P01 CA42745-14.
RE-IRRADIATION AND HYPERTERMIA AFTER MACROSCOPIC COMPLETE RESECTION FOR LOCOREGIONAL RECURRENT BREAST CANCER IN PREVIOUSLY IRRADIATED AREA: AN UPDATE

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Background
Local control of locoregional recurrent breast cancer in previously irradiated area is poor. Retrospectively a cohort of 77 patients was analysed to evaluate the therapeutic effect and side effects of adjuvant re-irradiation (RT) and hypertermia (HT) for locoregional recurrent breast cancer in previously irradiated area, after excision or complete remission (CR) after chemotherapy (CT). All patients treated in the AMC from 1979-2001 were included.

Patients/methods
All patients, 76 female and 1 male, were previously irradiated to an equivalent dose of \( \geq 50 \) Gy in 5 weeks and most had received one or more lines of systemic therapy. Primary tumor stage included stage 1-4 (37.7, 36.4, 13 and 1.3%, respectively). Concurrent metastases occurred in 5 (6%) patients. Thirty patients (39%) had one or more previous locoregional recurrences before current treatment. Median time interval between primary treatment and current recurrence was 67 months. At start of RT+HT there was no macroscopically detectable tumor. This was achieved by surgery in 74 patients and by CT in 3 patients.

RT for the current recurrence consisted of 20-40 Gy/ 3-5 weeks, given twice a week. Four (1-9) sessions of superficial hypertermia were added once a week within 60 minutes after radiation, using CFMA-434 MHz applicators. Aim temperature was 41-43°C for one hour. Temperatures were measured on the skin and occasionally also invasively, using 7 sensor thermocouples. Different flexible CFMA applicators were applied, depending on the size and location of the target area.

Results
16 out of 77 patients had invasive temperature measurements. Mean steady state \( T_{10}, T_{50}, T_{90} \) were 43.2 (± 0.5), 42.2 (± 0.6), 41.1 (± 0.7) °C measured on the skin and 42.3 (± 0.9), 41.0 (± 0.8), 40.0 (± 0.8) °C measured invasively. Mean CEM 43°C \( T_{90} \) was 22.2 (± 17.9) measured on the skin and 6.6 (± 6.3) measured invasively.

Median survival was 46 months with a median follow up time of 56 months (3-121). 3 and 5-year local control rates were 66% and 61%, respectively.

Predictors for local control were: number of previous recurrences, time interval from start of the primary treatment to the current loco-regional recurrence and original TNM classification. So far, none of the thermal parameters analysed correlated with local control.

Most commonly seen early complications were blisters (22.1%), ulceration (13%) and fat necrosis (1.3%) Severe late toxicity included osteo radionecrosis (11.7%), frozen shoulder (10.4%), rib fracture (2.6%) and brachial plexopathy (1.3%)

Discussion/Conclusion
Interpretation of these results is difficult due to the small size and heterogeneity of this group. However, the combination of resection of macroscopic tumour, re-irradiation and hypertermia appears to achieve good loco-regional control with an acceptable risk of side effects, particularly in view of the poor prognosis and resistance to previous treatments.
LOCAL HYPERTHERMIA AND RADIATION THERAPY IN THE TREATMENT OF RECURRENT PRETREATED SUPERFICIAL TUMOURS

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In this study 48 patients with superficial recurrent or metastatic lesions (< 3 cm in depth from the body surface) were enrolled. Patients were divided into four different groups depending on the site of tumour lesion (breast or chest wall -G1-, head and neck-G2-, melanoma-G3-and others-G4)(See table). All of them were previously submitted to other anticancer treatments and two third also experimented radiation. In particular 100% of G1, 90% of G2, 83 % of G3 were surgically treated. Most of them received chemotherapy contemporary to surgery (90% of patients ) and some of them received radiotherapy also (92% of G1, 55% of G2; 100% of G3 and G4. therapy. In this study patients were irradiated using megavoltage photons or electrons. Dose fraction was 1.8 to 2 Gy per day, 5 days a week. Both previously irradiated and unirradiated patients received from 20 Gy to 60 Gy depending on the location of the previous dose. Alba Hyperthermia system operating at 434 MHz/45-75W was used for external heating with alfa or beta CCMAs applicators depending on the lesion size and depth. Temperature ranged from 38,5°C (T_min) to 44°C (T_max). Maximal allowed temperature was 45°C. Probes were located on the skin surface. Hyperthermia treatment was delivered twice a week during radiation therapy session. Tumour site was kept at an average temperature of 41 °C for 30 minutes. Skin cooling system never exceeded 37°C on the skin surface. The effects of the combined treatment were evaluated in terms of complete response (CR) and partial reponse (PR) at 6 months and persistent local control in the following 18 months. 96 % (68 % CR + 28 % PR) of G1, 60 % (30 % CR + 30 % PR) of G2, 53 % (35 % CR + 18 % PR) of G3, and 50 % of G4 showed sensitivity to the combined treatment (See Table). Among sensitive lesions local control at 18 months was 72 % for G1, 50 % for G2, 44 % for G3 and 50 % for G4 (Table II).Results obtained are in agreement with literature. In particular we can confirm that this combination is effective in the group of patients previously irradiated, for whom giving a full dose additional radiotherapy was not possible. This study also confirms that hyperthermia treatment performed with modern equipments is a safe method. Sessions, in fact, were generally very well tolerated. None of our patients experienced severe, neither acute or chronic, injuries (data not shown).We confirm efficacy of combining radiation therapy to hyperthermia. Local hyperthermia is feasible, effective and safe. It improves patients outcome.

<table>
<thead>
<tr>
<th>Lesions</th>
<th>No of patients</th>
<th>Age (years)</th>
<th>Tumor size (cm)</th>
<th>Follow up % (3 months)</th>
<th>Follow up % (18 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CR</td>
<td>PR</td>
</tr>
<tr>
<td>Breast and chest wall</td>
<td>25</td>
<td>65 (52-80)</td>
<td>1.4 (0.3-7)</td>
<td>68</td>
<td>28</td>
</tr>
<tr>
<td>Melanoma</td>
<td>12</td>
<td>69.7 (51-85)</td>
<td>2.5 (1-4)</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>9</td>
<td>70 (51-89)</td>
<td>3.8 (0.5-8)</td>
<td>35</td>
<td>18</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>52.5 (52-53)</td>
<td>3.5 (3-4)</td>
<td>0</td>
<td>50</td>
</tr>
</tbody>
</table>

RT: radiotherapy; Gy: Greys HT: hyperthermia; CR: Complete response; PR: Partial response; NR: No response; LC: local control; NC: No control.
THE PALLIATIVE EFFECT OF RADIOTHERAPY AND HYPER- THERMIA IN RECURRENT SUPERFICIAL MELANOMA

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Background

Radiotherapy combined with hyperthermia is the standard treatment for recurrent melanoma in the Academical Medical Center of Amsterdam. Two randomized studies reported response rates of > 80% in a selected group of patients (Overgaard 1995, Jones 2005). Question was whether this high response rate could also be achieved in an unselected group of patients in daily clinical practice.

Patients and Methods

Between 1997 and 2005 59 patients with 94 lesions of superficial and recurrent melanoma were treated with radiotherapy and hyperthermia and analyzed retrospectively. All patients had either multiple skin lesions, bulky lesions (skin or lymphnodes > 3 cm) or a combination of both. Hyperthermia was applied in the majority of lesions (86%) with a 434 MHz microwave antenna and in 14% with a 70 MHz antenna. Mostly three sessions were applied (range 1-4). Temperature was measured interstitially in 40 lesions and in 47 lesions the thermal probes were superficially attached to the affected skin. Several radiation schedules were used, but most used schemes were 3 x 8, 3x 9 Gy, 7 x 5 Gy and 8 x 4 Gy. Radiation schedules were converted into their biological equivalent dose with an $a/\beta$ of 4 Gy. Median follow up time was 4 months (range 1-64). Response was evaluated by regression of the tumor size and by regression of the symptoms (palliative response) and was evaluable for 87 lesions. In six lesions the treatment was interrupted because of tumor progression or clinical deterioration. Regression was scored as Complete (CR), nearly Complete (nCR, > 95% remission), partial (PR), stable (SD) or progression (Progr). The following patient and tumor characteristics were evaluated for prognostic value on response and survival: Performance, sex, symptom type, tumor size and localization, presence of lymphnodes or distant metastasis, pre-treatment types, radiation dose and hyperthermia dose.

Results

Overall median survival after start of treatment was 13 months. Tumor regression occurred in 44%, SD in 39% and progression in 17%. A palliative response (CR/PR) occurred in 54%. Significant factors for response were clinical performance, tumor size and radiation dose: 51% of the patients with a WHO performance of I/II (n=74 lesions) showed tumor regression versus 0% for patients with a performance of III/IV (n=11). There is no linear trend for a size-effect relationship: A tumor size of 15-30 mm showed a response of 67% (n=25), versus 24% (n=24) and 43% (n=37) for size < 15 mm and > 30 mm respectively. The highest radiation doses (3 x 9 and 7 x 5 Gy) showed a higher response rate compared to the lower dose group (3 x 8 Gy or less): 58% versus 35%, respectively (p=0.038). No correlation was found between thermal dose and response rate.

Conclusion

Response rates of recurrent melanomas after radiotherapy plus hyperthermia were lower compared to those from the randomized trial by Overgaard et al. Prognostic factors for response were clinical performance and radiation dose.
TEMPERATURE AND POWER DATA ANALYSIS OF CERVICAL CANCER PATIENTS TREATED WITH HYPERThERMIA DURING 1991-2005

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Purpose
Analysis of RF-temperature and power data of primary cervical cancer patients to evaluate 15 years performance of loco-regional deep hyperthermia (DHT) with four configurations of the BSD-2000 system.

Materials and methods
Patients (n=444) were treated with the Sigma-60 applicator connected to one of four configurations of the BSD-2000 system from 1991 to 2005. The patients were grouped in three weight-groups: <61kg, 61-70kg, and >70kg. Temperature indices were calculated per patient, per treatment, per lumen and per tissue type. Ten power-related parameters were calculated for individual treatments. Then, the relationships between different temperature and power indices were computed per configuration, per weight-group, and over the time-period. Also percentages of normalized net integrated power per pelvic area and vagina T50 were calculated and the relationship between these was evaluated.

Results
No substantial variations were found for temperature and power indices over the four BSD configurations. The power indices increased from weight-group 1 to 3, however, the power data per pelvic area (or per weight) and also temperatures decreased slightly. Large variations were seen in the power-related parameters over the 1st time-period (1991-996), but they were much lower over the 2nd time-period (1997-2005). The average frequency of switched-off time was remarkably higher (2.6-fold) in the 2nd time-period. In contrast, the average duration of each switched-off was substantially lower in the 2nd time-period (75s vs. 44s). The yearly average of vagina T50 was in the range of 39.3-40.2°C (1st time-period) and 40.0-40.5°C (2nd time-period). In 40% of the patients, a positive correlation (mean: 0.7, range: 0.5 – 0.99) was found between the normalized power and temperature.

Conclusions
The small variation for the yearly average of applied-power and achieved temperatures in the last nine years shows the reproducibility of the application of loco-regional DHT to primary cervical cancer. A global view of the four BSD configurations indicates that the power outputs are almost similar; additionally, the achieved temperatures show that the four systems have provided relatively low doses of HT in the treatment area with a very small difference in the averages of temperature. An overall view of the three weight-groups shows that the applied powers increased from low-weight to the high-weight patients but the achieved temperatures decreased slightly from the low-weight to the high-weight patients. The experience of staff-members and changes in the treatment protocols certainly affected the switched-off strategy.
Acknowledgement

This work was supported by the Dutch Cancer Society grant 2003-2884. The first author was supported financially by the Shahrekord University of Medical Sciences (related to the Iranian Ministry of Health, Treatment and Medical Education). The authors would like to thank all hyperthermia staff-members of the Daniel den Hoed Cancer Center in Rotterdam for their technical assistance.
A RADIOFREQUENCY HYPERTHERMIA WITH SIMULTANEOUS INTERSTITIAL HDR BRACHYTHERAPY IN ADVANCED CERVICAL CANCER: INTERIM ANALYSIS OF A RANDOMIZED TRIAL

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Objectives
In cervical cancer the clinical benefit of hyperthermia combined with external beam radiation was demonstrated. Nevertheless, due to logistic and technical problems this treatment is rarely used. Hyperthermia used simultaneously with brachytherapy is more convenient alternative, however its efficacy is unknown.

Material and methods
From November 2006 to March 2007, 34 patients with advanced cervical cancer after standard chemoradiation were randomly allocated to either interstitial HDR brachytherapy given simultaneously with 500 kHz hyperthermia (N=17) or to the same brachytherapy alone (N=17). The total dose of 30 Gy was delivered in 7.5 Gy per fraction. In the hyperthermia group, the same applicators were used both for HDR brachytherapy, heating and temperature measurement. The sample size of 228 patients was calculated to detect 20% difference in local control.

Results
Mild bleeding after needles removal was the only side effect which occurred 5 times in 2 patients in brachytherapy + hyperthermia group (5/68 procedures, 7%) in comparison with 4 times in 3 patients in brachytherapy alone group (4/68 procedures, 6%).

Conclusion
The study should be continued, as simultaneous brachytherapy and hyperthermia well tolerated and accrual is satisfactory.
THE DUCTH DEEP HYPERTHERMIA TRIAL: UPDATED RESULTS IN CERVIX CANCER


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Background
The local failure rate in patients with locoregionally advanced cervical cancer is 41-72 % following radiotherapy alone (RT). Local control is a prerequisite for cure. The Dutch Hyperthermia Trial showed that combining radiotherapy with hyperthermia (RT+HT) improves local control at 3 years from 41 to 61 % 1,2. However, the follow-up in the early report was relatively short with a median of 43 months.

Purpose
To evaluate long-term results of a randomized phase III trial comparing RT with RT+HT after 12 years follow-up

Material and Methods
Eleven radiotherapy institutes participated in the study. One hundred and fourteen patients were randomized (n = 56 RT, n = 58 RT+HT) between 1990 and 1996. Prognostic factors were equally distributed over both groups. RT was given in 23-28 daily fractions of 1.8-2 Gy and brachytherapy (2 HDR applications of 17 Gy or 20-30 Gy LDR). HT was given 5-6 times, once weekly. The primary endpoint was local control; secondary endpoints were overall survival and toxicity.

Results
At 12 years follow-up, local control remains better in the RT+HT group (36% vs 56%, p = 0.02). The advantage of combined RT+HT was also reflected in a persistently better overall survival after 12 years from 20% (RT) to 37% (RT+HT). In a univariate Cox regression analysis, FIGO stage and WHO performance status (WHO-PS) were significant prognostic factors both for local control and survival. The benefit of HT remained significant after correction for these factors. In patients with continuing pelvic control, 30 % developed distant metastasis in the RT-group compared to 25 % in the RT+HT group (p = 0.4). The incidence of EORTC grade 3-5 radiation-induced toxicity was comparable in both groups.

Conclusions
Adding hyperthermia to radiotherapy in inoperable cervical cancer results in long-term major improvement of local control and survival, without an increase in toxicity.
References


HYPERTHERMIA IN THE TREATMENT OF GYNECOLOGIC CANCER:
A REVIEW OF THE CERVIX CANCER EXPERIENCE

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PURPOSE
Several randomized studies demonstrate a benefit to adding cisplatin (CDDP) based chemotherapy to radiotherapy (RT) for cervix cancer. The Dutch phase III pelvic tumor trial demonstrates a survival and local control benefit to the addition of hyperthermia (HT) to RT. We review the literature on CDDP, RT, and HT for cervix cancer, and discuss an ongoing international phase III trial centered on the role of HT in locally advanced cervix cancer (LACC).

METHODS
Patients with locally advanced cervix cancer are screened for eligibility on the basis of FIGO stage, tumor histology, renal function, performance status, and suitability for hyperthermia treatment. Eligible patients, after informed consent, are randomized to chemoradiation versus chemoradiation with weekly hyperthermia.

RESULTS
To date, 83 patients have enrolled on this trial. The overall grade 3 and 4 toxicity appears balanced between the two arms, and the hyperthermia toxicity to date has all been grade 1. Patient demographics and early toxicity data will be reviewed in detail. As mandated by the NCI data safety and monitoring board, no formal comparisons of failure free survival and overall survival are made at this time.

CONCLUSION
In phase II series published to date, trimodality therapy resulted in an excellent clinical response and was well tolerated. The addition of HT to chemoradiotherapy represents a promising new strategy which deserves continued multiinstitutional and international collaborative efforts.

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HYPERTHERMIA ENHANCES ANTI-ANGIOGENIC EFFECT OF MANGANESE Porphyrin Mimetic of Superoxide Dismutase

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Purpose
The objective of our study was to determine the effect of hyperthermia (41°C) combined with MnTE-2-PyP5+, a manganese porphyrin mimetic of superoxide dismutase with anti-angiogenic properties, on tumor growth delay and angiogenesis in murine melanoma tumors.

Methods and Results
C57/B6 mice with B16F10 melanoma tumors implanted on the right flank were randomized into 4 groups (n=8/each): control (saline), MnTE-2-PyP5+ alone, hyperthermia alone, or hyperthermia with MnTE-2-PyP5+. MnTE-2-PyP5+ (5mg/kg) was delivered subcutaneously BID for the duration of the experiment. Mice were exposed to localized hyperthermia to the right flank a total of three times for 1 hr each at 41°C. Tumors were harvested at sacrifice and animals were examined for lung and other organ metastasis. Tissue sections were stained for HIF-1α and VEGF. Animals treated with MnTE-2-PyP5+ alone, hyperthermia alone, and with combined therapy exhibited a substantial delay in tumor growth when compared to the saline control (p<0.05). Tumor growth was most inhibited in the group receiving combined therapy (MnTE-2-PyP5+ and HT). Preliminary assessment of angiogenic activity revealed HT and MnTE-2-PyP5+ combination was the most effective in inhibiting HIF1α and VEGF immunoreactivity.

Conclusions
Our data show hyperthermia has an enhanced effect on tumor growth delay when given in combination with anti-angiogenic therapy. Furthermore, the mechanism of tumor growth delay may be attributable to impaired angiogenesis consistent with decreased HIF1α stabilization and transcriptional activity of the potent angiogenic factor, VEGF. In addition to the above histological staining, we are continuing to investigate the mechanism behind HT mediated tumor growth delay. Currently, we are investigating changes in microvessel density (CD31), macrophages (ED-1), oxidative stress (8-OHdG), and hypoxia (CA9) between the control and treatment groups.
THE NEW VASCULAR DISRUPTING AGENT – OXi4503 – SIGNIFICANTLY ENHANCES THE ANTI-CANCER EFFECT OF RADIOTHERAPY COMBINED WITH MILD HYPERTHERMIA

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Purpose of the study

Vascular Disrupting Agents (VDAs) are drugs that target dividing endothelial cells, facilitating a tumor specific activity. Numerous studies have demonstrated that VDAs can significantly enhance the effect of chemo-, radio- and/or thermotherapy. The leading VDA is the clinically relevant Combretastatin-A4-disodium-phosphate. A new and more potent analogue, Combretstatin-A1-disodium-phosphate (OXi4503), has recently been made available. The purpose of this study is to investigate the effect of OXi4503 on hyperthermia especially in combination with radiotherapy.

Materials and methods

All experiments were performed using our well established murine C3H-mammary carcinoma grown subcutaneously in the rear right foot of female CDF1 mice. Treatments were performed when tumors reached a size of 200 mm³. Hyperthermia was performed locally by submerging the tumor bearing foot into a thermostat controlled waterbath set 0.2 °C above the targeted temperature. OXi4503 (supplied by OxiGene Inc. Watertown, MA, USA), was administered intraperitoneally (i.p.) at a dose of 50 mg/kg (injected at a relative volume of 0.02ml/g). Radiation was administered as a single local dose using a conventional X-ray machine. Radiation treatment was assessed using a tumor control assay. The number of animals showing local control 90 days after treatment was recorded for each treatment group and the radiation dose required to control 50% of the tumors calculated (TCD50). Hyperthermia and VDA-treatment was assessed using a Tumor Growth Time (TGT) assay. Tumor volume was registered 5 times weekly, and the time required to reach 5 times the treatment volume recorded (TGT5).

Results

The linear relationship between heating time at a specific temperature and TGT5 revealed slope values in the range of -0.003 days/min to 0.09 days/min at temperatures from 40.0 °C to 42.5 °C. When giving 50 mg/kg OXi4503 3 hours prior to heat treatment this was significantly enhanced to between 0.008 days/min and 0.03 days/min at temperatures from 39.5 °C to 41.0 °C. No increase was observed above these temperatures. The radiation dose required to control 50% of the tumors was 52 Gy. This was significantly lowered to 41 Gy when injecting 50 mg/kg OXi4503 1-hour after radiation treatment. An additional decrease to 37 Gy was observed when heat treatment (41.5 °C for 1 hour) was applied 3 hours after the OXi4503 injection.

Conclusions

The new VDA OXi4503 significantly enhances mild hyperthermia. A synergistic effect is only registered at temperatures that do not induce growth delays as a monotherapy. Furthermore, OXi4503 significantly enhanced the response to radiotherapy as well as radiotherapy combined with mild hyperthermia.

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VASCULAR DISRUPTING AGENTS FOR IMPROVING THERMORADIOThERAPY: DEPENDENCY ON DRUG TYPE AND HEATING TEMPERATURE

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Purpose
Vascular disrupting agents (VDAs) are drugs that specifically damage tumour vasculature and as a result of the subsequent decrease in tumour blood flow they can preferentially enhance tumour response to thermoradiotherapy. The aim of this study was to investigate the role of the drug type and heating temperature on this enhancement.

Methods
C3H mammary carcinomas grown in the right rear foot of female CDF1 mice were used when at 200 mm³ in size. The VDAs were prepared fresh before each experiment and injected intraperitoneally at a standard volume of 0.02 ml/g body weight. They included combretastatin A-4 disodium phosphate (CA4DP; 25 mg/kg) and the A-1 derivative (OXi4503; 50 mg/kg), and the TNF producing drugs flavone acetic acid (FAA; 150 mg/kg) and its derivative 5,6-dimethylxanthenone-acetic acid (DMXAA; 20 mg/kg). Radiation (240 kV X-rays) and heat (temperatures of 39.5 °C-42.5 °C for 60 minutes) were given locally to the tumour following immersion of the tumour bearing foot in a water bath. Timing and scheduling were radiation – 1 hour – VDA – 3 hours – heat. Response was the percentage of mice showing local tumour control at 90 days after graded radiation doses, and following logit analysis of the radiation dose response curves the TCD50 value (radiation dose producing tumour control in 50% of mice) was calculated. Statistical analysis performed using a Chi-square test (p<0.05).

Results
The TCD50 results for the different treatments are summarized in table 1.

Table 1: Effect of combining radiation, VDAs and heat on local tumour control

<table>
<thead>
<tr>
<th>VDA</th>
<th>Heating temperature (°C)</th>
<th>Controls*</th>
<th>39.5</th>
<th>40.5</th>
<th>41.5</th>
<th>42.5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>53 Gy (51-55)</td>
<td>---</td>
<td>55 Gy (51-59)</td>
<td>47 Gy (44-51)*</td>
<td>47 Gy (44-50)*</td>
<td></td>
</tr>
<tr>
<td>CA4DP</td>
<td>48 Gy (46-51)*</td>
<td>---</td>
<td>---</td>
<td>33 Gy (31-37)*</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>OXi4503</td>
<td>41 Gy (38-46)*</td>
<td>---</td>
<td>---</td>
<td>37 Gy (32-42)*</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>FAA</td>
<td>42 Gy (39-45)*</td>
<td>---</td>
<td>---</td>
<td>28 Gy (22-35)*</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>DMXAA</td>
<td>47 Gy (42-52)*</td>
<td>44 Gy (41-48)*</td>
<td>41 Gy (38-44)*</td>
<td>30 Gy (26-35)*</td>
<td>---</td>
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</tr>
</tbody>
</table>

Results show TCD50 values (with 95% confidence intervals). Those significantly different from radiation alone* or radiation + VDA* are indicated. *Heated at 25°C.
Conclusions

The heat enhancement of tumour radiation response was temperature dependent; it became larger at higher temperatures. All the VDAs tested enhanced the tumour response to radiation alone and the combination of radiation with heat. For this latter effect there was no significant drug type dependency, but did appear to be dependent on the heating temperature; the results with DMXAA showed that the higher the temperature the larger the effect.

Supported by a grant from the Danish Cancer Society.
WHAT DO WE MEAN “HEATING-UP THE TUMOR”?  

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Introduction, Objective
Hyperthermia in oncology has very controversial judgments and opposite reasoning among clinicians. However, the mainly historical results and the supposed universal ability to complement all the existing traditional methods are not enough to prove its efficacy on the evidence-based level. Although the temperature measurement is not satisfactorily solved in tumors, it is regarded as the quality parameter and a comparison basis of various hyperthermia techniques. Terms “heat-dose”, “temperature”, “energy dose” are used frequently as synonyms. We address the question: what we really mean on heating up the tumor?

Method
The dose thinking expects a value, which is volume/mass dependent, its proportioning could depend on the actual area/volume/mass. The temperature as a thermodynamic parameter measures an area/volume/mass independent equilibrium situation, expect isotherm-characterization of the tumor, supposing the only temperature changes in the area due to the “heating-process. However, the energy pumped into the tumor are is consumed by numerous effects which modify the temperature differently than a simple heating of a lifeless material (phantom). The trivially presented physiology reacts and drastically modifies the energy distribution: the blood-flow the metabolic rate, the electrolyte concentrations, pH and charge-distribution changes, lipid reactions and protein syntheses (HSP) are stimulated by the actual energy-intake. All these processes are energy-consuming, and their energy will be missing from the simple unchanged phantom-calculations. Nevertheless, some assumptions and corrective calculations could approximate these effects and modify the actual phantom-compared situation. However, an important factor, for what the treatment exists, is not calculated: the energy, which we expend on the distortion of the tumor structure and the malignant cells! Despite of the very complicated temperature equivalence standardization [1], [2], the scientific considerations [3], as well as the clinical experiences [4], well demonstrate the limit of the temperature control alone. The uncalculated and unmeasured missing incorporated energy is responsible for the curative hyperthermic changes in the tumor, and neglecting this could also explain numerous controversial results.

Discussion
Theoretical considerations showed the problem of the temperature dose-concept, and calculated a temperature dependent correction, about 2°C at 42.5, [5]. On the other hand, it is shown [6], that the thermal energy does not limit the electromagnetic effects through the membranes in the tissue. Our main approach is to use the constrained heat-flow through the cellular membranes of the malignant cells, forcing extra ionic currents and electro-osmotic processes to damage the membrane [7]. This situation technically could be constructed by capacitive coupling [8], using the impedance selection for focusing and the forced heat flow by non-equal specific absorption rate [SAR] in microscopic regions. The treatment is safe and well reproducible, [9].

Conclusion
Over-estimating the role of temperature damages the progress of the oncologic hyperthermia and simultaneously makes the treatments extremely complicated and expensive. The qualitative quality control by the absorbed energy combined by the ionic concentration and mobility
(impedance measurements) could be a method of control with acceptable complexity. It is time to think differently: study and apply the non-equilibrium processes during the heating procedure.

**References**


EARLY GLOBAL GENE EXPRESSION *IN VIVO AND IN VITRO* AFTER TREATMENT WITH HYPERThERMIA

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**Purpose**
Early global gene expression was analyzed after treatment with hyperthermia *in vivo* and *in vitro*. We have previously presented that both a metronomic dosage regimen of CTX (p = 0.006) and hyperthermia (p < 0.001), significantly delayed the time for the tumor to reach four times the initial volume in an experimental brain tumor model. A combination of the two regimens exhibited significantly better tumor control than the two modalities separately (both p < 0.001).

**Materials and methods**
BT4An aggressive rat glioblastoma-like tumors were serially transplanted orthotopically on the right hind foot in BD IX rats. One group was treated with a metronomic dosage regimen of the alkylating agent cyclophosphamide (CTX) at doses of 35 mg/kg i.p. administrated three times a week for two weeks. Another group received local water-bath hyperthermia at 44.1 ±0.1 °C administrated for one hour. A third group had both modalities combined, and a fourth group served as placebo treated controls. In a separate experiment tumor cells were also treated *in vitro* with hyperthermia at 43°C for one hour. We collected samples *in vivo* and *in vitro* up to three hours after completed treatment day zero, isolated mRNA according to standard protocols, and analyzed early global gene expression using Applied Biosystems Rat Genome Survey Microarray analyzing 26,857 genes.

**Results**
SAM analyses revealed 1213 genes that were differently expressed after treatment with hyperthermia *in vivo*. 127 of these we differently expressed also *in vitro* (t-test). Sorting the genes after biological processes according to the database of the Gene Ontology Consortium, we found significantly increased number of genes involved in processes like apoptosis, transcription, immune response, angiogenesis, cell signaling and protein metabolism. Interestingly the immune system (both lymphocyte and myeloid leucocytes) seems to be depressed by hyperthermia in our model system. There is upregulation of genes involved in protein folding (among others heat shock proteins) and overrepresentation of a cluster of genes involved in protein amino dephosphorylation (among them dual specificity phosphatases) indicating that protein modifications relevant for signal transduction, as well as transcriptional regulation may be important mediators of the effect of hyperthermia. An interesting observation was a significant upregulation of DNAJB4 mRNA after treatment with hyperthermia. DNAJB4 is recently shown to be a novel tumor suppressor.

**Conclusion**
Global gene expression reflects direct cell damage and simultaneous cell survival responses. To our best knowledge, this is the first full genome microarrays analysis focused hyperthermia versus placebo in the treatment in a malignant tumor *in vivo* and *in vitro*. The data may provide a basis for new hypotheses for the mechanisms involved.
NUMERICAL FEM MODELS FOR THE PREDICTION OF TEMPERATURE DURING SUPERFICIAL MW HYPERTHERMIA TREATMENTS

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Introduction
There are different approaches for microwave hyperthermia treatments. Local applicators allow superficial treatment of tumours that is effective and non-harmful, with minimal side effects and improved patient comfort. Thermal distribution in the target area depends not only on the power applied and the exposure time, but is also closely correlated with tissue blood perfusion [1], dielectric properties [2] and tissue-to-applicator matching [3]. It is important to take all these factors into account when planning treatment. Various numerical models will be presented and discussed.

Methods
Some simple numerical models of a local microwave applicator operating at 915 MHz (MA-100, BSD Medical Corp., Salt Lake City, UT, USA) were developed and solved to evaluate temperature distribution after 60- and 90-minute transients. The MW-power applied was initially set to a fixed value; a parametric study was performed to evaluate the effect of different power levels. Different vessel positions within the tissue were studied. A finite-element code was used to solve coupled electromagnetic and thermal problems with material characteristics dependent on temperature. We started with simple models, then added more details and compared the results.

Results
The penetration depth is in a good agreement with the typical clinical range. At 100 W, the tissue temperature ranges from 41 to 46 °C, depending on the model. The tissue blood perfusion [1] does have a strong effect on the overall temperature distribution, bringing a diffuse cooling effect (Figg.1-2). The water inside the bolus can be kept still or flowing; however, when water flow is taken into account, conduction continues to be the predominant aspect in tissue-to-water thermal exchange, as convection does not introduce clear differences compared to conduction only. The presence of a larger blood vessel near the treatment zone produces a local sink effect, thus introducing hot spots which make the heating less homogeneous and lower the overall treatment effectiveness (Fig.2). When temperature-dependent tissue dielectric properties are taken into account [2], we obtain a thinner and much hotter deposition pattern, even at lower power levels. A study on the optimal power level for each situation was then performed in the course of a time-dependent parametric analysis (Fig.3).

Conclusions
Local hyperthermia effectiveness is highly dependent on the temperature distribution in the tissue and on the temperature of the circulating water bolus. This is in turn influenced by tissue properties and vascularisation, which in their turn again depend on temperature. The numerical models presented attempt to describe these phenomena but further investigations are necessary to validate them in clinical application.

References

Fig. 1 – Thermal deposition on fatty tissue and hot spot marker; power applied: 100 W; treatment time: 60 minutes.

Fig. 2 – Thermal deposition on fatty tissue with Ø 1.5 cm blood vessel and hot spot marker; power applied: 100 W; treatment time: 60 minutes.

Fig. 3 – Hot spot temperature transients for various power levels (25÷300 W) and target tissue temperature (42.5 °C) in red dashed line; treatment time: 60 minutes.
HIPEC (HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY)
FOR PERITONEAL CARCINOMATOSIS – HOW TO ESTABLISH THE
APPROPRIATE DOSE OF CYTOSTATICS?

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There are only few therapeutic options for peritoneal carcinomatosis. Hyperthermic intraperitoneal chemotherapy (HIPEC) was developed as a unique technology combining more modalities. There is only a narrow therapeutic range of current cytostatics. In HIPEC it is influenced by a number of variables - penetration, absorption, concentration, volume of administered fluid, indwelling time, temperature, previous surgery etc., all alternating the risk of both adverse and antitumor effects.

We are the only group in Czech republic performing HIPEC, thus our experience is unique. We use a simple dose calculation of mitomycin C, carboplatinum and adriamycin based on a systemic exposition as an endpoint. It estimates the absorption rate of particular agent into a systemic circulation. It results in at least 80% absorption according to the variables of our methodology (indwelling time 90 mins., temperature 42°C, isotonic solution). The calculated dose may be finally adjusted accordingly to pretreatment status, blood count, number of previous chemotherapy cycles etc.

118 cycles of HIPEC were administered in 104 pts. with advanced peritoneal involvement by various malignancies (peritoneal pseudomyxoma, primary peritoneal, colorectal, ovarian and gastric cancer). The dose resulting of calculation was 18–22 mg for mitomycin, 50–80 mg for adriamycin and 400–500 mg for carboplatinum. The incidence of side effects was compared with the risk rate related to a current systemic chemotherapy as declared in official documents (SPC). It does not significantly differ and remains within the expected range. The predominant side effect gr. III–IV was a reversible myelosuppression. There were 2 toxic deaths after mitomycin C HIPEC, however combined with subsequent 5-FU treatment.

The dose derived of the systemic exposure estimate is safe. Any suitable model of dose calculation is desirable due to a number of insufficiently explored variables influencing the risk of side effects. The use of cytostatics for HIPEC is usually “off-label” and treatment safety remains fully in physician’s responsibility despite HIPEC is a developed methodology. Thus the manufacturers are challenged to include HIPEC into standard indications of their drugs and to declare dosage.

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IN VITRO STABILITY AND DRUG RELEASE PROPERTIES OF PHOSPHATIDYLGLYCEROGLYCEROL CONTAINING THERMOSENSITIVE LIPOSOMES WITH ENCAPSULATED DOXORUBICIN

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Introduction
Thermosensitive liposomes (TSL) in combination with hyperthermia represent a powerful tool for tumour specific drug delivery. Lately, we reported that the novel synthetic phospholipid dipalmitoyl-sn-glycero-3-phosphoglyceroglycerol (DPPGOG) prolongs the circulation time and facilitates the content release of TSL (Clin Cancer Res. 2004). The objective of this study was to examine the in vitro characteristics of DPPGOG containing TSL with encapsulated doxorubicin (DOX).

Methods
DPPC/DSPC/DPPGOG 5:2:3 (m/m) TSL were prepared by the lipid film hydration and extrusion method. A pH gradient was used to load DOX. The size and zeta-potential was determined by Photon Correlation Spectroscopy. The lipid concentration was determined with a phosphate assay. DOX encapsulation efficiency was measured with HPLC. DOX release under certain thermal conditions was determined with fluorescence spectroscopy measurements.

Results
DOX was actively loaded to DPPGOG containing TSL with encapsulated 300 mM citrate, pH 4. The resulting drug:lipid ratio of 0.12 ± 0.01 (m/m) was confirmed independently by HPLC analysis and fluorescence spectroscopy. No signs of decomposition, e.g. hydrolysis of lipids, have been observed. At body temperature (37°C), the DOX leakage was 3.6 ± 1.1 % and 10.9 ± 4.0 % during a time period of one and three hours, respectively. Under heating conditions (41°C) almost 100 % of DOX was released within 5 minutes (74.6 ± 2.4 % during the first 60 sec). At 42 °C, 85.6 ± 1.3 % DOX was released in the first 60 sec. In the absence of serum (20 mM HEPES, 150 mM NaCl, pH 7.4), the DOX release rate constant was decreased from 263 ± 102 (*10^4 s^-1) to 55 ± 5 (*10^4 s^-1) at 42 °C.

Conclusion
DPPGOG containing DOX-TSL demonstrated promising in vitro characteristics with high stability at 37 °C and fast DOX release properties at elevated temperatures. The presented data warrant further investigation of DOX containing DPPGOG TSL for clinical application.
THE HYPERCOLLAR: A NOVEL PHASED-ARRAY APPLICATOR FOR HYPERTHERMIA TREATMENT IN THE NECK

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Purpose
Clinical phase III trials have established the benefit from adding hyperthermia (HT) to radiotherapy (RT). The possibilities of HT are interesting to study in advanced head and neck tumours as well, however, an appropriate applicator is not available. Therefore this work was directed at the design and construction of a HT applicator for heating of advanced carcinomas in the entire head and neck region.

Materials and methods
High-resolution 3D electromagnetic (EM) simulations were used to perform parameters studies to guide the design of the applicator. Investigated topics were: 1) operating frequency, 2) number of sources, 3) positioning of sources, 4) antenna design. A laboratory prototype was build to verify the possibilities of deep heating with the designed array. In a next step we build a clinical prototype (HYPERcollar) and measured the performance of the final antenna design. We also performed comfort tests by seven healthy volunteers. By treatment planning in SEMCAD X for laryngeal patients, and an oropharynx case (Figure 1), we investigated the specific absorption rate (SAR) patterns that will be possible in patients using the HYPERcollar.

Results
The comfort tests with healthy volunteers have revealed that the applicator provides sufficient comfort to maintain in treatment position for an hour. Using treatment planning we showed that the focus can effectively be steered towards a target region or even multiple target regions, e.g. a primary tumour and a lymphnode metastasis (Figure 2). Further, we showed that by adjusting the SAR optimisation settings we can effectively reduce the SAR level in the critical tissues.

Conclusion
A site-specific applicator was designed that enables a good control of the SAR pattern. A clinical feasibility study is ongoing.

\textbf{Figure 1:} SAR distribution in an example oropharynx patient (black = 0\%, white = 100\%).
\textbf{Figure 2:} Optimised 25\% iso-SAR volume coverage (white) of a primary larynx tumour (red) and an artificial lymphnode metastasis (red sphere). Further visible are the bony structures (yellow).
ORGAN PRESERVING, QUADRIMODAL TREATMENT OF T1-2N0M0 BLADDER CANCER: RESULTS AFTER TRANS-URETHRAL RESECTION AND SIMULTANEOUS RADIOCHEMOTHERAPY COMBINED WITH REGIONAL DEEP HYPERTHERMIA

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Purpose
Evaluation of the safety and effectiveness of a quadrimodal treatment of T1-2N0M0 transitional cell cancer of the bladder with trans-urethral resection (TUR) followed by simultaneous radiochemotherapy combined with regional deep hyperthermia.

Patients and method
Between 11/2003 and 09/2006, 37 consecutive patients were enrolled in this phase II-study. After trans-urethral resection the patients received external beam radiotherapy of the bladder and the pelvic lymph nodes up to 50.4 Gy (SD 1.8 Gy, range 50.4-54); followed by a local boost of the bladder up to a median total dose of 57.6 Gy (SD 1.8 Gy; range 54-61.3). The medium overall treatment time was 45 days (range 41-56). 95% (35/37) of the patients received a radiosensitizing chemotherapy, usually cisplatin and 5-fluorouracil during the first and fifth irradiation week. During radiotherapy, regional deep hyperthermia was performed once weekly with the BSD 2000 3D/PC-hyperthermia system.

Acute toxicity was graded with the Common Terminology Criteria for Adverse Events, Version 3.0.

The remission rate was re-evaluated 6 weeks after treatment by re-TUR, local control was assessed by periodical follow-up cystoscopies.

Results
The median follow-up was 20 months (range 4-39). The median age was 67 years (range 38-82).

76% (28/37) received more than 3 hyperthermia-fractions. Because of co-morbidities or request 21% (8/37) of the patients received ≤ 2 hyperthermia fractions. The median number of hyperthermia treatments was 5 (range 1-7).

Acute toxicity was low: Grade 3 gastrointestinal toxicity 5% (2/37), grade 3-4 hematotoxicity 16% (6/37). At the time of re-TUR the complete response rate was 94% (33/35). The local relapse free survival probability was 90.2% at 2 years. At the time of the last follow-up examination the bladder preserving rate was 100%.

Conclusion
The quadrimodal treatment of T1-2N0M0 bladder carcinoma was feasible and well tolerated. Local control and bladder preserving rates were encouraging. However, for a conclusive appraisal of the results longer follow-up is necessary. To clarify the additional effect of deep regional hyperthermia randomised trials are required.
Hyperthermia treatment planning: Real-time clinical use of MODEL GUIDED STEERING

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Introduction and purpose

Current hyperthermia treatment of cervical carcinoma makes use of an empirical steering protocol. On patient complaints the focus is shifted away from the complaint region. Optimized treatment, using model guided steering, is based on a real anatomy model. This type of steering is tested in a clinical study in patient treatments.

First purpose of this study is testing the feasibility of real-time model guided steering using optimization in a clinical setting and a comparison of tumor temperature between model guided and regular treatments. Secondary a reduction of patient complaints is a goal of the study.

Methods

The basis for treatment planning is the Hyperplan FEM-model. Additionally a dedicated optimization routine, maximizing SAR in the target area, is developed in our department.

Two possible goal functions are tested in the study. The first goal function optimizes target-SAR without taking into account possible hotspots. Only on patient complaints the objective function is adapted to reduce hotspots. The second optimization goal function takes into account hotspot in initial optimization. On complaints in a certain region the goal function is also adapted to give more weight to the concerning region.

Before the use in a clinical situation these goal functions are tested in a phantom test setup to evaluate the effectiveness of steering actions.

Treatment of patients starts with optimized settings. On complaints, in the goal function more weight is given to the complaint region, after which optimization is recalculated and new settings are applied.

Results

Phantom tests indicate that most effective steering is achieved in peripherical regions. In regions adjacent to the target, reduction is less.

Results of treatments performed with both optimization routines show the feasibility of real-time clinical use of model guided steering. Calculation times are less than one minute generally, which is fast enough for (almost) real-time adaptation of settings on patient complaints. Furthermore temperatures well within the therapeutic range, above 41°C in target region, are achieved during treatments using optimization.

At last, in temperature models results of different patients are compared for regular treatment settings and both optimization methods. On basis of these model better results in temperature are expected. Model temperature predictions for regular treatment and both optimization routines show expected temperature differences in the order of tenths of °C.

Conclusions

Real-time SAR-optimization has shown its feasibility in a clinical study. Results of a number of treatments show that intraluminal temperatures well within therapeutic range can be
achieved. Model predictions furthermore indicate an increase in tumor temperature using optimization treatment planning.

This work is supported by the Dutch Cancer Society, grant nr. 2003-2884.
PATIENT-SPECIFIC FOCUS STEERING IN ANULAR AND BOWL-SHAPED PHASED ARRAYS USED IN MR-MONITORED HYPERTERMIA TREATMENT

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Purpose
The ability to control the position and profile of the heating pattern determines the efficacy of hyperthermia treatments. In the case of deep seeded tumors, such as breast tumors and extremities’ sarcomas, patient’s discomfort associated with the overheating of sensitive regions of normal tissue, often limits the treatment dose. This effect can be significantly reduced with an accurate control of the temperature distribution within the target region. In radiofrequency phased arrays, phase and amplitude determine the outline and the location of the power deposition and consequently of the heating. Recent advances in MR imaging allow for non-invasive real-time 3D monitoring of temperature differences inside the body. In certain cases, when MR imaging is not available, a set of 2 or 3 invasive temperature probes can give sufficient information about the thermal map of the treated volume. The control software developed at Duke University allows the clinician to choose between manual, semiautomatic or fully automatic control based on temperature information received by MR images or multiple fluoroptic probes. Using the semiautomatic method presented here, the clinician can reshape and relocate the heating pattern within a large set of positions and shapes obtained interpolating pre-calculated power distributions in relatively complex geometrical models derived from the actual anatomical features of the patient.

Methods
The semi-automatic method uses relatively complex geometrical model derived from anatomical images (MR or CT). The model is used to calculate a priori a set of position and shapes that can be obtained with several amplitude and phase combinations. Initially an MR or CT image is imported in Ansoft HFSS and IMST Empire. The two programs use frequency and time domain simulation respectively to determine the electromagnetic field distribution inside the concave array structure (anular to treat extremities or bowl-shaped for breast). Amplitude and phase can be set in post-processing to determine the power deposition patterns corresponding to each setting. A set of 5 normalized amplitudes (0, 0.25, 0.5, 0.75, 1) and 10 phase settings (-180 to +144, every 36 degrees) per antenna has shown to be sufficient to accurately describe most of the feasible patterns. The position of the maximum power ($X_{\text{Max}}$ and $Y_{\text{Max}}$) and the half power beam size ($L_x$ and $L_y$) for the settings not obtained by the simulation are obtained by interpolation using Matlab. Using Labview as the control software, the beam can be steered and formed in any interpolated position and shape.

Results
The semiautomatic method has been tested in homogeneous and inhomogeneous phantoms. The power deposition pattern is measured with an isotropic SAR probe in a tissue equivalent liquid. The experiments confirm the simulation results:

- The center of the focus can be simply moved in the target volume mostly modifying the phases
- The closer the beam is to an antenna, the lower the power of that antenna is set to maintain the beam shape
• The system symmetry cannot be exploited in non-homogeneous phantoms where the preservation of the shape of the half power beam deforms at the interfaces between tissues
• The thickness of the water bolus affects both power and phase settings

Conclusion
A method that allows the clinician to accurately control in a semiautomatic and intuitive way the beam position and shape has been developed. Based on anatomical images of the patient, a series of phase and amplitude sets associated with several positions and shapes of the focal region is determined using commercial simulation software. Additional sets are obtained by interpolation. The method has been verified experimentally with success.

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COMBINED LAK-THERAPY AND WHOLE BODY HYPERTERMIA IN PEDIATRIC CANCER TREATMENT

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Objective
The prognosis of patients (pts) with refractory and metastatic solid tumors is very poor. Experimental studies have shown enhancement of antitumor effect in case of combination hyperthermia, chemotherapy and immunotherapy with LAK-cells.

Methods
Eleven children (boys-9, girls-2, median age 12) with relapsed and refractory diseases have been treated with thermochemobiotherapy (totally 13 courses). There were rhabdomyosarcoma (RMS)-4, germ-cell tumors (GCT)-3, PNET-2, renal-cell carcinoma (RCC)-1 and mesenchymal liver tumor (MLT) -1 ) WBH, 42-43°C, 120-160 min was induced by 13,56 MHz electro-magnetic energy and curried out concurrently with hyperglycemia (20-26 mmol/l) and chemotherapy (depending on type of tumor) under general anesthesia. At the end of WBH session when temperature decreases to 40,5ºC, LAK-cells (0,5-1,5·10⁹ cells) obtained after lymphopheresis and incubation PBMC in vitro with IL-2 for 2-3 days, infused i.v. over 3-4 hours with IL-2 (0,25-0,5 MU/m²). Second infusion of LAK-cells was given the next day without WBH. Two pts had 2 session of systemic thermochemobiotherapy.

Results
All the children well tolerated WBH as well as LAK-therapy. At the end of infusion LAK-cells usually we observed elevation of body temperature up to 39 ºC due to IL-2. CR was achieved in two pts with GCT and PNET. PR was registered in 4 pts (RCC, RMS, PNET and MLT). SD-in 4 pts (GCT-2, RMS-2) and one child with disseminated and refractory RMS showed progression after systemic thermochemobiotherapy.

Conclusion
WBH combined with LAK-therapy is tolerable treatment and might be one of the approaches for overcoming chemotherapy resistance in refractory pts. The optimal choice of treatment in this poor prognostic group of pts still merits further investigation.
For high-risk soft tissue sarcomas (HR-STS) of adults, new treatment strategies are needed to improve outcome with regard to local control and overall survival. Systemic chemotherapy has been integrated either after (adjuvant) or before (neoadjuvant) optimal local treatment by surgery and radiotherapy in HR-STS. The presentation summarizes the results of the combination with regional hyperthermia (RHT) as a treatment strategy to open a new therapeutic window.

Under the auspices of the European Organization for Research and Treatment of Cancer (EORTC) and the European Society of Hyperthermic Oncology (ESHO) we recently completed a randomized Intergroup phase III trial (EORTC 62961/ESHO RHT-95) of multimodal treatment in patients with primary (S1 group) and recurrent (S2 group) disease or after inadequate surgery (S3 group: resections with positive margins or macroscopic residual tumor) in high-risk STS (tumor size ≥ 5 cm + histologic grade of 2 or 3 + deep location + extracompartamental extension). In this trial, all patients with HR-STS to extremity and non-extremity received neoadjuvant systemic chemotherapy (four cycles of the EIA regimen) and were randomized in two arms: chemotherapy alone or combined with RHT, followed by definitive surgery and radiotherapy. Thereafter, in addition, four cycles of the EIA regimen were administered with or without RHT according to the initial randomization. The results in terms of overall outcome for extremity and non-extremity STS will be presented.
RF CAPACITIVE HYPERTHERMIA SYSTEM: EXPERIMENTAL RESULTS AND THERMAL MODELING

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Introduction

Radiofrequency capacitive hyperthermia, at 13.56 MHz, can be used as an adjuvant treatment of the traditional radiotherapy and chemotherapy for advanced inoperable malignant brain tumours. In this work, the authors show results of an experimental study on a human skull filled with water bags and results of electro-thermal FEM simulations on a 2D model of a human head. Moreover, experimental set up and a numerical analysis have been performed in order to demonstrate the effect of RF energy deposition on resulting heating compared with the one due to thermal conduction.

Methods

In fig.1a the experimental set-up for the RF capacitive hyperthermia application on a skull is shown. The experiments have been carried out with the Synchrotherm RF system in Verona hospital. In Fig.1b the 2D geometric model for FEM analysis is shown where the position of the four temperature probes are underlined.

![Fig.1a Experimental set-up](image1)

![Fig.1b 2D geometric model for FEM analysis](image2)

In a second part of the work, developed in Electroheat laboratory of Padova University, only the effect of thermal conduction during the treatment has been considered: an experiment and a numerical model have been performed imposing the temperature of the electrodes surfaces at the constant temperature of 39°C.

Results

In Tab.1 thermal results obtained from experimental measurements and results of numerical calculation after 10 and 25 minutes of RF application are compared on correspondent points. The initial temperature in the FEM simulation is set equal to ambient temperature at 25°C.

<table>
<thead>
<tr>
<th></th>
<th>measured</th>
<th>calculated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>15 min</td>
<td>38°C</td>
<td>25°C</td>
</tr>
<tr>
<td>25 min</td>
<td>37°C</td>
<td>24°C</td>
</tr>
</tbody>
</table>

Tab.1 thermal results measured and calculated after 10 and 25 minutes of RF application.
In Fig.2 temperature evolution obtained from experimental and numerical analysis, with the only effect of thermal conduction considered, are compared. In this case, the initial temperature is set to 20°C.

**Fig.2 Temperature evolution**

**Conclusion**

Thermal results measured and calculated (Tab.1) are very different due to difficulties encountered during experimental RF application on temperature acquisition. Fig.2 shows that time constant related to thermal conduction phenomena are so high that temperature raise up to therapeutic values, during RF application, can be reasonably attributed to RF energy deposition.

**References**

EXPERIENCE AND RESULTS WITH RADIOFREQUENCY HYPERHEMRIA: APPROACH IN GLIOBLASTOMA

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Recent studies have shown radiofrequency clinical hyperthermia to have anticancer effects, in particular in the case of brain neoplasias. In recent years interest in hyperthermia has grown in that it has been demonstrated that the drugs normally used in anticancer therapy may have greater efficacy at equal dosages, or preserve the same efficacy at lower dosages, when administered in combination with hyperthermia techniques.

In this paper we present our experience in a group of patients with glioblastoma treated with Radiofrequency Hyperthermia (RH). The trial was carried out on 16 patients between January 2001 and February 2007 (10 males, 6 females, mean age 45) affected by glioblastoma. All 16 patients underwent radiotherapy and chemotherapy and 1 was treated exclusively with radiotherapy. The criteria for inclusion in the trial was: inoperable cancer and patients already treated with chemo and radiotherapy at the highest doses tolerated, with life expectancy of 12 months or less.

We used an RH equipment at 13.56 MHz endowed with liquid-cooled flexible antennas, positioned bilaterally on the temples. Treatment was based on an average of three cycles, each consisting of eight 45-minute sessions every other day, using about 85-95 W per session, and administering, at the same time, 250 cc of mannitol followed by 20 mg of furosemide i. v. to prevent the formation of oedemas.

There were no side effects. The results were assessed not only through MR and CT, but also by means of a clinical examination carried out by out neurologist before and after treatment.

At the end of treatment, considerable improvement in the neurological symptoms was found in 9 patients. In another 3 patients improvements were observed even if they were not as outstanding, and in 2 cases became stabilised. In the remaining 2 cases the symptoms did not improve significantly. Mean survival in these patient was 17.31 months, median was 15 month with D.S. 6.52. 5 patients was alive at 18th month (29%) and 3 patients was alive at 24th month (18%).

The results obtained in this group of patients, albeit small in number seem to confirm the positive effect of hyperthermia in controlling tumor growth, in increasing survival and above all in improving the neurological symptoms and the general conditions. Finally namely the total absence of side effects and good tolerance of treatment afforded by the instruments used, which contributed to increasing heat delivery time without causing discomfort to these delicate and difficult patients.
THERMORADIOThERAPY AND RADIOCHEMOTHERAPY OF
LOCALLY ADVANCED LARYNX CANCER WITH LYMPH
NODES METASTASES

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Introduction

Patients with advanced larynx cancer (stage III-IV with lymph nodes metastases) have a dismal prognosis. Radiation therapy (RT) alone led to limited response and survival rates with majority of patients dying of locoregional recurrence. That’s why a number of alternative approaches were designed to increase the radiation effect.

Purpose of the study

To compare efficiency and toxicity of thermoradiotherapy and chemoradiotherapy at patients with stage III-IV of squamous cell larynx cancer with involved lymph nodes (T3-4N1-3).

Materials and method

From September 1994 to March 2001, eighty eight patients were included into a prospective non-randomized study, 76 of them completed the treatment (median age 56 years; 30.3% stage III tumors; 69.7% stage IV tumors; 75% supraglottic larynx; 25% glottic larynx). In the first group, 34 patients underwent a split-course of conventional radiation therapy up to total dose 68-70 Gy. In the second group, 42 patients were performed RT and 6-9 sessions of local microwave hyperthermia (HT). Heat was delivered for an hour up to 41.50-43°C in the tumor before irradiation (915 MHz, 45-50 Wt).

From December 2002 to April 2006, thirty seven patients were enrolled, 29 of them completed the course (median age 61 year; 24.1% stage III tumors; 75.9% stage IV tumors). The treatment protocol in the third group (16 patients) consisted of three courses of chemotherapy (5-FU+cisplatin) given in the 1st, 5th and 11th week and conventional split radiation therapy (6-9 and 12-14 weeks). In the forth group (13 patients), besides, patients were performed 6-8 sessions of local hyperthermia. Adverse events (skin and mucosal toxicity, dysphagia, xerostomia and hematological toxicity) were scored according to RTOG\EORTC criteria.

Results

One-years overall survival (OS) was 53.1% and 67.5%, 3-years OS – 12.5% and 35%, 5-years 9.4% and 25%, 10-years – 6.3% and 16.7% in RT and RT-HT group, respectively (Fig.1). Median survival was 12.9 months and 20.4 months. There was a statistically evident benefit for RT-HT vs RT patients (0.0270). Patients in local hyperthermia group demonstrated non-significant increase of grade 3+4 mucositis, dysphagia, skin and soft tissue toxicity (p=0.067). Hematological toxicity was low and identical in both groups.

One-years OS of patients, who underwent chemradiotherapy, was 75%, 3-years – 38.1% with MS 18.6 months (Fig.2). In CRT-HT group, one- and three-years survival was 72.2% and 16.2%, respectively with median survival 16.2 months without any difference between the groups (p=0.8835). Patients treated with chemradiotherapy and local hyperthermia more often developed grade 3+4 mucositis (45.5% vs 28%, p=0.0271) and dysphagia (41.6% vs 24.1%, p=0.0433) compared to those with chemradiotherapy alone. Stage 2-4 anemia developed in 43% and 25% cases (p=0.004), respectively.
Conclusions
Thermoradiotherapy and radiochemotherapy are of equal efficiency in case of advanced larynx cancer, but thermoradiotherapy doesn’t cause hematological toxicity. Thermoradiochemotherapy significantly increases toxicity of the treatment without any therapeutic benefit.
A PHASED ARRAY HEAD AND NECK APPLICATOR: MEASUREMENTS OF THE SAR DISTRIBUTIONS IN A CYLINDRICAL MUSCLE PHANTOM

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Purpose
In previous theoretical studies we found that a setup consisting of two rings of six antennas, operating at 433MHz, can be used to obtain the desired specific absorption rate (SAR) distributions in the Head and Neck (H&N) region. In the present study we report on the work to verify the SAR distributions that can be obtained and the dynamic SAR steering possibilities by measurements in a cylindrical muscle phantom.

Materials and methods
Using a specially constructed laboratory prototype head-and-neck applicator, including a neck-mimicking cylindrical muscle phantom, we performed SAR measurements by either the electric field (Schottky-diode sheet) or the power-pulse technique (fiberoptic thermometry and infrared thermography). We also measured phase steered SAR distributions in radial and axial directions. All measured distributions were compared with the predictions by a finite-difference time-domain–based electromagnetic simulator. In a next step we build the clinical prototype (HYPERcollar) and measured the SAR distributions in the applicator by infrared thermography.

Results
A central 50% iso-SAR focus of 3.5 cm in diameter and about 10 cm in length was obtained for all investigated settings. Furthermore, this SAR focus could be steered toward the desired location in the radial and axial directions with an accuracy of ~0.5 cm. The SAR distributions as measured by all experimental methods were well predicted by the simulations. The SAR measurements within the HYPERcollar show a similar SAR focus in the diameter of the phantom, however due to the finite size of the waterbolus, the length decreases to around 9 cm.

Conclusion
The results of our study have shown that focused heating in the neck is feasible and that this focus can be effectively steered in the radial and axial directions.

Figure 1: laboratory prototype

Figure 2: SAR in phantom for central phase settings
CLINICAL APPLICATION OF INTRALUMINAL HOT WATER BALLOONS COMBINED WITH LOCOREGIONAL HYPERTHERMIA FOR TREATMENT OF OESOPHAGEAL TUMOURS

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Purpose

To improve hyperthermia (HT) for oesophageal tumours with an intraluminal Hot Water Balloon (HWB) in combination with the standard AMC-4 waveguide system.

Methods

Five patients with an oesophageal tumour, median length 6 cm, were treated with neoadjuvant chemoradiation combined with weekly HT for 5 weeks. HT was given using the locoregional 70MHz AMC-4 waveguide system, with an additional thermal boost using an intraluminal HWB. Balloons were 1 cm in diameter and 6 cm in length, and were placed at tumour position under endoscopic guidance prior to each HT session. Water of 51-52°C was circulated through 3-lumen tubing by a rollerpump at a flow rate of 30 ml/min, resulting in a HWB temperature of ~43°C. Duration of HWB application was increased from 2.5 min during the steady state (SST) period of session I, to 15, 30, 45 and 60 min during session II, III, IV and V, respectively. Tumour temperature profiles were measured intraluminally using multisensor thermocouple probes mounted on the outside of the HWB, and expressed in terms of maximal \( T_{lumen}^{10} \) and minimal \( T_{lumen}^{90} \) luminal tumour temperature and the heterogeneity coefficient \( HC = \left( \frac{T_{lumen}^{10} - T_{lumen}^{90}}{T_{lumen}^{90} - 37^\circ C} \right) \). Thermal dose was expressed as cumulative equivalent minutes with \( T_{lumen}^{90} \) at 43°C (\( CEM T_{lumen}^{90} @ 43^\circ C \)) per session.

Results

For all treatment sessions of all patients \( T_{lumen}^{90} \) significantly increased, on average from 38.6 ± 0.2 °C (mean ± SEM) before HWB application to 42.1 ± 0.1 °C during HWB application, i.e. an increase of 3.5 ± 0.1 °C. By increasing HWB duration from 9.2 ± 1.6 min (2×5 min) to 57.9 ± 1.2 min (60 min), thermal dose increased from 9.2 ± 4.5 to 22.3 ± 4.1 \( CEM T_{lumen}^{90} @ 43^\circ C \). Temperature profiles along the tumour were more uniform during HWB application, as indicated by a significant decrease in HC from 0.48 ± 0.04 to 0.29 ± 0.03.

<table>
<thead>
<tr>
<th>Session</th>
<th>Time HWB</th>
<th>SST before HWB</th>
<th>SST during HWB</th>
<th>Total SST period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aim [min]</td>
<td>actual [min]</td>
<td>( T_{lumen}^{90} ) [°C]</td>
<td>HC</td>
</tr>
<tr>
<td>I</td>
<td>2 × 5</td>
<td>9.2 ± 1.6</td>
<td>38.9 ± 0.4</td>
<td>0.48 ± 0.21</td>
</tr>
<tr>
<td>II</td>
<td>15</td>
<td>16.8 ± 0.7</td>
<td>39.0 ± 0.5</td>
<td>0.35 ± 0.11</td>
</tr>
<tr>
<td>III</td>
<td>30</td>
<td>26.8 ± 4.3</td>
<td>38.3 ± 0.5</td>
<td>0.58 ± 0.14</td>
</tr>
<tr>
<td>IV</td>
<td>45</td>
<td>45.1 ± 0.7</td>
<td>38.6 ± 0.4</td>
<td>0.44 ± 0.11</td>
</tr>
<tr>
<td>V</td>
<td>60</td>
<td>57.9 ± 1.2</td>
<td>38.2 ± 0.2</td>
<td>0.53 ± 0.04</td>
</tr>
<tr>
<td>mean</td>
<td>-</td>
<td>-</td>
<td>38.6 ± 0.2</td>
<td>0.48 ± 0.04</td>
</tr>
</tbody>
</table>

*p<0.05 vs. before HWB; **p<0.01 vs. before HWB (determined by paired t-tests).
Conclusion

Hot Water Balloons are clinically feasible, simple and safe devices, which can be easily combined with locoregional hyperthermia to achieve an additional temperature rise in the vicinity of the HWB.

Supported by Dutch Cancer Society grant 2002-2622.
PRELIMINARY EXPERIENCE IN THE TREATMENT OF HCC RESIDUALS AFTER RF ABLATION USING CT-FLUOROSCOPY (CTF) GUIDE

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2 Institute of Anesthesiology, University of Insubria, Varese, Italy.

Purpose
To assess the feasibility and the effectiveness of RF ablation CTF-guided for HCC residuals after RF ablation.

Materials and Methods
In the last 6 months we performed 23 RF ablation to treat HCC nodules. During the follow-up CT scan performed 1 months after the procedure showed 9 pericapsular residuals (mean diameter: 2.4 cm). In all cases Ultrasound had not distinguished the residual from the necrotic tissue. RF ablation was performed with CTF guide (Aquilion 64®/Toshiba) using a coaxial needle electrode (Le Veen®/Boston Scientific) during contrast media injection. The results were assessed with CT performed soon after the procedure and 1 and 3 months later.

Results
We obtained an immediate technical success of 100% as showed by post-procedural CT. No major complication occurred. CT scan performed 1 and 3 months after the procedure confirmed complete necrosis of the residuals (clinical success of 100%).

Conclusions
RF ablation CTF-guided is an effective tool for the treatment of HCC residuals. Contrast media injection during CTF allows the localization of hypervascular area guiding the positioning of the needle. Post-procedural CT scan allows an immediate assessment of treatment success.
THE IMPORTANCE OF THE RECENT RESULTS OF THE CAPACITIVE HYPERTERMIA (HT) ASSOCIATE WITH CHEMIOTHERAPY IN TREATING INOPERABLE PANCREATIC TUMOURS: AN UPDATE

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Department of Clinical Hyperthermia. University of Rome, "Tor Vergata". Italy.

The latest medical studies about pancreatic adenocarcinoma show a remarkable increase in incidence, prevalently in the western countries. This kind of neoplasia afflicts especially masculine population and smokers, presenting a considerable incidence according to the increase of age.

Recent medical studies have pointed out to us that there is a correlation between pancreatic tumours and fats diets; debated the incident of consuming coffee. In general, obstructive icterus and pain associate to the involvement of retroperitoneali nerve fibres are symptomatic of head and body tumours. Frequently a poor digestion, in consequence of a bad state of the pancreatic enzymes synthesis, brings about taking off weight. Unfortunately the prognosis of this kind of neoplasia is unfavourable, patients come to survive less than 12 months. A lot of this kind of neoplasia are inoperable and often a treatment with chemiotherapy and radiotherapy is not successful. A new treatment called capacitive hyperthermia (HT) shows antitumoral effects associate with a chemiotherapy treatment based on new drugs. This treatment utilizes a modern and functional apparatus so that the patients have a good ability to tolerate it because of the short incidence of complications.

In this updated work we want to make a detailed report on the action of the HT associate with chemiotherapy, tested on a group of 25 patients suffering from pancreatic adenocarcinoma.

Apparatus and treatment

APPARATUS: We used an RH equipment at 13.56 MHz endowed with liquid-cooled flexible antennas.

TREATMENT PERIOD: from 01/01/2001 to 28/02/2007.

TREATMENT: 3 cycles of treatment, every cycle is structured in 8 sessions of 45 minutes each on alternate days.

PATIENTS: a group of 25 patients suffering from inoperable pancreatic tumor (13 male and 12 female).

Results

1. Patients who have undergone an palliative operation: 5
2. Patients who have undergone the chemiotherapy: 22 (21 cases with Fluoruracile-Gemcitabina, 1 case with octreotide and interferon α-2b).

3. Survival 12th month: 17 pts - 68%
4. Survival 18th month: 10 pts - 40%
5. Survival 24th month: 9 pts - 36%
6. Survival over 24th month: 7 pts - 28%
Conclusions
The application of capacitive hyperthermia therapy on this restricted group of patients has given out surprising results. The HT+ CHT can reduce the tumoral increase, can raise the survival of the patients and, above all, the HT can better the general conditions of those patients which are in keeping with this kind of treatment.
ASSESSMENT OF HYPERTERMIA COMBINED WITH RADIATION IN TREATMENT OF LOCALLY ADVANCED PROSTATE CANCER: LONG-TERM RESULTS OF DFCI 94-153

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Purpose

Hypertermia offers potential therapeutic advantage in combination with radiation for treatment of prostate cancer. A phase 2 study was undertaken at the Dana-Farber Cancer Institute (DFCI 94-153) to provide a preliminary assessment of efficacy of transrectal ultrasound hyperthermia in combination with radiation +/- androgen suppression in treatment of locally advanced prostate cancer.

Methods and Materials

Patients with ≥T2b disease who consented to participation on this IRB approved study received 3D conformal radiation therapy in combination with 2 hyperthermia treatments at least 1 week apart during the first 4 weeks of radiation. After 4 patients were accrued, in light of changing practice patterns, 6 months of androgen suppression was allowed. Hyperthermia was administered with a 16 element trans-rectal ultrasound applicator with rectal wall, normal tissue, and intra-prostatic temperature monitoring performed during all treatments.

Results

Thirty-seven patients received a total of 72 hyperthermia treatments between September, 1997 and April, 2002. The mean CEM T 90 43°C for all 37 patients was 8.4 minutes. Median follow-up was 60 months. 1992 AJCC clinical stage: T2b 19, T2c 8, T3a 5, and T3b 5 patients. Median Gleason score was 7 (6-9), and median PSA was 13.3 (2 -65) ng/ml. All patients completed radiation therapy with median dose of 6700 cGy as normalized to 95%. Thirty-three patients received androgen suppressive therapy initiated within 3 months prior to radiation. All but 2 of these patients received 6 months of AST. PSA failure was defined per the ASTRO consensus definition. With a median follow-up of 60 months (range 15-84 months) 65% of patients remain free of biochemical recurrence. Three patients developed metastatic disease of which one patient died of prostate cancer 30 months after treatment. Absolute rate of biochemical control at 24 months, the primary study endpoint, was 78% which compares favorably with a rate of 64% for similar patients on the 4 month androgen deprivation arm of RTOG 92-02 which served as the comparison group for this study.

Conclusion

Transrectal ultrasound hyperthermia combined with radiation for treatment of advanced clinically localized prostate cancer appears promising. Further study of hyperthermia in primary treatment of prostate cancer in combination with optimal radiation and systemic therapies is warranted.
QUALITY OF LIFE IN PATIENTS WITH LOCALLY ADVANCED PROSTATE CANCER TREATED BY RADIOTHERAPY PLUS HYPERTHERMIA


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Introduction
In locally advanced prostate cancer (LAPC) Conformal Radiotherapy (CRT) should be considered the first therapeutic option. CRT and IMRT, allowing a dose more than 80 Gy, may increase local control providing that patients accept a higher risk of rectal complications. Although dose-response data suggests that higher dosage is generally better, it is difficult to determine how much of the improvement in biochemical control is simply related to better patient selection or the better delivery of irradiation. Rectal grade 2-3 complications increase from 12 to 26% when dose is raised from 70 to 78 Gy. The use of Local Hyperthermia (LHT) combined with radiotherapy at intermediate dose should avoid the dose escalation hazards. LHT does not increase late effects when added to radiotherapy and it seems to enhance efficacy of combined treatment (Anscher 1997, Kalapurakal 2000). It is feasible and well tolerated allowing a heat uniform distribution in the prostate and in seminal vesicles, with optimal temperature levels. The primary endpoint of this study was to evaluate quality of life of patients treated by using radiotherapy and local hyperthermia. Secondary endpoints: to evaluate freedom from biochemical recurrence, disease-free survival, and overall survival.

Materials and method
From January 2000 to December 2004, 107 patients with LAPC were treated by using CRT plus LHT. Mean PSA levels and Gleason score of these patients were 13 ng/ml (range 6-90) and 7 (range 6-9), respectively. All patients were treated by using conformal radiotherapy (CRT) at median dose of 74 Gy (range 68-78 Gy) with fractionation of 2 Gy/fraction/5 fractions per week, delivered with six-field isocentric conformal radiotherapy by using MLC and photons of 6 or 10 MV. The clinical target volume (CTV) included prostate and seminal vesicles with a margin of 5 mm. LHT was delivered after radiotherapy session, 1 session/week during the four week of the radiotherapy course (mean maximum temperature of 41.17°C, and mean T90 of 40.36°C), by using BSD 2000 with Sigma-60 applicator®. Androgen suppression therapy (AST) was performed in 73 patients 3-6 months before the start and during the course of CRT as neoadjuvant-concomitant therapy, whereas in 57 patients AST was administered as adjuvant therapy. Of these patients 74 were recently recruited in a prospective study evaluating quality of life (QoL) by using UCLA Prostate Cancer Index (UCLA PCI) and Medical Outcome Study 36-item SF (SF 36) questionnaires modified for Italian people. Mean age of this group was 73.1 (-31.3 / +12.7). To evaluate the sexual function it’s important to note that the majority of these patients were married (81%), 12.2% were single, and 6.8% widowed.

Results
Among 107 patients, 13 (12.1%) died for progression disease, whereas 3 patients (2.8%) died for intercurrent disease. The UCLA PCI was delivered to all patients enrolled in the study, whereas SF 36 questionnaire was administered only to 54% of patients examined. In terms of
late toxicity, only 2 patients (1.8\%) reported grade 2 GI injuries. No late GU severe complications were reported. Only 5 patients (4.6\%) experienced a grade 1 toxicity. Twenty-one patients (28.3\%) achieved a normal sexual activity after AST interruption, considering the mean age of these patients.

**Conclusions**

In the randomized phase III study of MDACC 26\% of patients treated with 78 Gy experienced a grade 2 rectal toxicity, whereas Zelefsky, by using IMRT reported only 4\% of grade 2 GI. Unfortunately, he found a higher (15\%) GU toxicity. In our patients grade 2 GI rate is very low and very few grade 1 GU late complications were reported. In LAPC, LHT plus CRT at intermediate dose is a promising approach useful to enhance irradiation effectiveness without increasing treatment toxicity.
TRANSPERINEAL MICROWAVE THERMOABLATION IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA: A PHASE I STUDY WITH A NEW MINI-CHOKE MICROWAVE APPLICATOR

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Introduction
The rapidly increasing number of patients affected by lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) and health-related costs containment issues recently led to the development of several minimally invasive and inexpensive therapeutic methods and technologies. The transurethral microwave thermotherapy (TUMT) is nowadays considered to be a valid alternative to the standard surgical treatment (TURP); however, uncontrolled back heating effects exhibited by conventional microwave applicators may result in uncertain and not fully repeatable ablative lesion size and shape. Recently, a new microwave antenna for transperineal thermoablation (TT) has been designed—named AMICA-PROBE—comprising at once an integrated hydraulic circuit for applicator cooling and a miniaturized device (mini-choke) for reflected waves entrapment, in order to attain maximum control over radial and longitudinal coagulative lesion size and to fully overcome back heating effects, while keeping the applicator size at a minimum.

Purpose
We present a phase I study aiming to evaluate the tolerability and safety of the thermoablative treatment of BPH-related LUTS patients with this new mini-choke, internally cooled microwave applicator.

Materials and Methods
All 9 patients (mean age: 72.3) enrolled in our study matched the following inclusion criteria: absence of major diseases, failure of previous LUTS pharmacological treatments, International Prostate Symptom Score (IPSS) greater than 7, maximum urinary flow rate (Q_max) of <10 ml/s, PSA less than 4 ng/ml, post void residual urine volume (PVR) greater than 100 ml and prostate volume between 80 and 100 ml. All patients underwent a US-guided TT, upon administering of periprostatic local anaesthesia. Microwave energy was delivered through a coaxial mini-choke antenna with a 15mm long radiating tip, lodged in a 14G introducing needle (operating frequency: 2.45 GHz; power level: 20W; exposure time: 5 minutes per prostatic lobe). Real-time temperature monitoring of periprostatic tissues surrounding the treated region was performed by inserting interstitial thermocouple sensors. Patients were then divided in 3 groups: group 1 (3 patients) underwent transvesical prostatectomy (TP) 7 days after ablative treatment, group 2 (3 patients) after 15 days and group 3 (3 patients) after 30 days. A 18 Ch urethral catheter was placed in each patient before TT and removed upon TP. All surgical samples underwent pathologic analyses in order to evaluate the anathomopathologic characteristics of the lesion. A few days before TT and a few days after TP all patients filled in the validated Italian version of the International Index of Erectile Function (IIEF-5) and SF-36 questionnaires; during TT, the Visual Analogue Scale (VAS) pain score was recorded.
Results

None of the patients reported pain or other symptoms during TT (VAS mean: 1.2) nor exhibited urinary incontinence after TP. Pre-TT and post-TP questionnaires do not show any significant statistical difference (IIEF-5-pre: 18.1, IIEF-5-post: 20.6, SF-36-pre: 85.5, SF-36-post: 90.5; all p > 0.05). During all TT treatments, the mean temperature value detected by thermocouple sensors distributed around the lesion (about 3 cm from the antenna tip) was 39±1°C. No complications occurred during TT treatments. The macroscopic inspection of the surgical samples showed very well defined lesion margins and absence of overheating phenomena. The anathomopathologic analyses showed a quasi-spheroidal lesion (longitudinal axis: 16 mm; transversal axis: 18 mm), characterized by a central coagulative necrosis surrounded by an inflammatory infiltrate reaction (thickness: 2.1 mm), beyond which healthy tissue was found. Lesion sizes were approximately equal for all groups of patients, regardless of the amplitude of TT to TP latency, which shows the absence of time-dependent post-treatment effects and thus assures the predictability and reproducibility of TT results.

Conclusions

Our study proves the safety and tolerability of the transperineal thermoablative treatment of patients affected by BPH-related LUTS with the new AMICA-PROBE microwave applicator.
BIOMEDICAL EVALUATION OF THE SIMULTANEOUS EXTERNAL RADIATION AND HYPERThERMIA INDUCED BY A MINIATURE EM APPLICATOR (434 MHz)

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Purpose

to evaluate the antitumor efficacy of simultaneous application of radiation (RT) and local hyperthermia (LHT) applied with a radio-resistant miniature contact microstrip applicator (MCMA), operating at the frequency of 434 MHz.

Materials and methods

Female rats (strain IEPOR bred, with a body weight of 220-250g) bearing subcutaneous Guerin carcinoma were used. Tumors were transplanted into the right flank All experiments had been approved by the regional animal ethics committee. Treatments were performed when tumors reached a volume of 0.7-0.9 cm³. LHT was administered using a new radio-resistant contact microstrip applicator MCMA, operating at the frequency of 434 MHz (Istok Ltd., Russia). Tumor temperature (°T) was measured by means of semiconductor thermoprobes (0.7 mm diameter). One hyperthermic session per treatment was conducted (43°C, 45 min). Irradiation was carried out using a γ-rays (60Co unit, ROCUS-AM, Russia). The dose rate was 0.83 Gy/min. The total doses of RT were 15 Gy and 20 Gy as a single exposure. RT was commenced on the 15th min of LHT (°T under the tumor 43°C, usually). The antitumor effect of TRT was evaluated by means of standard criterias. The bioenergetic status of tumor was assessed by 31P NMR spectroscopy, tumor choline-containing substances were registered using 1H NMR. Each treatment group have 3-5 animals, experiments were repeated 2 times. Statistical methods included t-tests and correlation analysis.

Results

The combined RT and LHT treatment was feasible, any kind of serious complications were not registered. It was shown the significant deterioration of tumor bioenergetic under radiation that was accompanied by increase of hypoxic fraction in the tumor. Application of HT in combination with radiation enhances these effects, especially in “simultaneous” group. Cho/Cr ratio was decreased after radiation and not returned to the initial level after 24 and 48 h, thus indicating the significant damage of tumor cells as well as inhibition of their restoration after combined treatment.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TGD (day)</th>
<th>CR (%)</th>
<th>SR (scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 Gy</td>
<td>20</td>
<td>0</td>
<td>3.0</td>
</tr>
<tr>
<td>20 Gy</td>
<td>28</td>
<td>0</td>
<td>4.5</td>
</tr>
<tr>
<td>15 Gy, in 1.0 h HT (43°C, 45 min)</td>
<td>22</td>
<td>40</td>
<td>4.0</td>
</tr>
<tr>
<td>20 Gy, in 1.0 h HT (43°C, 45 min)</td>
<td>34</td>
<td>50</td>
<td>5.0</td>
</tr>
<tr>
<td>15 Gy, simultaneously HT (43°C, 45 min)</td>
<td>27</td>
<td>50</td>
<td>5.0</td>
</tr>
<tr>
<td>20 Gy, simultaneously HT (43°C, 45 min)</td>
<td>32</td>
<td>70</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Above mentioned data have shown that LHT combined with RT both in “sequential” and, especially, “simultaneous” regimes displays significant radiosensitizing effect. TER was calculated as 1.3 for the “simultaneous” schedule. At the same time, TGF value was obtained as 1.2 under these conditions due to the increase of the skin response to radiation simultaneously combined with LHT.

Conclusion

1) Simultaneous EM LHT and RT is feasible and leads to an increase of TER and TGF, though further investigations are warranted.

2) Obtained results allow recommend the new miniature contact microstrip applicator (MCMA) for the exploitation in the simultaneous application of radiation and local microwave hyperthermia in biomedical HT experiments.

Acknowledgement

This study is supported by the ISTC grant, project 2221.
SLOT-LINE ARRAY APPLICATOR FOR SUPERFICIAL HYPERTHERMIA TREATMENT

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Introduction
This paper describes a slot-line array applicator for hyperthermia treatment of superficial tumours in cases where it is important to have limited penetration inside the biological tissue. For this reason this applicator has been designed in order to obtain a homogenous heating until a depth of 1 cm from the surface. For its optimization a 3D electromagnetic field simulator was used and impedance matching was evaluated by aid of a vector analyzer.

Methods
This applicator is obtained repeating the structure of a single squared slot-line applicator on a matrix with dimensions 2 x 2. The applicator is designed on a planar structure composed by a dielectric board which thickness is 1.5 mm and relative permittivity $\varepsilon_r = 4.3$. This board is covered with a 0.03 mm metal layer on one side. The slot-lines are then obtained removing chemically the metal on this layer. This applicator is therefore composed by four main parts: the active parts, the ground plane, the slot-lines and the substrate. The active parts are the squared metal patches located inside the slot-lines. The dimensions of active part are such to allow the structure to resonate at the chosen working frequency of 2450 MHz. The rest of metal layer forms the ground plane of the structure. The slot-lines are squared loops with a width to allow the applicator to be impedance matched at the working frequency. The distance between the slot-lines has been chosen in order to have the best SAR distribution inside the biological tissue. The substrate is composed by a squared piece of the dielectric board described above with same dimensions as the ground plane.

All applicator dimensions have been optimized with the help of a 3D electromagnetic field simulator. The feeding is given by means of four coaxial cables connecting the internal conductors to the active part and external conductor on the ground plane. The position of these connections haven been chosen in order to obtain a symmetrical structure, a good impedance matching at the working frequency and first of all the best SAR distribution as possible inside the phantom. The phantom used to evaluate this applicator is and homogeneous agar phantom with relative permittivity similar to muscular tissue. The applicator has been also designed to work with a water bolus, with a thickness of about 10 mm, located between the applicator and the phantom.

Conclusion
The results of SAR distribution simulations and temperature measurements made on agar phantom have shown how it is possible to obtain a treatment with a depth within 1 cm depth. For this reason this kind of applicator is particularly suitable for superficial hyperthermia treatments.

Acknowledgement
This research is supported by Czech Research Program: "Transdisciplinary Research in the Area of Biomedical Engineering II" (MSM6840770012) and by Grant Agency of the Czech Republic project: Medical Applications of Microwaves: "Therapy and Diagnostics" (102/05/0959).
IN VITRO AND IN VIVO COMPARISON OF HEATING METHODS

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Introduction, objectives
Classical oncological hyperthermia is often characterized solely by the homogeneous temperature increase within the tumor. Our objective is to study the effect of the heating method in vitro and in vivo at fixed temperature (42°C).

Method
We have studied the effect of hyperthermia on various cell-lines in vitro HL60 (human leukaemia all line /suspension/), HepG2 (human hepatocellular carcinoma), A431 (human epidermoid carcinoma), with human fibroblast co-culture and xenograft models HT29 (human colonctal carcinoma) and A431 on nude mice (BalbC nu/nu) in vivo. The temperature was kept on 42 (±0.5) °C, measured by fluorescent optical-cable temperature sensors (Luxtron). The classical hyperthermic heating was in water-bath for the cell-cultures (HL60, HepG2, A431) and by infrared radiation for the invivo experiments. The other heating was made by electro-hyperthermia (oncothermia) arrangement, with a laboratory device especially developed for the experimental purposes (Oncotherm). The cell-counting was done by hemocytometer (Burker-chamber). The immunohistochemical reactions were carried out by a fluorescent method using anti-β-catenin (Zymed), anti-p120-catenin (Sigma) and anti-E-cadherin (Zymed). The secondary antibodies were Alexa594 and Alexa488, labelled anti-mouse-IgG. The samples were imaged by confocal microscope (Bio-Rad).

Results
We had observed definite lower cell-count in the culture treated by oncothermia compared to its classically heated counterpart in the case of HL60 cell-culture. The adherent connections (beta- and p120-catenins, as well as the E-cadherin) also significantly differ by the treatment procedures, the adherent activity is higher after oncothermia than after the classical hyperthermia. The time-relaxing of the samples also has definite differences. In A431 cell line co-cultured with fibroblast, the same results were shown – regarding the distribution changes in β-catenin and E-adherin – as in the experiments described above. In vivo, the oncothermia tumor treatment is observed to be more effective in destroying the tumor structure than its classical counterpart.

Conclusions
Our present observations show definite differences between the heating procedures by hyperthermia keeping the same temperature. These measurements address questions of the underlying mechanism of hyperthermia, and make it feasible to continue the investigations in this direction.
Efficacy of Thermochemotherapy Against Murine Lung Carcinoma

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Introduction

Significance of thermochemotherapy of different tumor types is well-known. It was interesting to investigate influence of this therapeutic approach for lung cancer using local laser (LH), water (WH) or ultrasound (USH) hyperthermia.

Methods

Mice C57BL6 with i.m. transplanted Lewis lung carcinoma were used. Treatment was started on 6-9th day after tumor inoculation into leg when tumor volume achieved 0.6-1.6 cm³. Tumors were heated up to 43-45°C during 5-10 min with LH or USH, and 20-30 min with WH. LH was performed with λ=810 nm. USH was performed using two frequencies simultaneously (2.64 and 0.88 MHz with 1 and 2 W/cm² correspondingly). WH was performed with thermal water in thermostat. The cytostatics (cisplatin, doxorubicin, cyclophosphamide, etoposide and others, their double or triple combinations) with the therapeutic doses were administrated to mice single i.v. or i.p. to be followed by hyperthermia at 0.5 – 5 h interval. There was 1 or 2 courses of thermochemotherapy with 48 or 72 h interval. Groups of comparison received only hyperthermia or chemotherapy. Control groups of mice received injections of saline (did not treat anything). Double time (Dt) of tumor volume was calculated, and it was used for tumor growth evaluation. As a criterion of efficacy coefficient «C»=Dtexp/Dtcontrol was used. Simultaneously during 2-3 weeks local and system side effects were registered after all kinds of treatment.

Results

Control groups had Dt=1.5-2 days. LH groups had Dt=2 days and «C»=1.3. Group WH had Dt=4 days and «C»=2.0. Group USH had Dt=4 days and «C»=2. Group USH with 2 courses of treatment s Dt=12 days and «C»=6. Groups receiving any kind of chemotherapy had Dt=3-9 days and «C»=1.5-6. Thermochemotherapy groups with 1 course of treatment had Dt=9-12 days and «C»=6-8. Thermochemotherapy groups with 2 courses of treatment had Dt=14-16 days and «C»=7-8. The highest activity was demonstrated by the 1 courses of LH thermochemotherapy with cyclophosphamide 200 mg/kg or 2 courses of USH thermo-chemotherapy with doxorubicin 4 mg/kg + cisplatin 3 mg/kg. Side effects of hyperthermia were revealed as a local toxicity with edema just after application and during 3-4 days. If the schedule of treatment included 2 course of hyperthermia alone >43°C such effects were more intensive up to the necrosis of soft tissue. Only after 1 course of thermochemotherapy with high dose of cyclophosphamide application the decrease of body weight in treated mice without death from toxicity was observed. After the 2nd course of thermochemotherapy with other cytostatics local side effects were the same.

Conclusion

The group with hyperthermia only demonstrated Dt>2.0-4.0 time as compared to the control group. All treated groups demonstrated Dt>1.3-5.8 time in comparison with hyperthermia alone, or Dt>2-3 time in comparison with chemotherapy alone. Thus, local water, laser or
ultrasound hyperthermia together with chemotherapy including cisplatin, doxorubicin, etoposid, cyclophosphamide or their combinations in therapeutical doses inhibit tumor growth more significantly than chemotherapy or hyperthermia alone. Two courses of USH thermo-chemotherapy with cisplatin led to increase of efficacy without any side effects or other types of toxicity.

**Acknowledgement**

This work was supported by Moscow Government (Russia).
Microwave radiometry is investigated for non-invasive measurement of subcutaneous temperature as well as for detection of pathologies that are characterized by the presence of local thermal anomalies [1]. First type applications have been proposed for the monitoring of the temperature in oncological hyperthermia [2] and during hypothermia treatment of neonatal ischaemia [3]. The diagnostic application has been explored mainly for detection of mammalian cancer [4], [5] as a complementary technique to mammography.

A two-channel radiation-balance microwave radiometer has been designed and assembled. In view of the medical application, a sensitivity better than 0.1 °C was specified for 1s integration time. Immunity to reflectivity changes in the range between 0 and 0.25 was also specified. The size of the microwave unit has been kept small in order to allow its positioning close to the antenna and the sensed body (Fig. 1). The radiometer besides has some interesting features. Among them we quote: i) the use of high performance PIN switches, which show low insertion losses and high insulation due to a resonant scheme; ii) miniaturized front-end which employs MMIC and microwires on bare chips; iii) use of COTS devices in order to have a low cost; iv) radiometer operation and data acquisition supervised by a microcontroller, in order to have flexibility and capability of adopting further measurement procedures.

A record of radiometric data is given in Fig. 2. In this experiment a matched load, connected to the radiometer input by a short coaxial cable, is immersed in a water tank whose temperature is controlled by a thermostat. Bath-temperature steps are recognized by the radiometer over instrumental noise, whose rms value is about 0.05 °C for 5 s of integration time. In this paper, recent advances on potential applications to the visibility of a breast malignancy are discussed.
HYPERTHERMIA IN COMBINATION WITH METRONOMIC DOSED CYCLOPHOSPHAMIDE INDUCE THROMBOSPONDIN 1 (TSP-1) IN TUMOR VASCULAR ENDOTHELIUM

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Purpose
Metronomic dosed CTX has been shown to induce the antiangiogenic protein thrombospondin 1 (TSP-1) in endothelial cells. We have previously presented that both a metronomic dosage regimen of CTX (p = 0.006) and hyperthermia (p < 0.001), significantly delayed the time for the tumor to reach four times the initial volume in an experimental brain tumor model. A combination of the two regimens exhibited significantly better tumor control than the two modalities separately (p < 0.001). Complete tumor regression was seen in 6 % of the rats treated with CTX, in 12 % of the rats treated with hyperthermia alone and in 41 % of the animals treated with both CTX and hyperthermia. The objective of this study was to elucidate whether the enhanced effect observed by adding hyperthermia to metronomic dosed CTX was related to induction of TSP-1.

Materials and methods
We administered the combination of a metronomic regimen of the alkylating agent cyclophosphamide (CTX) combined with hyperthermia in the BT4An aggressive rat glioblastoma-like tumor model, serially transplanted orthotopically on the right hind foot in BD IX/HanFoss rats. CTX was administrated at doses of 35 mg/kg i.p. three times a week for two weeks and local hyperthermia at 44.1 +/- 0.1 °C was administrated for one hour. From tumor samples taken within the first three hour after completed treatment day zero, we analyzed TSP-1 gene expression using RT-PCR, and TSP-1 protein by immunohistochemical (IHC) staining.

Results
IHC revealed a marked upregulation of TSP-1 in the endothelium of tumors receiving the combined treatment, and to a lesser extent in those treated with hyperthermia alone. There was no difference in the gene expression of TSP-1, but the vast majority of the cells in the samples were tumor cells, and therefore gene expression changes restricted to the endothelial cell are not detectable.

IHC staining of TSP-1

Control, 180 min  HT + CTX, 180 min
Conclusion

Metronomic dosed CTX induce TSP-1. A distinct upregulation of TSP-1 in the endothelium of tumors treated with hyperthermia combined with metronomic dosed CTX indicate that influence on TSP-1 is associated with the improved tumor response.
PERCUTANEOUS CT-FLUOROSCOPIC-GUIDED RADIOFREQUENCY (RF) ABLATION OF A SINGLE PANCREAS METASTASIS: A CASE REPORT

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Purpose
To describe a case of percutaneous RF ablation of a single metastasis from renal adenocarcinoma localized at body-tail portion of pancreas.

Methods and materials
A 77 years old male, with a history of left nephrectomy for renal adenocarcinoma 2 years before, came to our attention for ultrasound and computed tomography finding of a 2 cm pancreatic nodule suggestive for secondary lesion. As the patient refused surgical intervention, a percutaneous RF ablation treatment was proposed. Informed consent was obtained, and the protocol was approved by the institutional review board. An intermittent CT-fluoroscopic technique (CT Aquilion Toshiba 64 slices; 120 kVp, 10–40 mA) was used for placement and deployment of a 19 G needle electrode (Invatec Miras RC®). This model generates up to a 3-cm-diameter zone of necrosis. The patient was treated during monitored anesthesia care.

Results
No peri-procedural complications occurred. After the procedure the patient complained of diffuse abdominal pain and a slight increase in amylases serum level was observed (300 UI/l). The patient was discharged after 3 days. A CT scan performed at 1 month showed complete lesion ablation with a little fluid asymptomatic peripancreatic collection. Amylases serum level was normal.

Conclusions
RF ablation under CT-fluoroscopic guidance is a feasible technique in the treatment of small pancreatic lesions.
LASER ABLATION IN THE SURGERY OF PARASAGITTAL MENINGIOMAS: MONITORING OF TEMPERATURE WITH SEMICONDUCTOR VISION INFRARED THERMOGRAPH (SVIT)

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3 Research Institute of laser physics, SB RAS, Novosibirsk, Russia

Meningovascular tumors – meningiomas – are observed in 13-27% of all adult intracranial neoplasms, ranking second among all brain tumors. They rank second among other brain meningiomas in localization and make a significant portion of neurooncologic patients.

Nd-YAG laser is used in the Clinic of Neurosurgery of Novosibirsk RITO since 1995. This is a solid, yttrium aluminum garnet neodymium laser with wave length 1.06 mkm designed in Siberian Laser Centre (SB RAS Laser Physics Institute). Surgical laser operates in pulse-periodic regime with impulse duration 200 mks, irradiation frequency 100 Hz, and power 45-60 W. This type of laser irradiation penetrates into meningioma tissues up to 0.5 cm and, being fully absorbed by blood, exert high-degree coagulating effect. Surgical laser application is based on the effect of laser coagulation and laser vaporization of biological tissues.

From 1998 till present 216 patients with meningiomas of different localization were operated on using original laser technologies. All patients were divided into 3 groups: 9 patients (4.16%) with convexity meningiomas, 90 patients (41.66%) – with parasagittal and 117 (54.16%) - with skull base meningiomas. Nd-YAG laser was used at the stage of microsurgical removal of the tumor (coagulation and ablation of the stroma), in treating tumor matrix, hyperostosis and bone flap if it is involved in neoplastic process.

Temperature parameters in the region of laser action were controlled with the help of “SVIT” (Semiconductor Vision Infrared Thermograph), developed in the Institute of semiconductors of Novosibirsk Scientific Center. Thermograph works in the range of infrared spectrum 2.6-3.1 mkm and is characterized by high sensitivity (0.025°C), high registration speed (0.001 sequence per sec), and thermal filming function. This allows for its real time application.

In the course of tumor parenchyma coagulation the temperature in laser impingement point reached 71.45°C while the temperature of adjacent brain tissue in close proximity to laser operation point was 33.2°C. In treating the tumor original site of growth (matrix), namely sinus wall or falx, the temperature in laser impingement point varied from 70.14 to 102.33°C. The temperature in laser point at the bone flap reached 80.66°C.

Thus, the use of infrared laser (wavelength 1.06 mkm, power 45-60 W) is effective and safe technique for removal of meningo-vascular brain tumors of multiform localization. As intraoperative monitoring of temperature parameters has shown, ND-YAG laser coagulation of meningioma, its matrix, and bone flap creates strictly local high temperatures in the laser impingement point. The temperature of adjacent intact brain tissue remains within the physiological norm.
NANOMECHANICAL MOTION OF YEAST CELL MEMBRANE AS POSSIBLE SOURCE OF ELECTRIC FIELD

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Introduction

Local nanomechanical motion of yeast cell (*Saccharomyces Cerevisiae*) wall has been measured by Pelling et al. with atomic force microscope (AFM). By means of the Fourier transform of the measured signal they have found oscillations with amplitude of a few tenths of nm to a few nm’s lying around the frequency of 1 kHz. Frequency of these oscillations was temperature dependent. Background noise of the AFM was of the order of magnitude of $10^{-2}$ nm. Oscillations at a single frequency have been detected on the normal yeast cell wall and those at multiple frequencies different from the frequency on the normal cell wall have been detected on the bud scar. Oscillations of the yeast cell wall and of the bud scar ceased after addition of metabolic inhibitor, which suggests cellular metabolism is involved in the generation of motion.

Materials and Methods

This paper reports on the measurements of acoustic vibrations of the yeast cells in the region around kHz. Measurements were made with a Multimode IV, Veeco Digital Instruments AFM.

AFM has to be screened from the vibrational noise from the floor as well as from the noise generated by controlling electronic system. Background noise was below the level of 0.1 nm at frequencies above 0.5 kHz.

Results and discussion

The peaks of acoustic oscillations of yeast cell membrane were detected on the multiple frequencies around 1 kHz with amplitudes of about of 1 nm. Spectra of detected oscillations are presented.

The findings correspond to the Fröhlich’s postulate of coherent electrically polar longitudinal vibrations in biological systems. Vibrations of the electrically polar structures in the cell membrane imply generation of electromagnetic field. Therefore we suggest that electrical oscillations of similar frequencies should be detectable in the vicinity of yeast cells.
CAPACITIVE HYPERThERMIA PLUS CHEMoTHERAPY IN A CASE OF PREVIOUSLY IRRADIATED UNRESECTABLE GRADE III ASTROCYTOMA: A FEASIBILITY STUDY

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Introduction

Hyperthermia (HT) has been shown to inhibit glioma growth both in vitro and in vivo, as it reduces the severe hypoxia that is present in these tumors, thus enhancing the effect of radiotherapy and chemotherapy\(^1\). Various HT techniques have been applied for brain heating (interstitial, nanoparticles), which proved to be safe. While treatment for resectable grade III-IV gliomas is well defined (surgery plus radio-chemotherapy with Temozolomide), the treatment options for unresectable gliomas still vary among institutions. As the prognosis for this group of tumors is dismal, the association of HT to chemotherapy in the presence of progressive disease could be a valid option, though its efficacy is still to be proved by clinical trials.

Case description

We present the case of a 69 years woman, whose clinical history began with left focal seizures; a MRI showed an area of signal alteration in T2 and PD in the territory of right anterior and posterior cerebral arteries, with minimal mass effect and no contrast enhancement; the finding was interpreted as low grade astrocytoma, not suitable for surgery, and the patient was sent to simple wait and see policy. Eleven months later the initial lesion showed to be increased, now occupying the right thalamus-pulvinar region, joining the mesencafalon caudally, with a little mass effect and no contrast enhancement; it was now interpreted as diffuse astrocytoma (grade III) and sent to our department for radiotherapy. We performed a whole brain radiotherapy with a dose of 30 Gy in 10 fractions, 5 days per week for 2 weeks. One month after the end of the treatment, a new MRI showed no change of the diffuse brain lesion and we started chemotherapy with Temozolomide (100 to 150 mg per meter square for 5 days during each 28 day cycle). After 3 cycles, a new MRI showed increasing of the lesion, which now involved the putamen, so the patient was sent to HT treatment in parallel with Temozolomide.

Materials and methods

We performed the HT treatment with a capacitive system (Synchrotherm RF), with a couple of capacitive antennas (13.56 MHz, 600 W). Tests were made on a phantom before treating the patient, to assure the safety of the procedure. External thermometry revealed a temperature of 39- 40 °C. Each treatment sessions lasted 20 minutes on average. During the treatment session we performed an intravenous infusion of Mannitol 18% solution, 250 ml, to prevent brain edema. We performed 4 HT sessions, once weekly. Temozolomide therapy went on as planned; Temozolomide-related haematological toxicity was monitored.

Results

No HT-related neurological toxicity was seen during the treatment. During the 4 weeks of the HT therapy, the patient did not complain of seizures or other neurological problems. After the completion of the 4 weeks of HT, the patient started the 5\(^\text{th}\) Temozolomide cycle (up to 6 – 12 cycles are foreseen).
Conclusions

HT-chemotherapy proved to be safe in case of non-resectable progressive diffuse astrocytoma after radiotherapy.

References

Background
Concurrent chemoradiotherapy with weekly Cisplatin became a standard procedure in patients with locally advanced cervical cancer. However, in case of relapse, most cervical malignancies are associated with very poor prognosis. Efficacy of local and systemic therapy can be enhanced by increasing temperature of target tissue to 41-43 degrees which leads to local hyperaemia and increases the response to cytotoxic interventions. Addition of hyperthermia to radiotherapy has been proved to yield an advantage in survival and local control in pts affected by recurrent and local advanced cervical cancer in the Dutch Phase III trial so that the Consensus Forum of Kadoka included cervical cancer among tumours treatable with hyperthermia. Platinum derivatives have shown synergistic effect and the combination of both has elicited high response rates in recurrent cervical carcinoma.

Patients and method
Since January 2003 to now 16 patients affected by cervical cancer with stage IB2 through IVA N0-N+ pelvic or paraaortic started the treatment. Fourteen patients were treated at initial diagnosis and two patients after chemotherapy which had achieved stable disease. Treatment regimen consisted in 5 courses of weekly chemotherapy (cisplatin 40 mg/mq) with concurrent external radiotherapy to a total dose of 64-66 Gy on CTV1 and 45 Gy on para-aortic nodes plus boost in pts with enlarged nodes identified by imaging. Five weekly sessions of hyperthermia were performed by using BSD 2000 system and sigma 60 applicator.

Results
Our own experience has shown that adding hyperthermia to chemoradiotherapy is well tolerated by the patients: compliance, tolerability and clinical response rates are consistent with that of other reported experiences.

Conclusions
Triple modality treatment combining radiotherapy, chemotherapy and hyperthermia for the treatment of patients with locally advanced cervical carcinoma appears to be very promising.
3-D VERSUS 2-D STEERING IN PATIENT ANATOMIES: A COMPARISON USING HYPERTHERMIA TREATMENT PLANNING

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Introduction
The AMC-8 70 MHz phased-array waveguide system is an eight channel regional hyperthermia device consisting of two rings with each four waveguides. This system enables 3-D steering, where the single ring version of the system, the AMC-4 system, is capable of 2-D steering only. This 3-D steering is expected to result in improved regional hyperthermia treatment.

Purpose
A comparison was made between the performance of the AMC-4 and AMC-8 system based on tumour temperature and the occurrence of hot-spots for patients with a cervical carcinoma using hyperthermia treatment planning.

Methods
For five patients with a cervical carcinoma a CT-scan has been made in treatment position. After manual segmentation of the tumour, the anatomy was segmented into fat, bone, muscle tissue and inner air based on the Hounsfield units. Tissue properties were assigned using values from literature. Using a finite-difference-time-domain method, the electric fields induced by the individual antennas were calculated. The calculated electric fields were then used as input for a temperature-based optimisation procedure based on Pennes’ bioheat transfer equation. The objective of the optimisation procedure was to minimise the tumour volume with a temperature lower than 43 °C using a maximum temperature of 45 °C for the normal tissue as a constraint. This procedure was repeated for the AMC-8 system using different values for the ring distance (1, 3, 5, 7 cm).

Results
With large inter-patient variability, an increase in tumour temperature of 0.5 °C was typically predicted when using the AMC-8 system instead of the AMC-4 system. To obtain this result, doubling of the delivered amount of power was typically required. Variation of the ring distance can influence the achieved tumour temperature, but the dependency between tumour temperature and ring distance varies from patient to patient. Hot-spots are commonly found to be located at the same anatomical position when comparing both systems. At the right and/or left flank of the patient, in the region between the two rings, hot-spots were predicted in all five patient cases when using the AMC-8 system.

Conclusion
From these simulations it can be concluded that application of the AMC-8 system will lead to a clinically relevant increase in tumour temperature.

Figure 1: An example of a geometry used for FDTD calculations.
ELECTRO-HYPERTHERMIA (EHT) AND HEPATIC ARTERIAL CHEMOTHERAPY (HAC) IN PATIENTS WITH LIVER METASTASES FROM GASTROINTESTINAL CANCER (GIC)

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Purpose

HAC is a promising approach for the treatment of liver metastases from GIC. EHT have a direct anticancer effect and a synergistic activity by potentiating drug activity. We clinically examined 40 patients (pts) with unresectable metastatic liver cancer (MLC) from GIC who received EHT and HAC at our Division between January 2006 and December 2006. Aim of the current study was to define the toxicity and response to this combined therapy.

Methods and patients

There were 25 males and 15 females. Patient ages ranged from 43 to 77 years, with a mean of 55 years. Primary cancers consisted of pancreatic cancer (14 pts), biliary tract or gallbladder cancer (12 pts), colorectal cancer (11 pts) and gastric cancer (3 pts). 25 pts were previously untreated, 15 pts received one or more previous chemotherapeutic treatments. Main inclusion criteria were PS ECOG 0-2, liver replacement by tumor <50%, T.bili. <2.0 AST/ALT <4 times the upper limit of normal. Treatment consisted of combined HAC with three days of EHT: the day before, the same day and the day after HAC. Every session of EHT was delivered using a radiofrequency generator of 13.56 Mhz for 60 minutes at 80-140 W equivalent to 41-45°. Patients received HAC cycles as follows: FLEC regimen (leuderfolin, 5-fluorouracil, epirubicin hydrochloride, carboplatin) for MLC from pancreatic origin, ECF regimen (epirubicin hydrochloride, cisplatin, 5-fluorouracil) for MLC from biliary tract or gallbladder, FEM regimen (5-fluorouracil, epirubicin hydrochloride, mitomycin-C,) for MLC from colorectal or gastric origin.

The pts received the drugs by a catheter placed into the celiac axis or the hepatic arterial through an inguinal access. Median number of cycles was 4 (1 - 6).

Results

All pts are fully evaluable for toxicity. No relevant hematologic or extrahematologic (grade 3-4°) toxicity were observed. 5 pts complained of not relevant side effect due to EHT (local pain or burning) that were not of obstacle in carrying out the treatment. The response among pts was: 5 partial response, 17 stable disease and 18 progressive disease for an overall tumor growth control of 55%. From beginning of therapy 24 pts are alive.

Conclusion

The combined therapy with HAC and EHT showes a high response rate without increasing toxicity in this group of pts with severe prognosis.
MODIFICATION OF LUCITE HORN APPLICATOR WITH RESPECT TO FREQUENCY BANDWIDTH

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Introduction
This paper describes two possible modifications of the lucite horn applicator to achieve larger frequency bandwidth. The applicators are designed at working frequency 434 MHz. The results were obtained using 3D electromagnetic field simulator. These modified applicators can be also used as a receiving antenna to the monitoring of temperature in radiometry system. In this system is required to use the applicators with broadband impedance matching to the treated area.

Methods
The electromagnetic field is excited in the waveguide which has got geometrical dimensions to provide only dominant mode TE_{10}. The lucite horn with aperture of 125x90 mm is connected to the waveguide to achieve more uniform distribution of the electromagnetic field inside the aperture. Two centimetres thick water bolus (\( \varepsilon = 78 \)) is inserted between the aperture of the horn and agar phantom (\( \varepsilon = 0.8 \text{ S/m}, \sigma = 54 \)). The coaxial-to-waveguide adapter is optimized in 3D electromagnetic field simulator to developed lucite applicator with larger frequency. On the fig. 1A is shown classical adapter which is most often used adapter and its possible modifications (fig. 1B-C).

Fig. 1: Coaxial-to-waveguide adapters

For the classical adapter the obtained frequency bandwidth (\( S_{11} \) parameter is under -10 dB) is 60 MHz. For the both modified models we achieved similar frequency bandwidth of 100 MHz. The 3D SAR distribution in agar phantom didn’t change using modified coaxial-to-waveguide adapters.

Conclusion
Two possible modifications of the lucite horn applicator were developed with respect to achieve larger frequency bandwidth. The results of the 3D SAR distribution are presented as well.

Acknowledgement
This research is supported by Czech Research Program: "Transdisciplinary Research in the Area of Biomedical Engineering II" (MSM6840770012) and by Grant Agency of the Czech Republic project: Medical Applications of Microwaves: "Therapy and Diagnostics" (102/05/0959).
Using an MRI for non invasive thermometry is a suitable tool to control an hyperthermia treatment. The problem is the decoupling of the radiofrequencies used for hyperthermia and for simultaneous imaging without noise. Due to the electromagnetic interferences and different hyperthermia applicators, up to three different frequencies had to be filtered.

The BSD-2000 3D MRI system used at Charité Medical Center has a fixed treatment frequency of 100 MHz with a power of 1800W maximum. Using high power levels leads to a subharmonic signal inside the body coil tuning box of the MRI with 50 MHz, which has also to be filtered for proper imaging. A second capacitive hyperthermia system for local purpose uses a third frequency of 13,56 MHz working with 150 W maximum.

The filtering has to be done in the power path of the MRI. Only 4.5% signal attenuation for 63.5 MHz is acceptable in this part for normal imaging with the MRI.
FIRST RESULTS OF A PHASE II CLINICAL STUDY ON RELAPSED MALIGNANT GLIOMAS TREATED WITH ELECTRO-HYPERTHERMIA

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The purpose of this study was to evaluate the activity and toxicity of electro-hyperthermia (ET) on relapsed malignant glioma patients. Twelve patients with histologically diagnosed malignant glioma entered the study. Eight patients had glioblastoma multiforme, two had anaplastic astrocytoma grade III and two had anaplastic oligodendroglioma. All patients were pre-treated with temozolamide-based chemotherapy and radiotherapy. Hyperthermia with short radiofrequency waves of 13.56 MHz was applied using a capacitive coupling technique keeping the skin surface at 20 degrees C. The applied power ranged between 40-150 Watts and the calculated average equivalent temperature in the tumours was above 40 degrees C for more than 90% of the treatment duration. One complete remission and 2 partial remission were achieved, with a response rate of 25%. The median duration of response was 10 months (range 4-32). The median survival of the entire patient population was 9 months, with 25% survival rate at 1 year. ET appears to have some effectiveness in adults with relapsed malignant glioma.
ONLINE STEERING CONTROL BY MR-THERMOMETRY

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Introduction
RF-hyperthermia can be planned by different calculation methods like FDTD or FE. To overcome existing differences between the calculation and the real SAR distribution it is possible to correct the calculation by the use of MR-thermometry.

Material and Methods
In phantom measurements we used the double-echo proton resonance frequency method for MR-thermometry performing a drift correction with silicone oil tubes. For SAR calculation the FDTD method on a regular voxel grid was used. For each experiment a planning was performed with the exact position of the applicator to the phantom. After a transformation of the basefields in the grid of the MR measurements we performed an adaptation of the basefields by the results of the MR thermometry with known phase settings. Therefore a Gauss-Newton algorithm was used. The resulting adapted planning was used to steer the SAR in the region of interest.

Results
The FDTD planning itself shows good similarity to the MR measurement, but the adaptation of planning by MR-Thermometry improves the congruence with the real situation. The adapted planning is used for steering the SAR virtually in a region of interest. The result of a following experiment with the new calculated phases with the MR-thermometry of the experiment shows quite good congruence with the reality and better than the FDTD planning alone.

Discussion
In comparison to a standard planning the adapted planning by use of MR-thermometry shows an improvement of accuracy. Using the adapted planning for further optimisation gives better results than using FDTD planning alone. In the near future we hope to improve the velocity of the calculation for using it in patient treatments.
COMBINED TREATMENT OF ABLATIVE THERAPY WITH PERCUTANEOUS RADIOFREQUENCY AND CEMENTOPLASTY OF A SYMPTOMATIC METASTATIC LESION OF THE ACETABULUM: CASE REPORT

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Purpose
Bone metastatic disease is one of the most frequent complications in the oncologic population and represents an important cause of pain. Medical treatment of these patients can be difficult since it doesn't often allow a suitable control of pain. Conventional therapeutics options include surgery, radiotherapy, chemotherapy, hormone therapy and, recently, therapy using systemic radiopharmaceuticals and biphosphonates.

Materials and Methods
We report the case of a symptomatic metastatic lesion of the acetabulum from colon adenocarcinoma in a 82-year-old female patient treated by a combined approach of thermal ablation with percutaneous radiofrequency (RF) and cementoplasty.

Results
The following day the patient was completely free from pain without neurological damage at the sensorio-motor physical examination. Six months later the patient was still free from pain.

Conclusions
Combined treatment of percutaneous RF ablation and cementoplasty appears to be promising, technically feasible under combined CT and fluoroscopic guide, minimally invasive; it represents an alternative treatment to control pain in patients with bone metastases not suitable to surgery and with pain not responding to medical treatment.
HYPERTHERMIA COMBINED WITH CISPLATIN AND RADIOTHERAPY. A SHORT REVIEW OF PRECLINICAL STUDIES ON TRIMODALITY TREATMENT

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This review discusses available clinical and experimental data and the underlying mechanisms involved in trimodality treatment consisting of hyperthermia, cisplatin and radiotherapy. The results of phase I/II clinical trials show that trimodality treatment is effective and feasible in various cancer types and sites with tolerable toxicity. Based on these results phase III trials have been launched to investigate whether significant differences in treatment outcome exist between trimodality and standard treatment. In view of the clinical interest it is surprising to find so few preclinical studies on trimodality treatment. Although little information is available on the doses of the modalities and the treatment sequence resulting in the largest degree of synergistic interaction, the results from in vivo and in vitro preclinical studies support the use of trimodality treatment for cancer patients. Animal studies show an improvement in treatment outcome after trimodality treatment compared with mono- and bimodality treatment. Studies in different human tumor cell lines show that a synergistic interaction can be obtained between hyperthermia, cisplatin and radiation and that this interaction is more likely to occur in cell lines which are more sensitive to cisplatin.
CHEMO-RADIATION WITH RF HYPERTHERMIA – A NOVEL TRIMODALITY OPTION FOR ADVANCED HEAD AND NECK CANCER

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Chemo-radiation is the current standard of care in most of head and neck cancers. It has improved disease free survival, functional integrity and marginally the survival. Hyperthermia has been shown to improve survival when combined with radiation. There is a level I evidence for the same. Hyperthermia can also enhance the effects of chemotherapy by increasing tumour perfusion, altering cell membrane characteristics on inhibiting repair. Hence, combination of all the three modalities should in principle add to the response and overall survival. Importantly hyperthermia has non-overlapping targets along with chemo-radiation.

Materials and Methods

Patients with non-resectable advanced head and neck cancers were treated with trimodality treatment. Nasopharyngeal cancers were not included in this prospective non-randomized study of cancer. All patients were scoped and imaged before obtaining histological confirmation.

Twenty-three patients received radiation with conventional fractionation to a total dose of 70 Gy. Patients also received either 60mgs of paclitaxel or cisplatin 50 mg per week. Patients were evaluated periodically during and after the treatment. Initial response and toxicities were scored during and at the end of treatment. Initial response and toxicities were scored during and at the end of treatment.

Conclusion

Trimodality treatment was well-tolerated ten patients showed a complete response and thirteen showed PR. A randomized trial to assess the role of HT will be the next step.
POST RFA SYNDROME: ONE SINGLE CENTRE EXPERIENCE

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Purpose
To study and to evaluate prospectively post-radiofrequency ablation syndrome and to determine its impact on the quality of life in the 15 days after percutaneous radiofrequency ablation (RFA) treatment.

Materials and Methods
We performed an internal review board-approved prospective study of the delayed symptoms that occurred after 71 consecutive RFA sessions in 53 patients (12 women, 41 men; age range, 45-83 years; mean age, 71.6 years) with 45 primary liver tumours, 34 liver metastases, 3 renal cell carcinoma [RCC], 2 residual lesions from RCC after nefrectomy and 1 pancreatic metastases from RCC.

Results
Postablation symptoms occurred in 17/53 (32%) patients. Six out of 17 patients developed low-grade fever (from 37.5°C to 38.5°C). Other symptoms included delayed pain (9/17), nausea (7/17), vomiting (3/17) malaise (3/17) and myalgia (1).

Conclusion
Postablation syndrome is a common phenomenon after RFA of solid abdominal tumours. In our study, but also in the previous ones, the occurrence is observed in approximately one thirds of patients. Patients should be informed that these symptoms are self limiting after RFA and most patients should be able to resume near complete preprocedural levels of activity within 10 days after the procedure.
WHOLE BODY HYPERThERMIA IN THE MANAGEMENT OF ADVANCED MALIGNANCIES IN CHILDREN

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Purpose

Despite the worldwide using intensive chemotherapy, surgery and/or radiotherapy in advanced cancer in children, the outcome is disappointing and there is an urgent need for novel treatment strategies in this group of patients. We used whole body hyperthermia (WBH) and cytokines as an adjuvant to chemotherapy cycles for overcoming drug resistance in this very poor prognostic group of pediatric patients.

Methods

Since 1994, 71 children (girls-37, boys-34) with a median age of 12.5 (range 6-16) years, have been treated with chemotherapy cycles and WBH (3-4 procedures for every pts). There were 27 patients with soft tissue sarcoma, 12 – Ewing’s sarcoma, 9 – osteogenic sarcoma, 6 – renal-cell carcinoma, 5 – primary malignant hepatic tumors, 3 – germ-cell tumors, 3 – nephroblastoma and 4 – other tumors. WBH (41-43°C, 3 hours) with hyperglycemia (21-26 mmol/1) procedures induced by 13, 56 MHz EM under the general anesthesia. Besides systemic thermo-chemotherapy, patients were given cytokines: IL-2 in 12 cases, INF-α2b in 11 cases and LAK-therapy implicated in 9 patients. In 33 pts WBH was administered as an adjuvant to standard chemotherapy (adjuvant-group). In all pts were diagnosed high risk and metastatic malignant solid tumors. WBH was used as a salvage therapy with second line chemotherapy in 38 children with resistant tumor (non-responders) or early relapses of advanced tumor (salvage-group). In case of severe hyperthermia regimens (42, 5-43°C) urotropin was used for blocking thermal proteolysis.

Results

All pts well tolerated WBH and no treatment-related complication observed. Occasionally we observed superficial skin burns which did not require any surgical management. Eight-years overall survival (OS) rate was achieved in 55% of patients in adjuvant group. These results are considerably better than at the standard therapeutic approach. As a salvage therapy WBH in 38 pts with refractory and early relapsed tumors resulted in 15% OS.

Conclusion

Based on clinical experience from many years of treatment and follow up, we suggest that whole body hyperthermia might be one of the future approaches in improving the effectiveness of care in advanced, relapsed and refractory tumors in children. Further clinical studies are necessary for optimizing temperature regimes, therapy schemes with WBH and cytokines.
DOSE-ENHANCEMENT EFFECT OF CYTOSTATIC AGENTS ASSOCIATED WITH INCREASED TEMPERATURE IN VITRO

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Background
The combination of chemotherapy and hyperthermia may be a promising approach in the treatment of malignant tumors. In the present study, the effect of 8 different chemotherapeutic agents in vitro was compared at 37°C and 42°C.

Materials and methods
Human cervical carcinoma HeLa cells, 24 hours after seeding, were treated with different concentrations of carboplatin, vinorelbine, ifosfamide, doxorubicin, etoposide, oxaliplatin, docetaxel or gemcitabine and incubated for 60 min at 37°C or 42°C. After the treatment the cells were left for 48 hours in the incubator at 37°C. The influence of chemotherapy and temperature on cell proliferation and survival was evaluated by hemocytometer cell counting using the Trypan blue exclusion method.

Concentrations of each drug causing growth inhibition by 50% and 90% (IC50 and IC90) and 50% initial population killing (LC50) were determined. Thermal enhancement ratio (TER) for cell proliferation or cell death for each chemotherapeutic drug was calculated as IC50, IC90, or LC50 for a drug alone divided by IC50, IC90, or LC50 for the drug combined with hyperthermia.

Results
Reduced cell proliferation with increasing concentrations of chemotherapeutic agents was demonstrated. Hyperthermia alone caused only 10-20% growth inhibition. All the chemotherapeutic agents used demonstrated a dose-enhancement effect at elevated temperature. TER for cell proliferation for oxaliplatin, vinorelbine, carboplatin and ifosfamide exceeded 4, for doxorubicin and gemcitabine exceeded 2. TER for cell death did not exceed 1.3.

Conclusion
Synergism of hyperthermia and chemotherapy was clearly demonstrated for oxaliplatin, vinorelbine, carboplatin, ifosfamide and to a lesser extent for doxorubicin and gemcitabine. Thermal enhancement was most prominent with low drug doses.
COMBINATION OF HYPERThERMIA AND RADIOTHERAPY AS THE TREATMENT OF SUPERFICIAL MALIGNANT MELANOMA METASTASES

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Purpose

The aim of this study is an evaluation of an effectiveness and toxicity of radiotherapy and hiperthermia combination for superficial malignant melanoma (MM) metastases on a base of the retrospective material.

Material

The material is comprised of 37 cases of superficial MM metastases (14 W, 23 M). Mean of patients age was 63 years. In 18 cases PS of patients was Zubrod 0, in 15 – Zubrod 1 and in 4 - Zubrod 2. In 33 cases the primary MM was located on skin, in 2 in eye and in 2 cases the primary site remained unknown. In 21 cases lymph nodes and in 16 cases skin metastases were treated. In 14 cases tumors located on thorax and in axillas, in 10 on neck and in supraclavicular region, in 7 on abdomen and in inguinal region and in 6 on extremities were treated. Tumors sizes varied from 0.5 cm to 10 cm (mean 3.5). All patients were unsuitable for surgery or refused operation.

Method

Patients were treated with three 9 Gy radiotherapy fractions followed by three 60 min. hiperthermia sessions (43°C). Treatment was completed within 8 days. Patients were examined in the day of treatment end, 2 and 6 weeks later and next every three months. The regression of tumor size and skin reaction in 6 degrees scale (1- delicate erythema, 2 – intensive erythema, 3 – blisters, 4 – brown skin, 5 – necrosis, 6 – teleangiectasies) were evaluated.

Results

The number of controlled patients decreased rapidly during the follow up period because of natural history of disseminated MM. The percentage regressions of treated tumors were 12.5% - 2 weeks after the treatment, 31.2% - 4 weeks later and 23.3% - 4.5 months after the treatment. After this time tumors started to regrow, so progression was noted during next controls. Means of tumors sizes 0.5, 1.5, 4.5, 7.5, and 10.5 months after treatment completion were 2.7 cm, 2.7 cm, 2.4 cm, 3.5 cm and 4.8 cm respectively. Number of patients with following degrees of skin reaction during follow up is presented in Table I.

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Conclusion
Combination of hyperthermia and radiotherapy could be a valuable and safe option of the palliative treatment for patients suffering from superficial inoperable MM metastases.
**OXYGEN TENSION MEASUREMENTS IN TUMOR DURING HYPERTERMIA**

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**Introduction**

Oxygen tension measurements in tissue are required in some fields of medicine particularly in oncology. Drawback of hard invasive oxygen sensors is their affecting on vasoconstriction and thus oxygen supply. Other mode is based on spectral measurement of ratio hemoglobin/oxyhemoglobin. But this allows supervising oxygenation in blood vessels rather than in cells of tumor where oxygen tension can be tens of times less. Phosphorescent oxygen-quenching sensors [1, 2] have been rapidly developed recently, due to their high sensitivity, selectivity and stability. Lifetime-based sensors possess some intrinsic advantages over intensity-based sensors:

- minimal interference by external noise-based sources;
- unaffected by light source intensity and photodetector sensitivity drift;
- independence on dye concentrations.

Here we consider application of lifetime-based phosphorescent liquid probe for oxygen tension measurements in mice tumors during sessions of laser induced hyperthermia.

**Materials and methods**

Mice BDF with intramuscular inoculated melanoma were used as experimental models. Tumors heated by radiation of Nd:YAG laser (wave length of 1064 nm, power up to 10 W). Tumor temperature measured using thermocouple mounted into gilded medical needle (diameter of 0.35 mm). Palladium meso-tetra-(phenyl)-tetrabenzoporphin (Vinogradov and Wilson, 1995) was used as a phosphor. Dye was dissolved in medical liquid paraffin. Maximum absorption is at 629 nm. Phosphorescence emission is maximal at about 800 nm. Solution (3-10 mm³, concentration of 1.6 10⁻⁵ M) was injected into tumor as oxygen tension probe. He-Ne laser (50 mW) was used for phosphorescence excitation. Rectangular excitation pulses (pulse duration of ~15 mcs, pulses repetition frequency of 50 Hz) are formed using mechanical chopper and irradiate injected probe. Phosphorescence is collected by lens to photomultiplier tube (Hammamatsu R3896). The photomultiplier output is amplified with amplifier (Hamamatsu C1053-51) and digitized. The digitization starts at the time of excitation pulse. The data for multiple pulses are collected by summing into 16-bit buffer. The single-exponential calculation was performed by fitting the natural logarithm of phosphorescence intensity as a function of time to a straight line.

**Results**

Phosphorescence decay was near to exponential unlike water-soluble phosphorescent probe. It facilitates processing of measurement results. Oxygen tension kinetics during hyperthermia sessions is presented. Heating of a tumor is accompanied at first by vasodilatation, after that by vasoconstriction. Usually exposition during 15 min at temperature 45 ⁰C led to irreversible damage of tumor blood vessels.
References


CALCULATION OF 1-D DISTRIBUTION OF THERMAL DAMAGES IN TISSUE DURING SURFACE CYCLIC IRRADIATION BY POWERFUL LIGHT SOURCE

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Introduction
Thermostimulation of surface lesions using long continuous irradiation can result in thermal damage of underlaying intact tissue. Use of short heating with the subsequent cooling is advisable in these cases.

Materials and methods
We have developed the calculation program for kinetics of 1-D distribution of thermal necrosis in tissue during surface cyclic irradiation by powerful light source at following assumptions. The irradiation zone sizes are much more than depth of damage. Tissue is homogenous. In this case the photons concentration, N, in tissue is described by equation (1);

\[ N = N_0 \exp(-x), \]

where \( N_0 \) - surface photons concentration, \( x = \beta z \), \( \beta \) - effective absorption parameter, \( z \) – depth. Temperature distribution is described by the equation of heat conductivity. Following boundary conditions were used: 1) heat exchange on a surface is absent or 2) surface temperature is maintained as constant (for example, using intensive air-blowing). Rate, \( W \), of accumulation of the thermal damages resulting in further to cells death is described by Arrhenius equation (2) at temperature higher than 42°C:

\[ W = A \exp(-E/kT), \]

where \( k \) – Boltzmann constant, \( T \) - absolute temperature. Parameters \( A \) and \( E \) were determined from experimental data on thermal necrosis of mice tail skin in temperature range 42-46°C [1].

Results and discussion
Some examples of 1-D distributions of the share of killed cells in tissue every 2 min during 4 cycles (2 min - irradiation is "on", 8 min - irradiation is "off") are shown in Fig.1.

![Fig.1](image_url)

**Fig.1.** Distribution of the share of killed cells in tissue. a - heat exchange on surface is absent, \( P = 0.5 \) W/cm²; b – \( Ts = Tb \), \( P = 1 \) W/cm²; c - \( Ts = Tb + 9^\circ C \), \( P = 1 \) W/cm² (\( P \) – irradiation power density, \( Ts \) – surface temperature, \( Tb \) – body temperature).
The obtained results allow to conclude nonstationary irradiation techniques enable protecting underlaying intact tissue better than stationary irradiation. It is clear, surface tissue protecting can be provided using air-blowing if necessary.

References

The absence of biophysical model of hyperthermia effect on the tumor cells forces the researchers to develop the mathematical models based on the experimental data. The different approaches to these models development were considered in [1-3]. The main idea of models construction consists in adjusting of their parameters to obtain an admissible difference between modeling results and experimental data. In this connection the considering models belong to the class of adaptive models. The adaptive neural model named CRNN allowing representation the dependencies of tumor cell surviving fraction $Z$ (%) via duration of hyperthermia $t$ at the fixed temperature $T$ was proposed by authors earlier [2]. The feature of this model consists in its ability to produce the dependencies dynamically contrary to usual (static) neural approach.

The representation of survival curves as the collection of lines $t(T)$ each of them corresponds to the fixed value of parameter $Z$ is more convenient for analysis of experimental data by specialists and in biomedical practice. The neural model developed in this paper was used for constructing of such collection. We used the multilayer perceptron (MLP, [4]) that has universal abilities for approximation of continuous functions with several arguments. The MLP with two hidden layers including 8 and 5 neurons respectively was trained for approximation of function $t(T,Z)$. We used the experimental data of Chinese hamster V79 cells survival [5] for the computational experiment. The experimental sample was artificially enlarged by modeled points because of insufficient data for carrying out necessary researches (Fig. 1). The collection of equisurvival curves $t(T)$ corresponding to the different values of parameter $Z$ in logarithmic scale of variable $t$ is presented in Fig. 2.

The character of curve $\ln [t(T)]$ depicted in Fig. 2 can be useful for specialists in biophysics of hyperthermia effect on tumor cells.
References


RADIOFREQUENCY ABLATION (RFA) OF PRIMARY AND METASTATIC LUNG TUMORS: SINGLE CENTRE-SINGLE DEVICE EXPERIENCE

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Purpose
To assess feasibility and results of RFA in the treatment of primary and secondary lung tumors.

Materials and Methods
In the last 3 years we selected 22 patients (mean age 66.8 years) with 26 pulmonary lesions: 12 primitive and 14 metastases. The procedures were performed with CT guide with anesthesiological assistance using a coaxial Le Veen needle-electrode. The results were evaluated by post-procedural CT and after 1, 3, 6 and 12 months from the treatment and then every 6 months.

Results
We obtained a complete ablation of 22/26 lesions (84.6%). We observe 7 pneumothorax (4 spontaneously resolved and 3 drained through coaxial needle), 4 middle pleural reactions, 1 hemothorax drained surgically. During follow-up we observe a stability of 2/4 lesions that received partial ablation and a disease progression in 2/4. 22 tumors, that received a complete ablation, have mean follow-up of 12.2 months (range 6-36); in 3/22 lesions we observed a recurrence (2/3 received a further RFA); in 19/22 complete ablation was confirmed by CT. A systemic disease progression occurred in 7/22 patients.

Conclusions
RFA is a valid option of treatment in “not surgical” patients with primary and secondary lung tumors, with good results in the local tumor control.
COMBINED TREATMENT OF TRANSARTERIAL EMBOLIZATION (TAE) AND RADIOFREQUENCY (RF) FOR LARGE HEPATOCELLULAR CARCINOMA (HCC)

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Purpose
To describe the effectiveness of a combined treatment of TAE and RF for large HCC (> 5 cm).

Materials and Methods
Over the last year we treated 10 patients (mean age 72 years), affected by unresectable HCC (mean diameter of nodule 5.8 cm; range 5-7 cm) with TAE and RF. Embolization was performed through a superselective catheterism of afferent branches of hepatic artery and injection of polyvinyl alcohol particles (PVA) in 6 cases and an emulsion of Lipiodol plus doxorubicin in 3; RF of the same lesion was carried out under ultrasound guidance (LeVeen needle in 6 cases; Invatec needle in 3).

Results
All patients underwent CT at 1, 3, 6, 12 months (range 3-12). In 5 cases we obtained a complete necrosis of the nodule. We reported 2 cases of persistence of disease at 1 month, retreated with TAE with complete success after 6 months. In 3 cases at 6 months, we documented a relapse of the lesion that was retreated with TAE. A hepatic abscess developed in 1 patient.

Conclusions
TAE before RF increases the area and amount of necrosis. In our experience, this combined treatment is effective and promising in patients affected by large HCC.
PART BODY HYPERTHERMIA PLUS RADIO-CHEMOTHERAPY IN
THE PALLIATIVE TREATMENT OF LIVER METASTASES
FROM COLORECTAL CANCER

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Introduction

Colorectal cancer represents a very important cause of cancer death in Europe and USA. More
than 15% of patients in advanced stages develop synchronous liver metastases (15-20% after
surgery and adjuvant chemotherapy and 50% during the natural evolution of the disease);
only a small number (10-20%) of these lesions are radically resectable.

In chemonaive patients with metastatic colorectal cancer, the use of 5-Fluorouracil (5-FU)
plus Folinic Acid improves the median survival to 12 months, giving an objective response of
about 20-25%, while in previously chemo-treated patients 5-FU does not significantly im-
prove the overall survival. Furthermore, in patients with 5FU-resistant metastatic colorectal
cancer, the use of Irinotecan and Oxaliplatin yields further toxicity without a significant im-
provement in overall survival.

Radiofrequency Ablation (RA) with percutaneous technique is frequently used in the treat-
ment of liver metastases. The results of RA are comparable with those of surgery, but a pro-
spective randomized trial is still needed to demonstrate the efficacy of this invasive approach.
An important limitation of this technique is represented by the size of the metastases, which
determines the diameter of the coagulation necrotic volume that can be produced by a single
RA session. Furthermore, the majority of patients show multiple lesions with too large diame-
ters to be treated by RA, so that an alternative heating technique should be proposed.

Materials and Methods

From 2001 to 2006, we delivered a combined chemo- or radio-hyperthermia treatment in 16
patients who were heavily affected by liver-metastatic colorectal cancer and who had not re-
sponded to a conventional first-line chemotherapy. All patients were previously treated with a
first-line chemotherapy (FOLFOX or FOLFIRI) as adjuvant therapy. Chemotherapy con-
sisted of 5-FU 300 mg/mq per 7 days in bolus. Exceptionally, in one patient who refused in-
travenous 5-FU, an oral fluoropyrimidine (Capecitabine) was preferred. In 5 patients with
very poor general conditions, a conventional hypofractionated irradiation with palliative in-
tent was preferred. In all cases, hyperthermia was combined with radio- or chemotherapy.
Hyperthermia was delivered as Part-Body hyperthermia (PBHT), using a BSD 2000 radiofre-
quency equipment, with a sigma 60 annular phase array applicator®, and a total output of 400
W; the treatment was performed once weekly, for 4-6 weeks. In order to avoid the sequelae of
invasive techniques, a dedicated treatment planning has been used for the measurement of the
intratumoral temperature distribution in collaboration with a team from the University of
Padua (IPERCHEM Project). Hyperthermia was combined with a second-line chemotherapy
(5-FU via bolus or continuous infusion; Capecitabine in one patient). In 5 patients hyperther-
mia was combined with radiotherapy alone; in 3 patients with a good compliance to the com-
bined treatment, more than 6 fractions (range 9-20 fractions) were delivered with concomitant
chemotherapy in order to maintain a prolonged response.

Results

At follow-up (range 4-24 months), 13/16 patients died, 12 due to metastases progression and
one due to bowel injury probably because of irradiation. One patient was lost at follow-up.
The remaining 2/16 patients (12.5%) had a median overall survival of 11 months from the beginning of the combined treatment; this data are comparable to the ones published in the work of Hager. No severe complications referred to hyperthermia or combined treatment have been reported.

Conclusions

In patients affected by liver metastases, hyperthermia combined with radio- or chemotherapy is feasible and well tolerated. Hyperthermia seems to improve the efficacy of chemotherapy also in previously chemo-refractory tumors. Some technical aspects as the applied frequencies, the time of exposure, the optimal temperature level, the number of sessions, and the interval between radiochemotherapy and hyperthermia, have not been defined yet. In patients with metastatic colorectal cancer, Capecitabine showed a better overall response compared with 5-FU as first-line treatment. In order to allow a concomitant chemotherapy-hyperthermia treatment, Capecitabine could be a reasonable choice.

References

RADIO-HYPERTHERMO-CHEMOTHERAPY FOR SOFT TISSUE SARCOMAS

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Purpose

We performed radio-hyperthermo-chemotherapy (RHC) as a new neoadjuvant therapy for 19 patients with high-grade maligant soft tissue sarcomas of the limbs between 2002 and 2004. We report here the effectiveness of RHC for high grade soft tissue sarcomas.

Patients and Methods

Radiotherapy involved the delivery of radiation at a dose of 2 Gy once daily on 16 days to give a total dose of 32 Gy. Hyperthermia was conducted locally once a week, with a total of 5 sessions. The temperature was measured by inserting a hyperthermia needle into the tumor and inserting a thermocouple thermometer into the space. The objective of treatment was to achieve a temperature of 42.5 celsius or more for 60 minutes. Chemotherapy was performed by implanting a reservoir and administering cisplatin (90 mg/M) 3 times and Pinorubin (25mg/M) twice by intra-arterial infusion at weekly intervals. These drugs were administered alternately during hyperthermia sessions. We divided the patients into three groups; 1) complete hyperthermia: intratumoral temperature was more than 42.5 celsius 2) mild hyperthermia; intratumoral temperature was between 40 and 42.5 celsius 3) poor hyperthermia; intratumoral temperature was less than 40 celsius and we evaluated the effectiveness of RHC for those three groups.

Results

The eight patients of complete hyperthermia were all CDF and the histological evaluation were also excellent. Among the poor hyperthermia group, round cell sarcomas such as soft tissue Ewing’s sarcoma showed good response histologically.

Conclusions

RHC is currently the most potent and relatively safe treatment method for high-grade soft tissue sarcomas.
MINIATURE MICROWAVE EM APPLICATORS FOR HEATING MALIGNANT TUMORS OF RODENTS

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Heating of malignant tumors of rodents is a necessary and commonly used method of experimental studies of hyperthermia (HT) influence on the efficiency of radio- and chemotherapy treatments for malignant diseases in different combinations of the active agents and environmental conditions. As a rule, HT heating is produced by means of emerging the limb of the rodent in a heat water bath, whereas HT procedures in clinics are dominantly administered by EM or US heating. To eliminate this discrepancy, a miniature EM applicator, capable to heat the rodents’ tumors locally, was warranted to be developed. The principle ideologies of the capacity type CFMA applicator [1] and the inductive type applicator with a radiating loop perpendicular to the heated area [2] were taken as key points of the design. Both variants – the capacity and the inductive types – were investigated.

The capacity type applicator antenna, exciting the electrical component of the heating microwave EM field in the heated tissue, consists of two miniature coplanar active electrodes formed by means of photo-lithography technique on one side of a 1.5 mm thick two-side copper-foiled Fluoroplast substrate. Capacities between the two active electrodes, connected by a microstrip inductance, and a shield-electrode on the opposite side of the substrate compose a resonant circuit. To adjust this resonator at the operating frequency chip capacitors are used. The mini-applicators are manufactured with an aperture diameter 12 mm at frequencies of 434MHz or 915MHz. Their overall dimensions are 14 mm in diameter and 5 mm in height. The maximum permissible input microwave power is 5 W. This power is enough to heat the rodents’ tumors to temperatures up to 50 °C.

The inductive applicators, exciting in the heated tissues the magnetic component of the heating EM field, are developed from the same two-side copper-foiled Fluoroplast substrate. They are parallelepipeds made from this material 1.5 mm thick. The two-side copper foils are short-circuited at one side of the parallelepiped thus forming an inductive loop perpendicular to the surface of the heated tissue volume. To form a microwave resonator, chip capacitors shunt the loop at the side opposite to the short –circuited side of the parallelepiped. The perpendicular to the heated surface position of the loop ensures homogeneous heating of the heated area without hot spots. Inductive mini-applicators were designed and manufactured with two aperture dimensions – (10×12)mm2 and (16×18)mm2. The height dimension of the mini-applicators is 6mm. The maximum permissible input microwave power is 5 W.

The miniature dimension of the applicators being comparable with the dimensions of the sensor antenna does not allow measurements of the induced EM field distribution in tissue phantoms. Thus thermal testing of the developed applicators was performed at a piece of liver. Temperature measurements were accomplished by means of needle-like thermo-sensors. With an input microwave power of 1.5W there were achieved coagulation temperatures in a volume about 1cm3. The developed inductive mini-applicators with both aperture sizes are successful used in hyperthermia studies on rodents.

Besides, both types of the developed applicators - capacitive and inductive - provide the possibility of heating the rodent tumor simultaneously with radio- and chemotherapy.
References

ANALYSIS OF CLINICAL APPLICATION OF DIFFERENT METHODS OF HEATING OF WHOLE-BODY HYPERTERMIA

State Institution “N.N. Alexandrov Research Institute of Oncology and Medical Radiology”, Minsk, Belarus

The State Institution “N.N. Alexandrov Research Institute of Oncology and Medical Radiology” has gained experience in generating whole-body hyperthermia by two methods – water-flow and electromagnetic. The water-flow method was used from 1970 to 1999. Since 1988 whole-body electromagnetic hyperthermia has been employed in the Institute’s clinic.

The objective of the study is a comparative analysis of whole-body hyperthermia procedures with regard to the method of its generation, using the following criteria:
- time of reaching hyperthermic reference temperatures;
- rate of thermal damage of the integumentary tissues.

Materials and methods
The data on 638 procedures of water-flow hyperthermia and 987 procedures of electromagnetic high-frequency (13.56 MHz) hyperthermia carried out for cancer patients from 1986 through 2002 constituted the materials of the study.

Results and discussion
Investigation of time and temperature parameters of the procedures with different methods of whole-body hyperthermia generation revealed the following variations in the duration of reaching reference temperatures (Table 1).

<table>
<thead>
<tr>
<th>Method of heating</th>
<th>Time of reaching reference temperatures (rectal temperature)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>up 40° C</td>
</tr>
<tr>
<td>Water-flow (n=638)</td>
<td>64±13 min</td>
</tr>
<tr>
<td>Electromagnetic (n=987)</td>
<td>35.5±5 min*</td>
</tr>
</tbody>
</table>

*p<0.05

The time of reaching 40° C with the electromagnetic method is 1.8-fold less than that with water-flow, and the time of reaching 41-41.5° C with electromagnetic heating is 2-2.5-fold less.

For water-flow hyperthermia, the patient’s body was irrigated with water at 43-44° C. Skin and subcutaneous fat are the first to be affected by the heat flow, that is why pathophysiological reactions of the integument are most markedly manifested. The discharge of vasoactive substances into the blood is increased, which causes spasm of peripheral vessels. Impairment of peripheral microcirculation may result in trophic disorders of the skin and subcutaneous fat in the fulcra (Table 2).
Table 2

<table>
<thead>
<tr>
<th>Method of heating</th>
<th>Hyperthermic unit</th>
<th>Rates of thermal morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Indurations of subcutaneous fat</td>
</tr>
<tr>
<td>Water-flow (n=638)</td>
<td>Pigment</td>
<td>61 (9.7%)</td>
</tr>
</tbody>
</table>

Electromagnetic heating is performed without the integument overheating. One of possible complications of this heating method is local damage of subcutaneous fat and muscular tissue in the form of painful indurations. Skin burns were rare and generally occurred in the places of ECG monitor electrode fixation. The rate of manifestation and the degree of intensity of integument thermal damage were found to depend on the performance mode of the electromagnetic energy generator (pulsed or continuous) (Table 3).

Table 3

<table>
<thead>
<tr>
<th>Generator performance mode</th>
<th>Hyperthermic unit</th>
<th>Number of procedures</th>
<th>Number of complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Indurations of soft tissues</td>
</tr>
<tr>
<td>Continuous</td>
<td>Emona-Brig, Ptich</td>
<td>657</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>Pulsed</td>
<td>Yakhta-5</td>
<td>330</td>
<td>17 (5.2%)</td>
</tr>
</tbody>
</table>

In general, the patients tolerate the electromagnetic thermal exposure much better. The heart-rate with water-flow hyperthermia is within 120-155 per minute, while with high-frequency hyperthermia it is within 93-125 beats per minute.

In conclusion, judging by its controllability, reaching and maintaining therapeutic temperature modes, response of the cardiovascular system, electromagnetic heating of patients has advantages over the water-flow method.
TECHNIQUES FOR THE PROCEDURE OF WHOLE-BODY HYPERTHERMIA WITH INDUCED HYPERGLYCEMIA AND MULTIDRUG CHEMOTHERAPY

State Institution “N.N. Alexandrov Research Institute of Oncology and Medical Radiology”, Minsk, Belarus

The result of clinical application of modifying factors in the treatment of cancer patients, the trends in hyperthermic oncology the world over, employment of novel equipment facilitated improvement of whole-body hyperthermia techniques.

The techniques developed at the State Institution “N.N. Alexandrov Research Institute of Oncology and Medical Radiology” for the procedure of whole-body hyperthermia with induced hyperglycemia and multidrug chemotherapy is carried out with obligatory use of balanced anesthesia and controlled ventilation.

Setting up and sustaining of high temperature is implemented by means of electromagnetic high-frequency (13.56 MHz) hyperthermic units introduced into clinic in 1988.

The design of the hyperthermic units enables to reduce the heat burden on the integumentary tissues (skin and subcutaneous fat), to accurately control the hyperthermic mode, to promptly reach hyperthermic reference temperatures: 40° C is attained during 25-40 min, 41.8-42.2° C – 60-75 min from the start of heating.

The maximum temperature is limited by 41.8-42.2° C of rectal sensor reading and maintained as accurate as 0.2° C for 60-80 min (the period of temperature plateau). Depending on the treatment regimen, additional heating of gas mixture up to 40° C for controlled ventilation is performed. During the hyperthermic period, the patient’s head is air-cooled (10° C), the temperature in the upper third of the esophagus not exceeding 41.2° C.

Our investigation demonstrated that the combination of electromagnetic heating and co-planar lay-out of emitting aerials makes it possible to establish a temperature in tumour masses exceeding the rectal temperature by 0.5° C as a minimum, thus producing a maximal therapeutic effect. The skin temperature of the ventral and dorsal surface of the patient’s body remains within the limits of 41° C.

The indices of the patient’s central hemodynamics are the restricting factor for duration of a hyperthermic procedure.

Hyperglycemia is induced by infusion of 40% glucose solution concurrently with the start of heating. The glucose level in blood higher than 22 mmol/l is reached for 30 min and sustained for no less than 100 min.

Mono- or multidrug chemotherapy is administered with regard to the pharmacokinetics of the acting drugs.

Herpetic infection is prevented by acyclovir at a dose of 500 mg; antiemetic therapy includes ondansetron 8 mg, dexamethasone 16 mg or prednisolon 60 mg.

After the heating being completed, the patient’s body is cooled in the natural way. The overall duration of the hyperthermic period is 150-210 min, of anesthesiological aid – 180-240 min.
All the detected changes in biochemical blood indices, electrocardiographic findings and the patient’s general condition are corrected in the course of and after the completion of the procedure.

The established techniques of whole-body hyperthermia performance was implemented in 2100 treatment procedures, including those for childhood patients, carried out from 1988 through 2006.
LOCAL SUPERFICIAL HYPERTHERMIA IN COMBINATION WITH LOW-DOSE RADIATION THERAPY FOR PALLIATION OF SUPERFICIALLY LOCALIZED NON SMALL CELL LUNG CANCER METASTASES

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Purpose
The aim of this study is to evaluate the response of superficially located non small cell lung cancer metastases and local toxicity to microwave hyperthermia combined with radiation therapy.

Methods and Materials
From May 2003 through December 2006 36 patients (27 male, 9 female; mean age 61 years) with lymph nodes or skin metastases were treated with microwave superficial hyperthermia combined with low-dose radiation therapy. Hyperthermia was administered twice weekly with high frequency applicator (~900Mhz) with water bolus. The temperature was set to 43°C for 45 minutes. Radiotherapy was performed daily with dose 2 Gy or 4 Gy per fraction, to a total dose 20 Gy. There were 11 patients with squamous cell carcinoma 16 with adenocarcinoma 9 with type difficult to determine. Treated regions were mainly neck and supraclavicular (34 patients). The toxicity was evaluated using 6 step scale: 0-no skin reaction, 1- delicate erythema, 2- intensive erythema, 3-blisters, 4-brown mark, 5-necrosis. Presence of pain and it’s intensity were also analyzed. Diameter of tumor after the treatment was observed.

Results
Complete response was achieved in 7 patients (18%), and partial response in 22 patients (58%), no response was observed in 6 patients (16%) and progression of tumor in 3 patients (8%). No skin reaction was observed in 5 patients, delicate erythema in 17 patients, intensive erythema in 14 patients, blisters in 2 patients, no brown mark or necrosis was observed. The pain occurred in 3 patients but it was not the cause of stopping treatment.

Conclusions
Local superficial hyperthermia combined with low-dose radiation therapy is an effective and safe method of treatment in a proportion of patients with superficial non small cell lung cancer metastases. This combination of treatment modalities is well tolerated and is useful for palliation.
HIGH RESOLUTION HYPERTHERMIA TREATMENT PLANNING

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Hyperthermia treatment planning is expected to improve treatment outcome. It helps reduce hot-spots in healthy tissue, improve energy deposition in the tumor, determine the correct dose and it reduces the requirement for invasive temperature measurements without resorting to sophisticated MRI thermometry. However, studies have shown that high resolution treatment planning is required to correctly predict the SAR (Specific Absorption Rate) or temperature distribution and to capture hot spots [1]. A new hyperthermia treatment planning tool based on the SEMCAD X platform has been developed, and novel techniques have been devised that allow the performance of simulations at high resolution.

A) The first step when performing treatment planning is simulation of the electromagnetic (EM) fields of the various applicator antennas. A finite-difference time-domain (FDTD) method on a graded rectilinear mesh is used. The FDTD method can handle large grids (several tenth of Megacells) easily, and the graded meshes allow to work with high resolution where required (antennas, region of interest...) while using a coarser grid elsewhere, thereby reducing simulation time. Dedicated GPU based hardware acceleration cards are employed to speed up the algorithm by an additional factor of 20-100. An ADI (Alternating Direction Implicit) variant of FDTD is used to increase the stable time step. Finally, a conformal subcell method has been developed that reduces staircasing artifacts and diminishes the need for fine resolution in areas remote from the region of interest.

B) It is subsequently possible to determine the EM induced temperature increase using a model based on the Pennes Bioheat Equation (PBE) but with improved perfusion. Again FDTD on a graded mesh is the method of choice. Efficient internal boundary conditions allow the decoupling of subregions. This combined with an implementation which can solve the PBE on an arbitrarily shaped subregion means that the computational domain can be reduced and that materials that would impose a small timestep (air, metal) do not have to be considered. A reasonable starting distribution can be guessed to converge more quickly to the steady state.

C) The time consuming task of calculating tissue damage and thermal doses can be reduced by performing the calculations only in specified subregions or by neglecting transient effects.

D) The SAR or temperature distribution can be optimized using the fast generalized eigenvector method developed in [2]. Precomputing contribution matrices permits quick determination of an alternative treatment plan based on patient feedback. It furthermore allows fast Monte Carlo based estimations of the impact of steering parameter uncertainties. The implementation allows multiple targets that do not have to coincide with a specific solid.

E) A special segmentation tool to generate the required high resolution patient models within reasonable time has been developed.

The treatment planning tool has been used to study various realistic setups. It correctly predicts observed behavior (hotspots, distributions). The software allows the study of hyperthermia treatments at an unprecedented level of detail.

FAST AND FLEXIBLE HIGH RESOLUTION FIELD OPTIMIZER FOR SAR AND TEMPERATURE DISTRIBUTIONS

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²Department of Physics, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece.

Hyperthermia treatment planning attempts to improve treatment outcome by using simulations and optimization to reduce exposure of healthy tissue (hotspots) and to focus the energy deposition into the tumor. Various studies (e.g., [1]) have shown that it is crucial to work at high spatial grid resolution to correctly capture all effects. While electromagnetic fields and in some models even thermal fields can be precomputed, it would be highly valuable to be able to quickly produce a new optimized treatment based on patient feedback during the actual treatment. A useful optimization tool would furthermore allow the specification of multiple, arbitrarily shaped targets. Furthermore, special care should be taken to reduce the exposure of sensitive tissues.

A new, fast optimizer has been designed on the basis of the generalized eigenvector method developed by Koehler [2]. It reduces the possible choice of the optimization functional but offers a fast, non-iterative method of optimizing the antenna parameters (phases and amplitudes). The method can be used for both temperature and SAR (specific absorption rate) field optimization. It requires a set of matrices of integrals to be computed. We propose to precompute these matrices for various subregions of the optimization domain. Based on patient feedback during treatment, these subregion matrices can then be weighted, combined and used for quick reoptimization. Furthermore, storing the matrices allows quick reevaluation of the functional. This can be used to perform a fast Monte Carlo analysis to study the sensitivity of the proposed treatment to uncertainties in phase and amplitude of the individual antenna excitations.

The novel implementation allows the user to specify multiple targets that can be assigned different heating priorities and that do not have to correspond to specific tissues. Instead, arbitrarily shaped target volumes can be specified such as the tumor plus 2 cm safety margin. The user can fix maximal thresholds for individual tissues or subregions and specify sensitivity factors. An iterative hotspot reduction as proposed in [2] can be used to assign additional weight to hotspots thereby allowing the generation of an improved, hotspot suppressing protocol.

The optimization tool has been integrated into the SEMCAD X [3] simulation environment, allowing various visualization and postprocessing options. It has been tested using data from a series of patients and produces considerably improved treatment protocols.

INTRACAVITARY APPLICATOR FOR MICROWAVE THERMOTHERAPY

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Introduction

One of prospective domains of microwave thermotherapy is microwave angioplastic for treatment of atherosclerosis. Due to dysfunction of endothelium a sedimentation of cholesterol on a blood vessel wall can happen. This evokes its sequential closing. Basic principle of microwave angioplastic is, that heating gained by microwave energy irradiated into artery by microwave applicator, enables safe clear out of atherosclerotic plates in the wall of vessel.

Methods

This paper describes the design of special applicator for microwave angioplastic. As the most acceptable structure to create intracavitary applicator, coaxial quarter wave monopole, was chosen. The applicator in our model was inserted into vein with blood and surrounded by phantom of muscular tissue. First goal was to obtain good impedance matching between generator and microwave applicator. Then we studied the distribution of absorbed power (SAR) along the applicator. For the applicator working at 2.45 GHz there was maximum of SAR at point of termination of outer conductor.

Results

The function of the microwave applicator was experimentally evaluated by measurement of reflection coefficient. This tested applicator had good impedance matching, less than -20 dB. Then the distribution of the temperature along the applicator was measured with IR camera. Described applicator was placed in to the phantom of muscular tissue and exposed by 50 W during 1 minute. The temperature grew to 47 °C (fig. 1).

Fig. 1: The distribution of the temperature along the applicator.

Conclusion

This paper describes only technical solution to design the intracavitary applicator for microwave angioplastic. Into the future we plan the cooperation with medical doctors, who will provide us the medical information. Main goal of this project is to determine the optimal temperature for different stadium of this illness.

Acknowledgement

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SUPERFICIAL HYPERTHERMIA WITH LOW DOSE RADIOTHERAPY FOR TREATMENT OF SUPERFICIAL METASTASES

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Purpose
The aim of this study is evaluation of the tumor response after hyperthermia combined with radiotherapy.

Materials and methods
From May 2003 till November 2006 108 patients (61 male, 47 female, mean age 60 years) with superficial metastases were treated with microwave superficial hyperthermia combined with hypofractionated radiotherapy. Hyperthermia was administered twice a week with high frequency applicator (~900Mhz) with water bolus. The temperature was set to 43°C for 45 minutes. Radiotherapy was performed daily with dose 2 Gy or 4 Gy per fraction, to a total dose 20 Gy. Treated regions were head and neck-64, chest wall - 16, abdomen and groins - 12, upper limb – 5 and lower limb - 11 patients. Tumor regression was evaluated at the end of treatment, after 2 weeks, after 1,5 month and every 3 months if it was possible due to the natural course of disease. The toxicity was evaluated using 6 step scale: 0-no skin reaction, 1-delicate erythema, 2-intensive erythema, 3-blisters, 4-brown skin, 5-necrosis.

Results
After the first 2 weeks mean regression value was 18%, after 1,5 month it was 16%. After 4,5 months mean tumor diameter was the same as at the beginning of the treatment. After 7,5 and 10,5 months mean tumor diameter was respectively 16% and 53% larger, than at the beginning of the treatment. No skin reaction was observed in 16 cases, delicate and intensive erythema in 40 and 35 cases respectively. Brown skin was observed in 4 cases. Blisters were observed in 12 cases. No necrosis was observed.

Conclusions
Hyperthermia combined with radiotherapy provides regression lasting approximately 4 months and is safe treatment scheme.
A PATCH ANTENNA ELEMENT FOR THE HYPERCOLLAR APPLICATOR: DESIGN AND CHARACTERIZATION

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Purpose

Hyperthermia (HT) has a high potential to improve treatment results in Head and Neck (H&N) patients. However, an appropriate applicator that can heat both superficial and deep located target regions is not available. In previous studies we found that a setup consisting of two rings of six antennas, operating at 433MHz, can be used to obtain the desired specific absorption rate (SAR) pattern in the neck. In the present study we describe the design of the single antenna element, i.e. a probe-fed patch antenna. Further we analysed the characteristics of the antenna within the HYPERcollar.

Methods

As a first step, we selected the probe-fed patch antenna as most promising candidate and changed its design to meet the desired requirements for operation in a water environment. Using electromagnetic modeling tools (Ansoft Designer and SEMCAD X) we optimized the dimensions of a probe-fed patch antenna design for operation at 433MHz. The electrical properties of the optimized design were analyzed by using SEMCAD X. Further we conducted reflection measurements to verify the simulations and to investigate the properties of the antenna within the array.

Results

By several optimization steps we could converge to a theoretical reflection of -38dB and a bandwidth (-15dB) of 20MHz (4.6%). Theoretically, the electrical performance of the antenna was satisfactory over a waterbolus temperature range of 15-35°C, and stable for patient-antenna distances to as low as 4cm. In an experimental cylindrical setup using six elements of the final patch design, we measured the impedance characteristics of the antenna 1) to establish its performance in the applicator and 2) to validate the simulations. For this experimental setup we simulated and measured comparable values: -21dB reflection at 433.92MHz and a bandwidth of 18.5MHz. We further established that indeed operation between 15-35°C is possible when maximum 10% reflection is allowed.

Conclusion

On the basis of this study, we conclude that this patch antenna design is very suitable for the clinical antenna array. In future research we will verify the long duration electrical performance by measurements in a clinical feasibility study.
Figure 1: 3D configuration (left) and cross-section (right) of the patch antenna configuration and a cross-section, with the dimensions that are varied. The "Muscle layer" was present only in the setups that were used to investigate influence of a patient on the reflection characteristics.
One of the most important problems of electromagnetic hyperthermia in oncology is high temperature in exposed tissue control and maintenance. High temperature should be constant in strong limits, because overheat destroys healthy cells and insufficient heating stimulates malignant tumor growth. The leading role in this process is absorption energy maximization. In electromagnetic hyperthermia absorption are used distances or invasive thermometrical methods, but sideways methods don’t allow show real absorption maximum.

On the middle of last century J.Pätzold suggested selective absorption conception. This conception was based in selective heating tissue deepened frequency, and it came to pass conception was disallow. It has been proved that absorption maximum is bounded with exposure feature.

We carried out the analyze of “condenser plates – air-gaps - object” system behavior. In these investigations characteristic graphs for three main frequencies which are used in electromagnetic hyperthermia have been obtained. Characteristic graphs show absorption maximum depending on object electrical conduction. All of this characteristic graphs have absorption maximums in the presence of air-gaps. Characteristic graphs without air-gaps have linear dependence.

Our results show that absorption maximums found out J.Pätzold depend on air-gaps condenser plates. At constant frequency analysis characteristic graphs show that air-gaps change gives us a possibility maximal as well as minimal of absorption energy. Electric field frequency change appears equivalent to shift of air-gaps distance between plates and object.

Our results allow to develop real-time system for maximal energy absorption in object. This method allows to evaluate the maximal absorption energy in exposed tissues and determine “maximal absorption - temperature” dependence. The practical application of developed method allows to reduce side-effects for patient.

This method can realize in electromagnetic hyperthermia apparatuses with automatic (overlooker) resonant harmonizing system. Hardware and software method realization may be constructed by addition to any type of 13,56; 27,12 and 40,68 MHz physiotherapy apparatuses. Device design and working regime doesn’t vary.
REMARKABLE CYTOREDUCTION OF A BLADDER LESION POST CHEMOTHERAPY (CHT) IN ASSOCIATION WITH HYPERTHERMIA (HT)

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A 69 years old woman was admitted to our department with diagnosis of Muscle Invasive Bladder Cancer (MIBC) [TURB: 28/08/2006, pT1-G4].

The patient complained of two months history of emathuria and pelvic continous pain. The patient underwent therapy based on CDDP 70mg/m² d1 and Gemcitabine 1000 mg/ m² d1,8 every 3 weeks for a total of 3 cycle, associated with 5 cycles of local Hyperthermia (HT). Each cycle consist of eight 45-minute-sessions every other day, using about 300 W per session, administering, at the same time, CDDP.

All the cycles has been administered at full doses and at programmed day. At conclusion of CHT patient complained only symptoms linked to G3 leuconeutropenia and trombocytopenia, treated with growth factors and corticosteroids, respectively and allowing a good quality of life. Progressively, the vanishing of pain lead to suspension of analgesic drug.

Before treatment a pelvic ultrasonography documented presence of bladder lesion about of 5 cm in diameter.

At conclusion of the protocol (CHT+HT) another pelvic ultrasonography and a total body PET-CT scan showed a remarkable reduction of bladder mass (4-5 mm in diameter), confirmed at cystoscopy.

The use of CHT-HT combination may enhance efficacy vs CHT alone. This surprising result may confer a small, but probably, clinically significant improvement survival. However the result of larger collaborative international adjuvant CHT-HT trials will be needed in order to determine the true value of this combination.
Metastatic breast cancer is a chemosensitive disease. In fact, CHT regimens whether based on anthracycline (e.g. FAC) or methotrexate (e.g. CMF) produce 40-75% objective response rate with a median duration of response and survival of 6-12 months and 12-24 months, respectively. However, while these regimens frequently palliate the symptoms of disease, they do not substantially prolong the median survival nor result in the cure of patients.

More recently, taxane containing regimens showed to be the most active regimen in the treatment of metastatic breast cancer, but also with these regimens overall survival was only marginally improved. When patients relapse or show increase of metastatic lesion following first line chemotherapy, a 30-40% response is still achievable various drugs and regimens as second line treatment.

Theoretical advantage for the association of taxane with HT include the following: 1) synergism, else taxane increased cytotoxicity, 2) both of treatments possess relatively non-overlapping toxicities, 3) a good compliance of patients.

In this paper we present a case report of a 41 years old female patient in premenopausal state with diagnosis of metastatic breast cancer (MBC), treated by surgery (April 2003), chemotherapy (FEC), local radiotherapy (DTF 50+50 Gy) and ormonotherapy (tamoxifen 20 mg/die + zoladex 3.6 1fl q 28).

After treatment follow-up was free disease until November 2006, when a total body (TB) computed tomography (CT) scan showed multiple liver lesions of about 5 cm in maximum diameter.

The patient, in our department, underwent chemotherapy based on Paclitaxel 110 mg weekly for 3 weeks consecutively every 5 weeks, associated with 2 cycles of Radiofrequency Hyperthermia (RH), each consisting of eight 45-minute sessions every other day, using about 300 W per session. A successive TB 18FDG Positron Emission Tomography (PET)-CT scan documented absence of metabolic activity disease and a remarkable reduction of liver metastases in number and dimensions, confirmed by an abdominal ultrasonography (February 2007).

Weekly paclitaxel associated with local RH seem to be a promising treatment because this regimen has good efficacy and moderate toxicity.
RETROSPECTIVE CLINICAL STUDY FOR ADVANCED BRAIN GLIOMAS BY HYPERTERMIA TREATMENT, AN UPDATE

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Introduction

None of the established state-of-the-art treatments in malignant primary brain tumors, could show commonly accepted curative potential until today. Electro-hypertermia (HT) applied in combination with chemo- and/or radio-therapy is a new modality of brain-glioma (BG) treatments. This new method shows promising preliminary results1. One of the prospective phase II clinical study on relapsed gliomas treated with electro-hypertermia, showed markedly good results2,3.

Objective

This retrospective clinical study presents 222 patients with brain tumors or metastases-treated/followed from February 2000 to April 2007. With this study we would like to indicate the feasibility of HT for BG. The primary endpoint was the survival time.

Method

The study is an open-label, single arm, monocentric, retrospective study. The involved patients are being analyzed according to an intention-to-treat (ITT) schedule. Recruiting time was 64 months. The primary endpoints of the study were the overall survival time (OST) and the survival time from the first hypertermia treatment (TST). The applied test was Kaplan-Meier log-rank (KM). HT is capacitive coupling technique by short (RF) waves of 13.56 MHz. Two/three sessions per week for tree to six weeks was performed.

Results

Distribution of the BG patients by WHO-grade show mostly advanced cases: astrocytoma WHO II: 13; astrocytoma WHO III (anaplastic astrocytoma, (AA) = diffuse astrocytoma): 49, glioblastoma WHO IV, (GBM): 116, metastases deriving from peripheral cancers: 26, others: 18. Discontinuation of HT defined as <8 sessions: 47

Most of the patients failed to respond to the applied conventional therapies. Hythermia was applied in most of the cases in an adjuvant setting.

Conclusion

The results are well indicating the feasibility and the benefit of the hypertermia treatment showing a valid treatment potential and safe application. Our present data are only retrospective indications of the efficacy of the hypertermia method.

References

PATHOPHYSIOLOGICAL PHENOMENA ARISING FROM HIGH LEVEL GENERAL CONTROLLED HYPERTHERMIA

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High level general controlled hyperthermia (GCH) (up to 43.5 – 44.0°C) occupies a special place among contemporary techniques of intensive therapy. Up to date there is no conception on minimal, rational, and optimal monitoring of patient’s safety during high level GCH.

Objectives
To provide pathogenetic foundation of minimal monitoring of patient’s safety during high level GCH procedure.

Material and Methods
A total of 162 patients at the age of 16 to 65 years underwent high level GCH procedures between 2000 and 2007. Indications for this procedure were oncologic disease. Dynamic control of the brain biological activity (EEG) and cardiovascular monitoring (systolic and diastolic blood pressure, heart rate) were performed in all cases. All data were estimated and analyzed initially and at one-degree rise in temperature. The temperature was measured in external acoustic meatus.

Results
Clinical analysis of findings of neurophysiologic and hemodynamic monitoring revealed a phenomenon of “biological turning point” (EEG findings) indicating the approach to a “biological zero” in the brain; a phenomenon of “diastolic dystonia” which is specific for high level GCH, naturally accompanies subsequently alternating hyperkinetic and hypokinetic phases of blood circulation system, and indirectly reflects the onset of thermal hypermetabolism; and a phenomenon of “gaseous a-v inversion”, which indirectly discloses the dependence of hemodynamic response on the intensity of thermal stress.

Conclusions
The phenomenon of “biological turning point” appearing as 80% decrease in the brain biopotentials is the most informative criterion for phenomenon of “diastolic dystonia”, safety monitoring of high level GCH. The phenomenon of “diastolic dystonia” has a pathogenetic importance for adequate protection of a patient during high level GCH.
THERMORADIOThERAPy AND RADIoCHEMOTHERAPy OF LOCALLY ADVANCED PHARYNX CANCER WITH INVOLVED LYMPH NODES

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Purpose of the study
To prove an expected benefit of simultaneously given radiotherapy or chemoradiotherapy and local hyperthermia for the treatment of stage III and IV unresectable pharynx cancer a prospective non-randomized trial was initiated.

Materials and method
From March 1994 to October 2001, one hundred twenty two patients were enrolled, 111 of them completed the treatment (median age 53 years; 35.1% stage III tumors; 64.9% stage IV tumors; 64% oropharynx; 36% hypopharynx). In the first group, 59 patients underwent a split-course of conventional radiation therapy (RT) up to total dose 68-70 Gy. In the second group (RT+HT), 52 patients were performed RT and 6-9 sessions of local microwave hyperthermia (915 MHz, 45-50 Wt). Heat was delivered for an hour up to 41.50-430C in the tumor before irradiation.

From December 2002 to April 2006, fifty seven patients were included into the study, 46 of them completed the course (median age 57 years; 39.1% stage III tumors; 60.9% stage IV tumors; 71.7% oropharynx; 28.3% hypopharynx). The treatment protocol of chemoradiotherapy (CRT) consisted of three courses of chemotherapy (5-FU+cisplatin) given in the 1st, 5th and 11th week and conventional split radiation therapy (6-9 and 12-14 weeks). In the forth group (CRT+HT), besides, patients were performed 6-8 sessions of local hyperthermia. Adverse events (skin and mucosal toxicity, dysphagia, xerostomia and hematological toxicity) were scored according to RTOG\EORTC criteria.

Results
Patients treated with thermoradiotherapy had significantly better OS than those treated with standard fractionation (p=0.0225). One-year overall survival (OS) was 49.1% and 68.1%, 3-year OS – 15.1% and 34%, 5-year 11.3% и 23.4%, 10-year – 5.7% and 12.7% in RT and RT-HT group, respectively (Fig.1), with median survival 11.9 and 19.1 months. Patients in local hyperthermia group demonstrated non-significant increase of grade 3+4 mucositis, dysphagia, skin and soft tissue toxicity (p=0.067). Hematological toxicity was low and identical in both groups.

One-years OS of patients, who underwent chemoradiotherapy, was 85.7%, 3-years – 66.2% with undefined median survival (Fig.2). In CRT-HT group, one- and three-years survival was 87.5% and 30%, respectively, with median survival 23.7 months. There was no significant difference between the groups (p=0.2413). Patients treated with chemoradiotherapy and local hyperthermia more often developed grade 3+4 mucositis (52.9% vs 32.9%, p=0.0347) and dysphagia (28.6% vs 8.8%, p=0.0315) compared to those with chemoradiotherapy alone. Severe myelosuppression (WBC less than 2.500 cells/mkl) was observed in 10.3% of patients in the course of CRT and 29.4% of patients in the course of CRT+HT, p=0.0213. Grade 2-4 anemia developed in 34.5% and 52.9% cases, respectively.
Conclusions

There is an evident benefit for CRT vs RT and RT+HT for the treatment of locally advanced pharynx cancer. Thermoradiochemotherapy doesn’t improve survival, but significantly increases toxicity of the treatment.
PATCH ANTENNA ARRAY FOR THE TIME REVERSAL MICROWAVE HYPERTHERMIA

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Introduction
The E-field distribution of the applicator can be driven by changing amplitude and phase at the feed points of the individual antennas. The E-field is typically focused by optimizing the SAR or the temperature distributions in the treated area. The time reversal method offers the another approach. The wave front of the source is propagated through the patient model from a virtual antenna placed in the tumour of the patient. The simulated radiated field is then "measured" using the computer models of the surrounding antenna system. The real antenna system is then transmitting the field in a time reversed order. It is the invariance of the wave equation under time-reversal in lossless media that enables optimal refocusing of the time-reversed signal at the original source.

In this paper, we investigate an antenna array design for time reversal based microwave hyperthermia. Our previous results, conducted in 2-D realistic anatomy models of neck and breast, have shown that the algorithm focuses EM energy better at high frequencies hence these fit well to treatment of small tumours. The level of absorbed energy is also strongly dependent on size of treated area through penetration depth of EM waves, thus selection of the frequency depends on treated area sizes as well as tumour volume. For this reason the broadband techniques is used in the patch antenna design.

Methods and Results
The proposed applicator is immersed in the matching liquid and consists of 8 to 12 identical triangular patch elements. The triangular patch antenna is chosen as the applicator element. By placing shorting wall the edge of a triangular patch antenna with a V-shaped slot, two resonant modes can be excited simultaneously and they can be coupled together to achieve the broadband operation. Two different models, with and without V-shaped slot respectively, are presented.

The matching liquid reduces hot spots and increases the impedance matching between biological tissue and the applicator. The relative permittivity $\varepsilon$ of the matching liquid strongly affects the operating frequency of the antenna. Thus by changing of this parameter it is possible to tune the applicator to required optimal frequency. Both operating frequency and bandwidth of proposed models are similar, whereas SAR distributions on the surface of the phantom have different shapes. The bandwidth of the single element achieves 50%. The center frequency variates according to relative permittivity $\varepsilon$ of the matching liquid from 350 MHz to 700 MHz for $\varepsilon = 78$ and $\varepsilon = 30$.

Conclusions
SAR distributions of both applicators are calculated for phantom and realistic anatomy model of the Head and Neck region. The results are compared with the applicator consisting of dipole elements. The performance indices show that application is encouraging for treatment of all tumour volumes and positions in this region. In comparison with the dipole applicator, the proposed applicator offers more favourable SAR distribution in the treated area. The single patch element may also be individually mounted in a planar array and can be use for the superficial hyperthermia.
CAN RADIATION INDUCED SARCOMA OF THE CHEST WALL BE TREATED WITH RE-IRRADIATION AND HYPERThERMIA?

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Background
Radiation induced sarcomas occur in about 0.5 per thousand irradiated patients, are often angiosarcomas, are believed to bear an extremely poor prognosis and to be radiation resistant. A series of eight radiation induced sarcoma’s of the chest wall, treated by re-irradiation and hyperthermia in the Academic Medical Centre is presented.

Patients and methods
From 1984 to 2007 eight patients were referred. Seven women, one man, mean age 71 years (48-82). Mean interval between the previous cancer (breast/Hodgkins disease) and the sarcoma was 74 months (19-132). Five were angiosarcoma, three not otherwise specified (NOS). One patient was metastasized at diagnosis, the others were referred after one (3 pts) two (2 pts) or three (1 pt) attempted resections or systemic treatment (1 pt), with a mean interval since diagnosis of 6.5 months (3-16). One patient had no apparent tumor at referral. The others a mean largest tumor size of 12 cm (1-25), usually an area of multiple nodules. Radiotherapy was applied to the tumour area plus a generous margin. One patient received 6 fx of 2.5 Gy in 2 weeks, one received one fraction of 6 Gy (and refused further treatment), the other six patients 8 fx of 4 Gy in 4 weeks. Hyperthermia was administered with the 434 MHz AMC wave guide system, aiming at 41 °C for an hour, at least once a week.

Results
One patient stopped treatment after one session and is unevaluable for response. One patient had progression shortly after treatment. Two patients had a minor/partial remission during treatment and too short follow-up, and four had a complete response. One patients is alive without disease after 29 months. One patient is well with regressing tumour shortly after treatment. One patient died of suicide two weeks after start of treatment, one died of unknown cause after two months, and three after 6,8, and 8 months respectively of pleuritis, believed to be sarcomatous. One patient is alive with pulmonary metastases and thrombo embolic complications.

Discussion
It is difficult to draw conclusions from a small and heterogeneous patient cohort. With four complete and one partial remission in 7 evaluable patients, and only one patient with documented local progression it may be concluded that the tumour is sensitive to irradiation plus hyperthermia. Survival is poor due to fast hematogeneous spread. The only patient alive and free of disease for longer than two years is the patient in whom adjuvant reirradiation plus hyperthermia was performed shortly after first resection.
APPLICATOR FOR MICROWAVE THERMOTHERAPY

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Introduction
Microwave thermotherapy (hyperthermia) is currently a commonly used method for cancer treatment in medicine. To achieve an effective treatment of some types of cancer, applicators with small size and large aperture are required. This article deals with the design of a waveguide strip-horn applicator with a frequency of 434MHz which fulfils these demands. Our main contribution is the applicator design and optimalization by means of numerical models and experimental measurements.

Materials and Methods
The applicator is composed of a waveguide and a horn which has lateral sides made from dielectric material (relative permittivity = 4). To decrease the cutoff frequency it is filled with essential water (relative permittivity = 81). Electromagnetic field is excited in the waveguide at frequency 434 MHz and subsequently passed along the strip horn into biological tissue. Impedance matching is performed by a capacity screw. The dimensions of the waveguide (60x30mm) support the excitation of the dominant mode only and the dimensions of the strip-horn support the large aperture. The impedance matching as well as the SAR distribution inside a biological tissue were first evaluated and then optimized by aid of numerical models based on FDTD. Instead of a biological tissue we used material with parameters $\varepsilon_r=54$, $\sigma=0.5$ S/m, $\rho=1300$ kg/m$^3$ for computation and an agar phantom for experimental measurement.

Results
The impedance matching is measured by a vector analyzer based on sixport and SAR distribution by using IR-camera. We achieved very good value of impedance matching $S_{1,1}=-27$dB. In Fig.1 is imaged a result of temperature distribution which shows the effective aperture of the applicator.

![Fig.1](image)

The temperature distribution measured on surface of an agar phantom.

Conclusion
Our main contribution was the design of applicator which has small size and large aperture, and its verification by means of experimental measurements. We found that the use of a strip-horn could be used to get larger aperture. Our results show that this type of applicator is suitable for tumor treatment.

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MEASUREMENT PROBES FOR COMPLEX PERMITTIVITY DETERMINATION - EVALUATION OF REFLECTION METHOD

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The knowledge of complex permittivity is important e.g. for the design and impedance matching of the thermotherapeutic applicators (to treated area) in microwave hyperthermia cancer treatment. Also in the medical diagnostics the knowledge of dielectric parameters of biological tissues enables to diagnose a tumor cell nest in the human body. Common to all papers in the field of dielectric measurements is a more or less extensive tabulation of the dielectric properties of tissues selected to illustrate the theoretical deliberations provided by the authors. The objective of the research reported here is to analyze an open ended coaxial line sensor for in vivo and nondestructive measurements of complex permittivity, and to develop a precision measurement system. It involves also feasibility study of different types of measurement probes.

Figure: Example of measurement probes (coaxial and waveguide type) and obtained values of complex permittivity (real and imaginary part) on author’s arm by aid of coaxial probe. We can see good agreement between the data from experimental measurement and data from numerical simulation.

The reflection measurement method is convenient method for the determination of dielectric parameters of biological tissues. It was found that our coaxial probe is useful in frequency range from 40 MHz. The description by two-element equivalent circuit (fringing capacitance and radiating conductance) is necessary because of the probe radiation at higher frequencies (dimensions of the probe are comparable with the wavelength). The planar probe and waveguide probe are suitable – achieved reflection coefficient is sufficient. This enables us to consider the use of measurements in reconstruction method of biological tissue.
EXPERIENCES WITH COMBINED TELERADIOOTHERAPY AND SUPERFICIAL HYPERTERMIA IN PATIENTS WITH HEAD AND NECK CANCERS

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Background
The combination of teleradiotherapy and superficial hyperthermia is used in the treatment of patients with Head and Neck Cancers in our department, especially in cases with superficial tumours or lymph node metastases.

Patients and methods
From 9/2002 till 2/2007 we treated 90 patients by combination of teleradiotherapy and superficial hyperthermia. There were patients treated for the first time with curative intent, patients with relapse after previous radiotherapy as well as patients with primary palliative intent. All of them were clinical stage IV. Linear accelerators with energy 5MeV or 6MeV were used for radiotherapy, with dose per fraction 2-3Gy, 5 fractions a week. For superficial hyperthermia was used Hyperthermia System 4010 from Lund Science AB (Sweden). The hyperthermia was applied after radiotherapy once a week, 60 minutes for one application.

Results
From the group of 90 patients with combined teleradiotherapy and superficial hyperthermia, 76 of them finished the planned treatment (64 men, 12 women). 62 patients were treated with curative intent, 14 patients were treated with palliative intent. Among these 76 patient were 12 patients with reirradiation (8 patients - curative intent, 4 patients - palliative intent).

Responses:
Curative intent: CR 41 pts. (66,12 %), PR 13 pts. (20,96 %), SD 6 pts. (9,67 %), PD 0 pts. (2 pts. were not evaluated).
Palliative intent: CR 0 pts., PR 10 pts. (71,42 %), SD 2 pts. (14,28 %), PD 2 pts. (14,28 %).
The responses were evaluated 1-2 months after finishing of treatment by clinical or pathological examination and imaging assesment (CT, USG).

Conclusion
In this group of patients were achieved relatively high rate responses after the treatment. The problem in evaluation is short follow-up period (average 10 months).
CLINICAL EXPERIENCES USING A CONTACT FLEXIBLE MICROSTRIP APPLICATOR OPERATING AT 70 MHZ FOR EXTERNAL HYPERTHERMIA

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Introduction
At our department occasionally patients are presented with a superficial tumor with extension in depth beyond the range of the regular superficial CFMA-434 applicator operating at 434 MHz. For this group of patients the Contact Flexible Microstrip Applicator operating at 70 MHz (CFMA-70) was introduced. This applicator combines flatness, lightness and flexibility with a high penetration depth in the range generally used for regional hyperthermia systems. The objective of this study is to evaluate the performance of the CFMA-70 and its applicability for superficial hyperthermia on deep seated tumors.

Method
So far 6 patients have been treated with the CFMA-70 applicator. All patients selected had advanced primary or recurrent breast cancer and were previously treated with radiotherapy, chemotherapy and in three cases an ablazio mamma. The depth of the tumors was 4 cm or more, too large to be treated adequately with the CFMA-434 applicator. The aim was four treatments at a tumor temperature between 41 and 43°C. Temperatures were measured with multi-point thermocouples, with 2 to 4 non-invasive thermocouples placed at the skin below the applicator and up to 3 invasive thermocouples. The geometry of the volume to be heated was considered to be difficult to treat in all patients as in most cases the breast or tumor was vast, irregular and quite rigid.

Results
The penetration depth of the EM-field appeared to be sufficient and the applied power levels, on average 220 W, and were well below the maximum level of 300 W. An additional flexible bolus was placed on the breast to reduce power reflection as it proved difficult to conform the shape of the antenna to the shape of the breast. The temperature distributions were rather inhomogeneous and T50 was rather low: T10, T50 and T90 of the invasive tumor temperature points averaged over all patients are 41.0°C, 39.6°C and 38.5°C respectively.

Discussion & Conclusions
Based on the extended penetration depth of the CFMA-70 most benefit is expected for patients with large superficial tumors with a depth exceeding 4 cm, too large to be treated adequately with the CFMA-434. However, relatively low average temperatures are achieved in the cases presented. This was caused by the irregular shape of the target and by occurrence of hot spots which significantly limit the applied power (mainly below the ends of the applicator where the normal E-field component is largest).

Alternative applications for which this applicator may be useful: as the SAR pattern of this applicator is insensitive to the bolus thickness it may act as a replacement of the CFMA-434 for situations where a uniform bolus thickness is difficult to achieve (e.g. uneven surfaces). Also, the CFMA-70 may enable treatment of (deeper) tumors located beyond the human trunk at sites that are difficult to approach using the less flexible and bulky phased array systems.
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